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Imaging Markers of Left Ventricular Function in Patients with Aortic Stenosis: A Clinical Epidemiology Perspective

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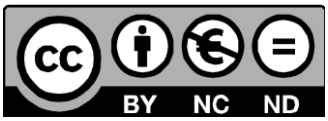
Droits d’auteurs



Summary

Figures list

Tables list

Abbreviations

ACC/AHA: American College of Cardiology / American Heart Association
ARF: acute rheumatic fever
AS: Aortic stenosis
ATTR: transthyretin amyloidosis
AVA: aortic valve area
BAV: bicuspid aortic valve
CI: confidence intervals
CMR: cardiac magnetic resonance
DI: dimensionless index
ESC: European Society of Cardiology
GBD: Global burden disease
GLS: global longitudinal strain
HR: hazard ratio
LDL: low density lipoprotein cholesterol
LGE: late gadolinium enhancement
LMICs: Low middle-income countries
Lp(a): lipoprotein(a)
LV: left ventricular
LVH: left ventricular hypertrophy
LVM: left ventricular mass
NYHA: New-York Heart Association
PG: peak gradient
RAAS: Renin-Angiotensin-Aldosterone System
ROS: reactive oxygen species
RVD: rheumatic valve disease
SAVR: surgical aortic valve replacement
TAVR: transcatheter aortic valve replacement
VICs: valvular interstitial cells
Vmax: peak maximal velocity
VTI: velocity-time integral
WHO: World Health Organization

Introduction

Aortic stenosis (AS), a cardiovascular disease characterized by narrowing of the aortic valve orifice, represents a major public health problem worldwide. As a common cause of morbidity and mortality in the elderly, this pathology implies a considerable burden on healthcare systems and affects patients' quality of life. Indeed, AS can silently and progressively lead to heart failure, angina pectoris, arrhythmias and even premature death when not timely and appropriately managed[1].

Over the decades, the incidence of AS has increased significantly in industrialized countries. This may be related to the combination of aging of the population together with metabolic disorders epidemic. Practically, both prevalence and incidence of AS will markedly increase worldwide. Southern countries will not be spared by this epidemic. Indeed, the epidemiological transition illustrated by a gradual shift from infectious to metabolic and chronic diseases will, during likely fairly long period, favor the presence of a double burden that is particularly generative for AS[2].

The AS is characterized by a long silent asymptomatic phase in which myocardial and pulmonary-vascular consequences develop. The general population screening of AS is still limited to physical examination, questioner and auscultation. Delayed diagnoses and insidious progression contribute to heightened healthcare costs, morbidity, and mortality. Costly diagnostic procedures and the primary treatment, aortic valve replacement, place significant financial strain on individuals, healthcare systems, and society at large. The disease's chronic nature demands prolonged medical management and exacerbates healthcare resource utilization[3]. Furthermore, AS-related comorbidities, productivity loss, and informal caregiving elevate societal costs and impact vulnerable populations disproportionately. The psychological toll on patients, coupled with frequent hospitalizations and disability-adjusted life years, underscore the disease's far-reaching societal implications. Evaluating cost-effectiveness, integrating palliative care, and promoting early detection and disease prevention are crucial strategies to mitigate the burden. Public-private collaborations, patient-centered care models,

and global data sharing are essential to optimize healthcare resource allocation and improve patient outcomes, fostering a comprehensive approach to addressing the complexities of AS.

In recent years, the cornerstone of AS management has been early detection, motivated by impetus toward early intervention. This is mainly related to the lack of medical treatment or prevention action allowing slowing progression of AS. In this regard, many efforts have been made by investigators to identify the earliest pathophysiological consequences of AS. Up to 2010, the current management of patients with AS was based on a “watch-for-symptoms” strategies, where the patients were only operated in the presence of symptoms and/or left ventricular (LV) dysfunction. Since then, a real paradigm shift has taken place, and indications for intervention are increasingly directed towards patients who are increasingly less severe, or at least identified earlier in the natural history of their disease. As compared to both 2017 American College of Cardiology / American Heart Association (ACC/AHA)[4] or European Society of Cardiology (ESC)[5], the most recent guidelines[6,7] highlighted this shift in paradigm allowing aortic valve intervention in patients with severe AS but only slight myocardial consequences.

Today, there is an increasingly robust body of evidence suggesting that it is preferable to intervene in patients with AS as early as possible, i.e. in the absence of symptoms or myocardial consequences that are too advanced or even irreversible. Mainly, many studies have demonstrated that the earliest the intervention, the best myocardial, clinical and functional outcome. Ultimately, the prognosis of patients is also well better when there are operated earlier.

The aim of the present work is to synthetize our contribution to the paradigm shift towards early intervention in patients with AS. In this regard, we will identify and discuss promising avenues of research that could improve patients risk stratification, management and outcome. Purposely, our theoretical frameworks and our approach to the question will be those of Public Health.

Partie I. Calcific Aortic Stenosis

I.1. Mechanisms and Pathophysiology

I.1.1. Mechanisms

The primary mechanism underlying AS is the calcification of the aortic valve leaflets. This process shares some similarities with atherosclerosis, both in terms of physiological mechanism and risk factors[8]. This involves the deposition of lipids, inflammatory cells, and calcium within the valve tissue. While the exact triggers for calcification are not fully understood, several factors contribute to its initiation and progression. Endothelial injury, oxidative stress, and chronic inflammation play critical roles in promoting the transformation of valvular interstitial cells (VICs) into osteoblast-like cells, which leads to the production and deposition of calcific nodules within the valve leaflets. In addition, genetic factors are also involved in AS development and progression[9].

I.1.1.1. Inflammatory process and endothelial injury

Initially, AS is a non-inflammatory process, but as the disease progresses, inflammatory mediators such as cytokines, chemokines, and matrix metalloproteinases are upregulated within the valve tissue[10]. These molecules promote the infiltration of immune cells, particularly macrophages and T lymphocytes, further exacerbating the inflammatory response. Ultimately, this inflammatory milieu contributes to the remodeling of the extracellular matrix and the promotion of calcification (Figure 1).

Nevertheless, inflammatory process in AS often begins with endothelial injury and dysfunction. Various risk factors, such as hypertension, hyperlipidemia, and smoking, contribute to endothelial damage, leading to increased permeability and the expression of adhesion molecules. These adhesion molecules facilitate the recruitment and migration of immune cells, particularly monocytes, into the valvular tissue.

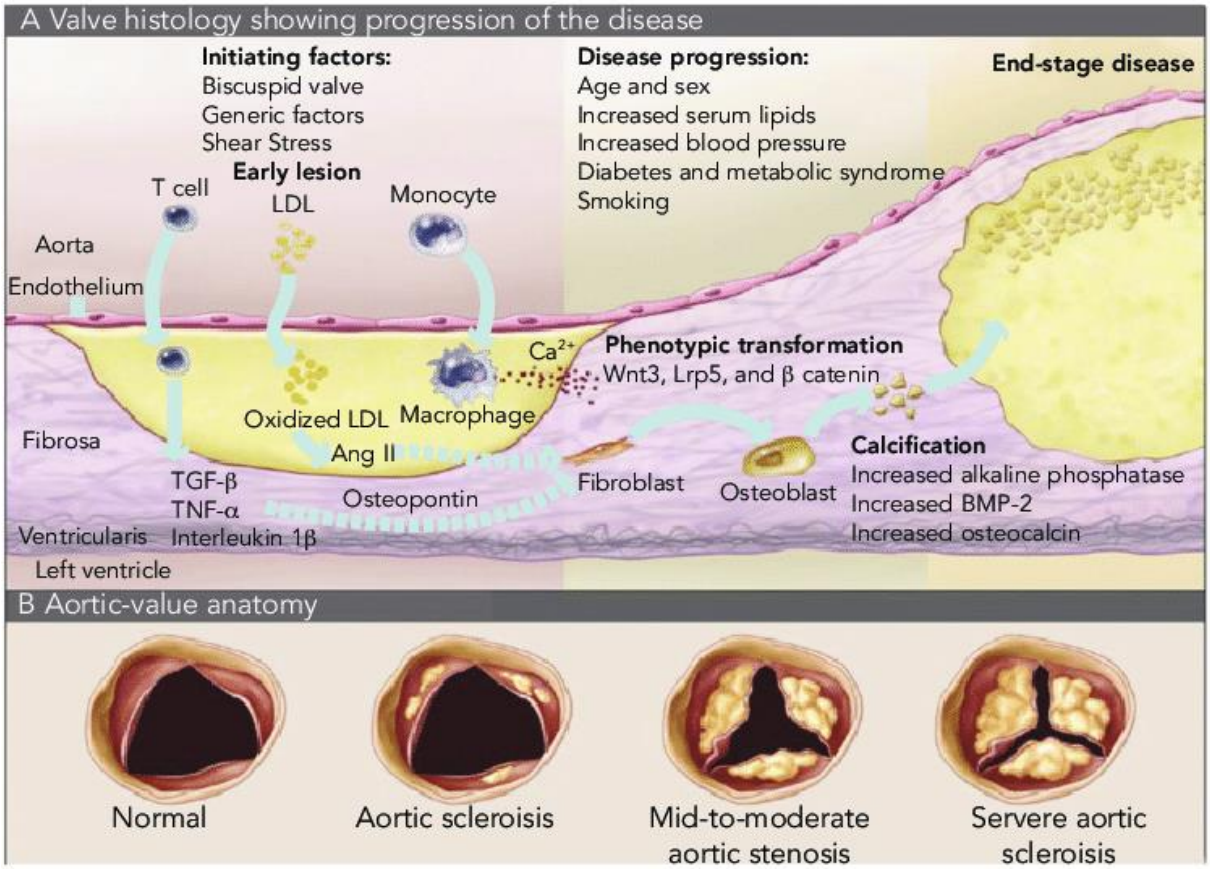
In the details, the inflammatory and endothelial injury response involves a complex interplay of various cellular and molecular components within the valvular tissue.

- ✓ Monocytes are among the first immune cells to infiltrate the valve tissue in response to the inflammatory signals. Once inside the tissue, these monocytes differentiate into macrophages, which are critical players in the inflammatory response. Macrophages release pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-1 beta, promoting a cascade of inflammatory events.
- ✓ The VICs are resident fibroblast-like cells within the aortic valve leaflets. In response to the inflammatory environment, VICs undergo phenotypic changes and differentiate into myofibroblast-like cells. These activated VICs play a central role in the calcification process by promoting the deposition of extracellular matrix proteins, such as collagen and fibronectin[11].
- ✓ Osteoblastic differentiation: one of the key features of AS is the transformation of VICs into osteoblast-like cells, a process known as osteoblastic differentiation. This process is stimulated by factors like bone morphogenetic proteins, Wnt signaling, and inflammation-induced upregulation of various osteogenic genes[12,13]. As VICs undergo osteoblastic differentiation, they produce bone-like nodules within the valve tissue, leading to progressive calcification.
- ✓ Extracellular matrix remodeling: chronic inflammation within the valve tissue leads to the remodeling of the extracellular matrix. Increased expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases disrupts the delicate balance between matrix synthesis and degradation. This dysregulation contributes to the degradation of valve tissue and the accumulation of calcium and lipid deposits[14].
- ✓ The inflammatory processes are also associated with increased production of reactive oxygen species (ROS). ROS play a dual role in AS pathogenesis – they promote oxidative stress, leading to further endothelial damage and inflammation, while also contributing to the activation of VICs and promoting calcification. Other presence of inflammatory cells, such as macrophages and T lymphocytes, contributes to the ongoing inflammatory response within the valve tissue. These immune cells release

pro-inflammatory cytokines and chemokines, further amplifying the inflammatory cascade and perpetuating valvular damage.

- ✓ Toll-like receptors are essential components of the innate immune system and play a role in recognizing pathogens and damage-associated molecular patterns. Activation of TLR signalling in AS can further amplify the inflammatory response, leading to the release of pro-inflammatory mediators.

Figure 1: Mechanisms involved in AS progression*.



**Reproduced with permission from Lerman et al.* [15]

Overall, the chronic inflammatory process in AS creates a hostile microenvironment within the valve tissue, promoting the differentiation of VICs into osteoblast-like cells, leading to the progressive formation of calcific nodules. This calcification process stiffens the valve leaflets, impairs their proper opening and closing during the cardiac cycle, and ultimately results in AS.

Understanding the intricate details of the inflammatory mechanisms involved in AS provides valuable insights into potential therapeutic targets to halt or reverse disease progression.

I.1.1.2. Genetic Factors and familial clustering

Genetic factors play a significant role in the pathogenesis of AS, contributing to an individual's predisposition to develop valvular calcification and stenosis. Mutations in genes encoding proteins involved in valve development and homeostasis, such as NOTCH1, GATA5, and SMAD6, have been identified as being associated with an increased risk of valve calcification and stenosis. These genetic predispositions, combined with other environmental factors, may accelerate the onset and progression of the disease in susceptible individuals.

The AS can run in families, indicating a strong genetic component. Studies have identified multiple genes associated with familial clustering of AS, including NOTCH1, GATA5, SMAD6, and others. Familial AS is often characterized by early-onset and severe valve calcification.

- ✓ The Notch signaling pathway is crucial for valve development and maintenance. Mutations in the NOTCH1 gene have been associated with aortic valve calcification and stenosis. NOTCH1 mutations can lead to impaired Notch signaling, affecting valve interstitial cell differentiation and function, ultimately promoting the calcification process.
- ✓ GATA transcription factors play essential roles in embryologic cardiovascular development. GATA5 transcription factors are involved in regulating the differentiation of cardiac and intestinal cells and are crucial for the development of these tissues. Mutations in the GATA5 gene have been linked to familial AS. GATA5 mutations may disrupt valve development and function, contributing to the disease's pathogenesis.
- ✓ The SMAD family of proteins is involved in the transforming growth factor-beta (TGF-β) signaling pathway, which regulates cellular processes like proliferation and differentiation. Mutations in the SMAD6 gene have been associated with aortic valve

calcification and stenosis. The SMAD6 mutations can impair the inhibition of TGF-β signaling, leading to dysregulated valvular remodeling.

- ✓ Elevated levels of lipoprotein(a) (Lp(a)) in the blood have been identified as a genetic risk factor for AS. Lp(a) is a lipoprotein particle that contains both LDL cholesterol and apolipoprotein(a). High levels of Lp(a) are associated with increased valvular calcification and disease progression.
- ✓ Calcific aortic valve disease susceptibility loci: genome-wide association studies have identified specific genetic loci associated with an increased risk of CAVD, providing further evidence of the genetic basis of AS. These loci often involve genes related to valvular and vascular biology, extracellular matrix remodeling, and lipid metabolism.

In addition to the common genetic factors mentioned above, rare variants in various genes have been associated with AS in specific cases. These variants may impact valve development, function, or cellular processes involved in valve calcification. Furthermore, epigenetic changes, such as DNA methylation and histone modifications, can influence gene expression without altering the underlying DNA sequence. Epigenetic mechanisms have been implicated in the regulation of genes involved in AS pathogenesis. Environmental factors may also influence epigenetic changes that contribute to disease development.

Finally, bicuspid aortic valve (BAV) is also a familial and genetic condition markedly associated with the development of AS. The BAV is a congenital condition where the aortic valve has two leaflets instead of the usual three. It is a common genetic factor associated with AS. Individuals with BAV have altered flow patterns in the ascending aorta, leading to changes in shear stress on the valve and an increased risk of valve calcification and stenosis.

To conclude, it remains important to note that AS is a multifactorial disease, and both genetic and environmental factors interact to determine an individual's susceptibility to the condition.

The exact interplay between genetic predisposition and environmental factors, such as lifestyle choices and comorbidities, remains an active area of research. Understanding the genetic basis of AS provides valuable insights into disease mechanisms, risk prediction, and potential targeted therapies for affected individuals and those at risk.

I.1.2. Pathophysiology

As the valve leaflets undergo calcification and stiffen, they become less flexible and lose their ability to open and close efficiently during the cardiac cycle. This results in increased resistance to blood flow through the aortic valve, leading to pressure overload on the LV. The LV compensates initially by undergoing concentric hypertrophy to maintain adequate cardiac output. However, over time, the ventricular wall becomes thickened and less compliant, leading to impaired diastolic filling and ultimately, LV dysfunction.

The consequences of AS extend beyond the valve and ventricular level. The increased pressure gradient across the stenotic valve induces changes in the arterial system, including arterial remodeling and hypertrophy. This process is known as ventricular-arterial coupling and contributes to the pathophysiology of AS by increasing the workload on the heart and further compromising cardiac function.

Clinically, patients with AS may remain asymptomatic for a considerable period, making early detection and intervention challenging. As the disease progresses, however, patients often develop symptoms related to reduced cardiac output, such as exertional dyspnea, fatigue, chest pain, and syncope. Angina pectoris may occur due to increased myocardial oxygen demand secondary to LV hypertrophy, or it can be the result of coronary artery disease frequently coexisting with AS.

Left untreated, severe AS can lead to life-threatening complications, such as heart failure, arrhythmias, infective endocarditis, and sudden cardiac death. Once symptomatic severe AS is diagnosed, surgical or transcatheter aortic valve replacement (SAVR or TAVR) is the

definitive treatment, as medical therapies have not shown significant efficacy in reversing or halting disease progression.

I.2. Epidemiology

The AS is one of the most common cardiovascular diseases worldwide. According to the World Health Organization (WHO) data, it affects millions of people across different continents and poses a major concern for healthcare systems[16,17]. The epidemiology of AS remains unclear worldwide and is characterized by marked disparities between geographical zone and, inside a given area, by economic status, lifestyle or health literacy. The etiology of AS is different from different regions in the world, and even inside a same region. Consequently, this multiplies challenges in assessing its exact prevalence and incidence. Roughly, whereas rheumatic-related AS predominantly affects young women, calcification-related AS rather mainly arise in old men. This markedly impact screening campaign in a given target population and sample.

In low- and middle-income countries, AS is still related to the rheumatic disease burden which mainly affects the poorest people. By contrast, in Western countries, where rheumatic fever and infection is no longer considered as a public health issue, the AS is rather a disease of elderly, with atherosclerotic-related risk factors. Nevertheless, even in high-income countries, rheumatic fever may still be an important epidemiologic trigger for AS in the poorest, unhealthy or insalubrious areas or among immigrants and older adults[18–20].

I.2.1. High-income countries epidemiology

The incidence of AS has significantly increased worldwide in recent decades, primarily due to the aging population and advancements in medical care that have led to longer life expectancy. Industrialized countries are more affected by this rising incidence, mainly due to their markedly higher aging populations than other countries. Additionally, the adoption of sedentary lifestyles, unhealthy diets, and other lifestyle-related risk factors has also contributed to the increasing prevalence of AS in these regions. Of note, the increase in AS prevalence and incidence parallels increase metabolic disorders and obesity pandemics in Western countries.

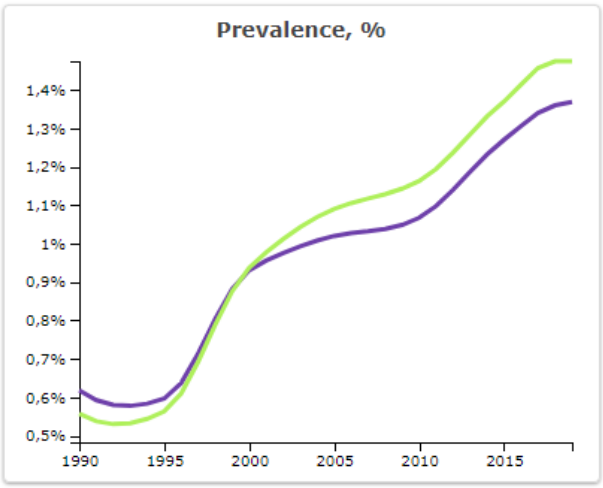
The Framingham Heart Study estimated the prevalence of AS to be approximately 2% in individuals aged 60 to 69 years and 4% in those aged 70 to 79 years. In a meta-analysis including subjects >75 years old, any grade of AS has been estimated to reach 12.4% of the population [2]. Of interest, 3.4% of them may have severe AS and approximately 3 quarters of them were symptomatic. In the Valvular Heart Disease (VHD) II survey, among the 5 219 included patients with native severe valve disease, 41.2% have AS, making such valve disease the most prevalent[21].

As life expectancy continues to rise, the burden of AS is expected to grow. Additionally, the prevalence of AS may vary across different populations, with some studies suggesting a higher prevalence among males compared to females. The incidence of AS is also relatively understudied: the Tromsø Study reported an incidence rate of 4.9‰/year[22].

In France, AS represents a growing public health concern due to demographic transitions leading to an aging population. According to national epidemiological data and similarly than in the rest of Western countries, the prevalence of AS has significantly increased over the past few decades. With an aging population and improved disease detection through advances in medical imaging, the number of diagnosed cases has risen significantly.

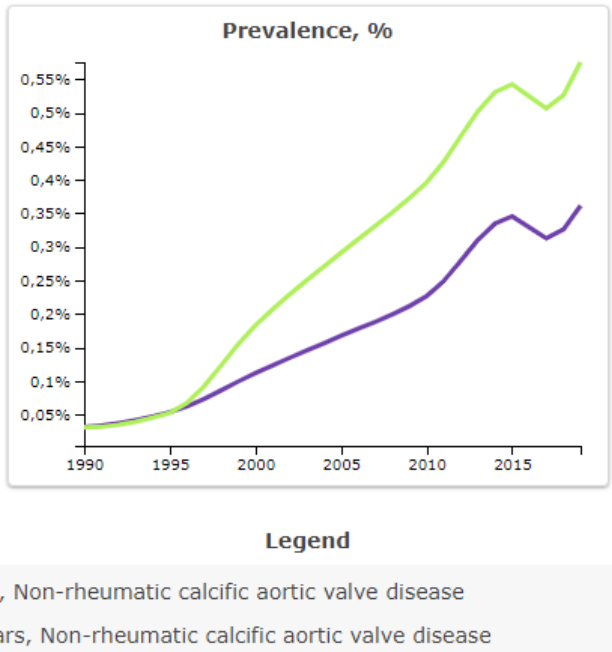
According to Global Burden Disease data, the prevalence of non-rheumatic aortic valve disease (i.e. mainly AS) markedly increase from 1990 to 2019. The impact of AS on death and injury in high-income countries seems also be increased around 1% since 90's (Figure 2). Similar trends occur in France both in male and female (Figure 3).

Figure 2: Prevalence of non-rheumatic calcific aortic valve disease in high-income countries from 1990 to 2019 in males and women >55 years old*.



**Data derived from the 2019 Global Burden of Disease (GBD) study.*

Figure 3: Prevalence of non-rheumatic calcific aortic valve disease in France from 1990 to 2019 in males and women >55 years old*.



**Data derived from the 2019 GBD study.*

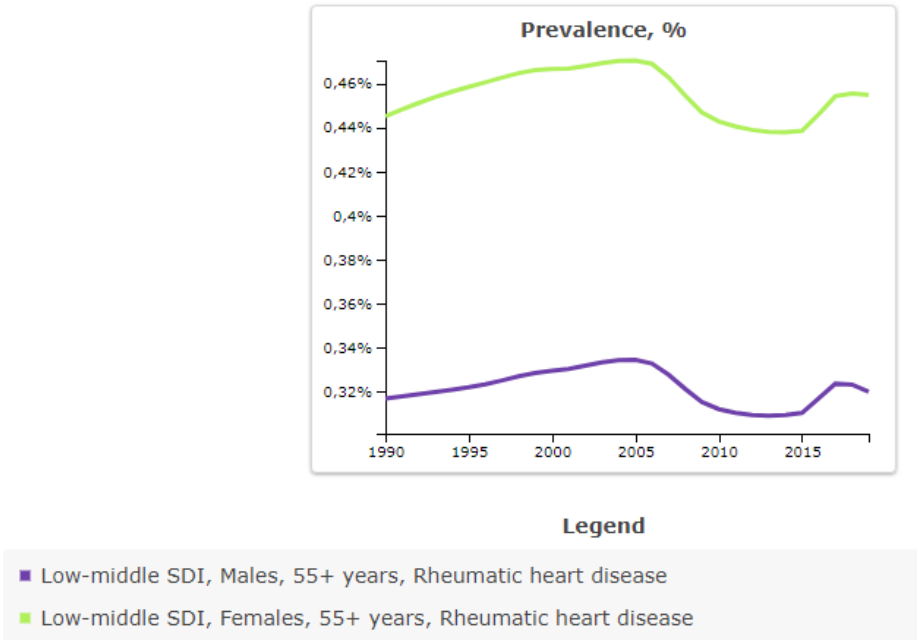
In conclusion, AS is a concerning cardiovascular disease, both globally and in France. Its incidence is steadily increasing due to the aging population and evolving associated risk factors. A better understanding of its epidemiology is essential to guide public health policies, improve early screening, and enable optimal patient management. Collaborative efforts to prevent and treat this major cardiac pathology are needed to reduce its impact on public health and enhance the quality of life for affected individuals.

Predicting the epidemiological projections for AS in the next 10 years and beyond involves considering various factors, including demographic changes, advances in medical technology and screening, changes in risk factors, and potential interventions. While it is challenging to provide precise projections, some trends can be anticipated based on existing data and research.

I.2.2. Low- and Middle-income Countries epidemiology

By contrast with high-income countries, rheumatic heart disease remains the leading cause of valve disease in low- and middle-income countries (LMICs). The epidemiology of rheumatic valve disease (RVD) in LMICs is poorly explored and data are scarce. The most recent data from GBD demonstrate approximately minor change in the prevalence of RVD in LMICs between 1990 to 2019 (Figure 4).

Figure 4: Prevalence of rheumatic heart disease in low-middle income countries from 1990 to 2019 in males and women >55 years old*.



**Data derived from the 2019 (GBD) study.*

The RVD often affects children and young adults, leading to lifelong cardiac complications. This higher prevalence of RVD in LMICs by comparison with high-income countries can be attributed to limited access to healthcare, crowded living conditions, and a lack of access to antibiotics for the prevention of acute rheumatic fever (ARF), which is the precursor to RVD.

The incidence of ARF is significantly higher in low-income countries, but within these same countries there are still major disparities, both geographically and in terms of political and economic situation. The ARF is triggered by untreated streptococcal throat infections, and in LMICs, inadequate access to antibiotics, suboptimal healthcare infrastructure, and poor hygiene practices contribute to a higher incidence.

Socio-economic factors, such as poverty, overcrowding, and limited access to clean water and sanitation facilities, play a significant role in the epidemiology of RVD in LMICs. These conditions promote the spread of streptococcal infections and increase the risk of developing ARF. Limited access to healthcare services in many LMICs results in delayed diagnosis and treatment of RVD. This often leads to advanced disease presentation and a higher likelihood

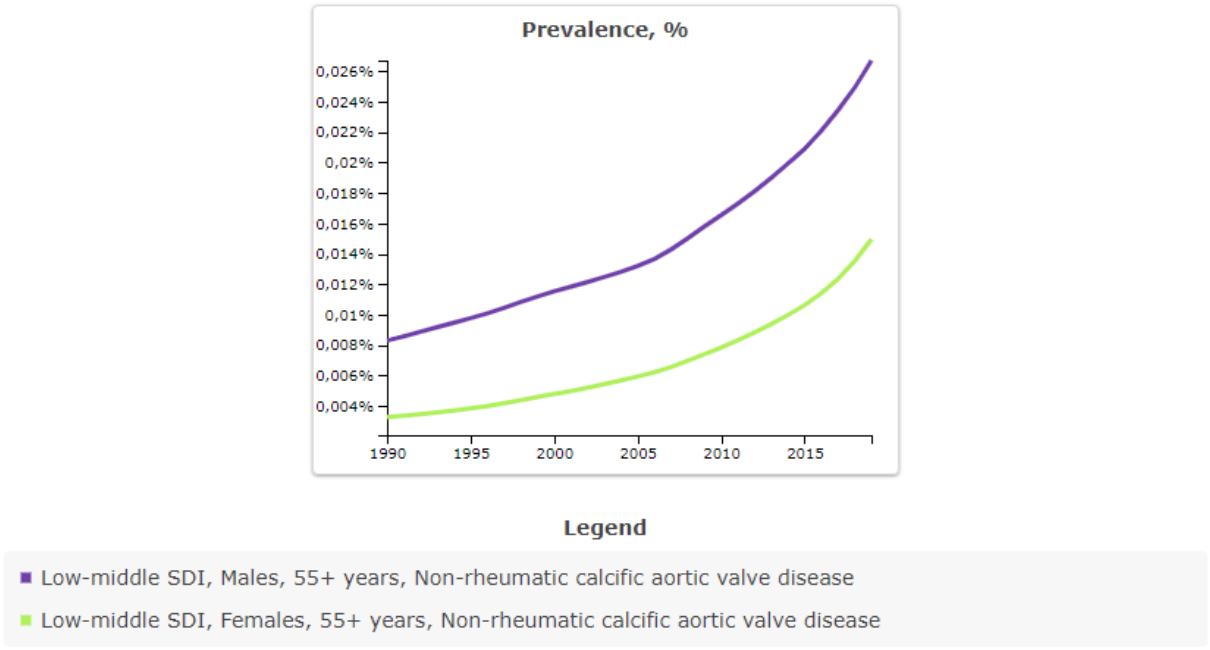
of complications. The diagnosis of RVD can be challenging in resource-constrained settings due to the lack of advanced imaging and diagnostic tools. As a result, RVD may go undiagnosed or be diagnosed at a later stage. Access to cardiac surgical interventions, such as valve dilatation, repair or replacement, is often limited in LMICs due to cost, infrastructure, and expertise constraints. This can further result in suboptimal management of RVD cases.

Some LMICs have implemented public health initiatives to raise awareness about RVD, improve access to antibiotics for streptococcal infection prevention, and enhance early diagnosis and treatment. These efforts, while promising, may not be widespread or adequately funded in all LMICs. In many of these countries, access to antibiotics is now easier, and some excesses in their use have been documented. Nonetheless, this is gradually limiting the epidemiological tension surrounding RVD. Nowadays, the long-term RVD-related complication, including heart failure, stroke, and infective endocarditis, may further strain healthcare resources and have significant societal and economic impacts in LMICs.

In summary, the epidemiology of rheumatic valve disease in low- and middle-income countries is characterized by a higher burden of disease due to a combination of socio-economic factors, limited access to healthcare, challenges in prevention and diagnosis, and inadequate treatment resources. Addressing RVD in LMICs requires a multifaceted approach that includes improved access to antibiotics, enhanced healthcare infrastructure, increased awareness, and efforts to mitigate the risk factors contributing to the disease's prevalence.

In contrast, the evolution of the epidemiology of non-rheumatic VHD in LMICs has not been documented yet. The epidemiological transition that is taking place in these countries, with metabolic disorders becoming increasingly prevalent, should encourage the emergence of pathologies linked to atherosclerosis. In this context, non-rheumatic VHD is set to increase progressively in subjects over 50 in LMICs. For example, calcific AS, despite remaining uncommon, shows progressive increase in prevalence since 1990 with obvious acceleration in 2005-2010 in LMICs (Figure 5).

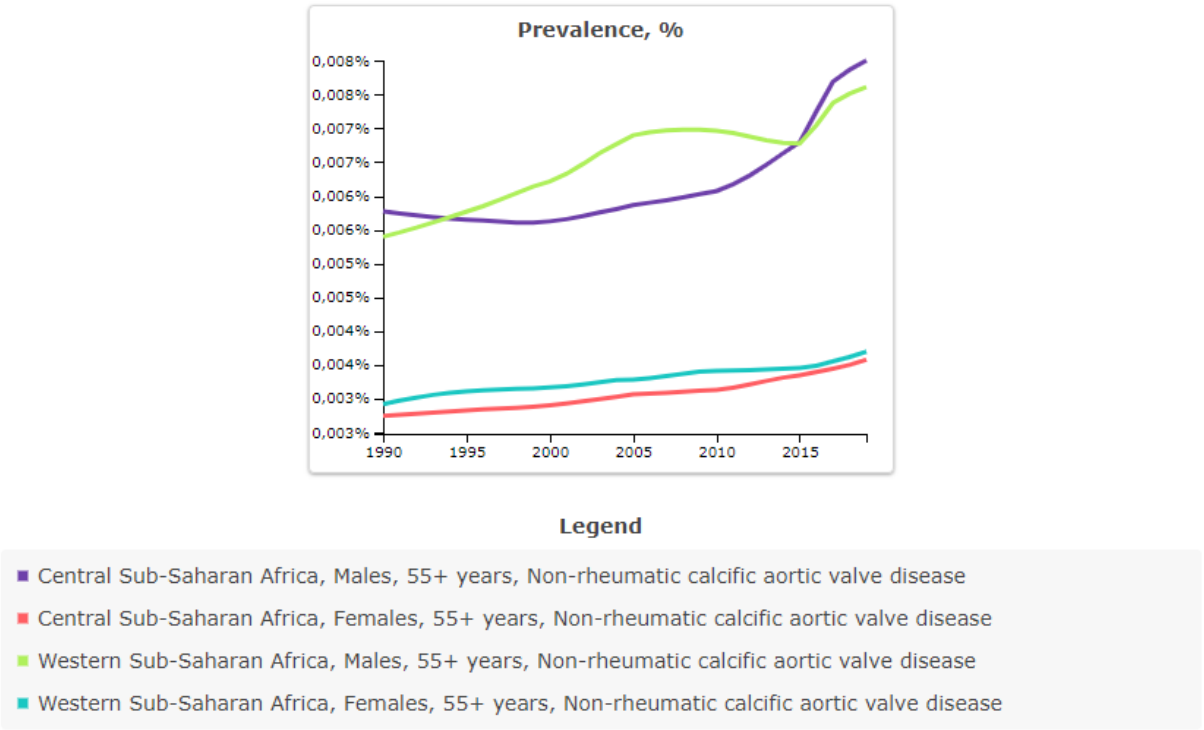
Figure 5: Prevalence of non-rheumatic calcific aortic valve in low-middle income countries from 1990 to 2019 in males and women >55 years old*.



**Data derived from the 2019 (GBD) study.*

Similar trends seem to be found in Sub-saharan Africa (Figure 6).

Figure 6: Prevalence of non-rheumatic calcific aortic valve in Sub-Saharan Africa from 1990 to 2019 in males and women >55 years old*.



**Data derived from the 2019 (GBD) study.*

Nevertheless, these numbers should be cautiously interpreted. The open source data from GBD arise from models in whom multiple assumption are performed and mainly using administrative database. The exhaustivity and quality of these data are frequently jeopardized. Consequently, this underlined the profound need for large program investigating VHD in LMICS and producing rigorous data.

I.2.3. Risk Factors

Several risk factors contribute to the mechanisms underlying the development and progression of AS. These factors can be broadly categorized into modifiable and non-modifiable risk factors (including genetic factors, and bicuspid aortic valve [BAV]). Understanding these risk factors is essential for identifying individuals at higher risk for AS and implementing preventive measures to reduce the burden of this condition. Briefly, every factors or condition promoting

oxidative stress, inflammation, lipid or macrophage intra-valvular deposit, endothelial stress or calcific process can be seen as a potential risk factor for AS.

I.2.3.1. Non-modifiable risk factors

I.2.3.1.1. Age and gender

Beyond genetics factors and BAV, that are already discussed above, age and gender play an important role in developing AS. Advancing age is the most significant non-modifiable risk factor for AS. It is predominantly a disease of the elderly population, with the prevalence increasing significantly after the age of 65. As people age, wear and tear on the aortic valve over time can contribute to calcification and valvular dysfunction. Men have a higher incidence of AS compared to women, although the reasons for this gender difference are not fully understood. However, the level of severity of AS is not homogeneous between men and women. Indeed, women may have a similar level of AS severity, despite lower calcific load or rigidity.

I.2.3.1.2. Amyloidosis

An intriguing and emerging area of research in AS is its association with amyloidosis. Amyloidosis can manifest in different forms, with light chain amyloidosis and transthyretin amyloidosis (ATTR) being the two most common types. The link between AS and amyloidosis has drawn increasing attention due to several factors. Firstly, both conditions are typically diseases of aging, with AS primarily affecting the elderly population, while the risk of amyloidosis, particularly ATTR amyloidosis, also increases with age. Secondly, there is growing evidence to suggest that amyloid deposition may be a contributory factor in the progression of AS. Several studies demonstrated that patients with severe AS exhibited a high prevalence of transthyretin amyloid deposits in their aortic valves[23]. These amyloid deposits were associated with increased aortic valve calcification and inflammation, possibly accelerating the progression of AS. Additionally, amyloidosis can lead to aortic root thickening and stiffness, which may have implications for the development of AS. Furthermore, AL amyloidosis has been linked to cardiac involvement, leading to a restrictive cardiomyopathy

phenotype that can mimic symptoms seen in AS. This overlapping clinical presentation can create diagnostic challenges and highlights the need for comprehensive cardiac evaluation in patients with both conditions.

As for the underlying pathophysiological mechanisms linking AS and amyloidosis, there is ongoing research seeking to elucidate the precise interactions. It is proposed that inflammation and oxidative stress, common features of both AS and amyloidosis, may play a role in the progression of these conditions. In particular, proinflammatory cytokines and immune cell activation observed in systemic amyloidosis may contribute to the inflammation and calcification of aortic valves in AS. Moreover, the accumulation of amyloid deposits in the aortic valve tissue can alter its structural integrity, possibly making it more susceptible to calcification and impairment of valve function. This suggests a complex interplay between AS and amyloidosis, where each condition may exacerbate the progression of the other.

The clinical implications of the AS-amyloidosis relationship are significant. Patients with both AS and amyloidosis present a unique clinical challenge, and early diagnosis and appropriate management are paramount. Cardiologists and clinicians should maintain a high index of suspicion for amyloidosis in AS patients, especially in cases with unexplained LV hypertrophy or rapidly progressive heart failure. Timely identification is crucial because the presence of amyloidosis can influence the treatment strategy for AS. Furthermore, understanding the shared mechanisms between these conditions may lead to novel therapeutic approaches that could slow disease progression and improve patient outcomes.

An evolving body of evidence supports an intricate relationship between AS and amyloidosis, wherein amyloid deposition may exacerbate the progression of AS, and AS can complicate the clinical presentation of amyloidosis. While the precise mechanisms underlying this relationship are still a subject of active investigation, the clinical and therapeutic implications are significant. A multidisciplinary approach, involving both cardiology and amyloidosis specialists, is essential for the optimal management of patients with concurrent AS and amyloidosis.

I.2.3.1.3. Osteoporosis

The relationship between AS and osteoporosis is not fully understood and several factors need to be considered[24,25]. Some risk factors for AS and osteoporosis overlap. These include older age, genetic predisposition, and certain lifestyle factors such as smoking and poor nutrition. Some studies suggest that individuals with osteoporosis may have a higher likelihood of developing calcified aortic valves[26–29], but this relationship is still debated[25,30].

In addition to chronic inflammation which plays a role in both AS and osteoporosis, hormonal imbalances, particularly in postmenopausal women, are known to increase the risk of both AS and osteoporosis. Estrogen, for example, has a protective effect on bones and may also influence cardiovascular health. Changes in hormonal levels during menopause may contribute to both conditions[31].

Of note, despite such obvious pathophysiological and mechanistic links between AS and osteoporosis, more research is needed to fully elucidate the nature of this relationship. The presence of one condition does not necessarily cause the other, but the shared risk factors and pathways suggest a potential association.

I.2.3.2. Modifiable risk factors

I.2.3.2.1. Hypertension

High blood pressure and hypertension is a significant modifiable and highly prevalent risk factor (>50% of patients with AS) for AS. Chronic hypertension can directly contribute to valvular dysfunction and calcification through various mechanisms[32,33]. The risk of AS is 40% higher in patients with hypertension as compared to those without[34].

Hypertension leads to chronic mechanical stress on the endothelium, the inner lining of blood vessels, including the aortic valve. This mechanical stress can lead to endothelial dysfunction, impairing the ability of the endothelium to maintain vascular homeostasis. In turn, endothelial dysfunction contributes to inflammation, oxidative stress, and alterations in vascular tone.

Hypertension is also known to be associated with low-grade chronic inflammation in the vasculature. As discuss above, inflammatory process is one of the main mechanisms promoting AS. Furthermore, hypertension is linked to increased production of ROS in the blood vessels, including the aortic valve. ROS play a role in the oxidative modification of lipids and proteins, further contributing to endothelial dysfunction and inflammation within the valve tissue.

Mechanically, high blood pressure results in increased pressure within the aorta, creating hemodynamic stress on the aortic valve leaflets and endothelium. This increased pressure gradient can lead to the valve thickening and stiffening, making it more susceptible to calcification and impairing its normal function. Furthermore, hypertension can lead to alterations in the composition and structure of the extracellular matrix within the valve tissue. Excessive production and deposition of matrix proteins can contribute to the formation of fibrotic tissue and calcific nodules.

The alteration of blood flow patterns resulting from hypertension may also create abnormal shear stress on the aortic valve. Disturbed flow patterns, particularly in individuals with a bicuspid aortic valve, can trigger pathological changes in valvular endothelial cells and contribute to valve remodeling and calcification.

The Renin-Angiotensin-Aldosterone System (RAAS) activation is another modifiable risk factor related to hypertension. It is also involved in developing and progression of AS. Hypertension activates the RAAS, which may, in turn, promote fibrosis, inflammation, and morphological changes in myocardium, vessels and also aortic valve[35–38].

Lifestyle modifications, such as adopting a heart-healthy diet, regular physical activity, weight management, and reducing sodium intake, can help to control hypertension and may be a potential target to slow the progression of AS. Additionally, antihypertensive medications are commonly prescribed to manage blood pressure and reduce the risk of associated cardiovascular complications. Nevertheless, no trial, to the best of our knowledge, are currently exploring such research pathway (source: clinicaltrial.gov, July 2023).

Overall, hypertension is a complex risk factor that impacts various aspects of valvular homeostasis and can contribute to the development and worsening of AS. Management of hypertension is essential not only for reducing the risk of AS but also for overall cardiovascular health.

I.2.3.2.2. Metabolic disorders

As the prevalence of obesity has been increasing worldwide, its impact on cardiovascular diseases, including AS, has garnered increased attention. Obesity is a well-known marker of risk of AS, mainly due to its association with others metabolic disorders. However, it could be also another significant risk factor associated with the development and progression of AS[39].

Indeed, obesity is characterized by chronic low-grade inflammation due to the release of pro-inflammatory cytokines and adipokines from adipose tissue. This inflammatory state can promote the infiltration of immune cells, such as macrophages, into the valve tissue, initiating and perpetuating the inflammatory response implicated in AS. Obesity often coexists with other risk factors for AS, such as hypertension, diabetes, dyslipidemia, and ultimately metabolic syndrome. These risk factors can have synergistic effects, accelerating valvular calcification and disease progression.

Elevated levels of lipids in the blood, particularly low-density lipoprotein (LDL) cholesterol, are associated with an increased risk of AS. Dyslipidemia contributes to the formation of lipid-rich plaques within the valve tissue, triggering inflammation and calcification. Patients with diabetes have an elevated risk of AS. Type-1 and type-2 diabetes are associated with 2-fold and 1.6-fold increase in risk of AS development, respectively[40]. Few hypotheses suggest that diabetes-related metabolic disturbances, such as hyperglycemia and insulin resistance, may accelerate the calcification process within the aortic valve. Insulin resistance can lead to endothelial dysfunction, oxidative stress, and inflammation, all of which contribute to the pathogenesis of AS.

I.2.3.2.3. Other modifiable risk factors

Although its prevalence decreases in western countries and over age, smoking has been linked to the development and progression of AS. Smoking promotes oxidative stress and inflammation, contributing to valvular calcification and dysfunction. Consequently, smokers increase their individual risk to develop AS. A large cohort study reported that compared with never smokers, the HR was 1.46 (95% CI: 1.16-1.85) in current smokers of ≥30 pack-years. Former smokers who had quit smoking 10 or more years previously had similar risk for AVS as never smokers[41]. Similarly, smoking was associated with faster AS progression. History of smoking multiply by more than 3 the risk of mean transaortic pressure gradient progression >5mmHg/year (relative risk =3.06; 95% confidence interval = 1.09-8.61; p = 0.034).

Patients with chronic renal disease are at higher risk of developing AS, while it remains difficult to judge whether it is only a marker or a real risk factor. It is documented that occurs 10-20 years earlier in patients on dialysis compared with the general population[42]. AS is twice as prevalent in patients with renal failure as compared to the general population. In addition, AS progresses at a faster rate and is associated with a higher risk of death and poorer quality of life in patients on dialysis[43]. In incident cases of AS, patients with chronic renal failure are more and more frequent. In Canada, from 2000 to 2016, age-standardised proportions of patients with AS with dialysis and pre-dialysis increased by 41% and by 45%, respectively. Inversely, age-standardised proportions of dialysis and pre-dialysis among non-AS patients decreased by 63% and by 32%, respectively, during the same study period[44]. The precise mechanisms linking renal disease and AS are not fully understood, but chronic inflammation, mineral imbalances, and impaired calcium-phosphate metabolism may play a role.

Radiation exposure may exacerbate calcification via pro-inflammatory and pro-fibrosis process. Prior radiation therapy to the chest, especially in childhood or early adulthood, is associated with an increased risk of AS. The damaging effects of radiation on the aortic valve may manifest years or even decades after the radiation exposure. Mainly, radiation exposure

may lead to formation of micro-calcification. These microcalcifications may serve as the nidus for further calcification, initiating the process of valvular calcification and narrowing

Finally, the most frequent risk factor for AS worldwide still remains rheumatic fever. Although less common in Western countries, except in specific area impacted by poverty and unhealthy conditions, Southern countries are still affected by rheumatic fever secondary to streptococcal infection.

History of rheumatic fever, particularly in childhood, can lead to valvular damage, including AS, due to the autoimmune response triggered by group A streptococcal infections.

I.2.3.3. Synergy between risk factors

Of note, many of these risk factors are interconnected, and individuals may have multiple risk factors simultaneously. For instance, hypertension often coexists with other risk factors for AS, such as hyperlipidemia and diabetes and/or metabolic syndrome. These risk factors can synergistically promote valvular calcification and disease progression. Moreover, the interaction between genetic predisposition and environmental factors likely plays a significant role in determining an individual's susceptibility to AS. Identifying and managing these risk factors through lifestyle modifications and appropriate medical interventions are essential and could be a path for prevention or delaying the onset of AS and its associated complications.

I.3. Medico-economic burden

The global medico-economic burden of AS is substantial and is expected to increase further with the aging population and rising disease prevalence. The costs associated with AS include medical care costs such as hospitalizations, outpatient visits, diagnostic tests (e.g. echocardiography, cardiac MRI, CT scans and even biology), and consultations with specialists[16]. Management of patients with AS in Heart Valve Clinic or expert centers, as proposed and recommended[7], would also further increase the global cost of this disease.

Surgical and interventional procedures like surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) can also contribute significantly to the

economic burden. Moreover, medication costs for symptom management, comorbidities, and post-procedure care further add to the financial impact. The costs of post-surgery rehabilitation, follow-up care, and management of complications may also substantially contribute to the overall economic burden, but major discrepancies between countries and practices remains, limiting a global evaluation of these costs[6]. Additionally, AS can lead to a decreased ability to work or engage in daily activities, resulting in lost productivity and economic impact for both patients and their caregivers[45]. Furthermore, the disease's impact on the quality of life of affected individuals and their families results in intangible costs that are challenging to quantify.

In France, AS poses a considerable medico-economic burden, particularly due to an aging population. Healthcare costs in France are mainly driven by hospitalizations for SAVR/TAVR, outpatient consultations, and diagnostic tests[46]. The increasing adoption of TAVR in France has both clinical benefits and economic implications. While TAVR can offer significant advantages over SAVR in certain patient populations, it may initially involve higher upfront costs. Moreover, managing comorbidities associated with AS can lead to additional healthcare expenses. Frequent follow-up visits, monitoring, and rehabilitation for AS patients can also strain healthcare resources. Additionally, the impact of AS on patients' and caregivers' daily

I.4. Current Assessment and Management of AS

Since there is no currently available effective medical treatment for patients with AS, the indication and timing of SAVR or TAVR is the cornerstone of the management of these patients. Consistently, the guidelines provide clear algorithm to carefully assess indication and identify the best timing of intervention. In addition, the place of heart-team decision-based is know well established in all international recommendation. In brief, the management of patients regarding the indication of intervention is based on 3 main questions:

1- Is the AS severe?

2- Is the patients symptomatic?

3- Is the LV function impaired?

I.4.1. Severe AS

Defining and identifying severe AS is crucial for appropriate clinical management, treatment decisions and timing of intervention. There are several key parameters, derived from echocardiography, used to define and identify severe AS:

1. Aortic Valve Area (AVA):

The AVA is a fundamental parameter for assessing the severity of AS. Severe AS is typically defined as an AVA < 1.0 cm^2, which reflects a significant reduction in the valve's effective orifice area. The AVA is commonly measured using echocardiography, with the continuity equation. The AVA may also be indexed for body surface area in order to take into account the systemic demand. When indexed, severe AS is defined as an AVAi < 0.6cm^2/m^2.

2. Mean Transvalvular Pressure Gradient (PG):

The mean transvalvular PG represents the average pressure difference between the LV and the aorta during systole. Therefore, it represents the loss of energy (spread as heat) developed by the ventricle to eject blood. Severe AS is usually defined as a mean PG ≥ 40 mmHg. Doppler continuous-wave is used to measure the PG non-invasively.

3. Peak Transvalvular Velocity (Vmax):

The peak transvalvular velocity is the highest velocity of blood flow across the aortic valve during systole. Severe AS is commonly defined as a Vmax ≥ 4.0 m/s. This parameter is also measured using Doppler echocardiography.

4. Dimensionless Index (DI):

The dimensionless index is calculated as the ratio of Vmax to the velocity time integral (VTI) of blood flow through the LV outflow tract (LVOT). A DI < 0.25 is suggestive of severe AS.

It is important to note that the assessment of AS severity should be based on the integration of multiple parameters rather than relying solely on one measurement. For instance, a patient with a small AVA but low transvalvular gradients might still have severe AS due to reduced left ventricular function or low cardiac output. This scenario is often encountered in patients with low-flow, low-gradient AS. Over the past 20 years, the gradation of AS severity has become much more complex, with the integration of sub-entities and different classifications. The use of artificial intelligence may help AS severity assessment[47]. Nevertheless, the vast majority of patients may be correctly evaluate simply using AVA, mean transvalvular PG and Vmax.

I.4.2. Evaluation of symptoms

In addition to the echocardiographic parameters, clinical evaluation and patient symptoms are critical components in the assessment of AS severity. Symptoms of severe AS may include angina (chest pain), dyspnea (shortness of breath), pre-syncope or syncope (fainting), and reduced exercise tolerance. These symptoms are indicative of significant obstruction to blood flow and increased afterload on the LV.

Symptoms can vary widely among individuals and may range from mild to severe. Furthermore, the occurrence of symptoms is subtle, progressive and slowly initiate, following a long asymptomatic phase. Consistently, patients may unconsciously adapt their lifestyle, expectation and habits to the symptoms, making particularly difficult their assessment and identification of onset.

The assessment of AS symptoms involves a combination of patient history (including questioning family and next of kin), physical examination, and functional evaluation. Here are the key steps in assessing symptoms in AS:

I.4.2.1. Patient History

Obtaining a comprehensive patient history is the first step in symptom assessment. Key points to address during the history-taking process include:

- Onset and progression of symptoms: Inquire about when the symptoms began and whether they have worsened over time.

- Specific symptoms: Ask the patient about the presence and characteristics of symptoms such as chest pain (angina), shortness of breath (dyspnea), dizziness, fainting (syncope), fatigue, and reduced exercise tolerance.

- Activity limitation: Assess how symptoms impact the patient's ability to perform daily activities and engage in physical exercise.

- Positional symptoms: Some patients may report symptoms that worsen or improve with changes in body position (e.g., orthopnea or paroxysmal nocturnal dyspnea).

- Medical history: Identify any comorbidities or other medical conditions that could exacerbate or mask AS symptoms.

I.4.2.2. Physical Examination

A thorough physical examination can provide valuable clues about the severity and impact of AS. Key elements of the physical examination include:

- Auscultation: Listening to the heart sounds, particularly the presence of a systolic ejection murmur over the aortic area (second right intercostal space) that may radiate to the carotid and/or subclavian arteries.

- Pulse assessment: Palpating the arterial pulses to evaluate for the presence of a slow-rising and diminished carotid pulse (pulsus parvus et tardus).

- Blood pressure measurement: Observing for a narrow pulse pressure (the difference between systolic and diastolic blood pressure) indicative of reduced stroke volume.

I.4.2.3. Functional Evaluation

Functional evaluation aims to assess the impact of AS symptoms on a patient's daily activities and exercise tolerance. It should be note that in patients with resting symptoms, exercise test is strictly contra-indicated. Common tools for functional evaluation include:

- New York Heart Association (NYHA) Functional Classification: A widely used system that classifies heart failure symptoms based on the patient's level of activity and tolerance to exertion. Class I indicates no limitation, and Class IV represents severe limitations.

- 6-Minute Walk Test: This test measures the distance a patient can walk in six minutes, reflecting their exercise capacity and functional status.

- Exercise stress test may be useful to identify subtle exercise symptoms, changes in ECG and blood pressure fall, which is an indication for intervention in patients with severe AS.

- Peak exercise oxygen consumption (VO2) measurement have also been found as a parameter of interest in assessing patients with AS[48]. More particularly when there is a doubt regarding absence of symptoms at rest and to identify “true” asymptomatic patients[49]. Peak VO2 seems also better reflect total LV hemodynamic afterload (i.e. not only valvular load)[50]. Assessing peak exercise VO2 involves performing a cardiopulmonary exercise test which may be sometimes difficult to interpret in patients with AS, particularly in elderly patients.

Typically, exercise capacity and peak VO2 are reduced in patients with AS, as compared to age-matched individuals without significant cardiovascular disease. Peak exercise VO2 has prognostic significance and has been shown to be a strong predictor of adverse outcomes in patients with AS. Lower peak exercise VO2 is associated with increased mortality and cardiovascular events.

Nevertheless, although the current guidelines recommend exercise testing (i.e. without gas-exchange analysis), there is no place for peak VO2 assessment. This is related to the relative lack of data showing the incremental value of peak VO2 measurement in the assessment and risk stratification of patients, by comparison to conventional hemodynamic or physical parameters.

I.4.3. LV function assessment

From a hemodynamic standpoint, AS increases LV afterload. The natural response of LV is concentric remodeling, increase in LV mass (LVM) and development of LV hypertrophy (LVH). This process aims to maintain wall stress and cardiac function. Although this appears to be compensatory in the early stages, preclinical studies have suggested that cardiac performance can be preserved in the absence of hypertrophy[51,52]. Moreover, the remodeling response is progressively followed by cell death and fibrosis, driving the transition to symptoms, heart failure, and adverse cardiovascular events. Therefore, in parallel to the AS progression and increase severity, consequences on LV myocardial morphological structure and function occur. The parameters evaluating LV function should follow such impairment and be as sensitive as possible to detect every function depress. The LV function is a major trigger of symptoms and of reduced outcome. Guidelines promote a careful appraisal and follow of LV function in patients with AS. However, only LV ejection fraction (LVEF) is mandatory to assess the changes in LV function. In the absence of coronary artery disease, the LVEF remains preserved in AS, and the concomitant presence of severe AS and reduced LVEF (<50%) is uncommon (3), especially when patients are still asymptomatic. Thus, although the Class I indication for aortic valve intervention is unquestionable in severe AS with depressed LV function evidenced by reduced EF (4,5), in the vast majority of patients, symptoms occur well before a reduction in LVEF. The literature commenting the limited value of LVEF in patients with AS is proliferating. The drawback of LVEF are well-know:

1- Vast majority of asymptomatic patients have LVEF >50-55%

2- LVEF is not associated with LV afterload or AS severity and its progression

3- LV morphological and structural abnormalities may occur even when LVEF>50-55%

4- Patients with LVEF 55-60% may have reduced survival as compared to age- and sex-matched general population and patients with AS and LVEF>60%

5- Intervention when LVEF<50-55% is associated with limited improvement in LV function, only partial reverse remodelling and reduced mid-term survival

Finally, evidence suggesting that the best post-intervention outcome is achieved in patients with preserved LVEF, are robust. Altogether these facts underline the deep need for other parameters than LVEF in order to better assess the LV function and unmask subclinical dysfunction. In this regard, many efforts from many research groups worldwide studied the diagnostic and prognostic value of other LV function assessment parameters. Purposely, such works attempted to identify parameters, allowing unmasking asymptomatic patients with subclinical dysfunction and subtle myocardial impairment. Among these parameters, LV global longitudinal strain (GLS), LV mechanical dispersion, or LV first phase EF were the most promising.

I.5. Objectives

The general objective of this work was, in a **clinical epidemiology perspective**, to identify imaging markers of LV function allowing better risk stratification of patients with AS, in order, ultimately, to improve their management and outcome.

The specific objectives were:

1- To assess the relevance of changes in LVEF threshold.

2- To perform an individual participant data meta-analysis in order to (1) describe the distribution, (2) identify the most predictive cut-off values, and (3) assess the impact of LV GLS on mortality in asymptomatic patients with significant AS and preserved LVEF.

3- To evaluate the added prognosis value of 2 new imaging markers of LV function:

   a. First phase ejection fraction

   b. Mechanical dispersion

4- To debate about the relevance of early intervention for asymptomatic patients with AS.

In this regard, we will first still discuss the current threshold of LVEF, specifically in patients with bicuspid aortic valve, in the light of new results.

Second, demonstrate the prognostic value of LV GLS in patients with AS and discuss its place in the assessment and management of these patients, more particularly in comparison with LVEF and its current threshold in patients with AS.

Third, we will evaluate the incremental assessment and prognostic values of 2 new imaging markers (i.e. first phase ejection fraction and mechanical dispersion) and their current supporting evidence.

Fourth, we will report and discuss current data in favor of early intervention in patients with AS and present the advantaged of a tailored individualized approach.

Partie II. Threshold reappraisal in Bicuspid Aortic Valve

This section relates to the following article [53]:

Donal E, Magne J, Cosyns B. Left Ventricular Ejection Fraction Thresholds Reappraisal: Also for Bicuspid Valve Disease? *J Am Coll Cardiol* 2022;80:1085–1087.

The BAV (ie, an aortic valve constituted with only 2 cusps) may lead to early aortic valve stenosis and/or regurgitation. Despite remaining asymptomatic for a long time, patients with BAV may require aortic valve intervention earlier than patients with tricuspid aortic valve disease (frequently <55 years of age)[54].

BAV creates 3 challenges for clinicians: 1) although uncommon in the general population[55], screening and early diagnosis is crucial; 2) once diagnosed, close monitoring of the disease's progression and consequences to the heart are mandatory; and 3) since operated at an early stage, choice of device (ie, valve repair vs mechanical prosthesis vs biological prosthesis) should deal with the appropriate balance between long-term anticoagulation consequences and risk of early degeneration.

Regarding the second challenge, similarly to in patients with tricuspid AS or regurgitation, recent guidelines focused on the need for LVEF assessment to improve timing of intervention in patients with BAV. Cut-off of LVEF related to the decision to intervene has been raised in current guidelines (from 50% to 55%-60%), but this choice is empiric, resulting from consensus, and the level of evidence remains low. Furthermore, the cutoffs proposed in guidelines are mainly based on studies including patients with isolated tricuspid aortic regurgitation or stenosis. Given that patients with BAV may have a mixed form of VHD and particular natural history, there is a profound need for data on outcome and on the impact of LVEF (specifically derived from patients with BAV).

The Journal of the American College of Cardiology published a study from Hecht et al.[56] reporting the fundamental importance of monitoring consequences of BAV on LVEF. Using an international network, the authors built a database with an initial international cohort from 5

centers expanded with additional centers, resulting in a large cohort (n=1,493) retrospectively analyzed. During a reported median follow-up of 56 months, the authors identified 117 primary endpoints (i.e., overall death regardless of occurrence of aortic valve intervention) and 675 secondary combined endpoints (i.e., aortic valve intervention or overall death).

The authors confirm the prognostic value of LVEF in aortic valve stenosis and regurgitation. The risk of combined event increased when LVEF was <60% (<50% for death in the isolated AS) in the whole cohort as well as in the AS and aortic regurgitation groups. The proposed cutoff is <55% in mixed aortic valve disease. There is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease. Of course, this is only a registry. The indication for surgery is part of the main clinical endpoint and remains a subjective parameter. Nevertheless, death is not subjective. Its risk increases according to the degree of decrease in LVEF. In addition to the limitations raised by the authors, several points suggest that the clinical implication of the present study must be tempered. First, an epidemiological registry needs an accurate definition of the data collection process and quality control, which is not detailed in the present study. Second, sample size is an obvious strength of the study. Nevertheless, the period of inclusion is large, including patients in the 1990s and early 2000s, implying various management strategies that may have an impact on outcome and, more particularly, on indication for AVR. Third, the present data set is based on a smaller number of patients than previous publications, despite the larger number of centers included. This may imply a selection bias. Fourth, symptoms are not reported, limiting the interpretation of a secondary combined endpoint.

Beyond these limitations, the present study underlines again the crucial role of myocardial damage and its assessment in patients with VHD. When the decision to intervene is taken too late, patients do not benefit from AVR because myocardial damage can be irreversible[57]. Waiting for symptoms might lead to myocardial damage that is too advanced, and it might be even more relevant in BAVD than other heart valve diseases. The present report stresses that a delayed diagnosis at the presentation time of symptoms and of significant damage (or

remodeling) could have a significant impact on prognosis in patients who are relatively young. Therefore, it also highlights the importance of taking the evaluation of the LV function into account during the screening of asymptomatic first relatives at the time of BAVD diagnosis and to follow-up on these patients regularly. Teaching the use of hand-held ultrasound devices is potentially an opportunity, but increasing the awareness about the prognostic importance of valvular disease (especially BAVD) is of crucial importance.

Guidelines are still restrictive for surgical indications, but the awareness is improving. The work from Hecht et al. should be highlighted, and it will potentially (with others) influence the next guidelines. The myocardial damage assessment is crucial and should help in promoting earlier interventions. We should look at the valve but not only at the valve. We should look at the consequences of heart valve diseases.

It has been previously demonstrated that LVEF is of crucial importance in stenotic and regurgitant aortic valve diseases, and the recent guidelines took into consideration the new cutoff of 55% instead of 50%. However, LVEF is not LV systolic function. Other imaging opportunities exist to best manage our patients.

The role of hypertrophy could be interesting to study in the BAVD population. The amount of myocardial fibrosis by CMR could also bring additional information regarding the risk stratification in the various BAVD subgroups of presentation[58].

In addition, LV global longitudinal strain might be even better in assessing the LV consequences of the hemodynamic alterations related to the BAVD. It was not studied by Hecht et al.5 They focused on a large number of patients, but only on classical measurements that could be done in echocardiography. Myocardial fibrosis as well as strain or myocardial work indexes have not been mentioned. These have, however, the strength of being more robust and should probably be advised in addition to LVEF, which could be considered too versatile for being used alone to guide a surgical indication. The enlargement of the interstitial space with reactive fibrosis and subsequently with replacement fibrosis and cell death has been suggested to be the main driver of the transition to symptoms, heart failure, and adverse

cardiovascular events even after aortic valve replacement. A “preserved” EF in the presence of a small LV cavity equates to a low stroke volume, which is the primary problem in low flow low gradient AS[59]. LV GLS is a more reliable parameter than standard 2-dimensional LVEF. Despite its influence by preload and afterload, it is sensitive enough to unmask patients with structural and functional myocardial damage that LVEF cannot reveal. An individual participant data meta-analysis demonstrated that in asymptomatic patients with significant AS and normal LVEF, impaired LV GLS (cutoff −14.6%) is associated with reduced survival. The recently suggested use of the myocardial work seems even more promising for detecting the myocardial damage earlier[60–62].

Despite the inherent limitations of the study, mainly related to its design, the authors should be congratulated for their tremendous effort in collecting the largest amount of data with follow-up of patients from several international centers. The present findings improve our knowledge about BAVD and the prognosis impact of LVEF, for which reappraisal of cutoff may be discussed in the light of present results. It should encourage further prospective works, using LVEF or other parameters of LV systolic function derived from TTE or CMR, to best define the timing for surgery. We should be aware and work for decreasing risk of disability and death in patients with BAVD.

Partie III. Imaging Markers of Early LV dysfunction

III.1. LV Global Longitudinal Strain

This section relates to the following article [63]:

Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, Kearney L, Lancellotti P, Marwick TH, Sato K, Takeuchi M, Zito C, Casalta A-C, Mohty D, Piérard L, Habib G, Donal E. Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis: An Individual Participant Data Meta-Analysis. *JACC Cardiovasc Imaging* 2019;12:84–92.

III.1.1. Background

The assessment of LV function using LVEF has a central place in the current guidelines for the management of patients with severe AS, particularly when still asymptomatic. The current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommend as class I indication (level of evidence B) to perform aortic valve intervention in asymptomatic patients when LVEF becomes <50%[4,5]. However, these concomitant findings are rare and symptoms generally occur well before decrease in LVEF which, in turn, remains preserved for long in patients with AS. Several recent studies demonstrate, using cardiac magnetic resonance, that LV structural and functional abnormalities may be frequent despite LVEF >50%[64–69]. This may partially explain the reduced postoperative survival of patients with LVEF 50-60%[64,70]. Furthermore, aortic valve intervention in patients with LVEF <50% frequently results in suboptimal postoperative LV function recovery, contributing to persistent symptoms, limited functional capacity and quality of life and increased risk of events. Consequently, this underlines the need to identify echocardiographic parameters better than LVEF to more accurately assess the consequences of AS-related LV pressure overload, on LV function.

The impairment of LV longitudinal shortening is associated with myocardial fibrosis[71,72], which is, in turn, a potential prognostic marker in patients with AS[67,73]. Hence, LV longitudinal function assessment, using speckle-tracking echocardiography, may provide a surrogate imaging

marker of myocardial damage. Indeed, there is growing evidence suggesting the potential prognostic role of LV myocardial longitudinal function, as assessed by GLS, in asymptomatic patients with AS. However, the available data are mainly derived from relatively small series and/or from single center studies. In addition, current series report various unstandardized cut-off values.

Our objective was therefore to perform an individual participant data meta-analysis in order to (1) describe the distribution, (2) identify the most predictive cut-off values, and (3) assess the impact of LV GLS on mortality in asymptomatic patients with significant AS and preserved LVEF.

III.1.2. Methods

We searched MEDLINE, Embase, and the Cochrane Library database using the key terms “aortic valve stenosis” and “longitudinal strain” between 2005 and 2017 without language restriction. The protocol of this individual participant data meta-analysis was validated by the Research & Innovation Committee of the European Association of Cardiovascular Imaging and the study was conducted on behalf of all members of the Committee. The PRISMA statement[74] was followed to conduct the individual participant data meta-analysis.

III.1.2.1. Inclusion criteria

Studies were selected for the meta-analysis if they included patients with all of the following criteria: (1) asymptomatic, (2) preserved LVEF (i.e. >50%), (3) ≥ moderate AS as defined by current guidelines at the time of the study, (4) quantification of the LV GLS using 2-dimensional speckle tracking, (5) availability of outcome of interest for the current analysis i.e. all-cause death.

No inclusion criterion was applied regarding sample size.

III.1.2.2. Selection of studies

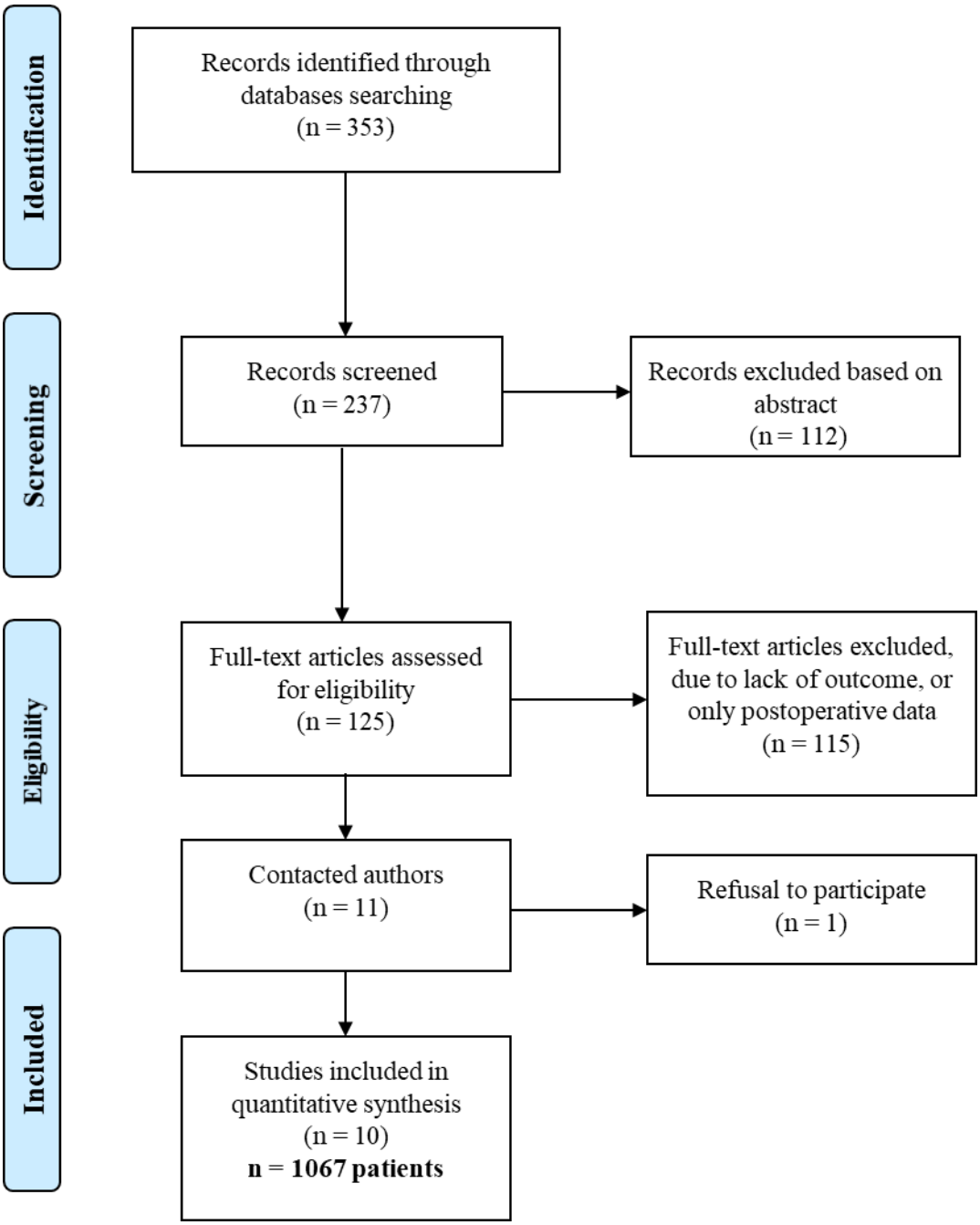
A first selection of the studies was based on the title and on the abstract. The full articles of all selected studies were then consulted in order to verify all pre-specified inclusion criteria. The

selection of the studies was performed simultaneously during specific meeting (JM, BC and ED). The flow chart illustrating the selection of the studies process is reported in Figure 7. Great care was taken to avoid inclusion of various studies based on the same cohort population in order to avoid redundancy in the meta-analysis.

Finally, all corresponding authors and/or first, second or last authors of the paper were contacted by email in order to propose them to participate to the meta-analysis. Responding authors were invited to share a short-anonymized database including a limited number of variables. The required variables were age, gender, comorbidities (coronary artery disease, hypertension, diabetes, dyslipidemia), AS severity, LVEF, LV GLS and outcome data.

The data were then computerized in a dedicated database.

Figure 7: Flow chart



III.1.2.3. Primary end-point

The primary end-point of this individual participant data meta-analysis was all-cause death. Purposely, combined end-point including need for aortic valve intervention was not used in the meta-analysis. This is justified by the fact that the decision-making regarding indication for intervention may considerably vary between centers.

III.1.2.4. Statistical analysis

Extraneous data was removed from the database and units of continuous variables were standardized and continuous variables were dichotomized.

Descriptive analysis was performed and mean ± standard deviation or proportion was reported. The distribution of LV GLS was compared according to each included study using one-way analysis of variance.

A univariate Cox proportional hazards model was used to derive, for each study, the hazard ratio (HR), standard error and 95% of confidence interval (95%CI) related to LV GLS (as continuous variables) and occurrence of death. Log transformation was performed and inverse variances as weights were then calculated for each study. The meta-analysis was performed using random effects models and forest plots were generated to express the pooled effect. Heterogeneity was assessed using I^2. Stratified analysis were performed according to LVEF with a pre-specified arbitrary cut-off value of 60%.

In order to assess the potential impact of vendor difference on the results, a stratified analysis was performed according to vendor.

The best cut-off value of LV GLS associated with death was derived from receiver operating characteristics curve analysis and selected using the best compromise between sensitivity and specificity and the Youden index. This cut-off was then used to generate Kaplan-Meier analysis and to assess the impact of LV GLS on death in multivariate Cox proportional Hazard model.

To assess the incremental prognostic value of LV GLS over LVEF, we calculated integrated discrimination improvement as recommended[75].

To simplify the interpretation and discussion of the results, although negative, LV GLS is reported as positive values.

All statistical analyses were performed using SPSS V23 and STATA V13.

III.1.3. Results

A total of 10 studies, including 1 067 asymptomatic patients with LVEF >50% were used for the present individual participant data meta-analysis. The dataset was completed for LV GLS and outcome data. There was 0.8% of missing values for LVEF (i.e. patients with LVEF >50% but without exact value).

The selected studies are summarized in Table 1, the description of the population is reported in Table 2 and Table 3.

The median LV GLS was 16.2% (from 5.6% to 30.1%). A LV GLS>13.7% was observed in 75% of patients and less than 15% of patients had LV GLS>20% (i.e. preserved LV longitudinal function). In patients with severe AS (i.e. indexed aortic valve area [AVAi] <0.6cm²/m²), the median LV GLS was 16.3% (from 6% to 30.1%).

Table 1: Description of selected studies

References	Years	Design	Population available n=1 067	AVAi (cm^2/m^2)	Vendor	LV GLS cut-off	Outcome
Lancellotti et al.[76]	2010	Prospective/bi-centric	n=163	0.45±0.09	GE	15.9%	MACE
Zito et al.[77]	2011	Prospective/monocentric	n=82	0.40±0.10	GE	18%	MACE
Dahl et al.[78]	2012	Prospective/monocentric	n=65	0.46±0.19	GE	Quartile	MACE
Kearney et al.[79]	2012	Prospective/monocentric	n=77	0.56±0.23	GE	15%	All-cause death
Yingchoncharoen et al.[80]	2012	Prospective/monocentric	n=78	0.39±0.13	Siemens	15%	MACE
Kusunose et al.[81]	2014	Retrospective/monocentric	n=137	0.42±0.2	Siemens	Quartile	All-cause death
Sato et al.[82]	2014	Retrospective/multicentric	n=142	0.42±0.11	GE	17%	MACE
Carstensen et al.[83]	2015	Prospective/multicentric	n=104	0.49±0.13	GE	15%	MACE
Nagata et al.[84]	2015	Prospective/multicentric	n=102	0.42±0.10	TomTec	17%	MACE
Salaun et al.[85]	2017	Prospective/multicentric	n=117	0.47±0.11	GE	Tertile	All-cause death

GE indicates General Electrics, AVAi, indexed aortic valve area and MACE, major adverse cardiac event.

Table 2: Population characteristics.

Variables	Whole pooled cohort (n=1 067)
Age, years	74±10
Body surface area, m^2	1.79±0.26
Male gender, %	56
Comorbidities	
Coronary artery disease, %	26
Hypertension, %	63
Diabetes, %	28
Dyslipidemia, %	44
Echocardiographic data	
Indexed aortic valve area, cm^2/m^2	0.49±0.17
Severe AS*, %	82
LVEF, %	63.5±8
LVEF >60%, %	65
LV global longitudinal strain, %	16.2±3.6

LV indicates left ventricular. * severe AS is defined as an indexed aortic valve area <0.6cm^2/m^2.

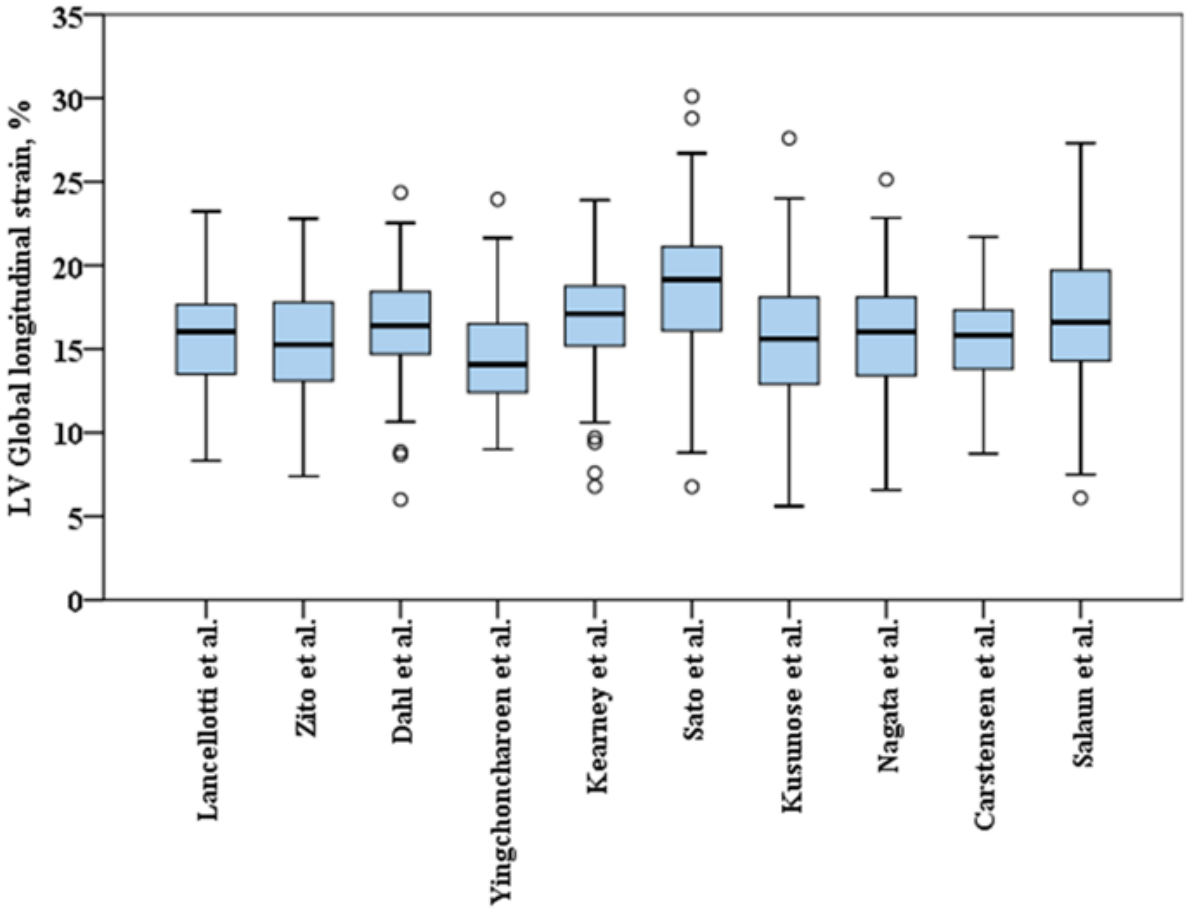
Table 3: Population characteristics of each included studies

Variables	Lancellotti et al. n=163	Zito et al. n=82	Dahl et al. n=65	Kearney et al. n=77	Yingchoncharoen et al. n=78	Kusunose et al. n=137	Sato et al. n=142	Carstensen et al. n=104	Nagata et al. n=102	Salaun et al. n=117
Age, years	70±10	73±11	70±10	75±11	77±12	70±10	78±8	72±9	78±10	72±11
Body surface area, m^2	1.83±0.17	1.77±0.18	1.83±0.38	1.85±0.24	1.94±0.25	2.00±0.30	1.47±0.17	1.94±0.19	1.50±0.17	1.81±0.21
Male gender, %	66	62	69	62	49	57	37	68	41	61
Comorbidities										
Coronary artery disease, %	…	16	…	40*	36	46*	26	…	18	…
Hypertension, %	51	50	41	84	63	79*	76	68	64	60*
Diabetes, %	17	21	11	30	23	17*	34	59	20	22*
Dyslipidemia, %	45	51	…	74	72	77*	39	12.5	39	44*
Echocardiographic data										
Indexed Aortic valve area, cm^2/m^2	0.45±0.09	0.40±0.11	0.46±0.18	0.67±0.24	0.75±0.13	0.42±0.10	0.42±0.11	0.49±0.13	0.42±0.10	0.47±0.11
LVEF, %	66.3±7.6	59.5±5.0	58±6.1	63.3±6.3	63.7±7.4	62.6±1.4	61.4±7.5	60.6±6.9	67.6±7.5	67.2±7.2
LVEF >60%, %	78	62	34	67	74	79	47	44	82.5	86
LV global longitudinal strain, %	15.8±3.1	15.3±3.3	16.3±3.4	16.8±3.1	14.3±3.0	15.6±3.8	18.6±3.9	15.6±2.7	15.8±3.4	16.8±4.0

LVEF indicates left ventricular ejection fraction.

The distribution of LV GLS according to selected studies is reported in Figure 2. Although the study from Sato et al.[82] reported significantly higher values and the study of Yingchoncharoen et al.[80] significantly lower values ($p<0.0001$), there was a good homogeneity between studies regarding LV GLS values (Figure 8). In studies using equipment only from the most commonly used vendor (GE Medical Systems), the median LV GLS was 16.6% (from 6% to 30.1%).

Figure 8: Distribution of LV GLS according to included studies.



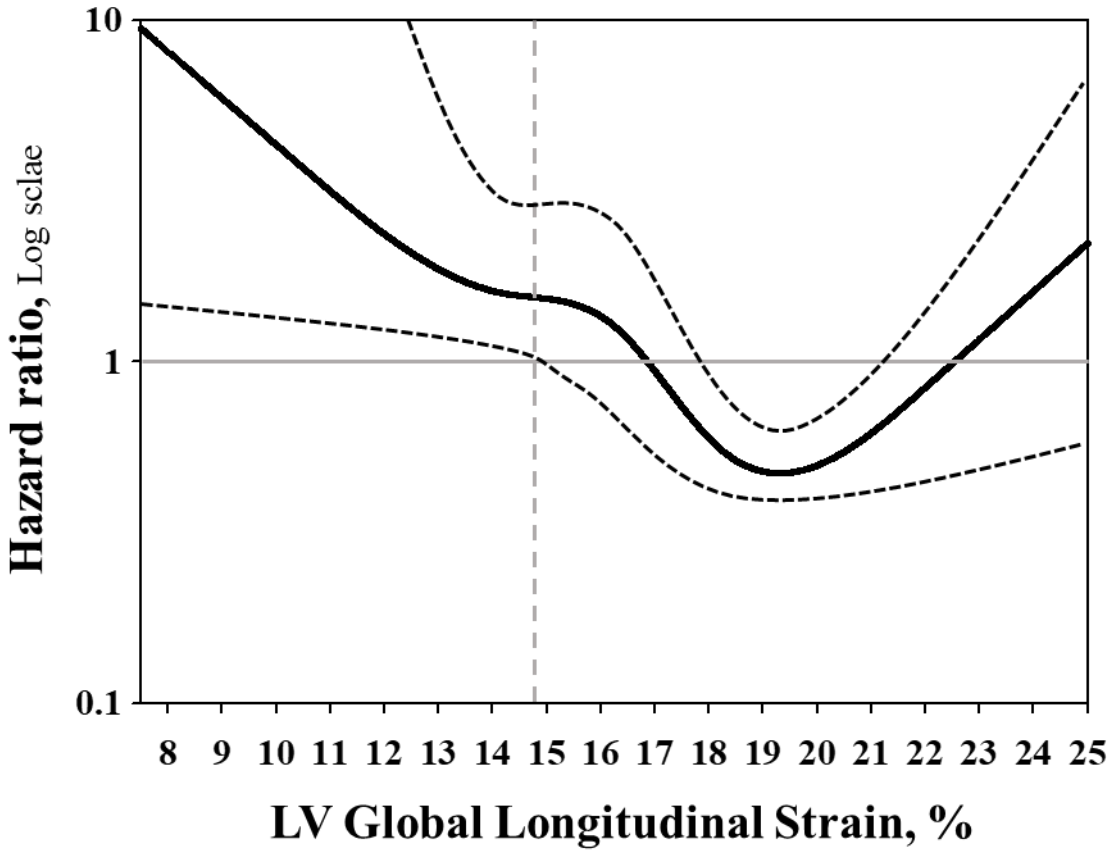
III.1.3.1. LV GLS and mortality

Among the 10 selected studies, 91 deaths were reported during a median follow-up of 1.8 years, from 0-8.5 years, resulting in a pooled crude rate of death of 8.5% (range 2.8% to 18.5%). In patients with LVEF>60% (n=734), 61 deaths occurred (8.3%, range 3.0% to 17.3%).

In the whole cohort, LV GLS was well associated with occurrence of death (area under the curve=0.68). The best cut-off value identified was LV GLS=14.7% (sensitivity=60%, specificity=70%). By comparison, LVEF depicted lesser association with occurrence of death (area under the curve=0.56). In patients with severe AS (i.e. AVA <0.6cm²/m²), area under the curve for LV GLS was 0.69).

The relationship between LV GLS and risk of death is assessed using spline function (Figure 9). The spline curve suggests a marked increase risk of mortality when LV GLS decrease below 15%.

Figure 9: Spline function reporting the relationship of LV global longitudinal strain and risk of mortality. The curve shows the relevance of a cut-off value between 14% and 15%. Black dashed lines represent 95% confidence intervals.



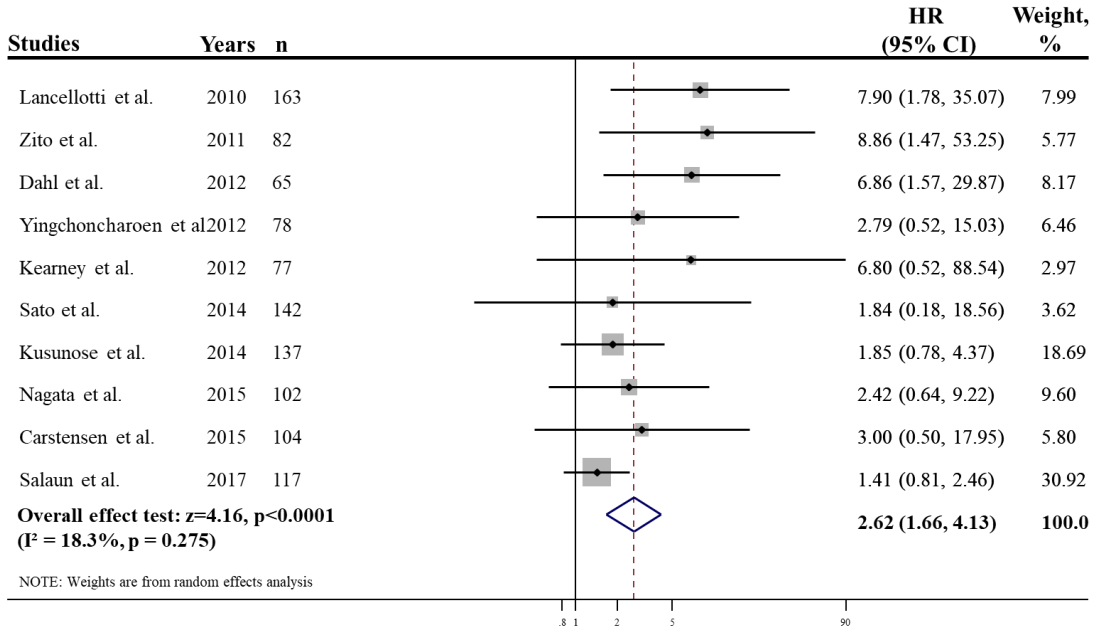
In studies performed with the GE machine, the predictive value of LV GLS was similar (area under the curve=0.69) and the best cut-off value was 14.7% (sensitivity=62%, specificity=74%). The predictive value in studies without GE machine was lower (area under the curve=0.62) and the best cut-off value was 11.9% with markedly lower sensitivity (35%) but higher specificity (86%).

In the whole cohort, impaired LV GLS<14.7% was found in 32.3% of patients, with significant difference between the studies (from 15.5% to 56%, p<0.0001). Applying this cut-off value to all selected studies allowed to generate a forest-plot (Figure 10, Panel A) showing that the risk of death for patients with LV GLS<14.7% was multiplied by >2.5 (HR=2.62, 95%CI: 1.66-4.13, p<0.0001), without significant heterogeneity (I^2=18.3%, p=0.275). The relationship between LV

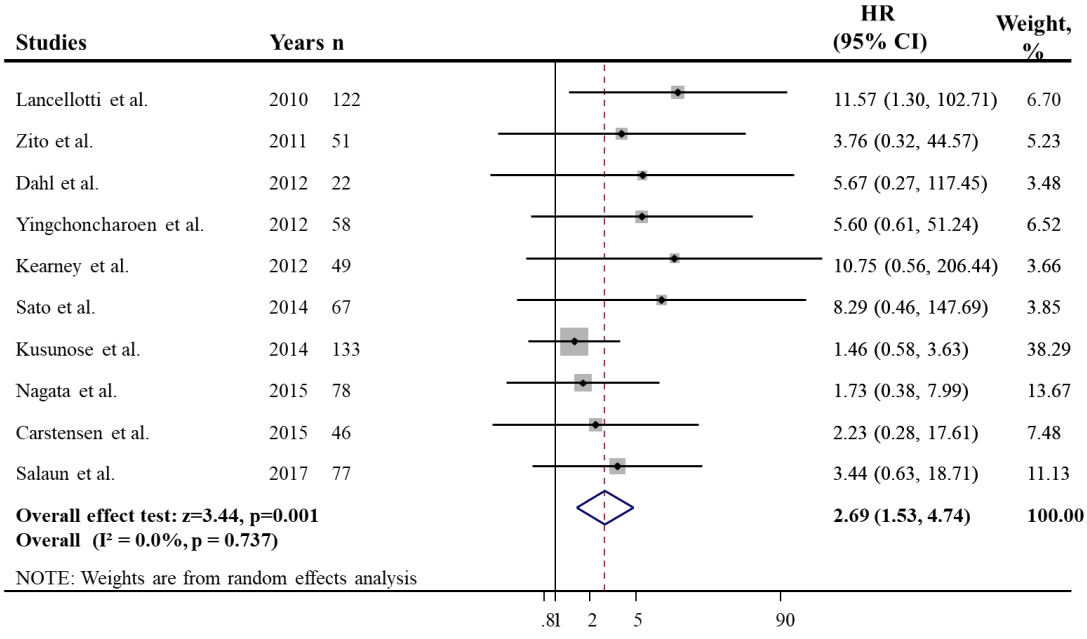
GLS<14.7% and mortality was also significant in patients with LVEF≥60% (Figure 10, Panel B).

Figure 10: Forest-plot on the impact of impaired LV GLS on mortality in the whole cohort (Panel A) and in patients with LVEF ≥60% (Panel B).

Panel A

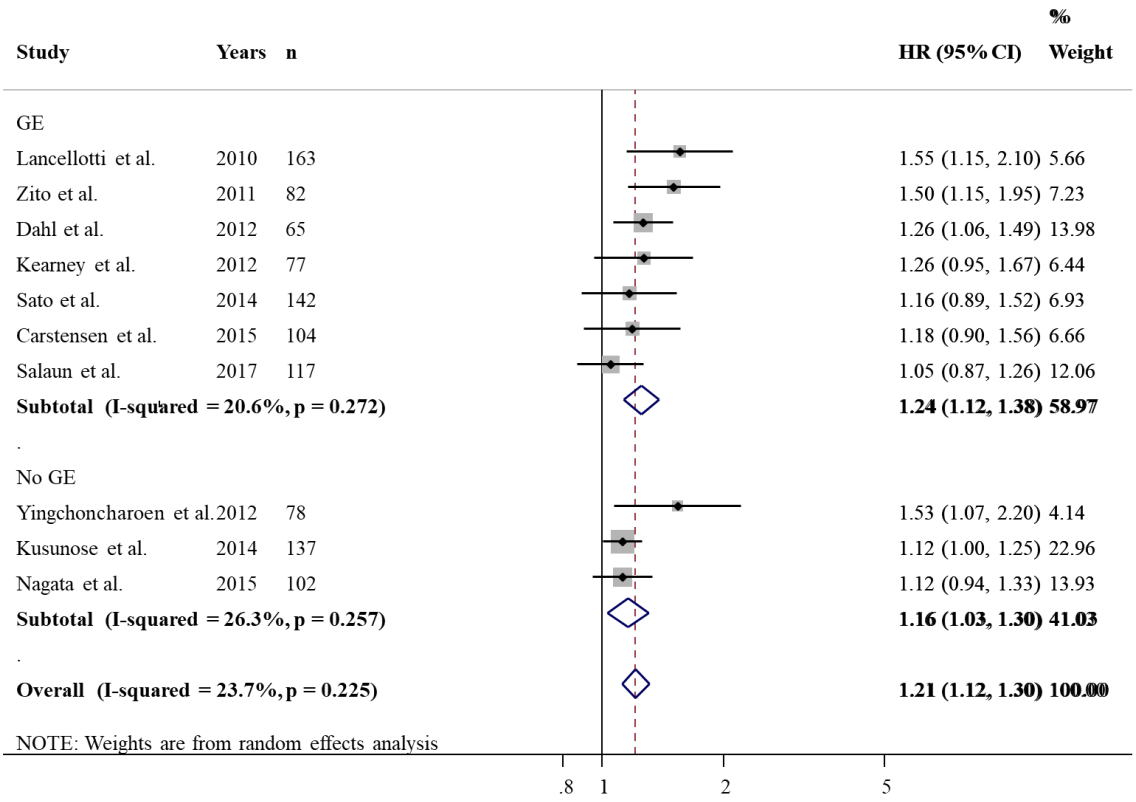


Panel B



With a stratification according to vendor (i.e. GE vs. others, Figure 11), similar results were found.

Figure 11: Forrest plot. Impact of left ventricular global longitudinal strain on survival stratified according to vendor (GE vs. others).



Because all patients from the Dahl et al.[78] study were referred for surgery, we performed a sub-analysis excluding this study. Similar results than in the whole cohort were found (HR=2.25, 95%CI: 1.47-3.43, p<0.0001; I^2=8.0%, p=0.369).

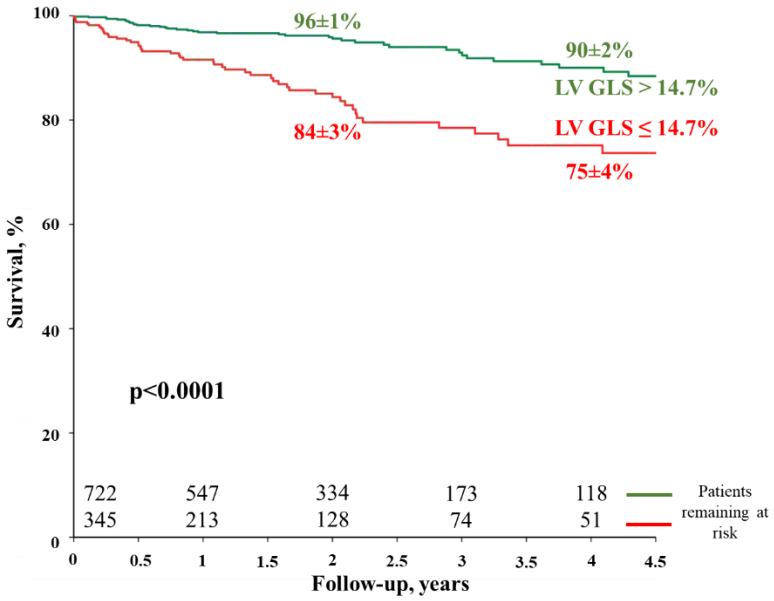
In patients with severe AS (i.e. AVAi <0.6cm²/m²), forest-plot showed that the risk of death in patients with LV GLS<14.7% was higher than in the whole cohort (HR=3.58, 95%CI: 1.84-6.99, p<0.0001, I^2=0, p<0.0001).

Using the cut-off of 14.7%, impaired LV GLS was associated with markedly reduced survival both in the whole cohort (p<0.0001, Figure 12, Panel A) and in patients with LVEF≥60% (p<0.0001, Figure 12, Panel B). Patients with LV GLS>18% have similar survival (at 2-year:

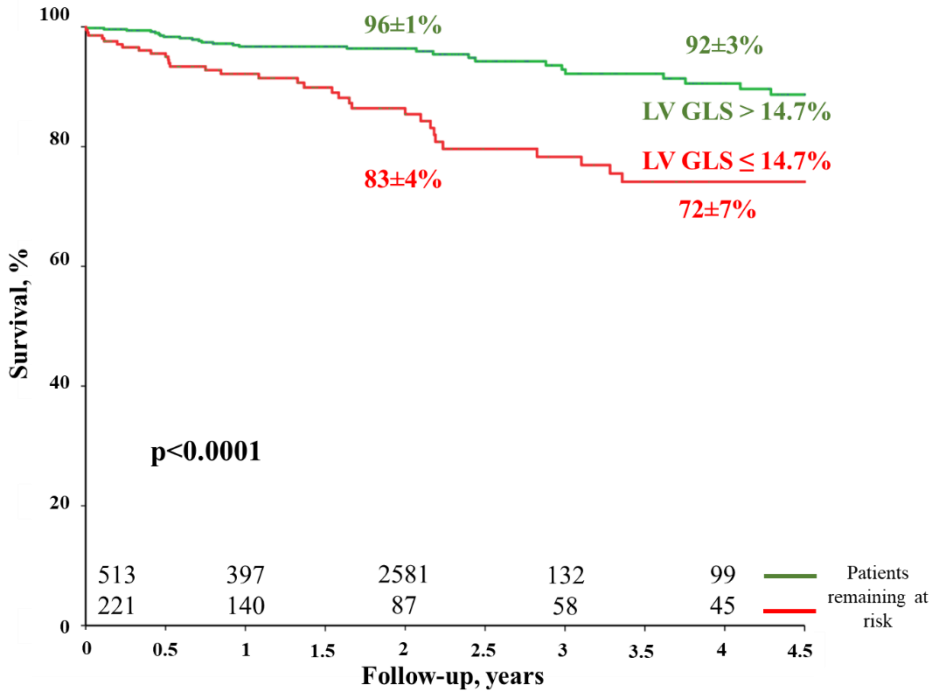
97±1%) than those with LV GLS between 16.2% and 18% (at 2-year: 95±2%, p=0.445) or even those with LV GLS between 14.7% and 16.2% (at 2-year 95±2%, p=0.207).

Figure 12: Mortality according to LV GLS in the whole cohort (Panel A) and in patients with LVEF ≥60% (Panel B).

Panel A

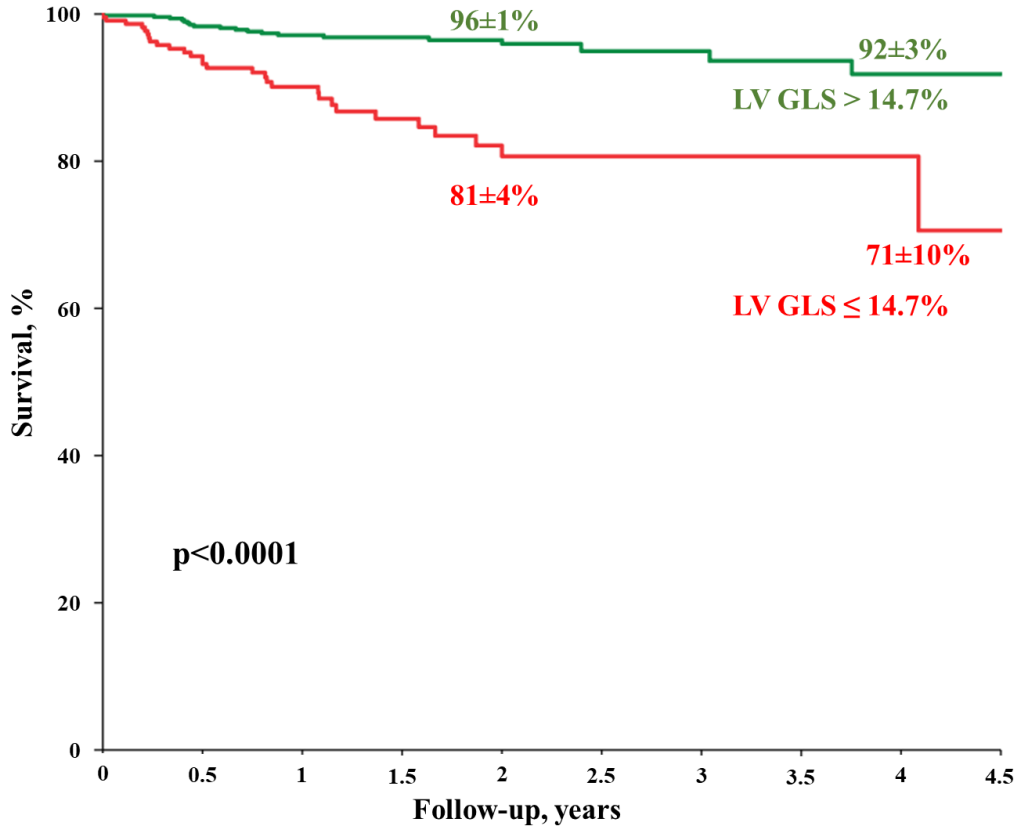


Panel B



In patients with severe AS (i.e. AVAi<0.6cm²/m²), 2-year survival was significantly lower in patients with impaired LV GLS than in those with preserved LV GLS (94±1% vs. 81±4%, p<0.0001, Figure 13).

Figure 13: Kaplan-Meier curve in patients with severe AS (i.e. indexed aortic valve area <0.6cm²/m²) according to LV global longitudinal strain.



In multivariate analysis, after adjustment for age, gender, indexed aortic valve area and LVEF, impaired LV GLS (i.e. <14.7%), was a strong independent determinant of survival (HR=3.59, 95%CI: 2.16-5.98, p<0.0001).

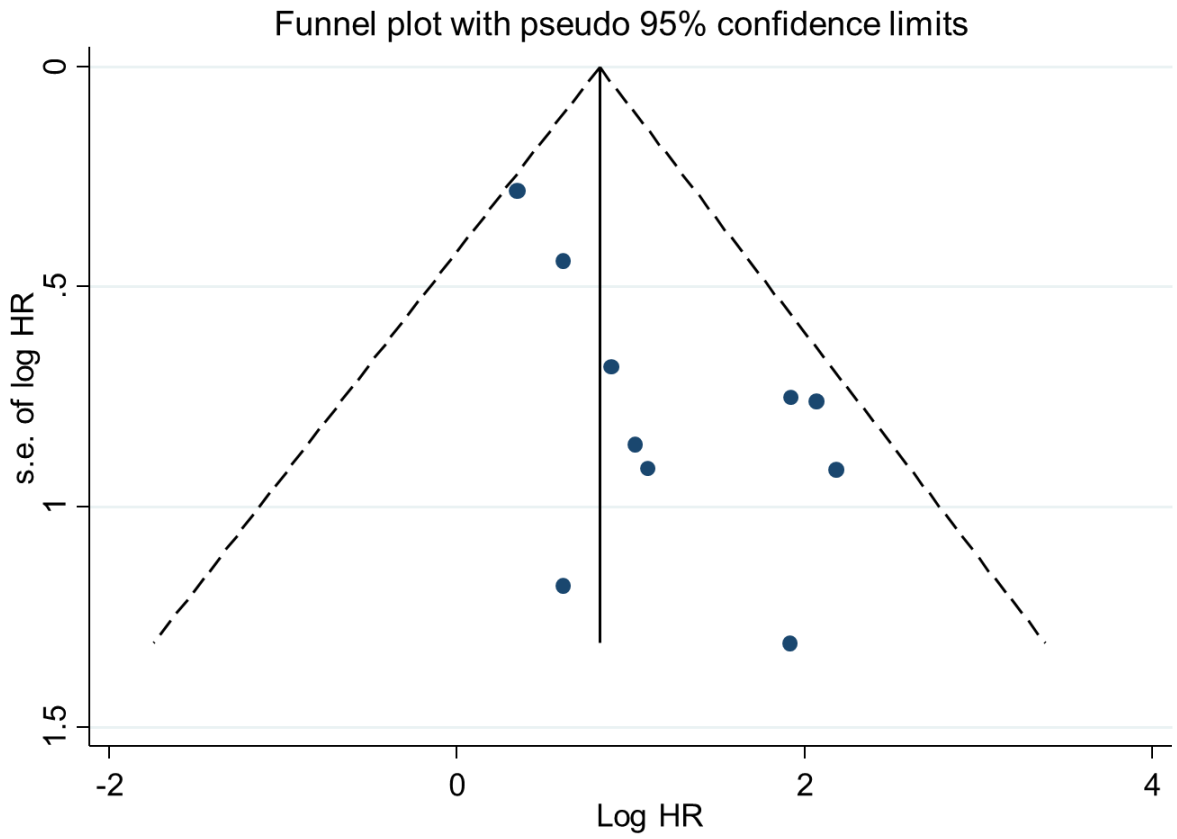
Adding impaired LV GLS to the multivariate model (i.e. including age, gender, indexed aortic valve area and LVEF) markedly improve its prediction (from χ^2=13.1 to χ^2=40.5). Comparing with LVEF, integrated discrimination improvement was positive for both LV GLS (i.e. as

continuous variable) or LV GLS <14.7% suggesting its incremental prognostic value over LVEF (0.028 and 0.026, respectively).

III.1.3.2. Publication bias assessment

Funnel plots, regarding impaired LV GLS and risk of death (Figure 14) demonstrated significant asymmetry (Egger's test, p=0.01) suggesting potential presence of publication bias. Funnel plots analysis demonstrates that this asymmetry may be related to discrepancy in publication in favor of studies reporting large effect size despite small sample size or large variance. In contrast, Begg's test demonstrated no significant risk of publication bias (p=0.18).

Figure 14: Funnel plots. Log HR represent the risk of death of patients with LV GLS < -14.7%.



III.1.4. Discussion

In asymptomatic patients with significant AS and preserved LV ejection fraction, the present individual participant data meta-analysis suggests that (1) LV GLS is relatively homogeneous

across available published cohorts, (2) LV GLS better than 20% is rare in this population, and (3) LV GLS is strongly associated with mortality, with >2.5-fold increase in risk of death in patients with impaired LV GLS. Of interest, the close independent relationship between LV GLS and mortality is sustained even when LV ejection fraction is ≥60%. A cut-off value of 14.7% appears to be associated with patients at a higher risk of death.

III.1.4.1. LV longitudinal function and myocardial fibrosis

The alteration of LV longitudinal function occurs in parallel to AS severity[86], LV morphological changes[87], LV myocardial damage and fibrosis proliferation[71]. Weidemann et al.[71] reported that the severity of myocardial fibrosis estimated with histological analysis was associated with impairment of LV longitudinal shortening as assessed by mitral annulus displacement using M-mode echocardiography. In addition, the presence of LV myocardial fibrosis may predict the risk of lack of LV function recovery following aortic valve replacement[73], and outcome[67]. Based on these studies, it appears that the development of LV fibrosis is the main pathophysiological mechanism involved in the reduction in LV longitudinal shortening in patients with AS. Nevertheless, these findings were obtained in cohorts with surgical indications or with markedly reduced LV ejection fraction, limiting the clinical usefulness of LV longitudinal function assessment. Indeed, the LV longitudinal function evaluation could be more relevant to detect sub-clinical LV dysfunction and manage asymptomatic patients with preserved LV ejection fraction.

The presence of transthyretin cardiac amyloidosis[88], which, in patients with AS, is frequently associated with impaired longitudinal LV shortening without apical sparing, could also partially explain the reduction in LV GLS.

III.1.4.2. LV GLS derived from speckle tracking echocardiography

Speckle tracking echocardiography is a non-Doppler modality, angle-independent, allowing measurement of myocardial deformation. The quantification of LV GLS is now the most common application of speckle tracking echocardiography and has already demonstrated added diagnostic and prognostic value in a wide range of conditions including VHD. Moreover,

LV GLS during exercise may identify LV dysfunction associated with the development of symptoms[89].

Derived from 2-, 3- and 4-chamber apical views, LV GLS can be easily calculated with good feasibility and both inter- and intra-observer reproducibility[90,91], even better than LVEF. The relative inter-observer and intra-observer variability of GLS approximately varies from 5% to 8% according to vendors. By contrast, 8% and 10% of variability are reported for LVEF, respectively32. Nevertheless, LV GLS remains load and geometry dependent and needs to be carefully interpreted in many cases.

III.1.4.3. LV GLS and LVEF

The obvious advantages of LV GLS over LVEF are its ability to unmask subclinical LV dysfunction, to identify early structural and morphological myocardial damage, and to better predict postoperative LV dysfunction and outcome[92]. Many cardiac magnetic resonance studies recently reported myocardial alterations, despite preserved LVEF. The presence of LV late gadolinium enhancement has been highlighted in patients with various degrees of AS, despite normal LVEF. A graded relationship between AS severity and longer T1 time, regardless of LVEF (assessed using cardiac magnetic resonance), has been shown5,7 and there have been good correlations between native T1 values and collagen volume fraction obtained by myocardial biopsies[68,93]. Of interest, a large proportion of patients with AS and with high presence of LV late gadolinium enhancement or with markedly elevated T1 values still have preserved LV ejection. Furthermore, LVEF does not follow AS severity whereas LV GLS has been found to gradually worsen when AS becomes more severe. Altogether, these recent data highlight the superiority of LV GLS over LVEF to assess LV myocardial function and predict outcomes of asymptomatic patients with AS.

III.1.4.4. Clinical implication

The present individual participant data meta-analysis shows, in a large cohort of patients, that LV GLS may have a close association with survival and could suggest a better risk stratification value than LVEF. However, the existing evidence has often considered aortic valve

intervention in a composite end-point, with the consequence that intervention influenced event-free survival. In the present study, LV GLS demonstrated its strong impact on mortality and, therefore, the crucial role that it may have in the risk stratification and management of patients with asymptomatic AS. The close relationship between death and impaired LV GLS suggests that this echocardiographic parameter could be implemented in future guideline recommendations, if the present results are confirmed by large multicenter studies. Indeed, a "Heart Team" discussion of early intervention (i.e. including transcatheter aortic valve replacement if necessary) in asymptomatic patients with preserved LVEF but impaired LV GLS<14.7% may be envisaged. Further confirmation about the need for intervention, related to myocardial morphological and structural damage, may be obtained by performing cardiac magnetic resonance and assessment of the presence of late gadolinium enhancement and/or quantification of native T1. Furthermore, the use of exercise stress echocardiography in these patients may also be discussed. Patients with good LV GLS>18% had an excellent outcome (i.e. 97±1% 2-year survival) supporting a conservative approach with clinical and echocardiographic assessment every 1-2 years, in the absence of other indications for intervention or abnormality during exercise stress echocardiography. Our results show that the survival of patients with depressed LV GLS between 14.7% and 18% is similar to those with preserved LV GLS>18% up to 2 years follow-up. With worse LV GLS values beyond 14.7% a marked increase in mortality seems to occur. This may rather promote shorter follow-up intervals (every 6-12 months), in order to assess subtle changes in LV GLS and/or symptoms and to propose prompt intervention.

III.1.4.5. Limitation

This study holds similar limitations to all meta-analyses. However, the use of individual data rather than data derived from publication only, may substantially improve the robustness of the reported results. Furthermore, the low degree of heterogeneity found indicates a relative consensus in the published data.

Although uncommon in asymptomatic patients with preserved LVEF, we cannot exclude that the presence of low flow/low gradient AS in the present cohort.

The lack of sub-analysis according to brain natriuretic peptide may limit our conclusion. However, this biomarker was not available in all selected studies and were not incorporated into guidelines when they were published.

The Egger's and Begg's tests produced discrepant results. However, analysis of the funnel plot suggests an asymmetry between studies' effect sizes and, therefore, a limited but potential publication bias. This is to be expected since positive studies may generally have higher chance to be published than negative ones. However, the studies selected in the present meta-analysis were positive on the basis of combined end-points, including aortic valve intervention. Of note, half of studies selected were negative with regards to all-cause mortality, further limiting the potential publication bias.

We report all-cause mortality as it is more objective, especially in retrospective studies. Cardiovascular death is difficult to assess in retrospective studies[94] and was not available in all publications. The need to perform aortic valve intervention with class I indication as recommended in current guidelines is a frequent end-point in patients with AS. However, the variety of centers and countries involved in the meta-analysis does not allow sufficient standardization to assess this end-point.

Exercise testing aimed at confirming the asymptomatic status of patients, was not systematically performed in all selected studies. Some apparently asymptomatic patients have abnormalities during exercise testing, and these may have been included in the meta-analysis.

The majority of studies included in the meta-analysis performed LV GLS measurement using a GE machine. Consequently, the present results could not be automatically transposed to all echocardiographs. However, LV GLS is known to have good reproducibility, limited difference between vendors and to be superior to conventional echocardiographic measurements.

III.1.5. Conclusion

This individual participant data meta-analysis demonstrates the strong relationship between LV GLS and all-cause mortality in asymptomatic patients with AS and preserved LVEF. These results support the systematic measurement of LV GLS for the risk stratification and the management of these patients and may promote its use in clinical practice as an important additive parameter for decision-making. A LV GLS<14.7% could be considered as a trigger for further imaging investigations and for early intervention. Nonetheless, a limited but potential risk of publication bias may be present in current literature, suggesting the value of a large prospective international study for confirming this key impact of GLS for our AS-patients.

III.2. Assessment of Subclinical LV Dysfunction

This section relates to the following article [95]:

Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of Subclinical Left Ventricular Dysfunction in Aortic Stenosis. *JACC Cardiovasc Imaging* 2019;12:163–171.

III.2.1. Introduction

The LV systolic dysfunction is recognized to be an adverse result of the pressure overload that occurs in severe AS. From a hemodynamic standpoint, AS increases LV afterload, and the natural response of the LV to the increased wall stress due to pressure overload is concentric remodeling, increase in LV mass, and development of LVH, which maintains wall stress and cardiac output. Although this appears to be compensatory in the early stages, preclinical studies have suggested that cardiac performance can be preserved in the absence of hypertrophy[51]. LVH is associated with impaired compliance, higher filling pressure, oxygen supply–demand mismatch, and myocardial ischemia[96]. Moreover, the LVH response is progressively followed by enlargement of the interstitial space with reactive fibrosis and, at a later stage, with replacement fibrosis and cell death. This mechanism is thought to be a major driver of the transition to symptoms, heart failure, and adverse cardiovascular events, and fibrosis is associated with heart failure, arrhythmias, and the resulting mortality risk even after

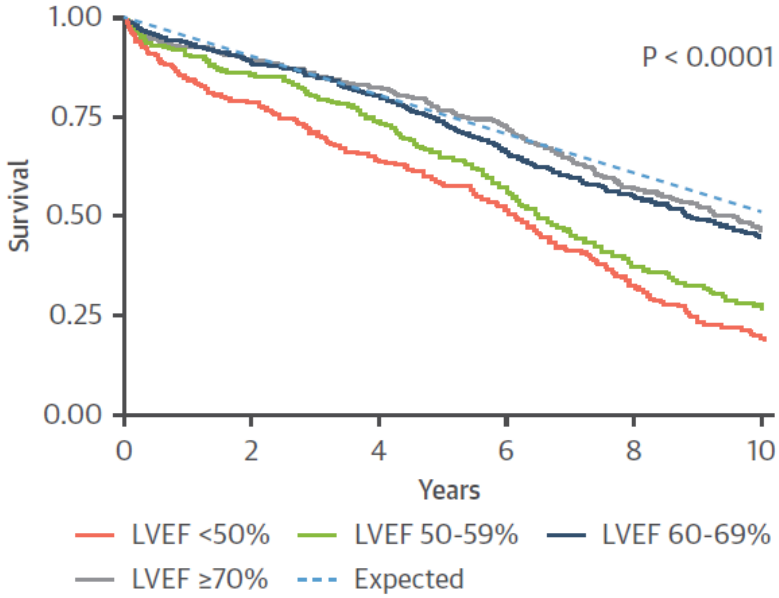
AVR. Early and accurate recognition of myocardial dysfunction offers the potential to optimize the timing of intervention in severe AS. Traditionally, LV systolic function has been expressed in terms of LVEF, referring to the fraction of LV end-diastolic volume ejected during systole. It is the most widely used measure of assessment of LV systolic function, is very familiar to patients and clinicians, and has been extensively used in clinical trials as well as in guideline recommendations for various diseases. LVEF is assessable by multiple imaging modalities that are based on similar principles of measurement. LVEF is a useful surrogate marker of LV function in many cardiac diseases and is ubiquitous among guidelines relating to a variety of topics. This review seeks to define whether the existing LVEF cutoff in AS should be modified or whether GLS should replace it as the marker of subclinical LV dysfunction.

III.2.2. LVEF Works but the Guidelines' Threshold for Intervention is Incorrect

In the absence of coronary artery disease, the LVEF remains preserved in AS, and the concomitant presence of severe AS and reduced LVEF (<50%) is uncommon[64], especially when patients are still asymptomatic. Thus, although the Class I indication for aortic valve intervention is unquestionable in severe AS with depressed LV function evidenced by reduced EF, in the vast majority of patients, symptoms occur well before a reduction in LVEF. However, patients adapt their lifestyle to reduced functional capacity, so symptoms in patients with AS may be difficult to detect. Thus, a strategy based on waiting for LVEF to fall to <50% to indicate aortic valve intervention may lead to suboptimal operative and post–operative outcome. Moreover, LVEF has a number of limitations that have led to decades of intensive research to identify markers that could replace LVEF. Multiple studies documented the independent prognostic value of LVEF in predicting outcomes in patients with AS[70,97,98] as well as with other cardiac conditions. Thus, LVEF persists as the preferred measure of LV function and still plays a pivotal role in the evaluation of any patient with AS. According to both the American College of Cardiology/American Heart Association and European Society of Cardiology VHD guidelines, LV systolic impairment is considered a Class I indication for AVR in severe AS, even in the patient without symptoms, and a specific LVEF cut-point of <50% has been used

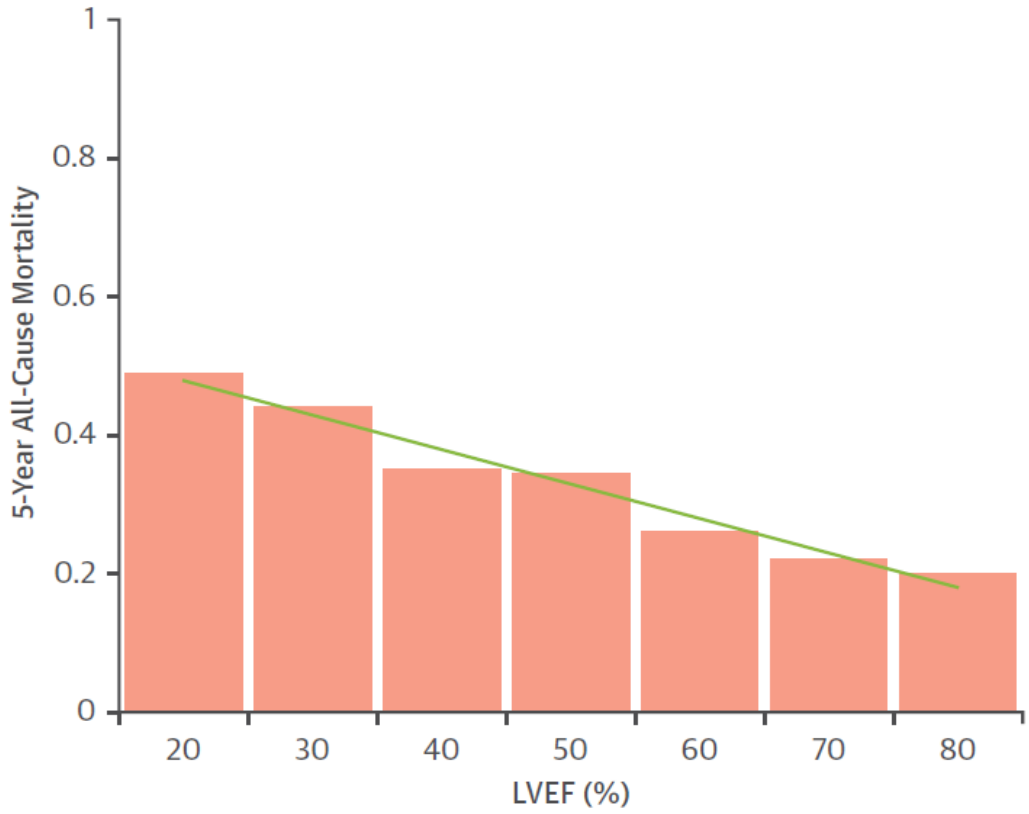
for this purpose. There are problems with this approach. First, echocardiography is the most widely used method of determining LVEF, and the guideline recommendations using echocardiography indicate that LVEF <52% for men and <54% for women should be considered abnormal[99], rather than the cutpoint of LVEF <50% as specified in VHD guidelines. Second, remarkably few data exist to substantiate this particular cut-point as a threshold for intervention in severe AS. In one of the first papers describing the effect of LVEF after AVR, O'Toole et al.[100] gathered a cohort of 93 patients with AS, aortic regurgitation, and mixed AS/aortic regurgitation who had LVEF estimated by ventriculography. Although not significant, there was a trend toward increased mortality in the subset of patients with AS and LVEF <50%, and the authors concluded that depressed LVEF might cause a moderate increase in post–operative mortality. Subsequent studies, comprising mostly symptomatic patients, have shown that reduced EF, variably defined, was a major predictor of survival in patients with severe AS. It should be noted that the occurrence of LVEF <50% in severe AS in the absence of symptoms is rare, with a prevalence of only 0.4% [101]. Consequently, in studies of the natural history of asymptomatic patients with severe AS, few patients have been noted to have LVEF <50%[102]. However, when LVEF is <50% in severe AS, prognosis is worse, with or without AVR. The paucity of available data supporting the selection of LVEF <50% as the cutpoint for referral to AVR led to studies of the impact of pre–operative LVEF on outcome after AVR in patients with severe AS. Dahl et al.[64] stratified 2,017 severe AS patients undergoing AVR into 4 groups according to LVEF: LVEF <50%, LVEF 50% to 59%, LVEF 60% to 69%, and LVEF >70%. In 300 patients (15%), LVEF was <50%, and these patients were characterized by having increased LV mass, low relative wall thickness, and larger LV cavities consistent with eccentric hypertrophy. Similar but less extensive changes were also present in patients with LVEF 50% to 59%. Patients with LVEF <50% experienced the worst outcome, with a 5-year mortality rate of 41%, although patients with LVEF 50% to 59% also experienced increased mortality (5-year all-cause mortality rate 35%) (Figure 15).

Figure 15: Graded relationship between impaired LVEF and reduced survival.



These findings were consistent, irrespective of the occurrence of ischemic heart disease or presence of symptoms. In the same population, 5-year all-cause mortality rates increased with decreasing LVEF in an inverse linear relationship (Figure 16). These findings suggested that not only patients with LVEF <50% but also those with LVEF 50% to 59% had a less favourable post–operative outcome.

Figure 16: Unadjusted 5-Year All-Cause Mortality Rates in 2,017 Patients With Severe Aortic Stenosis Undergoing Surgical Aortic Valve Replacement, according to pre-operative LVEF.



In line with these results, Capoulade et al.[103] demonstrated in more than 1,000 consecutive AS patients that the best LVEF cut-point value for all-cause mortality was 56%. Further corroborating these findings, Ito et al.[70] recently demonstrated in 928 consecutive patients with severe AS that patients with LVEF 50% to 59% had increased mortality compared with those with LVEF >60% irrespective of whether patients underwent AVR or not. This study showed that in patients with serial echocardiograms who present with LVEF <50% at the time of diagnosis of severe AS, LVEF had begun to decrease even when AS was moderate. An LVEF of 50% to 60% at the time that AS was moderate predicted further deterioration of LVEF. The findings from these studies thus suggest that the threshold of LVEF <50% may be too low and indicate that reduced LV function may already be present when LVEF is 50% to 59%. This "supranormal" threshold seen in AS may reflect that patients with severe AS have smaller cavities as a consequence of LV remodeling, requiring higher LVEF to preserve stroke volume. Failure to keep LVEF in the "supranormal" range may play an important role in the development

of low-flow low gradient AS with preserved LVEF, a condition with a poor prognosis compared with high-gradient AS patients. Although low-flow low-gradient AS is partly the result of progressive LV remodeling that leads to small concentric remodeled LV cavities, the decrease in stroke volume is accentuated by a decline of LVEF from supranormal ranges to normal ranges[104]. Despite its known limitations, the familiarity and wide availability of LVEF as a means of assessing systolic function provide ongoing importance to its role in assessment of the patient with AS. Nonetheless, to identify patients with subclinical LV dysfunction and who are at risk of poor outcomes, an LVEF threshold of <50% is inadequate. As risk has been shown to be increased above the standard LVEF cut-point, a safer threshold would be LVEF <60%, particularly when the LV cavity is small. Because of the variability between imaging modalities in determining LVEF, use of a single modality is optimal for serial assessment of the individual patient. Finally, despite a worse outcome when LVEF is reduced, this should not be used as a reason for denying AVR, which often leads to improved systolic function and remains the only effective treatment for severe AS.

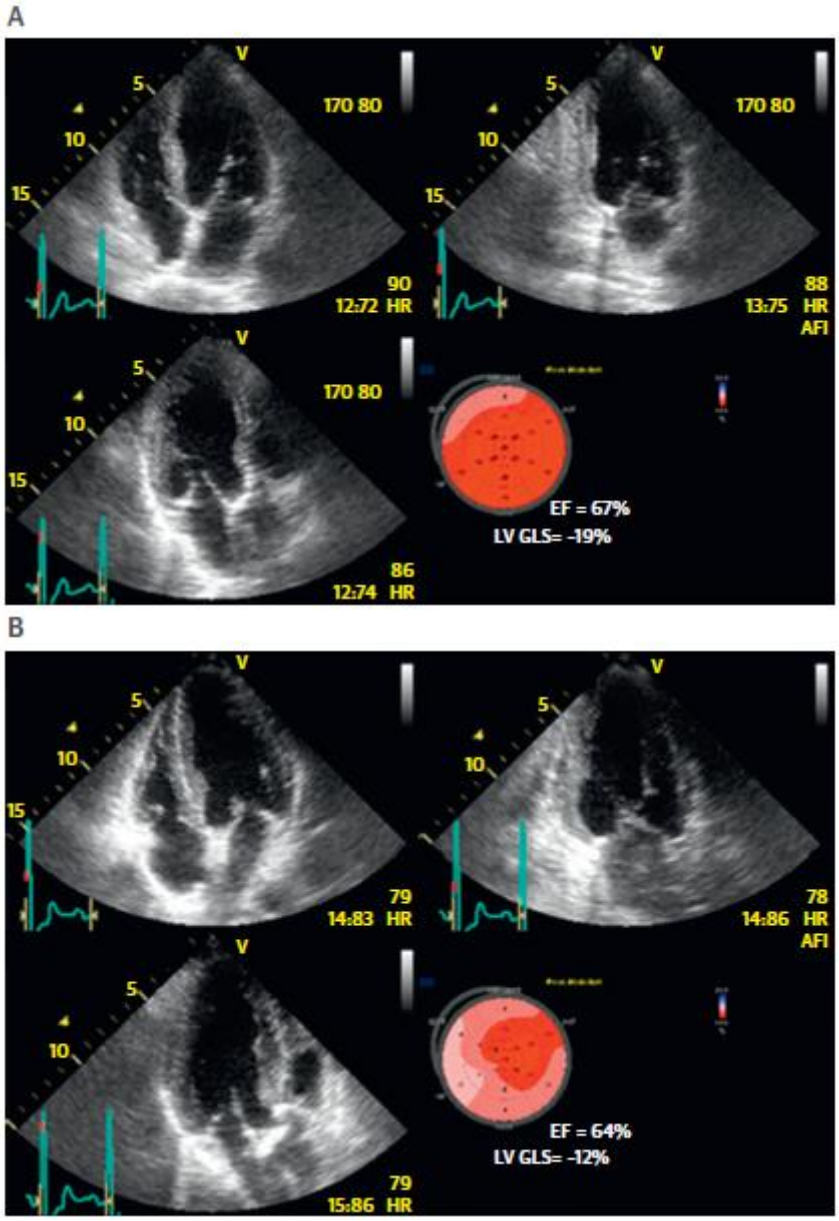
III.2.3. Role of GLS in Assessment of Subclinical LV Dysfunction in AS.

Despite the almost universal understanding and widespread use of LVEF, it has important limitations. It is load dependent[105,106] due to the mechanisms described by Starling et al.[107] and demonstrates imperfect reproducibility[108]. There exists an independent relationship between LVEF and relative wall thickness; thus, for a similar extent of intrinsic myocardial shortening, the LVEF will tend to increase in relation to the extent of LV concentric remodeling[109]. LVEF may thus be maintained despite reduced myocardial contractility by the use of preload reserve or changes in LV geometry. In contrast, a decreased LVEF may occur in the setting of preserved contractility due to afterload mismatch[108,110–113] but could also represent a failing LV. Thus, the interpretation of LVEF as a marker of LV contractility may be challenging in valvular diseases, where changes in afterload and preload are predominant. Impairments of LV structure and function are related to symptom severity and outcome in patients with AS, but as in other circumstances of “subclinical” dysfunction, LVEF is not an

ideal parameter. Specifically, in AS, EF is poorly correlated with AS severity parameters, both at rest or during exercise, and it has a low negative predictive value to detect LV myocardial damage. However, many other parameters have been identified as useful for the risk stratification both before and after intervention, including LV morphological and functional parameters other than LVEF[114]. Indeed, the presence of concentric remodeling, increased LV mass, and LVH are powerful markers of poor outcome, and even residual elevation of LV mass after intervention leads to reduced post–operative survival[115]. These considerations support the contention that focus on an LVEF <50% is overly simplistic in an era when the management of AS has evolved toward more complex decision-making and preservation of LV function. The era of tissue characterization with cardiac magnetic resonance (CMR) has provided new insights into LV responses to AS. Late gadolinium enhancement (LGE) has been identified in patients with various degrees of AS severity, despite normal LVEF[65–67]. In addition, the use of myocardial longitudinal magnetization relaxation time (native T1 time) allows more accurate assessment of diffuse changes in the interstitial space[116]. A graded relationship between AS severity and longer T1 time has been shown to be independent of CMR-derived LVEF[66,68], and good correlations have been shown between native T1 values and collagen volume fraction obtained by myocardial biopsies. A large proportion of patients with significant degrees of LV LGE or with markedly elevated T1 values still have preserved LVEF. Furthermore, both LGE and T1 values have been associated with outcome in patients with AS. These studies suggest that: 1) preserved LVEF does not mean preserved LV function and normal morphology; and 2) the use of LVEF <50% as a trigger for intervention very likely leads to operation in patients with LV myocardial abnormalities. The current published data demonstrate that LVEF does not effectively differentiate diffuse from focal fibrosis and therefore does not provide appropriate assessment of LV morphological and functional changes. As CMR tissue characterization is not a feasible option for the increasing numbers of patients with AS, a feasible and lower cost alternative is needed. In this regard, the use of LV GLS, derived from speckle tracking echocardiography, provides a semiautomated quantification of myocardial deformation (strain and strain rate) and may be an appropriate early marker of subclinical LV dysfunction. A

complete evaluation of LV mechanics would include measurement of deformation in the 3 planes (longitudinal, radial, and circumferential) as well as rotation and torsion[117]. Of these parameters, the feasibility of LV GLS calculation from standard 2-, 3-, and 4-chamber apical views has made this parameter the most common application of speckle tracking. GLS provides additional diagnostic and prognostic value in a wide range of conditions including VHD[118]. Its interobserver and intraobserver variability (5% to 8% relative difference) compares favorably with 8% to 10% for LVEF. The association of deformation indexes with invasive markers of LV contractility as dp/dt[119] and the end-systolic pressure–volume relationship[120] has led to the belief that GLS might be used as a surrogate of LV contractility. However, recent studies have demonstrated that GLS, similar to LVEF, also has important load dependency[121] and thus is also affected by AS severity[86,122]. The inability of LVEF and GLS to reflect LV contractility emphasizes one of the principal challenges of cardiac imaging. Imaging measures events occurring during the ejection phase, while contractility is the consequence of degradation/activation of actin myosin bonds that lead to building of systemic pressures in the LV and occurs during isovolumic contraction, a phase not easily measured with imaging. Newer methods of assessing myocardial stiffness may facilitate the assessment of cardiac function in AS but require further study[123,124]. Depression of LV GLS in patients with AS and preserved LVEF (Figure 17) is an early sign of LV dysfunction and is attributed to the susceptibility of longitudinal subendocardial fibers to myocardial damage and interstitial collagen deposition. Furthermore, the gradient of decreasing myocardial fibrosis from the base to the apex of the LV, evidenced by amount of LGE during CMR, is inversely correlated with peak systolic longitudinal strain[125], which may show a pattern of apical sparing (Figure 17).

Figure 17: Asymptomatic patients with preserved LVEF and normal LV GLS (A) or impaired LV GLS (B).

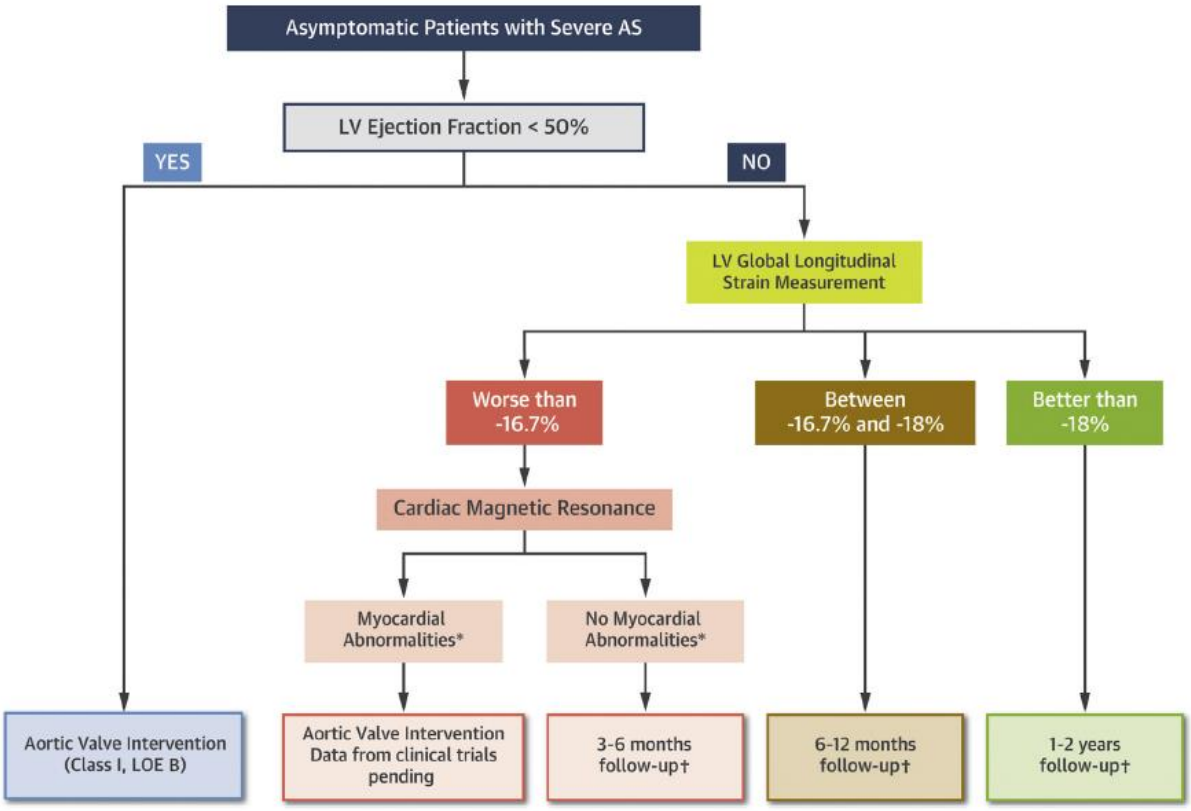


The degree of impairment of LV GLS worsens as AS becomes more severe, in contrast to the deterioration of LVEF at a later stage in the progression of AS. Ng et al.[86] showed that LV GLS worsened significantly from sclerosis to severe AS (from 20% to 15%), whereas LVEF remained preserved and did not change (from 62% to 61%). Furthermore, impaired LV GLS is strongly associated with requirement of aortic valve intervention, post–operative cardiac events, and survival in patients with AS, irrespective of LVEF and symptoms. In a recent

individual participant data meta-analysis of asymptomatic AS patients with preserved LVEF[63], the median LV GLS was 16.2% (interquartile range: 18.4% to 13.5%). These results confirm that LV GLS is a powerful marker of mortality in asymptomatic patients with AS and preserved LVEF (area under the curve: 0.68) with homogeneity between studies. Patients with LV GLS above the best cut-off value for prediction of death in the meta-analysis (GLS 14.7%) had a >2.5-fold increment of mortality. However, driven by the remaining small variability of GLS between vendors and the recognition that outcome of patients with AS is driven by a combination of factors including AS severity, abnormalities of the aorta (e.g., reduced compliance), and upstream consequences of AS (i.e., on LV, left atrium, and right ventricular size and function), it is unlikely that a specific number will be key. Aortic valve intervention allows regression of diffuse fibrosis and myocardial cellular hypertrophy, and this improvement is accompanied by structural, functional, and biomarker changes. The value of GLS is not limited to pre–operative patients. About 20% of patients who survive >1 year after AVR have abnormal postoperative LV GLS, despite preserved LVEF. This finding is independently associated with adverse events, and its presence despite LV mass regression suggests that it reflects an interstitial change. Experimental studies show that focal fibrosis and cardiomyocyte loss persists after AVR, suggesting the importance of intervention before the occurrence of irreversible myocardial damage. Paradoxical low-flow low-gradient severe AS is a well-known distinct entity of AS[126] in which preserved LVEF masks LV dysfunction. LGE has been frequently identified in this subgroup of patients[127], and impaired LV longitudinal function and reduced GLS are also frequently observed—to a similar extent to their manifestation in patients with depressed LVEF[128]. Consequently, LV GLS seems able to unmask occult longitudinal systolic dysfunction, not revealed by LVEF, and may be useful to explain the “paradox” (i.e., resolve the discrepancy of reduced LV flow despite preserved LVEF). The most recent American College of Cardiology/ American Heart Association and European Society of Cardiology VHD guidelines do not include a role for GLS assessment. However, the cumulative evidence demonstrating its powerful prognostic value may promote its incorporation in the next

recommendation. In the meanwhile, however, a proposed algorithm could be used in asymptomatic patients with preserved LVEF (Figure 18).

Figure 18: Proposed algorithm for the management of patients with asymptomatic severe AS.



*This approach integrates the use of left ventricular (LV) global longitudinal strain derived from speckle tracking echocardiography. *The presence of important late gadolinium enhancement, delayed native T1, or elevated extracellular volume in cardiac magnetic resonance. †Only if there is no other current guidelines indication for aortic valve intervention. LOE: Level of Evidence.*

In the absence of other current guideline indications for aortic valve intervention or exercise stress echocardiography abnormalities, the measurement of impaired LV GLS worse than <14.7% may be one of many features to guide a decision to intervene. If the optimal management is still unclear, patients with impaired GLS could be further studied using CMR; midwall LGE, abnormal native T1, or increased extracellular volume all provide evidence of LV impairment that could prompt surgery. In the absence of such CMR findings, close follow-up could be recommended (i.e., 3 to 6 months) to detect any changes in symptoms or LV function.

III.2.4. Take-home message

Consistent with the modern view of AS as a disease of the LV as well as the valve, the authors of this review emphasize the importance of LV dysfunction in decision-making about AS. At issue is how best to measure LV function:

- ✓ The current guidelines use of LVEF <50% is clearly wrong in an era where the measurement guidelines reference normal cutoffs of 52% in men and 54% in women.
- ✓ An EF <60% is associated with increased risk.
- ✓ A “preserved” EF in the presence of a small LV cavity equates to a low stroke volume—the primary problem in LFLG AS. The fundamental problem that a change of EF threshold cannot address is that it is difficult to assess the status of the LV without knowing the size of the LV cavity.
- ✓ LV GLS is a more reliable parameter than standard 2-dimensional LVEF. Despite its influence by preload and afterload, it is sensitive enough to unmask patients with structural and functional myocardial damage that LVEF cannot reveal.
- ✓ A reduced LV GLS corresponds to the presence of myocardial structural alterations by CMR and may promote early intervention in asymptomatic patients with severe AS.
- ✓ An impaired LV GLS despite preserved LVEF is a powerful predictor of outcome.

III.2.5. Conclusion

The central place of LVEF <50% in the assessment of LV function in patients with AS may be responsible for delays in aortic valve intervention in patients who could benefit and probably contributes to suboptimal postoperative clinical outcome in some patents. The current published data provide evidence to support the implementation of LV GLS in future recommendations.

Partie IV. New imaging markers of LV function in patients with AS

IV.1. First Phase Ejection Fraction

This section relates to the following article [129]:

Magne J, Aboyans V. First-phase left ventricular ejection fraction: a small step for myocardial assessment, a big leap for aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2021;22:658–659.

The quest of the most appropriate surrogate echocardiographic marker of LV systolic function able to assess accurately the impact of LV global afterload on LV myocardium in patients with AS is still in progress. Optimally, this marker should have good sensitivity and specificity, be easy and rapid to measure, with good reproducibility, cheap, well correlated with AS severity (and its chronicity) in addition to arterial afterload, and finally to patient's prognosis. Some of these characteristics are not fulfilled by LVEF, whereas we still continue to use it as the only recommended parameter for the assessment of LV function and decision for intervention in patients with AS. Consequently, many research efforts are done overtime to find better parameters than LVEF. Recently, the concept of first-phase LVEF ($LVEF_1$) has been studied in patients with increased LV afterload, initially in hypertensive patients, and then in those with AS. The biophysics of cardiac myocyte contraction stipulates that shortening deactivation[130] could participate to early (i.e. close to the first peak of LV pressure) and rapid decrease in myocardial wall stress, thus facilitating LV relaxation during diastole. In the presence of increased afterload and subsequent diastolic abnormalities, shortening deactivation and delayed peak shortening velocity of myocytes may occur in order to maintain elevated myocardial wall stress and preserved global LVEF[131]. This phenomenon may also protect the myocardium against wave reflections. The measurement of $LVEF_1$ allows the assessment of these pathophysiologic compensatory mechanisms and enables to unmask early LV myocardial morphological and functional alteration. Bing et al.[132] reported good relationship between increased AS severity or LV global haemodynamic afterload and reduced $LVEF_1$.

They also find that $LVEF_1$ is associated with CMR markers of LV myocardial fibrosis, such as late-gadolinium enhancement or indexed extra-cellular volume. Furthermore, Gu et al.[133] have shown that $LVEF_1$ <25% is associated with markedly reduced event-free survival or even all-cause mortality in patients with AS. Of interest, none of these studies found any significant correlation between global LVEF and $LVEF_1$, despite the use of LV end-diastolic volume in the calculation of both parameters. In addition to classical Simpson's rule, the quantification of $LVEF_1$ requires accurate measurement of time to-peak aortic flow velocity from continuous-wave Doppler.

Therefore, this delay needs to be replicated in bi-dimensional four and two-chamber views in order to measure the LV volume at peak aortic flow. Einarsen et al.[134] extended the knowledge's about $LVEF_1$ by studying a prospective series of 114 patients with at least mild AS and preserved LVEF (>50%). Of note, patients with arrhythmias, prior pacemaker, or known coronary artery disease were excluded. In other words, all patients with AS were free from any LV functional abnormalities despite few morphological changes (LV concentric remodeling or hypertrophy). Furthermore, the exclusion of patients with arrhythmias may ensure global suitable reproducibility of the measurements. Using transthoracic echocardiography, they quantified $LVEF_1$ and assessed its relationship with LV myocardial contractility and both LV and arterial haemodynamic load. The first results of interest from this study is the graded relationship between increase AS severity and decrease in $LVEF_1$, where $LVEF_1$ appears modestly reduced in moderate AS but much more in severe AS. In addition, the majority of patients with abnormal $LVEF_1$ has severe AS. This is crucial since $LVEF_1$ may reflect the pathophysiological continuum of AS and they consequences on LV myocardium. Of note, this relationship was also reported with LV GLS or other modern parameters of LV function but not with LVEF in contemporary series. Secondly, the reproducibility of $LVEF_1$, even derived from limited number of patients (n= 18), seems acceptable. This point is also fundamental for any new candidate parameter within the armamentarium of daily clinical practice LV function assessment. Although the quantification of $LVEF_1$ is not technically challenging, several small errors measurement may have major impact on the final results and

in this regard, a large-scale independent reproducibility study is still required. Third, regardless AS severity, the authors found that $LVEF_1$ is independently associated with LV global myocardial deformation, as assessed using strain rate. More interestingly, they also identify a strong association between $LVEF_1$ and arterial stiffness, as assessed using PP/SVi. This suggest that $LVEF_1$ may be used as a global parameter able to provide key findings on the real consequences of global LV haemodynamic afterload (i.e. both valvular and arterial) on LV myocardial function. The impact of such findings may be of importance since improving our assessment of LV systolic function in these patients. This may be helpful for the management of patients with AS since evidences in favour of early intervention (i.e. in the absence of symptoms or impaired LVEF) is growing. Despite preserved global LVEF, asymptomatic patients with $LVEF_1$ <25% could be considered for aortic valve intervention and discussed within dedicated Heart Team. Complementary LV function parameters, such as LV GLS or even CMR markers may also be used to corroborate early subclinical LV dysfunction. The present data elegantly strengthen the body of evidences suggesting the usefulness of $LVEF_1$ in patients with AS. Nevertheless, several points require clarification through further research. From a mechanistic standpoint, the delayed peak aortic flow velocity and LV shortening related to increased AS severity and global afterload lead to slower LV ejection and emptying. This is the rationale for $LVEF_1$ quantification in these patients. Nonetheless, such delay will automatically modify the emptying of LV, more particularly when LVEF is still preserved. Such pattern needs to be studied in patients with AS and modern multi-modalities imaging may be helpful. Despite a lack of data, serial measurement of $LVEF_1$ during the conservative follow-up phase of the management of patients with AS may be of interest. Following intervention, encouraging results have

been reported regarding the improvement of $LVEF_1$. These data suggested that around two-thirds of patients may markedly improve $LVEF_1$ when AS-related afterload is released and that patients remaining with reduced $LVEF_1$ frequently have myocardial irreversible sequela, such as infarct-like late-gadolinium enhancement. In patients with paradoxical low-flow severe AS, the poor prognosis may appear out of proportion regarding AS severity and even LV function

since LVEF is preserved. The use of $LVEF_1$ in these patients may participate to explain the paradox but also to better assess LV function and thus stratify the risk of patients. Nevertheless, the high prevalence of arrhythmias and atrial fibrillation in these patients may limit the application of $LVEF_1$. The load-dependency of $LVEF_1$ is obvious and already well studied.2,4 This could be an issue since $LVEF_1$ may only reflect the global LV hemodynamic increased afterload, as demonstrated by the present data, rather than the LV dysfunction. However, the relationship between $LVEF_1$ and outcome is independent from AS severity, underlining the usefulness of this parameter in the management of AS patients. Furthermore, the load-dependency of $LVEF_1$ strongly promote careful measurement and interpretation during echocardiographic exam. Concomitant assessment of blood pressure is mandatory and serial quantification of $LVEF_1$ during the exam may be recommended. The influence of white-coat effect on $LVEF_1$ also requires to be studied. All these points require further research in order to better understand and support the role of $LVEF_1$ measurement in the management of patients with AS. Meanwhile, $LVEF_1$ could be systematically quantified in these patients. A substantial learning curve is expected and this should encourage to start its quantification in daily practice as soon as possible in order to rapidly improve reproducibility.

Although promising, implementation of $LVEF_1$ in next guidelines may be premature, similarly than others echocardiographic parameters assessing LV function. Hence, randomized clinical trial comparing strategy's management based on the use of global LVEF vs. $LVEF_1$ (or LV GLS or LV dispersion) may be encouraged in order to provide stronger evidences.

IV.2. Mechanical Dispersion

This section relates to the following article [135]:

Magne J, Aboyans V. Mechanical left ventricular dispersion in aortic stenosis: another parameter within dispersed surrogates of myocardial function? *Eur Heart J Cardiovasc Imaging* 2019;20:749–750.

In patients with AS, the presence of LV systolic dysfunction, defined as a LV ejection fraction <50%, is a class I indication for valve intervention, regardless symptomatic status. Based on this definition, the prevalence of LV systolic dysfunction in strictly asymptomatic patients with severe AS is particularly rare. In addition, LV ejection fraction may remain normal for long in patients with severe AS and can mask structural and functional myocardial alteration. The use of LV ejection fraction and the cut-off of 50% in AS patients' is increasingly debated in the literature1. According to Starling and Laplace laws, LV ejection fraction is load dependent and is mechanically increased when LV concentric remodeling progresses, i.e. relative wall thickness increases leading to normal or supra-normal value of LV ejection fraction. These phenomena, combined with the concept of LV preload reserve, participate to maintain LV ejection fraction in a normal range in patients with AS without coronary disease. By opposition, even in the absence of reduced contractility, LV ejection fraction may be decreased due to afterload mismatch. Furthermore, its reproducibility is limited[108]. Altogether, these points underline that LV ejection fraction is not the most appropriate surrogate marker for LV systolic function and contractility in patients with AS. Consequently, many efforts have been recently made to develop and validate bio-imaging markers allowing identification of subclinical myocardial damage related to LV increased hemodynamic afterload. Cardiac magnetic resonance provides gold standard parameters for LV structure and function assessment but its cost, availability and processing time limit its daily use and, thus, could be mostly reserved to patients with poor acoustic windows and/or inconclusive echocardiography. Several

echocardiography-derived indices have been already studied and some of them are close to be routinely implemented in clinical practice (Table 4).

In the European Heart Journal – Cardiovascular Imaging, Prihadi et al.[136] studied the determinants and prognostic value of LV mechanical dispersion in patients with AS. This speckle tracking-derived parameter, well studied by the group of Haugaa and Edvardsen, reflects inhomogeneous LV myocardial contraction[137], is known to be independent of LV ejection fraction, and associated with subclinical dyssynchrony, ventricular arrhythmias and LV fibrosis in several cardiomyopathies[138]. Prihadi et al. retrospectively assessed LV mechanical dispersion in 630 patients from their previously published cohort of various degrees of native AS without other significant valve disease. They first reported a close relationship between LV mechanical dispersion and AS grade with markedly higher dispersion in patients with severe AS. Second, the authors identified older age, LV ejection fraction and mass, AS severity and QRS duration as correlates of LV mechanical dispersion. These results confirm that correlates of LV fibrosis in patients with AS are independent determinants of LV mechanical dispersion, even after adjustment for QRS duration. Third, the authors confirmed the results of Klaeboe et al.[139] showing the prognostic value of LV mechanical dispersion. Indeed after robust adjustment for cofounders including age, hypertension, QRS duration, aortic valve replacement, AS severity and classical parameters of LV function and morphology, they found the extent of LV mechanical dispersion as predictive of increased risk of mortality.

As compared to LV ejection fraction, the LV mechanical dispersion has several advantages and, from a pathophysiologic standpoint, appears as a better marker of consequences of LV hemodynamic afterload on ventricular myocardial structure and function. It is associated with AS severity, their determinants are related to LV fibrosis in non-ischemic pressure overload diseases, and its use could have incremental prognostic values as compared to LV ejection fraction. The present study obviously highlights all these benefits and suggests its wide used in clinical practice, although promoting further larger studies and trials based on this parameter. Indeed, some limitations in this study should be addressed in the future. First, the cut-off value

requires to be defined and validated. Second, the comparison of LV mechanical dispersion with LV ejection fraction is fair but many recent parameters also demonstrated added value as compared to LV ejection fraction (Table 4). Among them, the usefulness of LV global longitudinal strain in patients with AS could be compared to LV mechanical dispersion. Whether LV global longitudinal strain and mechanical dispersion provides similar or complementary information in the assessment of systolic function remains unknown in AS. A direct comparison also with myocardial biomarkers such as brain natriuretic peptides, high-sensitive troponin I or ST2 are also necessary. Third, to improve the management of AS, the prognostic value of LV mechanical dispersion should be studied in asymptomatic patients, i.e. with normal exercise test. Fourth, its reversibility following aortic valve intervention or under treatment targeting LV remodeling needs also to be addressed. Finally, cardiac magnetic resonance and histologic studies will be also required in the future to distinguish whether LV mechanical dispersion is a direct surrogate marker of LV fibrosis or, more largely, a surrogate of LV electrical conduction abnormalities related to LV morphological changes, including fibrosis, apoptosis or other mechanisms. Meanwhile, the data reported by Prihadi et al. are convincing, and support the implementation of LV mechanical dispersion within the catalogue of echocardiographic LV function related parameters.

Table 4: Main parameters of left ventricular systolic function developed in patients with AS.

LV parameters	Cut-off value	Predictive in asymptomatic patients	Severity of AS for the validation	Ref.
Echocardiographic				
Ejection fraction	50%	Yes*	Various	5
First-phase ejection fraction	25%	Yes	Moderate/severe AS	133
Global longitudinal strain	-14.7%	Yes	Significant AS	63
Basal strain	-13%	Yes	Moderate/severe AS	83
Indexed stroke volume	35mL/m²	No	Severe AS	140
Cardiac Magnetic Resonance				
Late gadolinium enhancement	…	No	Severe AS	67
Native T1	…	Yes	Moderate/severe AS	141
Extra cellular volume	Tertile	No	Severe AS	142

LV indicates left ventricular; AS, aortic stenosis. *asymptomatic patients with LV ejection fraction<50% are rare. Cut-off could be increased at 55-60%.

Partie V. Management and Early Intervention in Patients with AS

V.1. Intervention in Asymptomatic Patients

In 2023, the current recommendation for valve intervention in asymptomatic patients with AS have been softened as compared to previous guidelines (Table 5). Whereas in absence of symptoms, intervention was only recommended in patients with depressed LVEF<50% in all previous guidelines from 1998, both ACC/AHA 2020 and ESC 2021 guidelines innovated and introduced higher threshold for LVEF. Such evolution allowing to intervene earlier, before markedly high LV myocardial impairment. Indeed, American guidelines recommended to intervene on in asymptomatic patients with LVEF<60%. ESC guidelines were a bit cautious by introducing a threshold at 55%. Such change in cut-off are well supported by current data, despite lack of randomized trial.

Table 5 illustrate how far guidelines have evolved over the past 25 years, and in what direction. The number of parameters useful for the management of patients with AS has risen sharply, despite the lack A level of evidence. However, the new guidelines are increasingly permissive and clearly enable intervention at an earlier stage of the disease than ever. Management based on watchful waiting and watchful for symptoms strategy, involving very close monitoring and a particularly acute knowledge of the patient's disease, has less and less place in the management of patients with chronic asymptomatic AS. The same applies to the attitude of waiting for LVEF to fall below 50%. More parameters are now available to identify the myocardial consequences of AS. Based on these parameters, or even without their use, the next question to be answered by the community on the basis of robust data is whether all patients with chronic, severe and asymptomatic AS, with preserved LV function, are eligible for SAVR or TAVR intervention.

Table 5: Evolution from 1998 to 2021 of the recommendations for intervention in patients with AS.

	ACC/AHA 1998[143]		ACC/AHA 2006[144]		ESC 2007[145]		ESC 2012[146]		ACC/AHA 2014[147]		ESC 2017[5]		ACC/AHA 2020[6]		ESC 2021[7]	
	Class	**LOE**	**Class**	**LOE**	**Class**	**LOE**	**Class**	**LOE**	**Class**	**LOE**	**Class**	**LOE**	**Class**	**LOE**	**Class**	**LOE**
Severe AS and Symptoms	I	…	I	B	I	B	I	B	I	B	I	B	I	A	I	B
Severe AS undergoing CABG	I	…	I	C	I	C	I	C	I	B	I	C	I	B-NR	I	C
Severe AS undergoing surgery on the aorta or other valve	I	…	I	C	I	C	I	C	I	B	I	C	I	B-NR	I	C
Moderate AS undergoing CABG or surgery on the aorta or other valve	IIa	…	IIa	B	IIa	C	IIa	C	IIa	C	IIa	C	IIb	C-EO	IIa	C
Asymptomatic severe AS: LV syst. Dysf. (LVEF<50%)	IIa	…	I	C	I	C	I	C	I	B	I	C	I	B-NR	I	B
Abnormal response to exercise*	IIa*	…	IIb*	C	I† / IIa‡	C	I† / IIa‡	C	IIa‡‖	B	I†‡	C	IIa	B-NR	I† / IIa‡	C
Ventricular tachycardia	IIa	…	…	…	IIb§	C	…	…	…	…	…	…	…	…	…	…
Excessive LVH (≥15mm)	IIb	…	…	…	IIb	C	IIb	C	…	…	…	…	…	…	…	…
Very severe AS	IIb	…	IIb	C	IIa	C	IIa	C	IIa	B	IIa	C	IIa	B-NR	IIa£	B
Rapid progression	…	…	IIb	C	…	…	IIa	C	IIb	C	IIa	C	IIa	B-NR	…	…
Severe valve calcification#	…	…	…	…	…	…	IIa	C	…	…	IIa	C	…	…	IIa€	B
High BNP level	…	…	…	…	…	…	IIb	C	…	…	IIa	C	IIa	B-NR	IIa	B
Pulmonary hypertension	…	…	…	…	…	…	…	…	…	…	IIa	C	…	…	…	…
Ex.-induced ↗ in MPG>20mmHg	…	…	…	…	…	…	IIb	C	…	…	…	…	…	…	…	…
Progressive decrease in LVEF<60%	…	…	…	…	…	…	…	…	…	…	…	…	IIb	B-NR	…	…
LV syst. Dysf. LVEF<55%	…	…	…	…	…	…	…	…	…	…	…	…	…	…	IIa	B
Symptomatic Low gradient AS																
LV dysfunction and contractile/flow reserve	…	…	…	…	IIa	C	…	…	…	…	I	C	…	…	I	B
LV dysfunction and no contractile/flow reserve	…	…	…	…	IIb	C	IIb	C	…	…	IIa#	C	…	…	…	…
LF/LG reduced LVEF	…	…	…	…	…	…	…	…	IIa	B	…	…	I	B-NR	IIa	C
LF/LG preserved LVEF	…	…	…	…	…	…	…	…	IIa	C	IIa	C	I	B-NR	IIa	C

*hypotension or symptoms. †symptoms. ‡fall in blood pressure. §abnormal exercise test showing complex ventricular arrhythmias. ‖decrease exercise tolerance. £LVEF<55% and low procedure risk. #confirm severe AS with computed tomography calcium score. € severe valve calcification (ideally assessed by CT) and Vmax progression >0.3m/s/year. AS indicated aortic stenosis; CABG, coronary artery bypass graft; BNP, brain natriuretic peptide; MPG, mean pressure gradient; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; LF/LG, low flow/low gradient; NR, non-randomized; EO, expert opinion.

V.2. Debate: All patients with asymptomatic severe aortic stenosis need valve replacement.

This section relates to the following article [148]:

Iung B, Pierard L, Magne J, Messika-Zeitoun D, Pibarot P, Baumgartner H. Great debate: all patients with asymptomatic severe aortic stenosis need valve replacement. *Eur Heart J* 2023:ehad355.

V.2.1. Introduction

AS has become a significant health burden affecting 2%–6% of the population older than 65 years[149,150]. A recent study[151] estimated for 2017 globally 12.6 million patients with calcific AS—the most common etiology of AS—causing 102 700 deaths and a rapid increase in prevalence is observed with the aging population, particularly in Europe and North America[152]. Since calcific AS can easily be detected by echocardiography at a very early stage—when no or only mild hemodynamic consequences are present—develops slowly, and is an active process sharing pathophysiologic similarities with atherosclerosis[153], there is hope to find medical treatment that interferes with its progression. Unfortunately, all attempts to develop effective medical treatment over the last decades—in particular addressing cholesterol lowering and statin therapy[154] but also other innovative approaches[25,155]—were so far unsuccessful and the only treatment option currently remains AVR by a prosthetic valve when the stenosis has become severe. While studies reported a relatively good outcome for asymptomatic severe AS[102,156], the prognosis becomes dismal as soon as the patients develop symptoms. AVR has been shown to dramatically improve symptoms and survival at this stage of the disease[157–159]. Therefore, the strong indication for AVR in symptomatic severe AS is generally accepted. Whether and when to intervene in asymptomatic severe AS to improve outcome remains, however, controversial[160]. In a recent survey, asymptomatic patients accounted for 19% of patients with severe AS[21] and 17% of patients with severe high gradient AS referred to the participating centers[161], but the percentage in the general population must be expected to be much higher. Thus, the question of how to manage these patients is of critical importance. The potential rationale for intervening in asymptomatic severe VHD has recently been

summarized. Arguments include in particular the risk of life-threatening events and irreversible end-organ damage as well as practical limitations of a watchful waiting strategy in guaranteeing optimal timing of intervention.

The potential benefits of intervening in an asymptomatic patient must, however, be weighed against the operative/catheter interventional risk and the long-term risks associated with a valve substitute.

Over the years, a number of predictors of worse outcome in asymptomatic AS have been identified. These include clinical characteristics such as older age, atherosclerotic risk factors, and echocardiographic parameters such as degree of valve calcification, peak velocity and its progression, ejection fraction, increase in mean gradient > 20 mmHg with exercise, severe left ventricular hypertrophy, indexed stroke volume, left atrial volume, left ventricular global longitudinal strain, pulmonary hypertension, and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A). While these risk factors could be demonstrated to predict event-free survival, it must be kept in mind that in most studies, the predominating event was the development of symptoms requiring intervention. It still remains to be shown whether, in the presence of such risk factors, patients benefit indeed from early intervention when they are still asymptomatic.

Based on observational data, current guidelines recommend by expert consensus rather than by strong evidence to intervene in the following groups of asymptomatic patients with severe AS15 (the references cited after each recommendation are the ones provided in the guideline document to support the respective recommendation):

- Patients with systolic left ventricular dysfunction defined by ejection fraction <50% when no other causes are present (IB).
- When exercise testing reveals symptoms attributable to AS (IC).

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

- Patients with systolic left ventricular dysfunction defined by ejection fraction <55% when no other causes are present (IIaB).
- Patients with a sustained fall in blood pressure > 20 mmHg during exercise testing (IIaC).
- Patients with ejection fraction >55% and a normal exercise test who are at low procedural risk and present with one of the following parameters (IIaB):
    - Mean gradient ≥ 60 mmHg or peak velocity >5 m/s
    - Severe valve calcification and peak velocity progression ≥0.3 m/s/year
    - B-type natriuretic peptide levels >3 × age- and sex-corrected normal range confirmed by repeated measurements and without other explanations.

Current guidelines admit, however, that the management of patients with asymptomatic AS (including a normal exercise test) and normal left ventricular function remains controversial. Decision-making requires careful weighing of risk and benefit. In this regard, the fact that catheter interventional treatment of AS is rapidly evolving and recent data demonstrate that the risk of both, SAVR and TAVR have markedly decreased over the years has an obvious impact as this may change the threshold to intervene in asymptomatic patients when weighing risk vs. potential benefit. On the other hand, the complexity of long-term planning considering the consequences for later re-interventions, access to coronary arteries after TAVI, and other aspects have been recognized. New important data including randomized controlled trials comparing watchful waiting vs. early surgery in asymptomatic AS have also been provided. Thus, it appears timely to revisit the pro and cons of whether all patients with asymptomatic severe AS need a valve replacement.

V.2.2. Pro

The consequence of restricted indications for intervention in asymptomatic patients with severe AS is that the majority of patients are managed according to the so-called “watchful waiting” strategy, i.e. waiting for symptom onset. However, the rationale supporting the safety of

watchful waiting is challenged in clinical practice by a number of considerations derived from observational findings and recent trials.

V.2.2.1. Watchful waiting strategy in practice

V.2.2.1.1. Intervention is often unavoidable

Cardiac events, most often symptom onset requiring an intervention, will occur in as many as 80% of asymptomatic patients with severe AS within 3 years and in more than 20% within one year. The likelihood of remaining asymptomatic further decreases with AS severity and is very low among the subset of patients classified as very severe AS for whom an intervention is now recommended.

V.2.2.1.2. Follow-up is suboptimal in real life

Close follow-up is thus needed, at least twice a year to detect symptom onset. However, the watchful waiting strategy relies on two major principles that are often unsatisfactory in clinical practice: first, the patient immediately reports the occurrence of symptoms (patient compliance), and, second, a close follow-up could always be achieved (optimal follow-up). Thus, it has been shown that a third of asymptomatic patients with known severe AS are followed less than once a year and experience higher mortality. Although patients are informed to promptly report any change in symptoms, this is frequently not done in clinical practice.

V.2.2.1.3. Assessment of symptoms is challenging in the AS population

Symptoms are subjective and may develop insidiously and patients adapt to symptoms, which accounts for an underestimation of symptoms by both patients and practitioners[162]. Since AS frequently occurs in the elderly, impaired functional capacity may be attributed to ageing and/or comorbidities. Difficulties in symptom interpretation highlight the usefulness of exercise testing for an objective evaluation of exercise tolerance. However, in the recent valvular heart disease (VHD) II survey which included 2 152 patients referred to the hospital for severe AS, stress tests were used in only 6% of asymptomatic patients with severe AS[21]. Although exercise testing is now recommended in guidelines for asymptomatic severe AS, it was not performed

more frequently in VHD II than in the Euro Heart Survey in 2001. In addition, in the elderly AS population, a stress test may not be feasible in a significant proportion of patients.

V.2.2.1.4. Risk of sudden death

Sudden death rates are low in asymptomatic patients but higher than in the general population, and this very low risk of mortality is generally achieved in patients having strict follow-up in the context of heart valve clinics[159]. Although the rate of sudden death is low in true-asymptomatic patients, it significantly raises in those who developed symptoms during follow-up, especially if not reported and/or not recognized as shown in the RECOVERY trial[163].

V.2.2.1.5. Delaying intervention exposes to the risk of late referral with associated increased mortality and morbidity risk

A recent meta-analysis has shown that the risk of death under conservative management is high, that deaths are mostly of cardiac cause, and that sudden death only accounts for a part of it[164]. The VHD II survey attests to the late referral of patients with severe AS. More than a third of patients with severe AS were referred to hospital in outpatient clinics or in hospitalization in NYHA class III or IV and 16% had been hospitalized for heart failure during the preceding year[21]. These findings combine patients with undiagnosed AS and patients with known AS but in whom symptom onset has not been interpreted in due time. Late referral is also observed in patients followed in dedicated heart valve clinics. In a series of 103 asymptomatic patients aged ≥ 70 years with severe AS who were followed every 6 months in a heart valve clinic, an indication of aortic valve replacement occurred in 82 of them during a mean follow-up of only 19 months and 32 patients had severe symptoms at the time of aortic valve replacement, as defined by NYHA class ≥ III or CCS class ≥ 3.9 A total of 30 patients had impaired mobility due to comorbidities and this contributed probably to defer the identification of symptom onset. Severe symptoms or prior heart failure are associated with an increased risk of early morbidity and mortality after surgical AVR or TAVI, as compared with interventions performed in patients with few or no symptoms. Indications for intervention based only on the severity of AS appear as an effective approach to reduce late referral by avoiding delays in the interpretation of symptom onset.

V.2.2.1.6. Risk of irreversible consequences

Advanced left ventricular remodeling due to AS may compromise the quality of late results of aortic valve intervention. In contrast to ejection fraction, strain analysis detects subtle impairment of left ventricular function, and abnormal strain rate is associated with decreased event-free survival[63]. Left ventricular remodeling in AS is also related to the presence of ventricular fibrosis which has an incremental negative prognostic value[165–167]. Beyond the left ventricle, more than half of asymptomatic patients with moderate-to-severe AS present markers of left atrial or mitral valve damage, pulmonary hypertension, or right heart failure which are associated with impaired outcome[168]. Not all these features are direct consequences of AS; however, it is likely that they would be less frequent if intervention is performed early.

V.2.2.1.7. Waiting time and increased mortality

Excessive time delays in the identification of symptom onset and inherent late referral cumulate with time delays on the waiting list for intervention, which are associated with an increased risk of hospitalizations for heart failure and death before intervention[169,170].

V.2.2.1.8. Risk of intervention is now lower

The last decade has seen a marked decrease in the operative mortality and morbidity, in particular with transcatheter valve interventions in the elderly population. The risk of intervention increases with age and severity of the clinical presentation and the watchful waiting strategy is therefore intrinsically associated with an increased operative mortality.

V.2.2.2. Association between early intervention and outcome

V.2.2.2.1. Observational series

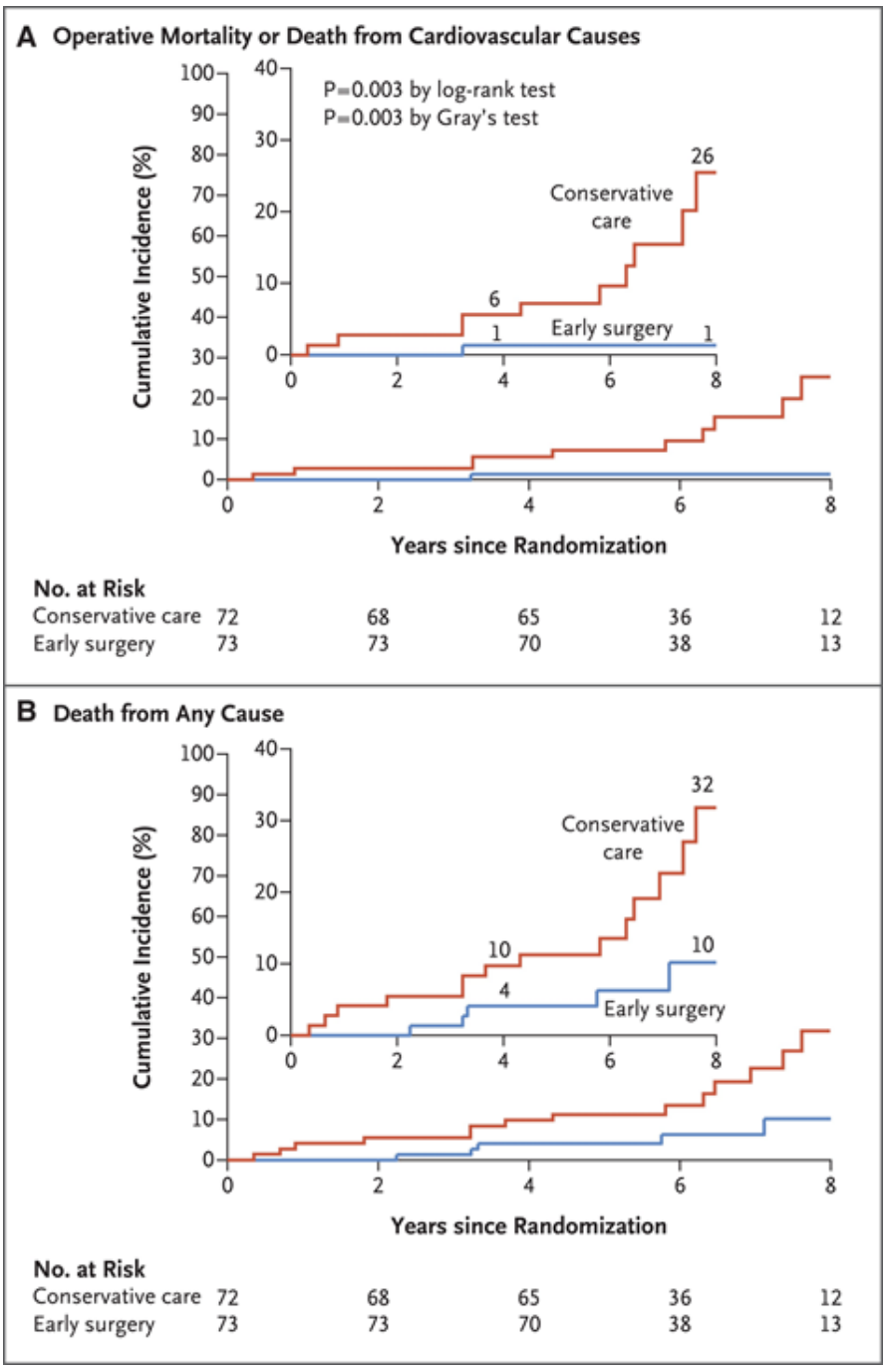
These have been used to compare the strategies of early intervention and watchful waiting. Their interpretation is hampered by inherent sources of bias which affect the comparability of therapeutic groups. Large series allow for adjusting on potential confounders, and this approach was used in the CURRENT AS registry which included 1 808 consecutive asymptomatic patients with severe AS, of whom 291 underwent early AVR and 1 517 were

managed conservatively[171]. In a comparison of two propensity-matched subgroups of 291 patients, there was a significant decrease in the incidence of hospitalization for heart failure and, more importantly, of all-cause mortality in asymptomatic patients who underwent early surgery as compared with conservative management.

V.2.2.2.2. Randomized controlled trials

Randomized trials are the only valid method to compare therapeutic strategies without bias due to measured and unmeasured confounders, although one should not forget their limitations due to open-label design and, as for all clinical trials, concerns on the generalizability of the findings. Two randomized trials comparing surgical AVR in asymptomatic patients with severe AS with a conventional conservative strategy have been published over the last two years, formally proving the benefit of an early intervention. The first randomized trial (RECOVERY) was conducted in four Korean centres and randomized 73 patients to early surgery and 72 patients to conservative strategy[163]. Inclusion criteria corresponded to a more severe degree of AS than usual criteria and were defined by valve area ≤ 0.75 cm^2 and (Vmax ≥ 4.5 m/s or mean gradient ≥ 50 mmHg). The absence of symptoms was based on case history and exercise testing was performed only in case of doubtful symptoms. The mean age was 64 years, and the mean EuroSCORE II was 0.9%. Outcome according to the primary endpoint of operative mortality or post-operative cardiovascular mortality was markedly better after early surgery as compared with conservative management [HR= 0.09; 95CI 0.01–0.67] (Figure 19). The benefit of early surgery was also consistent across the different secondary endpoints, even for all-cause mortality (HR= 0.33; 95% CI 0.12–0.90).

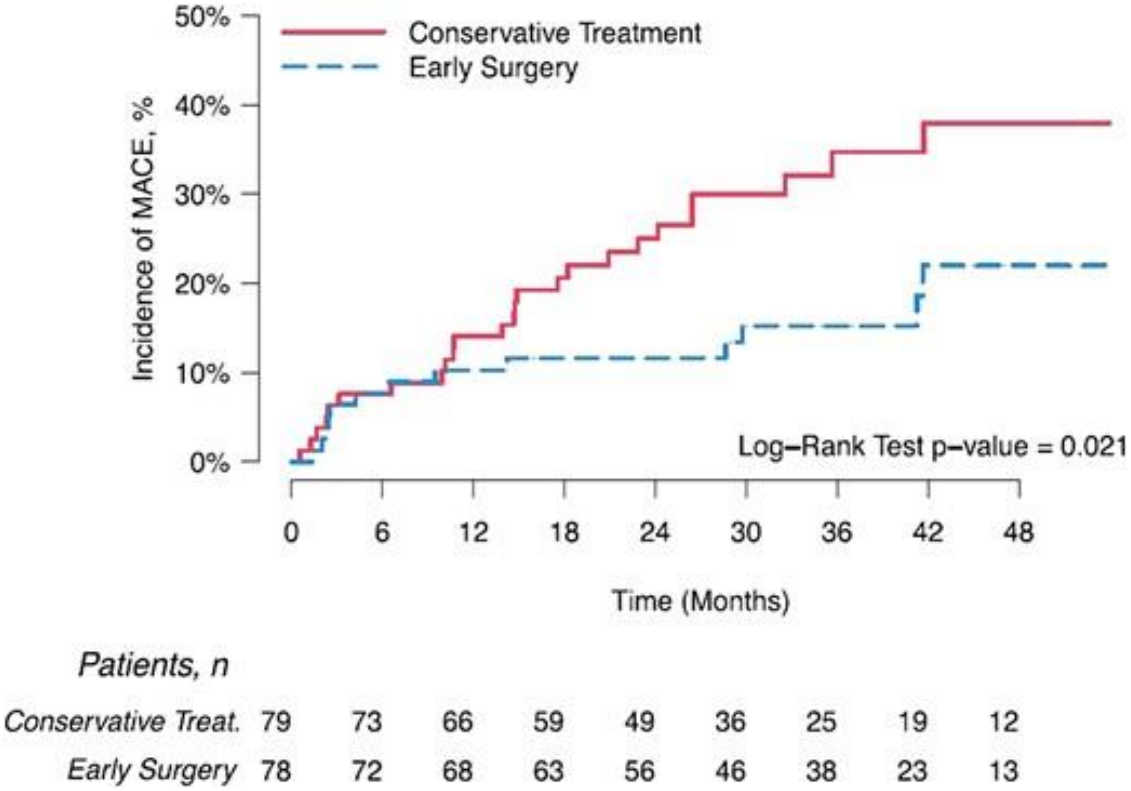
Figure 19: Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized RECOVERY trial. Reproduced with permission from Kang *et al*.[163]



More recently, the AVATAR trial included patients with commonly used definitions of severe AS (valve area ≤ 1.0 cm² and Vmax ≥ 4.0 m/s or mean gradient ≥ 40 mmHg)[172]. Exercise testing was mandatory to confirm the absence of symptoms, thereby corresponding to current guidelines. The mean age was 67 years, and the mean STS score was 1.7%; 78 patients were randomized to early surgery, and 79 patients to conservative strategy. The incidence of the

primary endpoint combining all-cause death or major adverse cardiac events was significantly reduced in the early surgery group as compared with conservative management (HR 0.46; 95% CI 0.23–0.90, p = 0.021) (Figure 20).

Figure 20: Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized AVATAR trial. Reproduced with permission from Banovic *et al.*[172]



Although not reaching statistical significance, the trend for all-cause mortality (HR 0.56; 95% CI 0.24–1.27, P = 0.16) and heart failure hospitalization were also in favour of the early surgery group (HR 0.32; 95% CI 0.08–1.19, p = 0.075). The absence of difference in cardiovascular mortality may seem paradoxical. However, of the 16 deaths which occurred in the conservative strategy group, four were caused by pneumonia, including three due to COVID-19. Severe AS may have contributed to worse outcome and highlighted the difficulties related to an accurate identification of the cause of death.

A meta-analysis combing 10 observational series (two prospective and eight retrospective) and the two randomized trials included 4130 patients and showed a significant association

between early surgery and significantly lower all-cause mortality as compared with conservative management (pooled odds ratio 0.40; 95% CI 0.35–0.45, $p < 0.01$)[164]. The restriction of the analysis to the two randomized trials showed also a lower all-cause mortality after early surgery (pooled odds ratio 0.45; 95% CI 0.25–0.82, $p < 0.01$) with no heterogeneity. Ongoing randomized controlled trials comparing the watchful waiting strategy and an early intervention using either surgical AVR or TAVI will formally demonstrate the superiority of one strategy vs. the other.

V.2.2.3. Implications on AS detection

Early intervention in asymptomatic patients as soon as AS becomes severe will require an increased awareness towards the diagnosis of AS. The underdiagnosis of heart valve disease in the community was first reported by Nkomo *et al.* in 2006[173], and confirmed more recently in the OxVALVE study[174]. In the OxVALVE cohort, systematic echocardiographic screening in the general practice of patients aged ≥ 65 years detected a prevalence of 6.4% of undiagnosed moderate or severe valvular disease (0.7% for AS), higher than the 4.9% prevalence of previously diagnosed valvular disease of the same severity.

V.2.2.4. Conclusion

In conclusion, although the watchful waiting strategy seems sound, its routine implementation is hampered by different issues, in particular, the considerable underuse of exercise testing and the frequent delay in the identification of symptom onset. This contributes to late referral, thereby compromising the safety and quality of the results of the valvular intervention. The results of the two recent randomized trials now provide evidence that early surgical aortic valve replacement in asymptomatic patients with severe AS is a valuable alternative to watchful waiting.

V.2.3. Contra

AS is the most frequent valvular heart disease. Both European and American guidelines recommend AVR (Class I or IIa) in patients with severe AS exhibiting symptoms and/or LVEF < 50%. However, for asymptomatic patients with severe AS and preserved LVEF, the management and, in particular, the timing of intervention remains highly controversial and challenging and is still based on a relatively lower level of evidence.

V.2.3.1. What are the current guideline recommendations for the management of asymptomatic severe AS?

Current guidelines recommend that asymptomatic patients with severe AS be followed closely in a heart valve clinic and be referred to a comprehensive heart valve center for confirmation of the indication of AVR and the selection of the type of AVR: i.e. surgical AVR (SAVR) with a mechanical or bioprosthetic valve or TAVI with a balloon-expandable or self-expanding valve. This should be a shared decision-making process with particular emphasis on patient preferences. Until now, AVR is not recommended for all patients with asymptomatic severe AS. Indeed, according to the guidelines, AVR is indicated (Class I) if the patient has a LVEF <50% or an indication for another cardiac surgery (Class I) or if symptoms can be demonstrated on exercise testing. However, specifically in such cases, the patient should not be considered as truly asymptomatic. Furthermore, AVR (SAVR or TAVI) may be considered (Class IIa) in the presence of specific risk markers (Table 6). Several studies lend support to this recommendation of early AVR in the presence of these risk markers. Nevertheless, these studies are only observational and cannot lead to a high level of evidence. In addition, these studies also show that the majority of asymptomatic patients with severe AS do not present with any of these risk markers and can be safely managed with conservative management.

Table 6: Indications for intervention in asymptomatic severe AS according to European guidelines.

Criteria	Class of indication and LOE	Comments
LVEF<50%	I, B	Applicable to very few (<2%) asymptomatic patients with severe AS and no CAD
Symptoms during exercise	I, C	If not, patients should be considered as truly asymptomatic
LVEF<55-60%	IIa, B	Recommendation only based on retrospective studies
Sustained fall in blood pressure>20mmHg during exercise	IIa, C	Despite being supported by pathophysiologic mechanisms, limited data are available. Recommendation requiring further investigation
LVEF>55% and: - Very severe AS (mean gradient ≥60 mmHg or *V*max >5 m/s) - Severe valve calcification and *V*max progression ≥0.3m/s/year - Elevated BNP levels (>three-fold higher than age- and sex-corrected normal range)	IIa, B	- Supported by strong evidence but true asymptomatic patients rarely have very severe AS. - CT is the gold standard for aortic calcium score measurement. *V*max progression is limited by measurement inter- intra-variability that may exceed the proposed cut-off. - Need to be cautiously interpreted in the context of patients with comorbidities

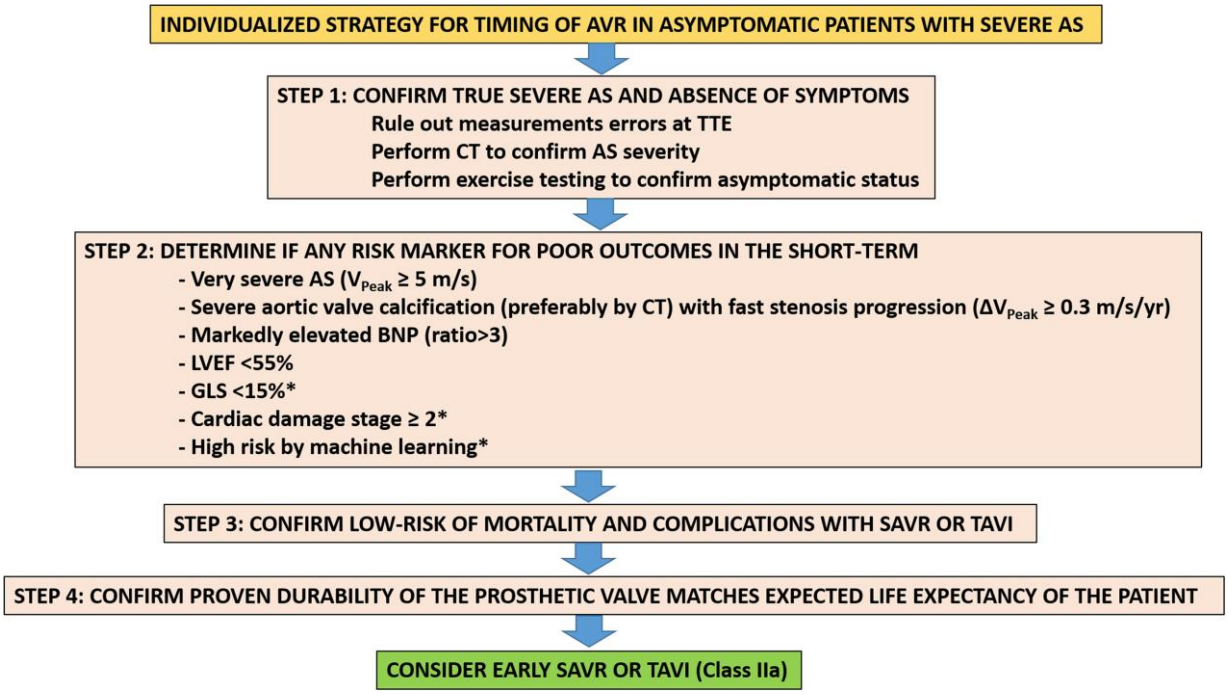
In light of the current evidence, we believe that early 'prophylactic' AVR strategy, i.e. in patients without current indication according to most recent guidelines, should not be applied to all asymptomatic patients but should be individualized by taking into account the patient's risk profile and personal preferences (Figure 21) and by addressing the four following key questions: (i) Is the patient really asymptomatic?

(ii) is the stenosis really severe?

(iii) does the risk of conservative management exceed the risk of early AVR?

(iv) does the proven durability of the prosthetic valve match the expected life expectancy of the patient?

Figure 21: Individualized strategy for the management of asymptomatic severe aortic stenosis.



*These are risk markers that are not presented in the guidelines and that will thus require further validation to be adopted in clinical practice. AVR, aortic valve replacement; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; VPeak, peak aortic jet velocity; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

V.2.3.2. Is the patient really asymptomatic?

Many patients with asymptomatic severe AS may have progressively reduced their level of activity to avoid symptoms or may deny or not report their symptoms. This issue is more important in older vs. younger patients and in women vs. men[175]. An exercise test is recommended to unmask symptoms and identify true asymptomatic patients.[176] Regrettably, only a minority (6.1%) of asymptomatic patients are submitted to an exercise test as shown in the EURObservational VHD II survey. Previous studies reported that at least one-third of patients claiming to be asymptomatic and submitted to an exercise test actually develop exercise-limiting symptoms. These falsely asymptomatic patients have an increased risk of adverse events in the short term and have a Class I indication for AVR according to current guidelines. Das et al. reported that the positive predictive value of exercise testing was good (79%) in patients younger than 70 years but only 57% for the older population[177]. These

findings underline the limitations of exercise test in the elderly population and provide an argument for the utilization of other tools to identify the asymptomatic patients who are at higher risk for adverse events and who may benefit from early AVR.

V.2.3.3. Is aortic stenosis really severe?

AS is considered severe when peak aortic velocity is ≥4 m/s, mean transvalvular pressure gradient is ≥40 mmHg, and aortic valve area (AVA) is <1.0 cm^2 (or <0.6 cm^2/m^2). However, AVA may be underestimated and thus AS severity may be overestimated because of the underestimation of left ventricular outflow tract diameter by echocardiography, which is squared in the continuity equation. Furthermore, Doppler echocardiography may overestimate pressure gradient and thus AS severity because of the pressure recovery phenomenon. Peak aortic jet velocity and pressure gradients and thus severity may also be underestimated if meticulous multiwindow interrogation with continuous-wave Doppler is not performed. Indeed, the exclusion of non-apical windows may result in the misclassification of AS severity in a significant proportion of patients. Hence, in asymptomatic patients with apparently severe AS, it is first essential to rule out measurements errors and to use additional parameters of AS severity to confirm the presence of true severe AS, particularly in patients with discordant grading at echocardiography (i.e. severe AVA but non-severe gradient). These parameters include Doppler velocity index < 0.25 to corroborate AVA, energy loss index < 0.55 cm^2/m^2 to account for pressure recovery, and computed tomography aortic valve calcium score >1200 AU in women and >2000 AU in men to assess the anatomic severity of AS.

V.2.3.4. Does the risk of conservative management exceed the risk of early AVR?

AVR consists in replacing a severe native aortic valve disease with another hopefully milder disease, which is the prosthetic valve. Early intervention is associated with a substantial risk of procedural mortality and complications including bleeding, coronary obstruction and myocardial infarction, stroke, permanent pacemaker implantation, and non-structural valve

dysfunction (paravalvular regurgitation and prosthesis-patient mismatch). Furthermore, an earlier intervention will expose the patients, sooner in their life, to the long-term risk of complications related to the prosthetic valve including valve thrombosis, thromboembolism, haemolysis, structural valve deterioration, valve failure, valve-related reintervention, or death. Furthermore, the risk of sudden cardiac death in asymptomatic patients with severe AS is low (<1% per year) and is actually lower than the risk of operative mortality with SAVR. When considering early AVR in a true asymptomatic patient, it is important to emphasize that AVR has no or minimal potential to improve the patient because he or she is not suffering from any symptom or side effect of the disease prior to AVR. In this context, it is crucial to not deteriorate the symptomatic status and quality of life of the patient with the intervention and to avoid any complication. Hence, early AVR can only be considered in these patients if the risk of procedural mortality and complications is very low.

Adopting a delayed intervention strategy in asymptomatic patients with severe AS may lead to the development of more advanced and potentially irreversible damage and dysfunction of the left ventricle and other cardiac chambers. Using a multi-echocardiographic parameter integrative approach for staging extra-valvular cardiac damage, Tastet et al. reported that 61% of patients with asymptomatic severe AS have advanced cardiac damage (i.e. Stage ≥ 2) and these patients display a higher risk of mortality in the short-term and may thus benefit from early intervention.7 However, in a substantial proportion of these patients, the advanced cardiac damage was likely not related to the AS per se but to other comorbidities, therefore undermining the potential benefit of early AVR in these patients. Moreover, close to 40% of the patients in this series were in Stage 0 or 1 (left ventricular damage only), and these patients harbored an excellent mid-term outcome with the management strategy currently recommended in the guidelines, i.e. intervention when symptoms or left ventricular systolic dysfunction develop or when one of the risk markers mentioned above occur.

V.2.3.5. Does the proven durability of the bioprosthetic valve match the expected life expectancy of the patient?

When selecting a type of AVR and valve substitute, it is essential to match the proven durability of the prosthetic valve vs. the expected life expectancy in order to reduce the risk of reintervention and ensuing complications[178]. Asymptomatic patients with severe AS are generally younger and have longer life expectancy and considering early AVR in these patients inherently raises the requirements in terms of long-term durability of the prosthetic valve. Hence, in most of these patients, the prosthetic valve should have a minimum durability of at least 10, if not 15, years. Few SAVR valves and no TAVI valves have such proven long-term durability, thus further limiting the consideration of early AVR in all asymptomatic patients with severe AS.

V.2.3.6. Current randomized trials of early AVR vs. conservative management in asymptomatic severe AS

Two small controlled randomized trials have been published until now. Kang et al. randomized 145 patients to early SAVR (within 2 months) vs. conservative management[163]. The primary endpoint, which was the composite of death within 30 days or cardiovascular death during the entire follow-up, occurred in only one patient in the early surgery group vs. 11 of 72 (15.2%) patients in the conservative group. In this group, the incidence of sudden death was 4% at 4 years and 14% at 8 years. There was no operative mortality in both the surgical group and the conservative group (17% submitted to surgery because of acute decompensation). Such outstanding results may be difficult to achieve in real-life practice and in all cardiac surgery centers. There are severe other limitations to this study. First, it included predominantly young patients (average: 64 years) with bicuspid valve disease, and all of them had very severe AS (peak aortic jet velocity > 5 m/s). Furthermore, several patients who developed symptoms did not undergo AVR and were thus not treated according to the guidelines.

The second trial, AVATAR (aortic valve replacement vs. conservative treatment in asymptomatic severe AS), randomized 157 patients (mean age 67 years; severe AS using the classical criteria; normal left ventricular function and negative exercise test) SAVR vs. conservative management[172]. The incidence of the primary endpoint, i.e. the composite of all-cause death, acute myocardial infarction, stroke, and unplanned hospitalization for heart failure, was lower in the SAVR vs. conservative management group (hazard ratio 0.46), and operative mortality in the SAVR arm was 1.4%. The sample size was, however, small, and although this was a multicenter trial, 73% of patients were recruited in one center. The study was prematurely stopped because of early superiority in the SAVR arm. There was no difference in cardiovascular death: 9.54% in the early SAVR group vs. 9.09% in the conservative group. The event curves diverged only after 18 months for both all-cause death and heart failure and the indications for delayed surgery in the conservative group were symptom onset (60%), AS progression (16%), and a decrease in LVEF (4%), which can all be identified during appropriate close (every 6 months) follow-up.

These two trials are interesting but do not provide any definitive answer regarding the timing of intervention in asymptomatic severe AS. We must wait for the results of large controlled trials (Table 7), such as ESTIMATE (early surgery for patients with asymptomatic aortic stenosis—NCT02627391), early TAVR (evaluation of trans-catheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis—NCT03042104), EVOLVED (early valve replacement guided by biomarkers of left ventricular decompensation in patients with asymptomatic severe aortic stenosis—NCT03094143), and EASY-AS (early valve replacement in severe, asymptomatic aortic stenosis study—NCT04204915). These trials plan to include 360, 901, 1000, and 2844 patients, respectively.

Table 7 : Summary of the design and results of the ongoing randomized trials in asymptomatic severe aortic stenosis.

Trial	Location	Design	*n*	Primary outcome	Main inclusion criteria	Main non-inclusion criteria	Sponsor	Comments
Early TAVR—evaluation of TAVR compared to surveillance for patients with asymptomatic severe aortic stenosis. https://classic.clinicaltrials.gov/ct2/show/NCT03042104	US and Canada	Randomized (TAVR vs. clinical surveillance). Open label	901	2-year combined all-cause death, all stroke, and unplanned cardiovascular hospitalization.	≥ 65 years old. Severe asymptomatic AS. LVEF ≥50%. Low risk (STS score ≤10).	>3 + mitral and/or aortic regurgitation. Patients unsuitable for TAVI.	Edwards lifesciences	Patients with class IIa indication can be randomized. Highly selected patients. Estimated primary completion date March 2024.
EVOLVED—early valve replacement guided by biomarkers of LV decompensation in asymptomatic patients with severe AS. https://clinicaltrials.gov/ct2/show/study/NCT03094143	UK	Randomized (4 arms according to results of cardiac MRI: mid-wall fibrosis or not). Open label.	400	Composite of all-cause mortality or unplanned AS-related hospitalization (mean follow-up of 2.75 years).	Severe asymptomatic AS.	LVEF <50%. Severe aortic or mitral regurgitation. Mild mitral stenosis. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis. Advanced renal impairment.	Academic	Patients with class IIa indication can be randomized. Randomization based on MRI results and not echocardiography. Patients with mid-wall fibrosis despite LVEF >50% will be randomized in no intervention group whereas their prognosis is already known to be reduced in absence of intervention.
EASY-AS—the early valve replacement in severe asymptomatic aortic stenosis study https://clinicaltrials.gov/ct2/show/NCT04204915	UK, Australia and NZ	Randomized (surgery vs. expectant management). Open label.	2844	3-year combined measure of cardiovascular death and hospitalization for heart failure	Severe asymptomatic AS.	Additional severe valvular heart disease. LVEF <50%. Other pre-inclusion cardiac surgery. Co-morbid condition that, in the opinion of the treating cardiologist, limits life expectancy to <2 years	Academic	Patients with class IIa indication can be randomized. No TAVI in the intervention arm.

The use of TAVI rather than SAVR in some of these trials may reduce the risk of short-term complications, but there are not yet any large studies on the potential benefits and more importantly the long-term valve durability and outcomes of TAVI in asymptomatic patients with severe AS.

In the event that these trials are positive and demonstrate the superiority of early AVR over conservative management, this would not necessarily imply that the results of these trials apply to all asymptomatic patients with severe AS and that early AVR is the best option for all patients.

V.2.3.7. Individualized strategy rather than early AVR for all asymptomatic patients with severe AS

The incidence of severe AS is expected to increase markedly in the next decades due to the aging of the population and rise of the prevalence of cardiometabolic risk factors involved in the initiation and progression of AS[2]. Furthermore, AS is currently under-detected and under-diagnosed[174,179] and the anticipated improvement in screening due to the implementation of digital tools and artificial intelligence may also contribute to the rise in the prevalence of asymptomatic severe AS. In the last 10 years, the number of AS-related interventions (mainly TAVI) has grown exponentially in both the US22 and European countries[180].

Currently, these issues may exceed the capacity of interventional cardiology and cardiovascular surgery departments to treat all patients with TAVI or SAVR. As a consequence, the waiting lists for AVR may increase. In the future, the diminished incidence of coronary artery disease due to better prevention may allow the healthcare systems to reallocate more resources to structural heart diseases. Furthermore, TAVI happened to be futile in a substantial number of patients[181–183]. And finally, it is estimated that about one-third of patients with symptomatic severe AS and Class I indication for AVR ultimately do not receive SAVR or TAVI because of various reasons. Hence, expanding AVR indication to all patients with asymptomatic severe AS may be questionable from both an ethical and healthcare resource standpoint.

Given that current evidence as well as current guidelines do not support the application of an early AVR strategy for all asymptomatic patients with severe AS and the results of the ongoing trials will likely not refute this statement, we would strongly favor the adoption of an individualized strategy including the following steps (Figure 21):

- Step 1: Confirm that the patient has true severe AS and is really asymptomatic.
- Step 2: Determine if the patients have any risk marker included in the guidelines (i.e. very severe AS, severe aortic valve calcification with fast stenosis progression, markedly elevated B-type natriuretic peptide, LVEF <55%) as well as other emerging risk markers (i.e. cardiac damage stage ≥ 2; global longitudinal strain <15%, etc.) pending further validation. In the future, machine learning algorithm using clinical, imaging, and/or blood biomarker data may help to identify the patients who are at higher risk of poor outcomes in the short term and who may thus benefit from earlier intervention[47].
- Step 3: Ascertain that the patient has a low risk for mortality and procedural complications with SAVR or TAVI.
- Step 4: Ascertain that the proven durability of the prosthetic valve selected for early AVR matches or exceeds the expected life expectancy of the patient.

If the patients do not meet the criteria described in these four steps, they should probably be managed conservatively. However, this conservative management should not be a passive, i.e. 'wait for symptoms' strategy but rather an active clinical surveillance with regular (every 3 to 6 months) clinical, echocardiographic, and blood biomarkers follow-up, ideally conducted in the context of a dedicated heart valve clinic[184].

V.2.3.8. Conclusion

In conclusion, early AVR is likely not the optimal strategy for all patients with asymptomatic severe AS. We rather advocate for an individualized strategy that would determine the best management for the given patient according to his or her risk profile, preferences, and life expectancy.

Partie VI. General Discussion

Our works identified and discussed new imaging markers that allow a better risk stratification of patients with asymptomatic AS. It has been highlighted that the threshold of LVEF used to decide intervention in patients with AS requires a deep reappraisal. Many works have already been published in this context, however, even if the current guidelines evolved and decreased to 55% the cut-off to intervene in asymptomatic patients (class IIa), the level of evidence provided remains low (LOE B) and based only on limited data. This promotes strong effort to accelerate research data generation to validate (i.e. using randomized clinical trial) an appropriate threshold of LVEF. Meanwhile, we have produced new evidence reinforcing the appropriateness of the use of LVGLS in patients with asymptomatic AS and preserved LVEF.

It has been shown that the distribution of LVGLS in these patients is much more homogeneous than expected, at least in Western countries. A cut-off value of <15% has been proposed and also requires further validation. Patients with depressed LVGLS represented around 1 third of all asymptomatic patients. These patients depicted excess risk of death >2.5 as compared to patients with LVGLS >15%. Similar results were also found in patients with LVEF >60%, suggesting the suitability of LVGLS to detect early subclinical LV myocardial impairment, and its relevance in clinical practice. Nevertheless, integrated approach using multi-modalities imaging seems more effective in these patients and their comprehensive assessment, including CMR-derived parameters, seems the optimal way for their management. This has been underlined in our new proposed management algorithm (Figure 18). Efficacy, security and cost-effectiveness of such strategy should also be validated using high standard methodology. Beyond the clinical relevance of all these new elements and their use in patient management, this work opens the debate on the benefits of early intervention in these patients, before the onset of symptoms or class IIa recommendation.

Proceed to valve replacement in all asymptomatic patients with severe AS is appealing and results of randomized trials seem promote this strategy. However, these trials still remain open-labelled and based on combined end-point including subjective criterion, not necessarily

adjudicated with independent committee. Furthermore, they compared early strategy versus conventional strategy. A direct comparison between early strategy versus new imaging markers-derived strategy should be tested. Unfortunately, sham design would not be ethical and, therefore, such trial would remain open-label. Therefore, adjudicated end-point are necessary in the design of a new trial.

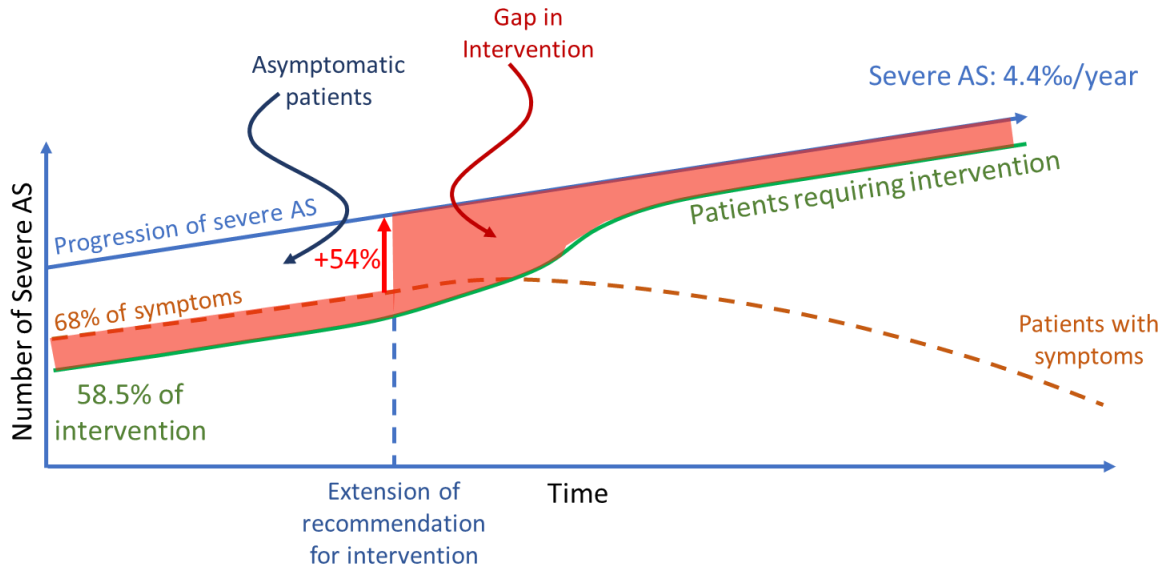
Defining the best trial design to test the superiority of early intervention as compared to new imaging markers-derived management is complex. The first step would be to find a consensus between experts in the field to define imaging markers-derived strategy and implement it inside Heart Team. The proposed algorithm (Figure 18) could be helpful but still requires to be refined and some definitions, e.g. myocardial abnormalities derived from CMR, need clarification. Secondly, the ideal end-point should be discussed. The Valve Academic Research Consortium (VARC)-2 initiative already debated extensively about appropriateness end-points[185]. Hard end-point, such as cardiovascular mortality, could be recommended. However, the majority of death occurring 1-year after TAVR is from non-cardiovascular in these patients[186], suggesting that overall death would be more representative of the natural course of the disease. Other cardiovascular events such as myocardial infarction and stroke may have clinical relevance as end-point for trial. Recent data from Partner-3 trial[187] demonstrated that such event are uncommon at 5-year following TAVR or SAVR with approximately 3% of myocardial infarction and 6% of strokes. Consequently, only combined end-points, including death from any cause, occurrence of myocardial infarction or stroke would be appropriate in order to well illustrate natural history of the disease and enabling to guarantee feasibility with reasonable sample size. Softer end-points, such as rehospitalisation (which remains the most frequent 5-year outcome in patients receiving SAVR or TAVR) or quality of life, could also have clinical interest. Nevertheless, in an open-label trial, such criteria should only be analysed as secondary end-points.

Ideally, testing the superiority of early intervention as compared to new imaging markers-derived management would require a multicentre open-label 1:1 randomized trial, with

intention-to-treat analysis of combined end-point (overall death, myocardial infarction or stroke) with independent adjudication committee.

Meanwhile, extend recommendation to all asymptomatic patients with severe AS may also rise some concerns in terms of public health. As demonstrated in the Table 5, both ACC/AHA and ESC guidelines are more and more permissive regarding criterion for the intervention in patients with severe AS. Indeed, many asymptomatic patients may already receive intervention. According to the Society of Thoracic Surgeons Predicted Risk of Mortality survey, asymptomatic patients represent 32% of all severe AS. This number is probably underestimate since in the absence of obvious symptoms and systematic screening, many patients with severe asymptomatic AS may not be diagnosed. Therefore, extent such indication to all asymptomatic patients with severe AS would imply to also modify the strategy of AS screening in order to identify the highest possible proportion of patients with asymptomatic AS and avoid gap in intervention. This may also involve significant concerns in term of public health system. It has been demonstrated that in France, the extension of recommendation for TAVR from high- and intermediate-risk patients to low-risk patients will increase by +54% the estimated annual number of patients requiring intervention[188]. Current trend in AS intervention demonstrated that during the last 10 years, the number of patients receiving TAVR markedly increased, whereas the number of SAVR performed a year remains almost similar. In the STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement[189,190] the annual trends show an approximate increase in >20% of TAVR every year since 2012. From France-TAVI registry[180,191] the number of AVR has doubled in a decade and TAVR has become the dominant intervention in 2018. Logically, extend indication from patients with symptoms to all asymptomatic patients would follow similar trend, as suggested by the Figure 22.

Figure 22: Schematic trends of the impact on the number of interventions required for patients with severe aortic stenosis (AS) if the recommendations were extended to asymptomatic patients*.



**Based on the data published by Durko et al. Eur Heart Journal, 2008*[188]*.*

The extension of recommendation for intervention have overt potential benefits for the patients, preventing progression of AS and its complications, and improving long-term quality of life and reducing the risk of premature death. Nonetheless, the related-costs of such management could be an issue. More intervention in asymptomatic patients would induce more TAVI in low-risk patients since patients and health professional may be more reluctant to surgically intervene in these patients.

For intermediate-risk patients with severe AS the costs at 1 year are higher for TAVR than for SAVR. The difference was mainly caused by the higher costs of the transcatheter valve and was not compensated by the lower costs for blood products and hospital stay in TAVR patients[192]. More generally, the cost-effectiveness of TAVR seems gradually reduced as the risk of patients decrease. Broadening the recommendations, therefore, would increase the financial burden on healthcare systems, insurers and patients. In addition, despite largely underestimated and understudied, the need and cost for ongoing monitoring following early intervention could also be a source of concerns for healthcare system. Asymptomatic patients undergoing a procedure need to be followed-up regularly to ensure that the procedure has

been successful and to detect any potential complications. Furthermore, intervention in younger and low risk patients may also lead to higher incidence of re-intervention, such as valve-in-valve (i.e. TAVR-in-TAVR or TAVR-in-SAVR). Cost and impact on healthcare resources and system is still not evaluated.

Finally, although TAVR appears beneficial even in patients over 90 years of age[193], the question of the futility of TAVR in certain patients is now open[194–196]. Some authors question whether TAVR, in patients with less than 6 months or 1 year of life expectancy, and with a very reduced quality of life, is useful and sustainable by a healthcare system. It remains surprising that, at a time when the futility of TAVR is discussed for the most at-risk, elderly and comorbid patients – in other words, for those for whom healthcare demand is the highest – many efforts have been done for the past 10 years to extend the indications to as many people as possible[197]. Intermediate and low-risk patients can now benefit from TAVR. The next stage will focus on all asymptomatic patients, including those without evidence of LV-afterload related consequences, i.e. impaired imaging or biologic (natriuretic peptides) markers. This final step cannot be taken without an in-depth analysis of the impact on the healthcare system and public health.

Conclusion

Early SAVR or TAVR is likely not the optimal strategy for all patients with asymptomatic severe AS. An individualized strategy determining the best management for the given patient, should still be promoted.

Following analysis of numerous prognostic studies, it now seems clear that sub-clinical LV myocardial dysfunction, a consequence of severe chronic AS, may be present in many asymptomatic subjects, despite a LVEF>50%. Failure to intervene in these patients increases their risk of cardiovascular events and death. Several imaging parameters seem relevant to unmask these patients. Among them, LVGLS seems the most relevant in view of the level of evidence available in the literature. Nevertheless, based the management of these patients on only one unique parameter, more particularly derived from echocardiography, could be a mistake. A more tailored and individualized approach could be recommended but still need to be tested. Integrating multiple factors from multiple modalities complicates management and makes decision-making heterogeneous. In this context, the development of artificial intelligence algorithms will be of considerable help to the heart team. Abundant works has already been published on this subject. However, their routine use, efficacy and safety have yet to be evaluated. Meanwhile and pending validation, much remains to be done to phenotype patients with AS as accurately as possible and offer them an optimal management.

References list

1. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–2270.

2. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJJC, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;**62**:1002–1012.

3. Harris AW, Pibarot P, Otto CM. Aortic Stenosis: Guidelines and Evidence Gaps. *Cardiol Clin* 2020;**38**:55–63.

4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**70**:252–289.

5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.

6. Writing Committee Members, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2021;**77**:450–500.

7. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W, ESC/EACTS Scientific Document Group, ESC Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021:ehab395.

8. Goody PR, Hosen MR, Christmann D, Niepmann ST, Zietzer A, Adam M, Bönner F, Zimmer S, Nickenig G, Jansen F. Aortic Valve Stenosis: From Basic Mechanisms to Novel Therapeutic Targets. *Arterioscler Thromb Vasc Biol* 2020;**40**:885–900.

9. Akahori H, Tsujino T, Masuyama T, Ishihara M. Mechanisms of aortic stenosis. *J Cardiol* 2018;**71**:215–220.

10. Lindman BR, Clavel M-A, Mathieu P, Iung B, Lancellotti P, Otto CM, Pibarot P. Calcific aortic stenosis. *Nat Rev Dis Primer* 2016;**2**:16006.

11. Kraler S, Blaser MC, Aikawa E, Camici GG, Lüscher TF. Calcific aortic valve disease: from molecular and cellular mechanisms to medical therapy. *Eur Heart J* 2022;**43**:683–697.

12. Liu Z, Dong N, Hui H, Wang Y, Liu F, Xu L, Liu M, Rao Z, Yuan Z, Shang Y, Feng J, Cai Z, Li F. Endothelial cell-derived tetrahydrobiopterin prevents aortic valve calcification. *Eur Heart J* 2022;**43**:1652–1664.

13. Liu Z, Wang Y, Liu F, Zhu D, Chen Y, Yim WY, Hu K, Rao Z, Pan X, Li F, Dong N. Long noncoding TSI attenuates aortic valve calcification by suppressing TGF-β1-induced osteoblastic differentiation of valve interstitial cells. *Metabolism* 2023;**138**:155337.

14. Moncla L-HM, Briend M, Bossé Y, Mathieu P. Calcific aortic valve disease: mechanisms, prevention and treatment. *Nat Rev Cardiol* 2023;**20**:546–559.

15. Lerman D, Prasad S, Alotti N. Calcific Aortic Valve Disease: Molecular Mechanisms And Therapeutic Approaches. *Eur Cardiol Rev* 2015;**10**:108.

16. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V, GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;**76**:2982–3021.

17. Cardiovascular diseases (CVDs)https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (26 July 2023)

18. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, Forouzanfar MH, Longenecker CT, Mayosi BM, Mensah GA, Nascimento BR, Ribeiro ALP, Sable CA, Steer AC, Naghavi M, Mokdad AH, Murray CJL, Vos T, Carapetis JR, Roth GA. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. *N Engl J Med* 2017;**377**:713–722.

19. Watkins DA, Beaton AZ, Carapetis JR, Karthikeyan G, Mayosi BM, Wyber R, Yacoub MH, Zühlke LJ. Rheumatic Heart Disease Worldwide: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2018;**72**:1397–1416.

20. Doukky R, Abusin SA, Bayissa YA, Kelly RF, Ansari AH. Rheumatic heart disease in modern urban America: a cohort study of immigrant and indigenous patients in Chicago. *Int J Cardiol* 2014;**175**:178–180.

21. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, De Bonis M, Tribouilloy C, Evangelista A, Bogachev-Prokophiev A, Apor A, Ince H, Laroche C, Popescu BA, Piérard L, Haude M, Hindricks G, Ruschitzka F, Windecker S, Bax JJ, Maggioni A, Vahanian A, EORP VHD II Investigators. Contemporary Presentation and Management of Valvular Heart Disease: The EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation* 2019;**140**:1156–1169.

22. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromsø study. *Heart Br Card Soc* 2013;**99**:396–400.

23. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, Gallet R, Teiger E, Côté N, Clavel M-A, Tournoux F, Pibarot P, Damy T. Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019;**74**:2638–2651.

24. Demer LL, Tintut Y. Hearts of Stone: Calcific Aortic Stenosis and Antiresorptive Agents for Osteoporosis. *Circulation* 2021;**143**:2428–2430.

25. Pawade TA, Doris MK, Bing R, White AC, Forsyth L, Evans E, Graham C, Williams MC, Beek EJR van, Fletcher A, Adamson PD, Andrews JPM, Cartlidge TRG, Jenkins WSA, Syed M, Fujisawa T, Lucatelli C, Fraser W, Ralston SH, Boon N, Prendergast B, Newby DE, Dweck MR. Effect of Denosumab or Alendronic Acid on the Progression of Aortic Stenosis: A Double-Blind Randomized Controlled Trial. *Circulation* 2021;**143**:2418–2427.

26. Hekimian G, Boutten A, Flamant M, Duval X, Dehoux M, Benessiano J, Huart V, Dupré T, Berjeb N, Tubach F, Iung B, Vahanian A, Messika-Zeitoun D. Progression of aortic valve stenosis is associated with bone remodelling and secondary hyperparathyroidism in elderly patients--the COFRASA study. *Eur Heart J* 2013;**34**:1915–1922.

27. Skolnick AH, Osranek M, Formica P, Kronzon I. Osteoporosis treatment and progression of aortic stenosis. *Am J Cardiol* 2009;**104**:122–124.

28. Chen C-L, Chen N-C, Wu F-Z, Wu M-T. Impact of denosumab on cardiovascular calcification in patients with secondary hyperparathyroidism undergoing dialysis: a pilot study. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA* 2020;**31**:1507–1516.

29. Elmariah S, Delaney JAC, O'Brien KD, Budoff MJ, Vogel-Claussen J, Fuster V, Kronmal RA, Halperin JL. Bisphosphonate Use and Prevalence of Valvular and Vascular Calcification in Women MESA (The Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2010;**56**:1752–1759.

30. Aksoy O, Cam A, Goel SS, Houghtaling PL, Williams S, Ruiz-Rodriguez E, Menon V, Kapadia SR, Tuzcu EM, Blackstone EH, Griffin BP. Do bisphosphonates slow the progression of aortic stenosis? *J Am Coll Cardiol* 2012;**59**:1452–1459.

31. Pirro M, Manfredelli MR, Schillaci G, Helou RS, Bagaglia F, Melis F, Scalera GB, Scarponi AM, Gentile E, Mannarino E. Association between circulating osteoblast progenitor cells and aortic calcifications in women with postmenopausal osteoporosis. *Nutr Metab Cardiovasc Dis NMCD* 2013;**23**:466–472.

32. Hungerford SL, Adji AI, Hayward CS, Muller DWM. Ageing, Hypertension and Aortic Valve Stenosis: A Conscious Uncoupling. *Heart Lung Circ* 2021;**30**:1627–1636.

33. Saeed S, Scalise F, Chambers JB, Mancia G. Hypertension in aortic stenosis: a focused review and recommendations for clinical practice. *J Hypertens* 2020;**38**:1211–1219.

34. Movahed MR, Timmerman B, Hashemzadeh M. Independent association of aortic stenosis with many known cardiovascular risk factors and many inflammatory diseases. *Arch Cardiovasc Dis* 2023;**116**:467–473.

35. Goel SS, Aksoy O, Gupta S, Houghtaling PL, Tuzcu EM, Marwick T, Mihaljevic T, Svensson L, Blackstone EH, Griffin BP, Stewart WJ, Barzilai B, Menon V, Kapadia SR. Renin-angiotensin system blockade therapy after surgical aortic valve replacement for severe aortic stenosis: a cohort study. *AnnInternMed* 2014;**161**:699–710.

36. Goel SS, Kleiman NS, Zoghbi WA, Reardon MJ, Kapadia SR. Renin-Angiotensin System Blockade in Aortic Stenosis: Implications Before and After Aortic Valve Replacement. *J Am Heart Assoc* 2020;**9**:e016911.

37. Martinsson A, Törngren C, Nielsen SJ, Pan E, Hansson EC, Taha A, Jeppsson A. Renin-angiotensin system inhibition after surgical aortic valve replacement for aortic stenosis. *Heart Br Card Soc* 2023:heartjnl-2023-322922.

38. Nadir MA. Aortic Stenosis, Left Ventricular Remodeling, and Renin-Angiotensin System Blockade. *J Am Coll Cardiol* 2018;**71**:2984.

39. Kaltoft M, Langsted A, Nordestgaard BG. Obesity as a Causal Risk Factor for Aortic Valve Stenosis. *J Am Coll Cardiol* 2020;**75**:163–176.

40. Rawshani A, Sattar N, McGuire DK, Wallström O, Smith U, Borén J, Bergström G, Omerovic E, Rosengren A, Eliasson B, Bhatt DL, Rawshani A. Left-Sided Degenerative Valvular Heart Disease in Type 1 and Type 2 Diabetes. *Circulation* 2022;**146**:398–411.

41. Larsson SC, Wolk A, Bäck M. Alcohol consumption, cigarette smoking and incidence of aortic valve stenosis. *J Intern Med* 2017;**282**:332–339.

42. Ahmad Y, Bellamy MF, Baker CSR. Aortic Stenosis in Dialysis Patients. *Semin Dial* 2017;**30**:224–231.

43. Candellier A, Hénaut L, Morelle J, Choukroun G, Jadoul M, Brazier M, Goffin É. Aortic stenosis in patients with kidney failure: Is there an advantage for a PD-first policy? *Perit Dial Int J Int Soc Perit Dial* 2021;**41**:158–167.

44. Khelifi N, Blais C, Jean S, Hamel D, Clavel M-A, Pibarot P, Mac-Way F. Temporal trends of aortic stenosis and comorbid chronic kidney disease in the province of Quebec, Canada. *Open Heart* 2022;**9**:e001923.

45. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde J-L, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe : The Euro Heart Survey on Valvular heart Disease. *EurHeart J* 2003;**24**:1231–1243.

46. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 2011;**8**:162–172.

47. Sengupta PP, Shrestha S, Kagiyama N, Hamirani Y, Kulkarni H, Yanamala N, Bing R, Chin CWL, Pawade TA, Messika-Zeitoun D, Tastet L, Shen M, Newby DE, Clavel M-A, Pibarot P, Dweck MR, Artificial Intelligence for Aortic Stenosis at Risk International Consortium. A Machine-Learning Framework to Identify Distinct Phenotypes of Aortic Stenosis Severity. *JACC Cardiovasc Imaging* 2021;**14**:1707–1720.

48. Domanski O, Richardson M, Coisne A, Polge A-S, Mouton S, Godart F, Edmé JL, Matran R, Lancellotti P, Montaigne D. Cardiopulmonary exercise testing is a better outcome predictor than exercise echocardiography in asymptomatic aortic stenosis. *Int J Cardiol* 2017;**227**:908–914.

49. Dulgheru R, Magne J, Davin L, Nchimi A, Oury C, Pierard LA, Lancellotti P. Left ventricular regional function and maximal exercise capacity in aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2016;**17**:217–224.

50. Dulgheru R, Magne J, Capoulade R, Davin L, Vinereanu D, Pierard LA, Pibarot P, Lancellotti P. Impact of global hemodynamic load on exercise capacity in aortic stenosis. *IntJ Cardiol* 2013;**168**:2272–2277.

51. Bartunek J, Weinberg EO, Tajima M, Rohrbach S, Katz SE, Douglas PS, Lorell BH. Chronic N(G)-nitro-L-arginine methyl ester-induced hypertension : novel molecular adaptation to systolic load in absence of hypertrophy. *Circulation* 2000;**101**:423–429.

52. Esposito G, Rapacciuolo A, Naga Prasad SV, Takaoka H, Thomas SA, Koch WJ, Rockman HA. Genetic alterations that inhibit in vivo pressure-overload hypertrophy prevent cardiac dysfunction despite increased wall stress. *Circulation* 2002;**105**:85–92.

53. Donal E, Magne J, Cosyns B. Left Ventricular Ejection Fraction Thresholds Reappraisal: Also for Bicuspid Valve Disease? *J Am Coll Cardiol* 2022;**80**:1085–1087.

54. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, Pellikka PA, Tajik AJ, Enriquez-Sarano M. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation* 2008;**117**:2776–2784.

55. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. *Am J Cardiol* 2005;**96**:718–721.

56. Hecht S, Butcher SC, Pio SM, Kong WKF, Singh GK, Ng ACT, Perry R, Poh KK, Almeida AG, González A, Shen M, Yeo TC, Shanks M, Popescu BA, Gay LG, Fijałkowski M, Liang M, Tay E, Marsan NA, Selvanayagam J, Pinto F, Zamorano JL, Evangelista A, Delgado V, Bax JJ, Pibarot P. Impact of Left Ventricular Ejection Fraction on Clinical Outcomes in Bicuspid Aortic Valve Disease. *J Am Coll Cardiol* 2022;**80**:1071–1084.

57. Généreux P, Pibarot P, Redfors B, Bax JJ, Zhao Y, Makkar RR, Kapadia S, Thourani VH, Mack MJ, Nazif TM, Lindman BR, Babaliaros V, Vincent F, Russo M, McCabe JM, Gillam LD, Alu MC, Hahn RT, Webb JG, Leon MB, Cohen DJ. Evolution and Prognostic Impact of Cardiac Damage After Aortic Valve Replacement. *J Am Coll Cardiol* 2022;**80**:783–800.

58. Hj L, H L, Sm K, Jb P, Ek K, Sa C, E P, Hk K, W L, Yj K, Sc L, Sw P, Dw S, Jk O, Sj P, Sp L. Diffuse Myocardial Fibrosis and Diastolic Function in Aortic Stenosis. *JACC Cardiovasc Imaging* 2020;**13**.

59. Flannery L, Etiwy M, Camacho A, Liu R, Patel N, Tavil-Shatelyan A, Tanguturi VK, Dal-Bianco JP, Yucel E, Sakhuja R, Jassar AS, Langer NB, Inglessis I, Passeri JJ, Hung J, Elmariah S. Patient- and Process-Related Contributors to the Underuse of Aortic Valve Replacement and Subsequent Mortality in Ambulatory Patients With Severe Aortic Stenosis. *J Am Heart Assoc* 2022;**11**:e025065.

60. De Rosa S, Sabatino J, Strangio A, Leo I, Romano LR, Spaccarotella CA, Mongiardo A, Polimeni A, Sorrentino S, Indolfi C. Non-Invasive Myocardial Work in Patients with Severe Aortic Stenosis. *J Clin Med* 2022;**11**:747.

61. Jain R, Bajwa T, Roemer S, Huisheree H, Allaqaband SQ, Kroboth S, Perez Moreno AC, Tajik AJ, Khandheria BK. Myocardial work assessment in severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J Cardiovasc Imaging* 2021;**22**:715–721.

62. Fortuni F, Butcher SC, Kley F van der, Lustosa RP, Karalis I, Weger A de, Priori SG, Bijl P van der, Bax JJ, Delgado V, Ajmone Marsan N. Left Ventricular Myocardial Work in

Patients with Severe Aortic Stenosis. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2021;**34**:257–266.

63. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, Kearney L, Lancellotti P, Marwick TH, Sato K, Takeuchi M, Zito C, Casalta A-C, Mohty D, Piérard L, Habib G, Donal E. Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis: An Individual Participant Data Meta-Analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92.

64. Dahl JS, Eleid MF, Michelena HI, Scott CG, Suri RM, Schaff HV, Pellikka PA. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circ Cardiovasc Imaging* 2015;**8**.

65. Dweck MR, Joshi S, Murigu T, Alpendurada F, Jabbour A, Melina G, Banya W, Gulati A, Roussin I, Raza S, Prasad NA, Wage R, Quarto C, Angeloni E, Refice S, Sheppard M, Cook SA, Kilner PJ, Pennell DJ, Newby DE, Mohiaddin RH, Pepper J, Prasad SK. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2011;**58**:1271–1279.

66. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, Jenkins W, Koo M, Mirsadraee S, White AC, Japp AG, Prasad SK, Semple S, Newby DE, Dweck MR. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. *JACC Cardiovasc Imaging* 2016.

67. Barone-Rochette G, Pierard S, Meester de RC de, Seldrum S, Melchior J, Maes F, Pouleur AC, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gerber BL. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J AmCollCardiol* 2014;**64**:144–154.

68. Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, Francis JM, Karamitsos TD, Prendergast BD, Robson MD, Neubauer S, Moon JC, Myerson SG. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart Br Card Soc* 2013;**99**:932–937.

69. Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuva AN, Sheikh A, López B, González A, Manisty C, Lloyd G, Kellman P, Díez J, Moon JC. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. *J Am Coll Cardiol* 2018;**71**:860–871.

70. Ito S, Miranda WR, Nkomo VT, Connolly HM, Pislaru SV, Greason KL, Pellikka PA, Lewis BR, Oh JK. Reduced Left Ventricular Ejection Fraction in Patients With Aortic Stenosis. *J Am Coll Cardiol* 2018;**71**:1313–1321.

71. Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G, Strotmann JM. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* 2009;**120**:577–584.

72. Mele D, Censi S, La Corte R, Merli E, Lo Monaco A, Locaputo A, Ceconi C, Trotta F, Ferrari R. Abnormalities of left ventricular function in asymptomatic patients with systemic sclerosis using Doppler measures of myocardial strain. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2008;**21**:1257–1264.

73. Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M, Rochitte CE. Prognostic significance of myocardial fibrosis quantification

by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol* 2010;**56**:278–287.

74. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–269, W64.

75. Pencina MJ, D'Agostino RB, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. *Stat Med* 2012;**31**:101–113.

76. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert J-C, Pierard LA. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. *Heart* 2010;**96**:1364–1371.

77. Zito C, Salvia J, Cusma-Piccione M, Antonini-Canterin F, Lentini S, Oreto G, Di BG, Montericcio V, Carerj S. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. *AmJ Cardiol* 2011;**108**:1463–1469.

78. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. *Circ Cardiovasc Imaging* 2012;**5**:613–620.

79. Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, Burrell LM, Srivastava PM. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2012;**13**:827–833.

80. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging* 2012;**5**:719–725.

81. Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, Grimm RA, Griffin BP, Desai MY. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. *Circ Cardiovasc Imaging* 2014;**7**:938–945.

82. Sato K, Seo Y, Ishizu T, Takeuchi M, Izumo M, Suzuki K, Yamashita E, Oshima S, Akashi YJ, Otsuji Y, Aonuma K. Prognostic value of global longitudinal strain in paradoxical low-flow, low-gradient severe aortic stenosis with preserved ejection fraction. *Circ J Off J Jpn Circ Soc* 2014;**78**:2750–2759.

83. Carstensen HG, Larsen LH, Hassager C, Kofoed KF, Jensen JS, Mogelvang R. Basal longitudinal strain predicts future aortic valve replacement in asymptomatic patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2016;**17**:283–292.

84. Nagata Y, Takeuchi M, Wu VC-C, Izumo M, Suzuki K, Sato K, Seo Y, Akashi YJ, Aonuma K, Otsuji Y. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. *JACC Cardiovasc Imaging* 2015;**8**:235–245.

85. Salaun E, Casalta A-C, Donal E, Bohbot Y, Galli E, Tribouilloy C, Hubert S, Magne J, Mancini J, Renard S, Avierinos J-F, Maysou L-A, Lavoute C, Szymanski C, Haentjens J, Habib G. Apical four-chamber longitudinal left ventricular strain in patients with aortic

stenosis and preserved left ventricular ejection fraction: analysis related with flow/gradient pattern and association with outcome. *Eur Heart J Cardiovasc Imaging* 2017.

86. Ng AC, Delgado V, Bertini M, Antoni ML, Bommel RJ van, Rijnsoever EP van, Kley F van der, Ewe SH, Witkowski T, Auger D, Nucifora G, Schuijf JD, Poldermans D, Leung DY, Schalij MJ, Bax JJ. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. *Eur Heart J* 2011;**32**:1542–1550.

87. Takeda S, Rimington H, Smeeton N, Chambers J. Long axis excursion in aortic stenosis. *Heart* 2001;**86**:52–56.

88. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879–2887.

89. Donal E, Thebault C, O'Connor K, Veillard D, Rosca M, Pierard L, Lancellotti P. Impact of aortic stenosis on longitudinal myocardial deformation during exercise. *EurJ Echocardiogr* 2011;**12**:235–241.

90. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt J-U. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2015;**28**:1171–1181, e2.

91. Mirea O, Pagourelias ED, Duchenne J, Bogaert J, Thomas JD, Badano LP, Voigt J-U, EACVI-ASE-Industry Standardization Task Force. Variability and Reproducibility of Segmental Longitudinal Strain Measurement: A Report From the EACVI-ASE Strain Standardization Task Force. *JACC Cardiovasc Imaging* 2018;**11**:15–24.

92. Kafa R, Kusunose K, Goodman AL, Svensson LG, Sabik JF, Griffin BP, Desai MY. Association of Abnormal Postoperative Left Ventricular Global Longitudinal Strain With Outcomes in Severe Aortic Stenosis Following Aortic Valve Replacement. *JAMA Cardiol* 2016;**1**:494–496.

93. Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM, McGregor C, Moon JC. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation* 2010;**122**:138–144.

94. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999;**34**:618–620.

95. Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of Subclinical Left Ventricular Dysfunction in Aortic Stenosis. *JACC Cardiovasc Imaging* 2019;**12**:163–171.

96. Bache RJ, Zhang J, Murakami Y, Zhang Y, Cho YK, Merkle H, Gong G, From AH, Ugurbil K. Myocardial oxygenation at high workstates in hearts with left ventricular hypertrophy. *Cardiovasc Res* 1999;**42**:616–626.

97. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;**15**:1012–1017.

98. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or =80 years. *EurJ CardiothoracSurg* 2006;**30**:722–727.

99. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.

100. O'Toole JD, Geiser EA, Reddy PS, Curtiss EI, Landfair RM. Effect of preoperative ejection fraction on survival and hemodynamic improvement following aortic valve replacement. *Circulation* 1978;**58**:1175–1184.

101. Henkel DM, Malouf JF, Connolly HM, Michelena HI, Sarano ME, Schaff HV, Scott CG, Pellikka PA. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: characteristics and outcomes. *J Am Coll Cardiol* 2012;**60**:2325–2329.

102. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;**111**:3290–3295.

103. Capoulade R, Le Ven F, Clavel M-A, Dumesnil JG, Dahou A, Thébault C, Arsenault M, O'Connor K, Bédard É, Beaudoin J, Sénéchal M, Bernier M, Pibarot P. Echocardiographic predictors of outcomes in adults with aortic stenosis. *Heart Br Card Soc* 2016;**102**:934–942.

104. Pellikka PA, She L, Holly TA, Lin G, Varadarajan P, Pai RG, Bonow RO, Pohost GM, Panza JA, Berman DS, Prior DL, Asch FM, Borges-Neto S, Grayburn P, Al-Khalidi HR, Miszalski-Jamka K, Desvigne-Nickens P, Lee KL, Velazquez EJ, Oh JK. Variability in Ejection Fraction Measured By Echocardiography, Gated Single-Photon Emission Computed Tomography, and Cardiac Magnetic Resonance in Patients With Coronary Artery Disease and Left Ventricular Dysfunction. *JAMA Netw Open* 2018;**1**:e181456.

105. Merillon JP, Neukirch F, Motte G, Aumont MC, Curien ND, Prasquier R, Gourgon R. The left ventricular end-systolic pressure-volume ratio. Studies during changes in load and inotropism in the human. *Eur Heart J* 1981;**2**:41–48.

106. Mérillon JP, Ennezat PV, Guiomard A, Masquet-Gourgon C, Aumont MC, Gourgon R. Left ventricular performance is closely related to the physical properties of the arterial system: Landmark clinical investigations in the 1970s and 1980s. *Arch Cardiovasc Dis* 2014;**107**:554–562.

107. Starling EH, Visscher MB. The regulation of the energy output of the heart. *J Physiol* 1927;**62**:243–261.

108. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2004;**44**:1030–1035.

109. Dumesnil JG, Shoucri RM. Effect of the geometry of the left ventricle on the calculation of ejection fraction. *Circulation* 1982;**65**:91–98.

110. Krayenbuehl HP, Rutishauser W, Wirz P, Amende I, Mehmel H. High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man. *Am J Cardiol* 1973;**31**:415–427.

111. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation* 1989;**79**:744–755.

112. Krayenbuehl HP, Hess OM, Ritter M, Monrad ES, Hoppeler H. Left ventricular systolic function in aortic stenosis. *Eur Heart J* 1988;**9 Suppl E**:19–23.

113. Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. *Circulation* 1979;**59**:679–688.

114. Potter E, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. *JACC Cardiovasc Imaging* 2018;**11**:260–274.

115. Gavina C, Falcao-Pires I, Pinho P, Manso MC, Goncalves A, Rocha-Goncalves F, Leite-Moreira A. Relevance of residual left ventricular hypertrophy after surgery for isolated aortic stenosis. *Eur J CardiothoracSurg* 2016;**49**:952–959.

116. Podlesnikar T, Delgado V, Bax JJ. Cardiovascular magnetic resonance imaging to assess myocardial fibrosis in valvular heart disease. *Int J Cardiovasc Imaging* 2018;**34**:97–112.

117. D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, Hatle L, Suetens P, Sutherland GR. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Review. *EurJ Echocardiogr* 2000;**1**:154–170.

118. Galli E, Lancellotti P, Sengupta PP, Donal E. LV mechanics in mitral and aortic valve diseases: value of functional assessment beyond ejection fraction. *JACC Cardiovasc Imaging* 2014;**7**:1151–1166.

119. Weidemann F, Jamal F, Kowalski M, Kukulski T, D'Hooge J, Bijnens B, Hatle L, De Scheerder I, Sutherland GR. Can strain rate and strain quantify changes in regional systolic function during dobutamine infusion, B-blockade, and atrial pacing--implications for quantitative stress echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2002;**15**:416–424.

120. Greenberg NL, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA, Drinko JK, Rodriguez LL, Thomas JD, Garcia MJ. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. *Circulation* 2002;**105**:99–105.

121. Yotti R, Bermejo J, Benito Y, Sanz-Ruiz R, Ripoll C, Martínez-Legazpi P, Villar CP del, Elízaga J, González-Mansilla A, Barrio A, Bañares R, Fernández-Avilés F. Validation of noninvasive indices of global systolic function in patients with normal and abnormal loading conditions: a simultaneous echocardiography pressure-volume catheterization study. *Circ Cardiovasc Imaging* 2014;**7**:164–172.

122. Kowalski M, Herbots L, Weidemann F, Breithardt O, Strotmann J, Davidavicius G, D'hooge J, Claus P, Bijnens B, Herregods M-C, Sutherland GR. One-dimensional ultrasonic strain and strain rate imaging - a new approach to the quantitation of regional myocardial function in patients with aortic stenosis. *Circulation* 2002;**106**: :II–421.

123. Pislaru C, Bruce CJ, Belohlavek M, Seward JB, Greenleaf JF. Intracardiac measurement of pre-ejection myocardial velocities estimates the transmural extent of viable myocardium early after reperfusion in acute myocardial infarction. *J Am CollCardiol* 2001;**38**:1748–1756.

124. Pislaru C, Alashry MM, Thaden JJ, Pellikka PA, Enriquez-Sarano M, Pislaru SV. Intrinsic Wave Propagation of Myocardial Stretch, A New Tool to Evaluate Myocardial Stiffness: A Pilot Study in Patients with Aortic Stenosis and Mitral Regurgitation. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2017;**30**:1070–1080.

125. Hoffmann R, Altiok E, Friedman Z, Becker M, Frick M. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography in comparison to late gadolinium enhancement cardiac magnetic resonance for analysis of myocardial fibrosis in severe aortic stenosis. *Am J Cardiol* 2014;**114**:1083–1088.

126. Magne J, Mohty D. Paradoxical low-flow, low-gradient severe aortic stenosis: a distinct disease entity. *Heart* 2015;**101**:993–995.

127. Herrmann S, Stork S, Niemann M, Lange V, Strotmann JM, Frantz S, Beer M, Gattenlohner S, Voelker W, Ertl G, Weidemann F. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol* 2011;**58**:402–412.

128. Adda J, Mielot C, Giorgi R, Cransac F, Zirphile X, Donal E, Sportouch-Dukhan C, Reant P, Laffitte S, Cade S, Le DY, Thuny F, Touboul N, Lavoute C, Avierinos JF, Lancellotti P, Habib G. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. *CircCardiovascImaging* 2012;**5**:27–35.

129. Magne J, Aboyans V. First-phase left ventricular ejection fraction: a small step for myocardial assessment, a big leap for aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2021;**22**:658–659.

130. Ezzaher A, Ouazzani T el, Crozatier B. Timing and velocity of ejection as major determinants of end-systolic pressure in isolated rabbit hearts. *Circulation* 1994;**90**:3055–3062.

131. Gu H, Li Y, Fok H, Simpson J, Kentish JC, Shah AM, Chowienczyk PJ. Reduced First-Phase Ejection Fraction and Sustained Myocardial Wall Stress in Hypertensive Patients With Diastolic Dysfunction: A Manifestation of Impaired Shortening Deactivation That Links Systolic to Diastolic Dysfunction and Preserves Systolic Ejection Fraction. *Hypertens Dallas Tex 1979* 2017;**69**:633–640.

132. Bing R, Gu H, Chin C, Fang L, White A, Everett RJ, Spath NB, Park E, Jenkins WS, Shah AS, Mills NL, Flapan AD, Chambers JB, Newby DE, Chowienczyk P, Dweck MR. Determinants and prognostic value of echocardiographic first-phase ejection fraction in aortic stenosis. *Heart Br Card Soc* 2020.

133. Gu H, Saeed S, Boguslavskyi A, Carr-White G, Chambers JB, Chowienczyk P. First-Phase Ejection Fraction Is a Powerful Predictor of Adverse Events in Asymptomatic Patients With Aortic Stenosis and Preserved Total Ejection Fraction. *JACC Cardiovasc Imaging* 2019;**12**:52–63.

134. Einarsen E, Hjertaas J, Gu H, Matre K, Chowienczyk P, Gerdts E, Chambers JB, Saeed S. Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2020.

135. Magne J, Aboyans V. Mechanical left ventricular dispersion in aortic stenosis: another parameter within dispersed surrogates of myocardial function? *Eur Heart J Cardiovasc Imaging* 2019;**20**:749–750.

136. Prihadi EA, Vollema EM, Ng ACT, Marsan NA, Bax JJ, Delgado V. Determinants and Prognostic Implications of Left Ventricular Mechanical Dispersion in Aortic Stenosis. *European Heart Journal Cardiovascular Imaging*.

137. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, Figulla HR, Poerner TC, Edvardsen T. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2012;**25**:667–673.

138. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, Galderisi M, Habib G, Knuuti J, Lancellotti P, McKenna W, Neglia D, Popescu BA, Edvardsen T, EACVI Scientific Documents Committee, EACVI Board members and external reviewers, EACVI Scientific Documents Committee, EACVI Board members and external reviewers. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:237–253.

139. Klaeboe LG, Haland TF, Leren IS, Ter Bekke RMA, Brekke PH, Røsjø H, Omland T, Gullestad L, Aakhus S, Haugaa KH, Edvardsen T. Prognostic Value of Left Ventricular Deformation Parameters in Patients with Severe Aortic Stenosis: A Pilot Study of the Usefulness of Strain Echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2017;**30**:727-735.e1.

140. Magne J, Mohty D, Boulogne C, Boubadara FE, Deltreuil M, Echahidi N, Cassat C, Laskar M, Virot P, Aboyans V. Prognosis importance of low flow in aortic stenosis with preserved LVEF. *Heart* 2015;**101**:781–787.

141. Lee S-P, Lee W, Lee JM, Park E-A, Kim H-K, Kim Y-J, Sohn D-W. Assessment of diffuse myocardial fibrosis by using MR imaging in asymptomatic patients with aortic stenosis. *Radiology* 2015;**274**:359–369.

142. Park S-J, Cho SW, Kim SM, Ahn J, Carriere K, Jeong DS, Lee S-C, Park SW, Choe YH, Park PW, Oh JK. Assessment of Myocardial Fibrosis Using Multimodality Imaging in Severe Aortic Stenosis: Comparison With Histologic Fibrosis. *JACC Cardiovasc Imaging* 2019;**12**:109–119.

143. Bonow RO, Carabello BA, Leon ACJr de, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH. ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on management of patients with valvular heart disease. *J Am Coll Cardiol* 1998;**32**:1486–1588.

144. Bonow RO, Carabello BA, Chatterjee K, de LA Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006

guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am CollCardiol* 2006;**48**:e1-148.

145. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Zamorano JL, Angelini A, Antunes M, Fernandez MA, Gohlke-Baerwolf C, Habib G, McMurray J, Otto C, Pierard L, Pomar JL, Prendergast B, Rosenhek R, Uva MS, Tamargo J. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;**28**:230–268.

146. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De BM, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Oppell UO von, Windecker S, Zamorano JL, Zembala M, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Popescu BA, Von SL, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;**33**:2451–2496.

147. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J AmCollCardiol* 2014.

148. Iung B, Pierard L, Magne J, Messika-Zeitoun D, Pibarot P, Baumgartner H. Great debate: all patients with asymptomatic severe aortic stenosis need valve replacement. *Eur Heart J* 2023:ehad355.

149. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care* 1988;**26**:724–735.

150. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *JAmCollCardiol* 1993;**21**:1220–1225.

151. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, Alahdab F, Alashi A, Alipour V, Arabloo J, Azari S, Barthelemy CM, Benziger CP, Berman AE, Bijani A, Carrero JJ, Carvalho F, Daryani A, Durães AR, Esteghamati A, Farid TA, Farzadfar F, Fernandes E, Filip I, Gad MM, Hamidi S, Hay SI, Ilesanmi OS, Naghibi Irvani SS, Jürisson M, Kasaeian A, Kengne AP, Khan AR, Kisa A, Kisa S, Kolte D, Manafi N, Manafi A, Mensah GA, Mirrakhimov EM, Mohammad Y, Mokdad AH, Negoi RI, Thi Nguyen HL, Nguyen TH, Nixon MR, Otto CM, Patel S, Pilgrim T, Radfar A, Rawaf DL, Rawaf S, Rawasia WF,

Rezapour A, Roever L, Saad AM, Saadatagah S, Senthilkumaran S, Sliwa K, Tesfay BE, Tran BX, Ullah I, Vaduganathan M, Vasankari TJ, Wolfe CDA, Yonemoto N, Roth GA, Global Burden of Disease Study 2017 Nonrheumatic Valve Disease Collaborators. Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990-2017. *Circulation* 2020;**141**:1670–1680.

152. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R, Kazakiewicz D, Benito Rubio V de, Ignatiuk B, Raisi-Estabragh Z, Pawlak A, Karagiannidis E, Treskes R, Gaita D, Beltrame JF, McConnachie A, Bardinet I, Graham I, Flather M, Elliott P, Mossialos EA, Weidinger F, Achenbach S, Atlas Writing Group, European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;**43**:716–799.

153. Mohler ER 3rd, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation* 2001;**103**:1522–1528.

154. Zhao Y, Nicoll R, He YH, Henein MY. The effect of statins therapy in aortic stenosis: Meta-analysis comparison data of RCTs and observationals. *Data Brief* 2016;**7**:357–361.

155. Diederichsen ACP, Lindholt JS, Möller S, Øvrehus KA, Auscher S, Lambrechtsen J, Hosbond SE, Alan DH, Urbonaviciene G, Becker SW, Fredgart MH, Hasific S, Folkestad L, Gerke O, Rasmussen LM, Møller JE, Mickley H, Dahl JS. Vitamin K2 and D in Patients With Aortic Valve Calcification: A Randomized Double-Blinded Clinical Trial. *Circulation* 2022;**145**:1387–1397.

156. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;**343**:611–617.

157. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *NEnglJ Med* 2010;**363**:1597–1607.

158. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J* 1988;**9**:57–64.

159. Lancellotti P, Magne J, Dulgheru R, Clavel M-A, Donal E, Vannan MA, Chambers J, Rosenhek R, Habib G, Lloyd G, Nistri S, Garbi M, Marchetta S, Fattouch K, Coisne A, Montaigne D, Modine T, Davin L, Gach O, Radermecker M, Liu S, Gillam L, Rossi A, Galli E, Ilardi F, Tastet L, Capoulade R, Zilberszac R, Vollema EM, Delgado V, Cosyns B, Lafitte S, Bernard A, Pierard LA, Bax JJ, Pibarot P, Oury C. Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. *JAMA Cardiol* 2018;**3**:1060.

160. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J* 2020;**41**:4349–4356.

161. Eugène M, Duchnowski P, Prendergast B, Wendler O, Laroche C, Monin J-L, Jobic Y, Popescu BA, Bax JJ, Vahanian A, Iung B, EORP VHD II Registry Investigators Group. Contemporary Management of Severe Symptomatic Aortic Stenosis. *J Am Coll Cardiol* 2021;**78**:2131–2143.

162. Arnold SV, Manandhar P, Vemulapalli S, Vekstein AM, Kosinski AS, Spertus JA, Cohen DJ. Patient-reported vs. physician-estimated symptoms before and after transcatheter aortic valve replacement. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:161–168.

163. Kang D-H, Park S-J, Lee S-A, Lee S, Kim D-H, Kim H-K, Yun S-C, Hong G-R, Song J-M, Chung C-H, Song J-K, Lee J-W, Park S-W. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. *N Engl J Med* 2020;**382**:111–119.

164. Costa GNF, Cardoso JFL, Oliveiros B, Gonçalves L, Teixeira R. Early surgical intervention versus conservative management of asymptomatic severe aortic stenosis: a systematic review and meta-analysis. *Heart Br Card Soc* 2023;**109**:314–321.

165. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, Bijsterveld P, Tastet L, Musa TA, Dobson L, Chin C, Captur G, Om SY, Wiesemann S, Ferreira VM, Piechnik SK, Schulz-Menger J, Schelbert EB, Clavel M-A, Newby DE, Myerson SG, Pibarot P, Lee S, Cavalcante JL, Lee S-P, McCann GP, Greenwood JP, Moon JC, Dweck MR. Extracellular Myocardial Volume in Patients With Aortic Stenosis. *J Am Coll Cardiol* 2020;**75**:304–316.

166. Musa TA, Treibel TA, Vassiliou VS, Captur G, Singh A, Chin C, Dobson LE, Pica S, Loudon M, Malley T, Rigolli M, Foley JRJ, Bijsterveld P, Law GR, Dweck MR, Myerson SG, McCann GP, Prasad SK, Moon JC, Greenwood JP. Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation* 2018;**138**:1935–1947.

167. Kwak S, Everett RJ, Treibel TA, Yang S, Hwang D, Ko T, Williams MC, Bing R, Singh T, Joshi S, Lee H, Lee W, Kim Y-J, Chin CWL, Fukui M, Al Musa T, Rigolli M, Singh A, Tastet L, Dobson LE, Wiesemann S, Ferreira VM, Captur G, Lee S, Schulz-Menger J, Schelbert EB, Clavel M-A, Park S-J, Rheude T, Hadamitzky M, Gerber BL, Newby DE, Myerson SG, Pibarot P, Cavalcante JL, McCann GP, Greenwood JP, Moon JC, Dweck MR, Lee S-P. Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis. *J Am Coll Cardiol* 2021;**78**:545–558.

168. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, Shen M, Capoulade R, Clavel M-A, Arsenault M, Bédard É, Bernier M, Beaudoin J, Narula J, Lancellotti P, Bax JJ, Généreux P, Pibarot P. Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis. *J Am Coll Cardiol* 2019;**74**:550–563.

169. Elbaz-Greener G, Masih S, Fang J, Ko DT, Lauck SB, Webb JG, Nallamothu BK, Wijeysundera HC. Temporal Trends and Clinical Consequences of Wait Times for Transcatheter Aortic Valve Replacement: A Population-Based Study. *Circulation* 2018;**138**:483–493.

170. Albassam O, Henning KA, Qiu F, Cram P, Sheth TN, Ko DT, Woodward G, Austin PC, Wijeysundera HC. Increasing Wait-Time Mortality for Severe Aortic Stenosis. *Circ Cardiovasc Interv* 2020;**13**:e009297.

171. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Nagao K, Inada T, Murakami T, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Sakata R, Kimura T, CURRENT AS Registry Investigators. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol* 2015;**66**:2827–2838.

172. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, Kotrc M, Glaveckaite S, Gasparovic H, Pavlovic N, Velicki L, Salizzoni S, Wojakowski W, Van Camp G, Nikolic

SD, Iung B, Bartunek J, AVATAR Trial Investigators*. Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial. *Circulation* 2022;**145**:648–658.

173. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011.

174. Arcy JL d', Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, Myerson SG, Prendergast BD. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J* 2016;**37**:3515–3522.

175. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex Differences and Similarities in Valvular Heart Disease. *Circ Res* 2022;**130**:455–473.

176. Redfors B, Pibarot P, Gillam LD, Burkhoff D, Bax JJ, Lindman BR, Bonow RO, O'Gara PT, Leon MB, Généreux P. Stress Testing in Asymptomatic Aortic Stenosis. *Circulation* 2017;**135**:1956–1976.

177. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *EurHeart J* 2005;**26**:1309–1313.

178. Pibarot P, Herrmann HC, Wu C, Hahn RT, Otto CM, Abbas AE, Chambers J, Dweck MR, Leipsic JA, Simonato M, Rogers T, Sathananthan J, Guerrero M, Ternacle J, Wijeysundera HC, Sondergaard L, Barbanti M, Salaun E, Généreux P, Kaneko T, Landes U, Wood DA, Deeb GM, Sellers SL, Lewis J, Madhavan M, Gillam L, Reardon M, Bleiziffer S, O'Gara PT, Rodés-Cabau J, Grayburn PA, Lancellotti P, Thourani VH, Bax JJ, Mack MJ, Leon MB, Heart Valve Collaboratory. Standardized Definitions for Bioprosthetic Valve Dysfunction Following Aortic or Mitral Valve Replacement: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2022;**80**:545–561.

179. Gaede L, Di Bartolomeo R, Kley F van der, Elsässer A, Iung B, Möllmann H. Aortic valve stenosis: what do people know? A heart valve disease awareness survey of over 8,800 people aged 60 or over. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol* 2016;**12**:883–889.

180. Nguyen V, Willner N, Eltchaninoff H, Burwash IG, Michel M, Durand E, Gilard M, Dindorf C, Iung B, Cribier A, Vahanian A, Chevreul K, Messika-Zeitoun D. Trends in aortic valve replacement for aortic stenosis: a French nationwide study. *Eur Heart J* 2022;**43**:666–679.

181. Puri R, Iung B, Cohen DJ, Rodés-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225.

182. Minha S, Marcus G. Can We Truly Predict Futility for TAVR Based on Pre-Procedural Indices? *Cardiovasc Revascularization Med Mol Interv* 2021;**23**:77–78.

183. Parikh PB. Predicting Futility in Aortic Stenosis: What's the Holdup? *J Am Coll Cardiol* 2022;**80**:801–803.

184. Chambers JB, Ray S, Prendergast B, Taggart D, Westaby S, Grothier L, Arden C, Wilson J, Campbell B, Sandoe J, Gohlke-Barwolf C, Mestres CA, Rosenhek R, Otto C.

Specialist valve clinics: recommendations from the British Heart Valve Society working group on improving quality in the delivery of care for patients with heart valve disease. *Heart* 2013;**99**:1714–1716.

185. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM van, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A van, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB, Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 2012;**42**:S45-60.

186. Østergaard L, Køber N, Petersen JK, Jensen AD, De Backer O, Køber L, Fosbøl EL. Long-Term Cause of Death in Patients Who Underwent Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2023;**193**:91–96.

187. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, Kodali SK, Kapadia SR, Cohen DJ, Pocock SJ, Lu M, White R, Szerlip M, Ternacle J, Malaisrie SC, Herrmann HC, Szeto WY, Russo MJ, Babaliaros V, Smith CR, Blanke P, Webb JG, Makkar R, PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years. *N Engl J Med* 2023.

188. Durko AP, Osnabrugge RL, Van Mieghem NM, Milojevic M, Mylotte D, Nkomo VT, Pieter Kappetein A. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. *Eur Heart J* 2018;**39**:2635–2642.

189. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, Kirtane AJ, Fitzgerald S, Michaels J, Krohn C, Masoudi FA, Brindis RG, Bavaria JE. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. *Ann Thorac Surg* 2021;**111**:701–722.

190. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, Kirtane AJ, Fitzgerald S, Michaels J, Krohn C, Masoudi FA, Brindis RG, Bavaria JE. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2020;**76**:2492–2516.

191. Nguyen V, Michel M, Eltchaninoff H, Gilard M, Dindorf C, Iung B, Mossialos E, Cribier A, Vahanian A, Chevreul K, Messika-Zeitoun D. Implementation of Transcatheter Aortic Valve Replacement in France. *J Am Coll Cardiol* 2018;**71**:1614–1627.

192. Osnabrugge RLJ, Head SJ, Genders TSS, Van Mieghem NM, De Jaegere PPT, Boon RMA van der, Kerkvliet JM, Kalesan B, Bogers AJJC, Kappetein AP, Hunink MGM. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg* 2012;**94**:1954–1960.

193. Arsalan M, Szerlip M, Vemulapalli S, Holper EM, Arnold SV, Li Z, DiMaio MJ, Rumsfeld JS, Brown DL, Mack MJ. Should Transcatheter Aortic Valve Replacement Be Performed in Nonagenarians?: Insights From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2016;**67**:1387–1395.

194. Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2014;**7**:707–716.

195. Terrosu P, Boccanelli A, Sabino G, Alboni P, Baldasseroni S, Bo M, Desideri G, Marchionni N, Palazzo G, Rozzini R, Ungar A, Vetta F, Zito G. Severe aortic stenosis and transcatheter aortic valve replacement in elderly patients: utility vs. futility. *Minerva Med* 2022;**113**:640–646.

196. Lantelme P, Lacour T, Bisson A, Herbert J, Ivanes F, Bourguignon T, Quilliet L, Angoulvant D, Harbaoui B, Babuty D, Etienne CS, Deharo P, Bernard A, Fauchier L. Futility Risk Model for Predicting Outcome After Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2020;**130**:100–107.

197. Patel KV, Omar W, Gonzalez PE, Jessen ME, Huffman L, Kumbhani DJ, Bavry AA. Expansion of TAVR into Low-Risk Patients and Who to Consider for SAVR. *Cardiol Ther* 2020;**9**:377–394.

Annexes

Annexes 1: Left ventricular ejection fraction thresholds reappraisal. Also for bicuspid Valve Disease?

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EDITORIAL COMMENT

Left Ventricular Ejection Fraction Thresholds Reappraisal

Also for Bicuspid Valve Disease?*

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Bicuspid aortic valve (BAV) (ie, an aortic valve constituted with only 2 cusps) may lead to early aortic valve stenosis and/or regurgitation. Despite remaining asymptomatic for a long time, patients with BAV may require aortic valve intervention earlier than patients with tricuspid aortic valve disease (frequently <55 years of age).[1]

BAV creates 3 challenges for clinicians: 1) although uncommon in the general population,[2] screening and early diagnosis is crucial; 2) once diagnosed, close monitoring of the disease's progression and consequences to the heart are mandatory; and 3) since operated at an early stage, choice of device (ie, valve repair vs mechanical prosthesis vs biological prosthesis) should deal with the appropriate balance between long-term anticoagulation consequences and risk of early degeneration.

Regarding the second challenge, similarly to in patients with tricuspid aortic stenosis or regurgitation, recent guidelines focused on the need for left ventricular ejection fraction (LVEF) assessment to improve timing of intervention in patients with BAV.[3,4] Cut-off of LVEF related to the decision to intervene has been raised in current guidelines (from 50% to 55%-60%), but this choice is empiric, resulting from consensus, and the level of evidence remains low. Furthermore, the cutoffs proposed in guidelines are mainly based on studies including patients with isolated tricuspid aortic regurgitation or stenosis. Given that patients with BAV may have a mixed form of valvular heart disease and particular natural history, there is a profound need for data on outcome and on the impact of LVEF (specifically derived from patients with BAV).

SEE PAGE 1071

In this issue of the *Journal of the American College of Cardiology*, the study from Hecht et al[5] reports the fundamental importance of monitoring consequences of BAV on LVEF. Using an international network, the authors built a database with an initial international cohort from 5 centers[6] expanded with additional centers, resulting in a large cohort (n = 1,493) retrospectively analyzed. During a reported median follow-up of 56 months, the authors identified 117 primary endpoints (ie, overall death regardless of occurrence of aortic valve intervention) and 675 secondary combined endpoints (ie, aortic valve intervention or overall death).

The authors confirm the prognostic value of LVEF in aortic valve stenosis and regurgitation.[7-11] The risk of combined event increased when LVEF was <60% (<50% for death in the isolated aortic stenosis) in the whole cohort as well as in the AS and AR groups. The proposed cutoff is <55% in mixed aortic valve disease. There is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease. Of course, this is only a registry. The indication for surgery is part of the main clinical endpoint and remains a subjective parameter.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Nevertheless, death is not subjective. Its risk increases according to the degree of decrease in LVEF. In addition to the limitations raised by the authors, several points suggest that the clinical implication of the present study must be tempered. First, an epidemiological registry needs an accurate definition of the data collection process and quality control, which is not detailed in the present study. Second, sample size is an obvious strength of the study. Nevertheless, the period of inclusion is large, including patients in the 1990s and early 2000s, implying various management strategies that may have an impact on outcome and, more particularly, on indication for AVR. Third, the present data set is based on a smaller number of patients than previous publications, despite the larger number of centers included.[5] This may imply a selection bias. Fourth, symptoms are not reported, limiting the interpretation of a secondary combined endpoint.

Beyond these limitations, the present study underlines again the crucial role of myocardial damage and its assessment in patients with valvular heart diseases. When the decision to intervene is taken too late, patients do not benefit from AVR because myocardial damage can be irreversible.[12] Waiting for symptoms might lead to myocardial damage that is too advanced, and it might be even more relevant in BAVD than other heart valve diseases. The present report stresses that a delayed diagnosis at the presentation time of symptoms and of significant damage (or remodeling) could have a significant impact on prognosis in patients who are relatively young. Therefore, it also highlights the importance of taking the evaluation of the left ventricular (LV) function into account during the screening of asymptomatic first relatives at the time of BAVD diagnosis and to follow-up on these patients regularly.[3] Teaching the use of hand-held ultrasound devices is potentially an opportunity, but increasing the awareness about the prognostic importance of valvular disease (especially BAVD) is of crucial importance.[13,14]

Guidelines are still restrictive for surgical indications, but the awareness is improving. The work from Hecht et al[5] should be highlighted, and it will potentially (with others) influence the next guidelines. The myocardial damage assessment is crucial and should help in promoting earlier interventions. We should look at the valve but not only at the valve. We should look at the consequences of heart valve diseases.

It has been previously demonstrated that LVEF is of crucial importance in stenotic and regurgitant aortic valve diseases, and the recent guidelines took into consideration the new cutoff of 55% instead of 50%.[3,4] However, LVEF is not LV systolic function. Other imaging opportunities exist to best manage our patients.

The role of hypertrophy could be interesting to study in the BAVD population. The amount of myocardial fibrosis by CMR could also bring additional information regarding the risk stratification in the various BAVD subgroups of presentation.[15]

In addition, LV global longitudinal strain might be even better in assessing the LV consequences of the hemodynamic alterations related to the BAVD. It was not studied by Hecht et al.[5] They focused on a large number of patients, but only on classical measurements that could be done in echocardiography. Myocardial fibrosis as well as strain or myocardial work indexes have not been mentioned.[16] These have, however, the strength of being more robust and should probably be advised in addition to LVEF, which could be considered too versatile for being used alone to guide a surgical indication.[17,18] The enlargement of the interstitial space with reactive fibrosis and subsequently with replacement fibrosis and cell death has been suggested to be the main driver of the transition to symptoms, heart failure, and adverse cardiovascular events even after aortic valve replacement.[15] A "preserved" EF in the presence of a small LV cavity equates to a low stroke volume, which is the primary problem in low flow low gradient AS.[19] LVGLS is a more reliable parameter than standard 2-dimensional LVEF.[17,18] Despite its influence by preload and afterload, it is sensitive enough to unmask patients with structural and functional myocardial damage that LVEF cannot reveal.[17,18] An individual participant data meta-analysis demonstrated that in asymptomatic patients with significant AS and normal LVEF, impaired LVGLS (cutoff −14.6%) is associated with reduced survival.[17,18] The recently suggested use of the myocardial work seems even more promising for detecting the myocardial damage earlier.[20,21]

Despite the inherent limitations of the study, mainly related to its design, the authors should be congratulated for their tremendous effort in collecting the largest amount of data with follow-up of patients from several international centers. The present findings[5] improve our knowledge about BAVD and the prognosis impact of LVEF, for which reappraisal of cutoff may be discussed in the light of present results. It should encourage further prospective works, using LVEF or other parameters of LV systolic function derived from TTE or CMR, to best define the timing for surgery. We should be aware and work for decreasing risk of disability and death in patients with BAVD.

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REFERENCES

1. Michelena HI, Desjardins VA, Avierinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*. 2008;117:2776–2784.

2. Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. *Am J Cardiol*. 2005;96:718–721.

3. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632.

4. Otto CM, Nishimura RA, Bonow CM, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450–500.

5. Hecht S, Butcher SC, Pio SM, et al. Impact of left ventricular ejection fraction on clinical outcomes in bicuspid aortic valve disease. *J Am Coll Cardiol*. 2022;80(11):1071–1084.

6. Kong WK, Delgado V, Poh KK, et al. Prognostic implications of raphe in bicuspid aortic valve anatomy. *JAMA Cardiol*. 2017;2:285–292.

7. Bohbot Y, de Meester de Ravenstein C, Chadha G, et al. Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. *J Am Coll Cardiol Img*. 2019;12:38–48.

8. Yang LT, Boler A, Medina-Inojosa JR, et al. Aortic stenosis progression, cardiac damage, and survival: comparison between bicuspid and tricuspid aortic valves. *J Am Coll Cardiol Img*. 2021;14:1113–1126.

9. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol*. 2018;3:1060–1068.

10. Yang LT, Takeuchi M, Scott CG, et al. Automated global longitudinal strain exhibits a robust association with death in asymptomatic chronic aortic regurgitation. *J Am Soc Echocardiogr*. 2022;35(7):692–702. https://doi.org/10.1016/j.echo.2021.10.018. e8.

11. Zhao Q, Zhang B, Ye Y, et al. Prognostic impact of left ventricular ejection fraction in patients with moderate aortic regurgitation: potential implications for treatment decision-making. *Front Cardiovasc Med*. 2021;8:800961.

12. Genereux P, Pibarot P, Redfors B, et al. Evolution and prognostic impact of cardiac damage after aortic valve replacement. J Am Coll Cardiol. Published online May 14, 2022. https://doi.org/10.1016/j.jacc.2022.05.006.

13. Iung B, Delgado V, Rosenhek R, et al. Contemporary presentation and management of valvular heart disease: the EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation*. 2019;140:1156–1169.

14. Neskovic AN, Skinner H, Price S, et al. Focus cardiac ultrasound core curriculum and core syllabus of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19:475–481.

15. Lee HJ, Lee H, Kim SM, et al. Diffuse myocardial fibrosis and diastolic function in aortic stenosis. *J Am Coll Cardiol Img*. 2020;13:2561–2572.

16. Meucci MC, Butcher SC, Galloo X, et al. Noninvasive left ventricular myocardial work in patients with chronic aortic regurgitation and preserved left ventricular ejection fraction. *J Am Soc Echocardiogr*. 2022;35(7):703–711. https://doi.org/10.1016/j.echo.2022.01.008. e3.

17. Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of subclinical left ventricular dysfunction in aortic stenosis. *J Am Coll Cardiol Img*. 2019;12:163–171.

18. Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *J Am Coll Cardiol Img*. 2019;12:84–92.

19. Flannery L, Etiwy M, Camacho A, et al. Patient- and process-related contributors to the underuse of aortic valve replacement and subsequent mortality in ambulatory patients with severe aortic stenosis. *J Am Heart Assoc*. 2022;11:e025065.

20. Taconne M, Le Rolle V, Paris V, et al. How myocardial work could be relevant in patients with an aortic valve stenosis? *Eur Heart J Cardiovasc Imaging*. Published online March 17, 2022. https://doi.org/10.1093/ehjci/jeac046.

21. Fortuni F, Butcher SC, van der Kley F, et al. Left ventricular myocardial work in patients with severe aortic stenosis. *J Am Soc Echocardiogr*. 2021;34:257–266.

KEY WORDS aortic regurgitation, aortic stenosis, bicuspid aortic valve, left ventricular ejection fraction, mixed aortic valve disease

Annexes 2: Distribution and Prognostic Significance of LV Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis.

JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 1, 2019

ORIGINAL RESEARCH

Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis

An Individual Participant Data Meta-Analysis

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ABSTRACT

OBJECTIVES In this individual participant data meta-analysis on left ventricular global longitudinal strain (LVGLS), our objective was to: 1) describe its distribution; 2) identify the most predictive cutoff values; and 3) assess its impact on mortality in asymptomatic patients with significant aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF).

BACKGROUND The evidence supporting the prognostic role of LVGLS in asymptomatic patients with AS has been obtained from several relatively small studies.

METHODS A literature search was performed for studies published between 2005 and 2017 without language restriction according to the following criteria: "aortic stenosis" AND "longitudinal strain." The corresponding authors of selected studies were contacted and invited to share their data that we computerized in a specific database. The primary endpoint was all-cause mortality.

RESULTS Among the 10 studies included, 1,067 asymptomatic patients with significant AS and LVEF >50% were analyzed. The median of LVGLS was 16.2% (from 5.6% to 30.1%). There were 91 deaths reported during follow-up with median of 1.8 (0.9 to 2.8) years, resulting in a pooled crude mortality rate of 8.5%. The LVGLS performed well in the prediction of death (area under the curve: 0.68). The best cutoff value identified was LVGLS of 14.7% (sensitivity, 60%; specificity, 70%). Using random effects model, the risk of death for patients with LVGLS <14.7% is multiplied by >2.5 (hazard ratio: 2.62; 95% confidence interval: 1.66 to 4.13; $p < 0.0001$), without significant heterogeneity between studies ($I^2 = 18.3\%$; $p = 0.275$). The relationship between LVGLS and mortality remained significant in patients with LVEF ≥60% ($p = 0.001$).

CONCLUSIONS This individual participant data meta-analysis demonstrates that in asymptomatic patients with significant AS and normal LVEF, impaired LVGLS is associated with reduced survival. These data emphasize the potential usefulness of LVGLS for risk stratification and management of these patients. (J Am Coll Cardiol Img 2019;12:84–92)

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The assessment of left ventricular (LV) function using LV ejection fraction (LVEF) has a central place in the current guidelines for the management of patients with severe aortic stenosis (AS), particularly when still asymptomatic. The current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines recommend as Class I indication (Level of Evidence: B) to perform aortic valve intervention in asymptomatic patients when LVEF becomes <50% (1,2). However, these concomitant findings are rare (3) and symptoms generally occur well before decrease in LVEF, which, in turn, remains preserved for long in patients with AS. Several recent studies demonstrate, using cardiac magnetic resonance, that LV structural and functional abnormalities may be frequent despite LVEF >50% (4–9). This may partially explain the reduced post-operative survival of patients with LVEF 50% to 60% (3,10). Furthermore, aortic valve intervention in patients with LVEF <50% frequently results in suboptimal post-operative LV function recovery, contributing to persistent symptoms, limited functional capacity and quality of life, and increased risk of events. Consequently, this underlines the need to identify echocardiographic parameters better than LVEF to more accurately assess the consequences of AS-related LV pressure overload on LV function.

SEE PAGE 93

The impairment of LV longitudinal shortening is associated with myocardial fibrosis (11,12), which is, in turn, a potential prognostic marker in patients with AS (6,13). Hence, LV longitudinal function assessment, using speckle-tracking echocardiography, may provide a surrogate imaging marker of myocardial damage. Indeed, there is growing evidence suggesting the potential prognostic role of LV myocardial longitudinal function, as assessed by global longitudinal strain (GLS), in asymptomatic patients with AS. However, the available data are mainly derived from relatively small series and/or from single-center studies. In addition, current series report various unstandardized cutoff values.

Our objective was therefore to perform an individual participant data meta-analysis to: 1) describe the distribution; 2) identify the most predictive cutoff values; and 3) assess the impact of LVGLS on mortality in asymptomatic patients with significant AS and preserved LVEF.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVAi = indexed aortic valve area
CI = confidence interval
GLS = global longitudinal strain
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction

METHODS

We searched MEDLINE, Embase, and the Cochrane Library database using the key terms "aortic valve stenosis" and "longitudinal strain" between 2005 and 2017 without language restriction. The protocol of this individual participant data meta-analysis was validated by the Research & Innovation Committee of the European Association of Cardiovascular Imaging and the study was conducted on behalf of all members of the Committee. The PRISMA statement (14) was followed to conduct the individual participant data meta-analysis.

INCLUSION CRITERIA. Studies were selected for the meta-analysis if they included patients with all of the following criteria: 1) asymptomatic; 2) preserved LVEF (i.e., >50%); 3) greater than or equal to moderate AS, as defined by current guidelines at the time of the study; 4) quantification of the LVGLS using 2-dimensional speckle tracking; and 5) availability of outcome of interest for the current analysis (i.e., all-cause death). No inclusion criterion was applied regarding sample size.

SELECTION OF STUDIES. A first selection of the studies was based on the title and on the abstract. The full articles of all selected studies were then consulted to verify all pre-specified inclusion criteria. The selection of the studies was performed simultaneously during specific meeting (J.M., B.C., and E.D.). The flow chart illustrating the selection of the studies process is reported in **Figure 1**. Great care was taken to avoid inclusion of various studies based on the same cohort population to avoid redundancy in the meta-analysis.

Finally, all corresponding authors and/or first, second, or last authors of the paper were contacted

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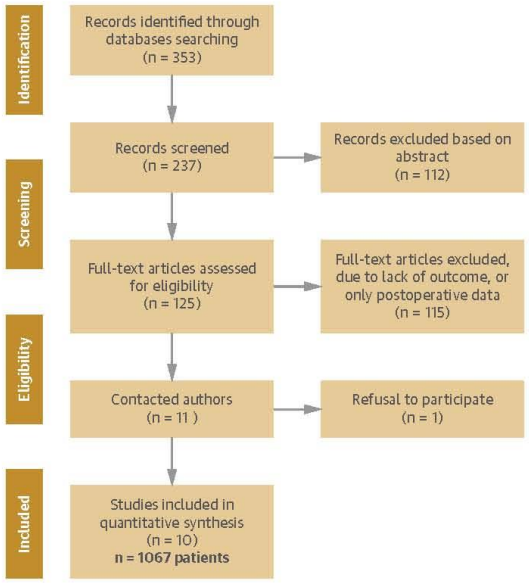
FIGURE 1 Flow Chart



Selection and inclusion of the studies.

by email to propose them to participate in the meta-analysis. Responding authors were invited to share a short, anonymized database including a limited number of variables. The required variables were age, gender, comorbidities (coronary artery disease, hypertension, diabetes, dyslipidemia), AS severity, LVEF, LVGLS, and outcome data. The data were then computerized in a dedicated database.

PRIMARY ENDPOINT. The primary endpoint of this individual participant data meta-analysis was all-cause death. Purposely, combined endpoint including need for aortic valve intervention was not used in the meta-analysis. This is justified by the fact that the decision-making regarding indication for intervention may considerably vary between centers.

STATISTICAL ANALYSIS. Extraneous data were removed from the database and units of continuous variables were standardized and continuous variables were dichotomized.

Descriptive analysis was performed and mean ± SD or proportion was reported. The distribution of LVGLS was compared according to each included study using 1-way analysis of variance.

A univariate Cox proportional hazards model was used to derive, for each study, the hazard ratio (HR), standard error, and 95% confidence interval (CI) related to LVGLS (as continuous variables) and occurrence of death. Log transformation was performed and inverse variances as weights were then calculated for each study. The meta-analysis was performed using random effects models and forest plots were generated to express the pooled effect. Heterogeneity was assessed using I^2. Stratified analysis was performed according to LVEF with a prespecified arbitrary cutoff value of 60%.

To assess the potential impact of vendor difference on the results, a stratified analysis was performed according to vendor. The best cutoff value of LVGLS associated with death was derived from receiver operating characteristic curve analysis and selected using the best compromise between sensitivity and specificity and the Youden index. This cutoff was then used to generate Kaplan-Meier analysis and to assess the impact of LVGLS on death in multivariate Cox proportional hazards model.

To assess the incremental prognostic value of LVGLS over LVEF, we calculated integrated discrimination improvement as recommended (15). To simplify the interpretation and discussion of the results, although negative, LVGLS is reported as positive values. All statistical analyses were performed using SPSS version 23 (IBM, Armonk, New York) and STATA version 13 (StataCorp LP, College Station, Texas).

RESULTS

A total of 10 studies, including 1,067 asymptomatic patients with LVEF >50%, were used for the present individual participant data meta-analysis. The dataset was completed for LVGLS and outcome data. There was 0.8% of missing values for LVEF (i.e., patients with LVEF >50% but without exact value). The selected studies are summarized in **Table 1**, and the description of the population is reported in **Table 2**.

The median LVGLS was 16.2% (from 5.6% to 30.1%). A LVGLS >13.7% was observed in 75% of patients and <15% of patients had LVGLS >20% (i.e., preserved LV longitudinal function). In patients with severe AS (i.e., indexed aortic valve area [AVAi] <0.6 cm^2/m^2), the median LVGLS was 16.3% (from 6% to 30.1%).

The distribution of LVGLS according to selected studies is reported in **Figure 2**. Although the study

TABLE 1 Description of Selected Studies

First Author (Ref. #)	Year	Design	Population Available (n = 1,067)	AVAi (cm^2/m^2)	Vendor	LVGLS Cutoff	Outcome
Lancellotti et al. (32)	2010	Prospective/bicentric	163	0.45 ± 0.09	GE	15.9%	MACE
Zito et al. (33)	2011	Prospective/monocentric	82	0.40 ± 0.10	GE	18%	MACE
Dahl et al. (18)	2012	Prospective/monocentric	65	0.46 ± 0.19	GE	Quartile	MACE
Kearney et al. (34)	2012	Prospective/monocentric	77	0.56 ± 0.23	GE	15%	All-cause death
Yingchoncharoen et al. (17)	2012	Prospective/monocentric	78	0.39 ± 0.13	Siemens	15%	MACE
Kusunose et al. (35)	2014	Retrospective/monocentric	137	0.42 ± 0.2	Siemens	Quartile	All-cause death
Sato et al. (16)	2014	Retrospective/multicentric	142	0.42 ± 0.11	GE	17%	MACE
Carstensen et al. (36)	2015	Prospective/multicentric	104	0.49 ± 0.13	GE	15%	MACE
Nagata et al. (37)	2015	Prospective/multicentric	102	0.42 ± 0.10	TomTec	17%	MACE
Salaun et al. (38)	2017	Prospective/multicentric	117	0.47 ± 0.11	GE	Tertile	All-cause death

AVAi = indexed aortic valve area; GE = General Electric; LVGLS = left ventricular global longitudinal strain; MACE = major adverse cardiac event.

from Sato et al. (16) reported significantly higher values and the study of Yingchoncharoen et al. (17) significantly lower values ($p < 0.0001$), there was a good homogeneity between studies regarding LVGLS values (**Figure 2**). In studies using equipment only from the most commonly used vendor (GE Healthcare, Horten, Norway), the median LVGLS was 16.6% (from 6% to 30.1%).

LVGLS AND MORTALITY. Among the 10 selected studies, 91 deaths were reported during a median follow-up of 1.8 years, from 0 to 8.5 years, resulting in a pooled crude rate of death of 8.5% (range, 2.8% to 18.5%). In patients with LVEF ≥60% (n = 734), 61 deaths occurred (8.3%; range, 3.0% to 17.3%).

In the whole cohort, LVGLS was well associated with occurrence of death (area under the curve: 0.68). The best cutoff value identified was LVGLS of 14.7% (sensitivity, 60%; specificity, 70%). By comparison, LVEF depicted lesser association with occurrence of death (area under the curve: 0.56). In patients with severe AS (i.e., AVA <0.6 cm^2/m^2), area under the curve for LVGLS was 0.69.

TABLE 2 Population Characteristics (N = 1,067)

Age, yrs	74 ± 10
Body surface area, m^2	1.79 ± 0.26
Male, %	56
Comorbidities, %	
Coronary artery disease	26
Hypertension	63
Diabetes	28
Dyslipidemia	44
Echocardiographic data	
Indexed aortic valve area, cm^2/m^2	0.49 ± 0.17
Severe AS,* %	82
LVEF, %	63.5 ± 8
LVEF >60%, %	65
LV global longitudinal strain, %	16.2 ± 3.6

Values are mean ± SD or %. *Severe AS is defined as an indexed aortic valve area <0.6 cm^2/m^2.
AS = aortic stenosis; EF = ejection fraction; LV = left ventricular.

The relationship between LVGLS and risk of death is assessed using spline function. The spline curve suggests a marked increase risk of mortality when LVGLS decrease below 15% (Supplemental Figure 1).

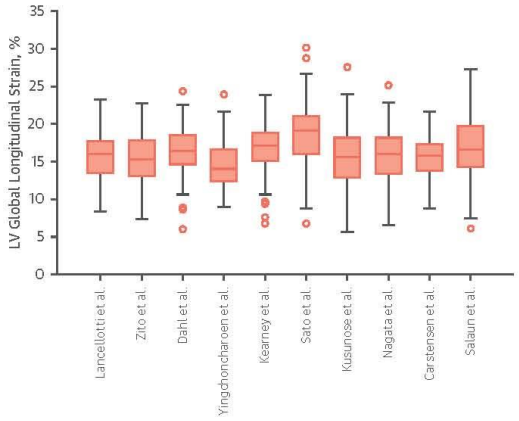
In studies performed with the GE machine, the predictive value of LVGLS was similar (area under the curve: 0.69) and the best cutoff value was 14.7% (sensitivity, 62%; specificity, 74%). The predictive value in studies without GE machine was lower (area under the curve: 0.62) and the best cutoff value was 11.9% with markedly lower sensitivity (35%) but higher specificity (86%).

In the whole cohort, impaired LVGLS <14.7% was found in 32.3% of patients, with significant difference between the studies (from 15.5% to 56%; $p < 0.0001$). Applying this cutoff value to all selected studies allowed to generate a forest plot (**Figure 3A**) showing that the risk of death for patients with LVGLS <14.7% was multiplied by >2.5 (HR: 2.62; 95% CI: 1.66 to 4.13; $p < 0.0001$), without significant heterogeneity ($I^2 = 18.3\%$; $p = 0.275$). The relationship between LVGLS <14.7% and mortality was also significant in patients with LVEF ≥60% (**Figure 3B**). With a stratification according to vendor (i.e., GE vs. others) (Supplemental Figure 2), similar results were found.

Because all patients from the Dahl et al. (18) study were referred for surgery, we performed a subanalysis excluding this study. Similar results than in the whole cohort were found (HR: 2.25; 95% CI: 1.47 to 3.43; $p < 0.0001$; $I^2 = 8.0\%$, $p = 0.369$).

In patients with severe AS (i.e., AVAi <0.6 cm^2/m^2), forest plot showed that the risk of death in patients with LVGLS <14.7% was higher than in the whole cohort (HR: 3.58; 95% CI: 1.84 to 6.99; $p < 0.0001$; $I^2 = 0$, $p < 0.0001$).

FIGURE 2 Distribution of LV Global Longitudinal Strain According to Studies



Circles indicate outliers. LV = left ventricular.

Using the cutoff of 14.7%, impaired LVGLS was associated with markedly reduced survival both in the whole cohort ($p < 0.0001$) (**Figure 4A**) and in patients with LVEF ≥60% ($p < 0.0001$) (**Figure 4B**). Patients with LVGLS >18% have similar survival (at 2 years, 97 ± 1%) than those with LVGLS between 16.2% and 18% (at 2 years: 95 ± 2%; $p = 0.445$) or even those with LVGLS between 14.7% and 16.2% (at 2 years 95 ± 2%; $p = 0.207$).

In patients with severe AS (i.e., AVAi <0.6 cm^2/m^2), 2-year survival was significantly lower in patients with impaired LVGLS than in those with preserved LVGLS (81 ± 4% vs. 94 ± 1%; $p < 0.0001$) (Supplemental Figure 3).

In multivariate analysis, after adjustment for age, gender, AVAi, and LVEF, impaired LVGLS (i.e., <14.7%) was a strong independent determinant of mortality (HR: 3.59; 95% CI: 2.16 to 5.98; $p < 0.0001$).

Adding impaired LVGLS to the multivariate model (i.e., including age, gender, AVAi, and LVEF) markedly improve its prediction (from chi square of 13.1 to chi square of 40.5). Comparing with LVEF, integrated discrimination improvement was positive for both LVGLS (i.e., as continuous variable) and LVGLS <14.7% suggesting its incremental prognostic value over LVEF (0.028 and 0.026, respectively).

PUBLICATION BIAS ASSESSMENT. Funnel plots, regarding impaired LVGLS and risk of death (Supplemental Figure 4), demonstrated significant asymmetry (Egger test; $p = 0.01$) suggesting potential presence of publication bias. Funnel plots analysis demonstrates that this asymmetry may be related to discrepancy in publication in favor of studies reporting large effect size despite small sample size or large variance. In contrast, Begg test demonstrated no significant risk of publication bias ($p = 0.18$).

DISCUSSION

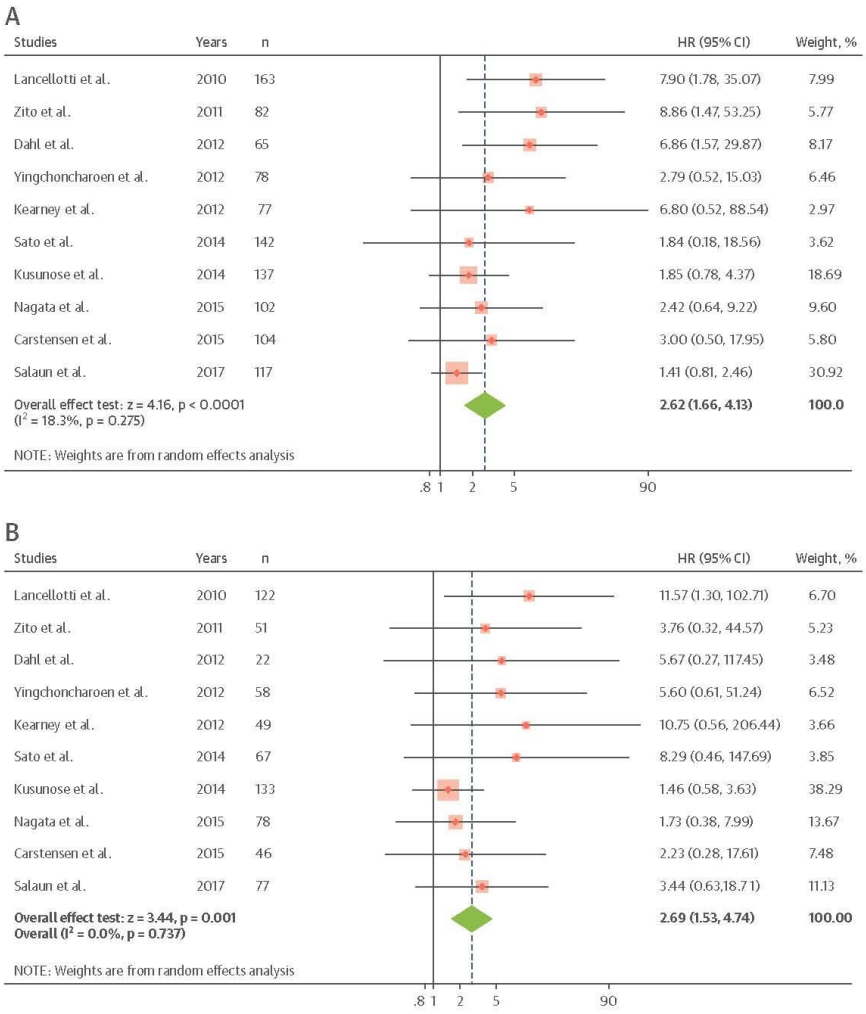
In asymptomatic patients with significant AS and preserved LVEF, the present individual participant data meta-analysis suggests that: 1) LVGLS is relatively homogeneous across available published cohorts; 2) LVGLS better than 20% is rare in this population; and 3) LVGLS is strongly associated with mortality, with >2.5-fold increase in risk of death in patients with impaired LVGLS. Of interest, the close independent relationship between LVGLS and mortality is sustained even when LVEF is ≥60%. A cutoff value of 14.7% seems to be associated with patients at a higher risk of death.

LV LONGITUDINAL FUNCTION AND MYOCARDIAL FIBROSIS. The alteration of LV longitudinal function occurs in parallel to AS severity (19), LV morphologic changes (20), LV myocardial damage, and fibrosis proliferation (11). Weidemann et al. (11) reported that the severity of myocardial fibrosis estimated with histologic analysis was associated with impairment of LV longitudinal shortening as assessed by mitral annulus displacement using M-mode echocardiography. In addition, the presence of LV myocardial fibrosis may predict the risk of lack of LV function recovery following aortic valve replacement (13) and outcome (6). Based on these studies, it seems that the development of LV fibrosis is the main pathophysiologic mechanism involved in the reduction in LV longitudinal shortening in patients with AS. Nevertheless, these findings were obtained in patients with surgical indications or with markedly reduced LVEF, limiting the clinical usefulness of LV longitudinal function assessment in these cohorts. Indeed, the LV longitudinal function evaluation could be more relevant to detect subclinical LV dysfunction and manage asymptomatic patients with preserved LVEF.

The presence of transthyretin cardiac amyloidosis (21), which in patients with AS is frequently associated with impaired longitudinal LV shortening without apical sparing, could also partially explain the reduction in LVGLS.

LVGLS DERIVED FROM SPECKLE TRACKING ECHOCARDIOGRAPHY. Speckle tracking echocardiography is a non-Doppler modality, angle-independent, allowing measurement of myocardial deformation

FIGURE 3 Forest Plot

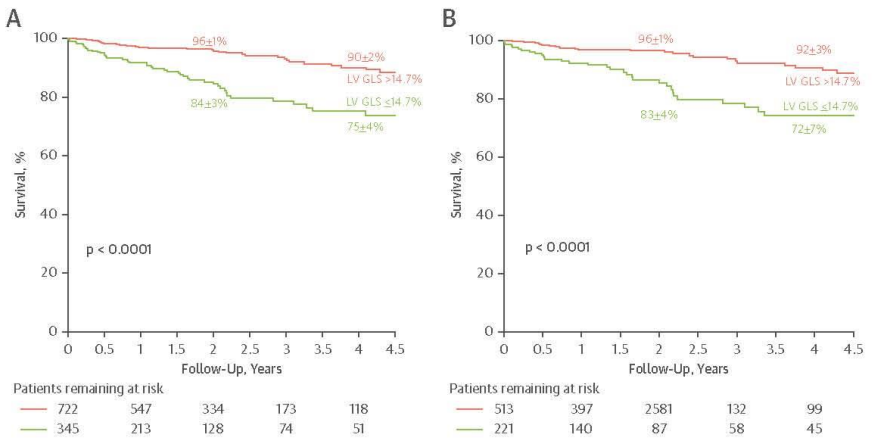


Forest plot reporting the pooled effect of impaired left ventricular global longitudinal strain (i.e., <14.7%) on mortality in the whole cohort **(A)** and in patients with left ventricular ejection fraction ≥60% **(B)**. CI — confidence interval; HR — hazard ratio.

(22). The quantification of LVGLS is now the most common application of speckle tracking echocardiography and has already demonstrated added diagnostic and prognostic value in a wide range of conditions including valvular heart disease (23). Moreover, LVGLS during exercise may identify LV dysfunction associated with the development of symptoms (24).

Derived from 2-, 3-, and 4-chamber apical views, LVGLS can be easily calculated with good feasibility and both interobserver and intraobserver reproducibility (25,26), even better than LVEF. The relative

FIGURE 4 Kaplan-Meier Survival Curves



Kaplan-Meier survival curves stratified according to left ventricular global longitudinal strain in the whole cohort **(A)** and in patients with left ventricular ejection fraction ≥60% **(B)**. Percentage in the graphs are survival rate at 2- and 4-year follow-up. LVGLS = left ventricular global longitudinal strain.

interobserver and intraobserver variability of GLS approximately varies from 5% to 8% according to vendors. By contrast, 8% and 10% of variability are reported for LVEF, respectively (25). Nevertheless, LVGLS remains load and geometry dependent and needs to be carefully interpreted in many cases.

LVGLS AND LVEF. The obvious advantages of LVGLS over LVEF are its ability to unmask subclinical LV dysfunction, to identify early structural and morphologic myocardial damage, and to better predict post-operative LV dysfunction and outcome (27). Many cardiac magnetic resonance studies recently reported myocardial alterations, despite preserved LVEF. The presence of LV late gadolinium enhancement has been highlighted in patients with various degrees of AS, despite normal LVEF (4–6). A graded relationship between AS severity and longer T1 time, regardless of LVEF (assessed using cardiac magnetic resonance), has been shown (5,7) and there have been good correlations between native T1 values and collagen volume fraction obtained by myocardial biopsies (7,28). Of interest, a large proportion of patients with AS and with high presence of LV late gadolinium enhancement or with markedly elevated T1 values still have preserved LV ejection. Furthermore, LVEF does not follow AS severity whereas LVGLS has been found to gradually worsen when AS becomes more severe (19). Altogether, these recent data highlight the superiority of LVGLS over LVEF to assess LV myocardial function and predict outcomes of asymptomatic patients with AS.

CLINICAL IMPLICATIONS. The present individual participant data meta-analysis shows, in a large cohort of patients, that LVGLS may have a close association with survival and could suggest a better risk stratification value than LVEF. However, the existing evidence has often considered aortic valve intervention in a composite endpoint, with the consequence that intervention influenced event-free survival. In the present study, LVGLS demonstrated its strong impact on mortality and, therefore, the crucial role that it may have in the risk stratification and management of patients with asymptomatic AS. The close relationship between death and impaired LVGLS suggests that this echocardiographic parameter could be implemented in future guideline recommendations, if the present results are confirmed by large multicenter studies. Indeed, a heart team discussion of early intervention (i.e., including transcatheter aortic valve replacement if necessary) in asymptomatic patients with preserved LVEF but impaired LVGLS <14.7% may be envisaged. Further confirmation about the need for intervention, related to myocardial morphologic and structural damage, may be obtained by performing cardiac magnetic resonance and assessment of the presence of late gadolinium enhancement and/or quantification of native T1. Furthermore, the use of exercise stress echocardiography in these patients may also be

discussed (29,30). Patients with good LVGLS >18% had an excellent outcome (i.e., 97 ± 1% 2-year survival) supporting a conservative approach with clinical and echocardiographic assessment every 1 to 2 years, in the absence of other indications for intervention or abnormality during exercise stress echocardiography. Our results show that the survival of patients with depressed LVGLS between 14.7% and 18% is similar to those with preserved LVGLS >18% up to 2 years follow-up. With worse LVGLS values beyond 14.7% a marked increase in mortality seems to occur. This may rather promote shorter follow-up intervals (every 6 to 12 months), to assess subtle changes in LVGLS and/or symptoms and to propose prompt intervention.

STUDY LIMITATIONS. This study holds similar limitations to all meta-analyses. However, the use of individual data rather than data derived from publication only may substantially improve the robustness of the reported results. Furthermore, the low degree of heterogeneity found indicates a relative consensus in the published data.

Although uncommon in asymptomatic patients with preserved LVEF, we cannot exclude the presence of low flow/low gradient AS in the present cohort.

The lack of subanalysis according to brain natriuretic peptide may limit our conclusion. However, this biomarker was not available in all selected studies and were not incorporated into guidelines when they were published.

The Egger and Begg tests produced discrepant results. However, analysis of the funnel plot suggests an asymmetry between studies' effect sizes and, therefore, a limited but potential publication bias. This is to be expected because positive studies may generally have higher chance to be published than negative ones. However, the studies selected in the present meta-analysis were positive on the basis of combined endpoints, including aortic valve intervention. Of note, half of studies selected were negative with regards to all-cause mortality, further limiting the potential publication bias.

We report all-cause mortality because it is more objective, especially in retrospective studies. Cardiovascular death is difficult to assess in retrospective studies (31) and was not available in all publications. The need to perform aortic valve intervention with class I indication as recommended in current guidelines is a frequent endpoint in patients with AS. However, the variety of centers and countries involved in the meta-analysis does not allow sufficient standardization to assess this endpoint.

Exercise testing aimed at confirming the asymptomatic status of patients was not systematically performed in all selected studies. Some apparently asymptomatic patients have abnormalities during exercise testing, and these may have been included in the meta-analysis.

Most studies included in the meta-analysis performed LVGLS measurement using a GE machine. Consequently, the present results could not be automatically transposed to all echocardiographs. However, LVGLS is known to have good reproducibility, limited difference between vendors, and to be superior to conventional echocardiographic measurements (25).

CONCLUSIONS

This individual participant data meta-analysis demonstrates the strong relationship between LVGLS and all-cause mortality in asymptomatic patients with AS and preserved LVEF. These results support the systematic measurement of LVGLS for the risk stratification and the management of these patients and may promote its use in clinical practice as an important additive parameter for decision-making. A LVGLS <14.7% could be considered as a trigger for further imaging investigations and for early intervention. Nonetheless, a limited but potential risk of publication bias may be present in current literature, suggesting the value of a large prospective international study for confirming this key impact of GLS for our patients with AS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prognostic value of LVGLS in patients with AS often arises from small, single-center studies, including heterogeneous grade and stage of AS. Impaired LVGLS (i.e., <14.7%) is strongly associated with mortality in asymptomatic patients with significant AS. This is confirmed in patients with severe AS (i.e., indexed aortic valve area <0.6 cm^2/m^2) and in patients with LVEF >60%. This individual participant data meta-analysis confirmed the usefulness of LVGLS in the management and risk stratification of these patients and may have incremental value as compared with the LVEF.

TRANSLATIONAL OUTLOOK: The effort to improve reproducibility of LVGLS measurement between vendors should be sustained. Large multicenter prospective study aiming to confirm our results is now mandatory. The usefulness of LVGLS, as trigger for surgery, should also be tested in experimental trial, more particularly to test its benefit as compared with LVEF.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

3. Dahl JS, Eleid MF, Michelena HI, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. Circ Cardiovasc Imaging 2015;8. https://doi.org/10.1161/CIRCIMAGING.114.002917.

4. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271–9.

5. Chin CWL, Everett RJ, Kwiecinski J, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. J Am Coll Cardiol Img 2017;10:1320–33.

6. Barone-Rochette G, Pierard S, de Meester de RC, et al. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. J Am Coll Cardiol 2014;64:144–54.

7. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart Br Card Soc 2013;99:932–7.

8. Lee H, Park J-B, Yoon YE, et al. Noncontrast myocardial T1 mapping by cardiac magnetic resonance predicts outcome in patients with aortic stenosis. J Am Coll Cardiol Img 2018;11:974–83.

9. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. J Am Coll Cardiol 2018;71:860–71.

10. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. J Am Coll Cardiol 2018;71:1313–21.

11. Weidemann F, Herrmann S, Stork S, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009;120:577–84.

12. Mele D, Censi S, La Corte R, et al. Abnormalities of left ventricular function in asymptomatic patients with systemic sclerosis using Doppler measures of myocardial strain. J Am Soc Echocardiogr 2008;21:1257–64.

13. Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56:278–87.

14. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657–65.

15. Pencina MJ, D'Agostino RB, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med 2012;31:101–13.

16. Sato K, Seo Y, Ishizu T, et al. Prognostic value of global longitudinal strain in paradoxical low-flow, low-gradient severe aortic stenosis with preserved ejection fraction. Circ J Off J Jpn Circ Soc 2014;78:2750–9.

17. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging 2012;5:719–25.

18. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging 2012;5:613–20.

19. Ng AC, Delgado V, Bertini M, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J 2011;32:1542–50.

20. Takeda S, Rimington H, Smeeton N, Chambers J. Long axis excursion in aortic stenosis. Heart 2001;86:52–6.

21. Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879–87.

22. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol 2011;12:167–205.

23. Galli E, Lancellotti P, Sengupta PP, Donal E. LV mechanics in mitral and aortic valve diseases: value of functional assessment beyond ejection fraction. J Am Coll Cardiol Img 2014;7:1151–66.

24. Donal E, Thebault C, O'Connor K, et al. Impact of aortic stenosis on longitudinal myocardial deformation during exercise. Eur J Echocardiogr 2011;12:235–41.

25. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt J-U. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28:1171–81.

26. Mirea O, Pagourelias ED, Duchenne J, et al. Variability and reproducibility of segmental longitudinal strain measurement: a report from the EACVI-ASE Strain Standardization Task Force. J Am Coll Cardiol Img 2018;11:15–24.

27. Kafa R, Kusunose K, Goodman AL, et al. Association of abnormal postoperative left ventricular global longitudinal strain with outcomes in severe aortic stenosis following aortic valve replacement. JAMA Cardiol 2016;1:494–6.

28. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138–44.

29. Huded CP, Masri A, Kusunose K, et al. Outcomes in asymptomatic severe aortic stenosis with preserved ejection fraction undergoing rest and treadmill stress echocardiography. J Am Heart Assoc 2018;7. https://doi.org/10.1161/JAHA.117.007880.

30. Marechaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J 2010;31:1390–7.

31. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618–20.

32. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364–71.

33. Zito C, Salvia J, Cusma-Piccione M, et al. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. Am J Cardiol 2011;108:1463–9.

34. Kearney LG, Lu K, Ord M, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging 2012;13:827–33.

35. Kusunose K, Goodman A, Parikh R, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ Cardiovasc Imaging 2014;7:938–45.

36. Carstensen HG, Larsen LH, Hassager C, Kofoed KF, Jensen JS, Mogelvang R. Basal longitudinal strain predicts future aortic valve replacement in asymptomatic patients with aortic stenosis. Eur Heart J Cardiovasc Imaging 2016;17:283–92.

37. Nagata Y, Takeuchi M, Wu VC-C, et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. J Am Coll Cardiol Img 2015;8:235–45.

38. Salaun E, Casalta A-C, Donal E, et al. Apical four-chamber longitudinal left ventricular strain in patients with aortic stenosis and preserved left ventricular ejection fraction: analysis related with flow/gradient pattern and association with outcome. Eur Heart J Cardiovasc Imaging 2018;19:868–78.

KEY WORDS aortic valve stenosis, left ventricular global longitudinal strain, meta-analysis, mortality

APPENDIX For a supplemental table and figures, please see the online version of this paper.

Annexes 3: Subclinical LV Dysfunction in Aortic Stenosis.

JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 1, 2019

REVIEW

STATE-OF-THE-ART PAPER

Assessment of Subclinical Left Ventricular Dysfunction in Aortic Stenosis

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ABSTRACT

Left ventricular (LV) systolic dysfunction is an adverse consequence of the pressure overload of severe aortic stenosis (AS). The enlargement of the interstitial space with reactive fibrosis and subsequently with replacement fibrosis and cell death has been suggested to be the main driver of the transition to symptoms, heart failure, and adverse cardiovascular events even after aortic valve replacement (AVR). Early and accurate recognition of myocardial dysfunction offers the potential to optimize the timing of intervention in severe AS. In the asymptomatic patient, an LV ejection fraction (EF) cutpoint of <50% has been used for this purpose. However, in most asymptomatic patients, an LVEF <50% is uncommon, and patients with an LVEF of 50% to 59% fare almost as badly. Moreover, the presence of a small LV cavity, the reliability and automation of the global longitudinal strain (GLS) signal, and the independent prognostic role of GLS are reasons why GLS could be expected to be a better marker of subclinical LV dysfunction in these patients. This review seeks to define whether the existing EF cutoff in AS should be modified or whether GLS should replace it as the marker of subclinical LV dysfunction. (J Am Coll Cardiol Img 2019;12:163–71) © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Left ventricular (LV) systolic dysfunction is recognized to be an adverse result of the pressure overload that occurs in severe aortic stenosis (AS). From a hemodynamic standpoint, AS increases LV afterload, and the natural response of the LV to the increased wall stress due to pressure overload is concentric remodeling, increase in LV mass, and development of left ventricular hypertrophy (LVH), which maintains wall stress and cardiac output. Although this appears to be compensatory in the early stages, preclinical studies have suggested that cardiac performance can be preserved in the absence of hypertrophy (1). LVH is associated with impaired compliance, higher filling pressure, oxygen supply–demand mismatch, and myocardial ischemia (2). Moreover, the LVH response is progressively followed by enlargement of the interstitial space with reactive fibrosis and, at a later stage, with replacement fibrosis and cell death. This mechanism is thought to be a major driver of the transition to symptoms, heart failure, and adverse cardiovascular events, and fibrosis is associated with heart failure, arrhythmias, and the resulting mortality risk even after aortic valve replacement (AVR). Early and

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

CMR = cardiac magnetic resonance

GLS = global longitudinal strain

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

accurate recognition of myocardial dysfunction offers the potential to optimize the timing of intervention in severe AS.

Traditionally, LV systolic function has been expressed in terms of left ventricular ejection fraction (LVEF), referring to the fraction of LV end-diastolic volume ejected during systole. It is the most widely used measure of assessment of LV systolic function, is very familiar to patients and clinicians, and has been extensively used in clinical trials as well as in guideline recommendations for various diseases. LVEF is assessable by multiple imaging modalities that are based on similar principles of measurement. LVEF is a useful surrogate marker of LV function in many cardiac diseases and is ubiquitous among guidelines relating to a variety of topics.

This review seeks to define whether the existing LVEF cutoff in AS should be modified or whether global longitudinal strain (GLS) should replace it as the marker of subclinical LV dysfunction.

LVEF WORKS, BUT THE THRESHOLD FOR INTERVENTION IS INCORRECT

In the absence of coronary artery disease, the LVEF remains preserved in AS, and the concomitant presence of severe AS and reduced LVEF (<50%) is uncommon (3), especially when patients are still asymptomatic. Thus, although the Class I indication for aortic valve intervention is unquestionable in severe AS with depressed LV function evidenced by reduced EF (4,5), in the vast majority of patients, symptoms occur well before a reduction in LVEF. However, patients adapt their lifestyle to reduced functional capacity, so symptoms in patients with AS may be difficult to detect. Thus, a strategy based on waiting for LVEF to fall to <50% to indicate aortic valve intervention may lead to suboptimal operative and post-operative outcome. Moreover, LVEF has a number of limitations that have led to decades of intensive research to identify markers that could replace LVEF.

Multiple studies documented the independent prognostic value of LVEF in predicting outcomes in patients with AS (3,6–8) as well as with other cardiac conditions. Thus, LVEF persists as the preferred measure of LV function and still plays a pivotal role in the evaluation of any patient with AS.

According to both the American College of Cardiology/American Heart Association and European Society of Cardiology valvular heart disease guidelines, LV systolic impairment is considered a Class I indication for AVR in severe AS, even in the patient without symptoms (9,10), and a specific LVEF cutpoint of <50% has been used for this purpose. There are problems with this approach. First, echocardiography is the most widely used method of determining LVEF, and the guideline recommendations using echocardiography indicate that LVEF <52% for men and <54% for women should be considered abnormal (11), rather than the cutpoint of LVEF <50% as specified in valvular heart disease guidelines. Second, remarkably few data exist to substantiate this particular cutpoint as a threshold for intervention in severe AS. In one of the first papers describing the effect of LVEF after AVR, O'Toole et al. (12) gathered a cohort of 93 patients with AS, aortic regurgitation, and mixed AS/aortic regurgitation who had LVEF estimated by ventriculography. Although not significant, there was a trend toward increased mortality in the subset of patients with AS and LVEF <50%, and the authors concluded that depressed LVEF might cause a moderate increase in post-operative mortality. Subsequent studies, comprising mostly symptomatic patients, have shown that reduced EF, variably defined, was a major predictor of survival in patients with severe AS (13,14). It should be noted that the occurrence of LVEF <50% in severe AS in the absence of symptoms is rare, with a prevalence of only 0.4% (15). Consequently, in studies of the natural history of asymptomatic patients with severe AS, few patients have been noted to have LVEF <50% (16). However, when LVEF is <50% in severe AS, prognosis is worse, with or without AVR (15).

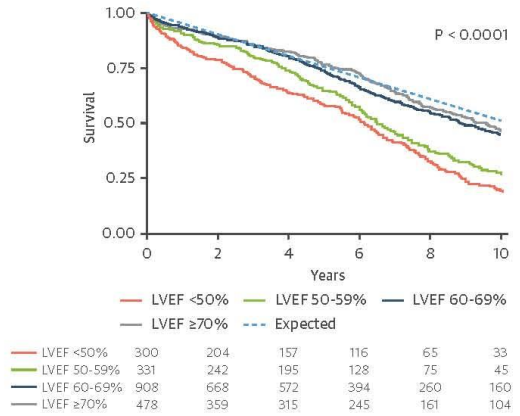
The paucity of available data supporting the selection of LVEF <50% as the cutpoint for referral to AVR led to studies of the impact of pre-operative LVEF on outcome after AVR in patients with severe AS. Dahl et al. (3) stratified 2,017 severe AS patients undergoing AVR into 4 groups according to LVEF: LVEF <50%, LVEF 50% to 59%, LVEF 60% to 69%, and LVEF >70%. In 300 patients (15%), LVEF was <50%, and these patients were characterized by having increased LV mass, low relative wall thickness, and larger LV cavities consistent with eccentric hypertrophy. Similar but less extensive changes were also present in patients with LVEF 50% to 59%. Patients with LVEF <50% experienced the worst outcome, with a 5-year mortality rate of 41%, although patients with LVEF 50% to 59% also experienced increased mortality (5-year all-cause mortality rate 35%) (**Figure 1**). These findings were consistent, irrespective of the occurrence of ischemic heart disease or presence of symptoms. In the same

population, 5-year all-cause mortality rates increased with decreasing LVEF in an inverse linear relationship (Figure 2). These findings suggested that not only patients with LVEF <50% but also those with LVEF 50% to 59% had a less favorable post-operative outcome. In line with these results, Capoulade et al. (17) demonstrated in more than 1,000 consecutive AS patients that the best LVEF cutpoint value for all-cause mortality was 56%. Further corroborating these findings, Ito et al. (7) recently demonstrated in 928 consecutive patients with severe AS that patients with LVEF 50% to 59% had increased mortality compared with those with LVEF >60% irrespective of whether patients underwent AVR or not (7). This study showed that in patients with serial echocardiograms who present with LVEF <50% at the time of diagnosis of severe AS, LVEF had begun to decrease even when AS was moderate. An LVEF of 50% to 60% at the time that AS was moderate predicted further deterioration of LVEF. The findings from these studies thus suggest that the threshold of LVEF <50% may be too low and indicate that reduced LV function may already be present when LVEF is 50% to 59%.

This "supranormal" threshold seen in AS may reflect that patients with severe AS have smaller cavities as a consequence of LV remodeling, requiring higher LVEF to preserve stroke volume. Failure to keep LVEF in the "supranormal" range may play an important role in the development of low-flow low-gradient AS with preserved LVEF, a condition with a poor prognosis compared with high-gradient AS patients. Although low-flow low-gradient AS is partly the result of progressive LV remodeling that leads to small concentric remodeled LV cavities, the decrease in stroke volume is accentuated by a decline of LVEF from supranormal ranges to normal ranges (18).

Despite its known limitations, the familiarity and wide availability of LVEF as a means of assessing systolic function provide ongoing importance to its role in assessment of the patient with AS. Nonetheless, to identify patients with subclinical LV dysfunction and who are at risk of poor outcomes, an LVEF threshold of <50% is inadequate. As risk has been shown to be increased above the standard LVEF cutpoint, a safer threshold would be LVEF <60%, particularly when the LV cavity is small (3,7,17). Because of the variability between imaging modalities in determining LVEF, use of a single modality is optimal for serial assessment of the individual patient (19). Finally, despite a worse outcome when LVEF is reduced, this should not be used as a reason for denying AVR, which often leads to improved systolic function and remains the only effective treatment for severe AS.

FIGURE 1 Outcomes Associated With LVEF Range in AS



Overall survival is shown as a function of pre-operative LVEF. The expected survival is based on mortality rates of the Minnesota white population with a similar age and sex (11). Patients with left ventricular ejection fraction (LVEF) <50% fare the worst, but those with LVEF from 50% to 59% have an outcome worse than expected. Patients with an LVEF ≥60% have a similar outcome to the remainder of the population.

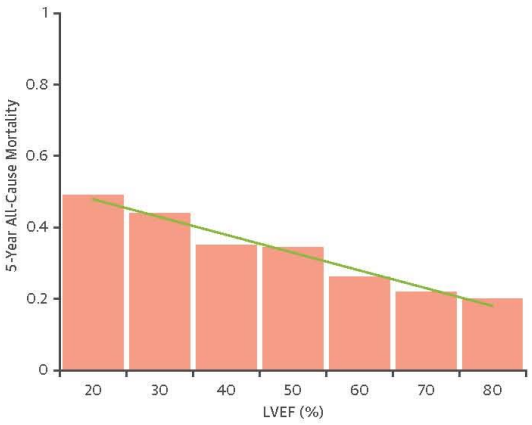
ROLE OF GLS IN ASSESSMENT OF SUBCLINICAL LV DYSFUNCTION IN AS

Despite the almost universal understanding and widespread use of LVEF, it has important limitations. It is load dependent (20,21) due to the mechanisms described by Starling et al. (22) and demonstrates imperfect reproducibility (23). There exists an independent relationship between LVEF and relative wall thickness; thus, for a similar extent of intrinsic myocardial shortening, the LVEF will tend to increase in relation to the extent of LV concentric remodeling (24). LVEF may thus be maintained despite reduced myocardial contractility by the use of preload reserve (25) or changes in LV geometry (26). In contrast, a decreased LVEF may occur in the setting of preserved contractility due to afterload mismatch (13,25,27,28) but could also represent a failing LV (13). Thus, the interpretation of LVEF as a marker of LV contractility may be challenging in valvular diseases, where changes in afterload and preload are predominant.

Impairments of LV structure and function are related to symptom severity and outcome in patients with AS, but as in other circumstances of "subclinical" dysfunction, LVEF is not an ideal parameter.

Specifically, in AS, EF is poorly correlated with AS severity parameters, both at rest or during exercise,

FIGURE 2 Unadjusted 5-Year All-Cause Mortality Rates in 2,017 Patients With Severe Aortic Stenosis Undergoing Surgical Aortic Valve Replacement



Patients were divided into 7 groups according to pre-operative left ventricular ejection fraction (LVEF). The inverse relationship between LVEF and outcome is evident across a range of LVEF.

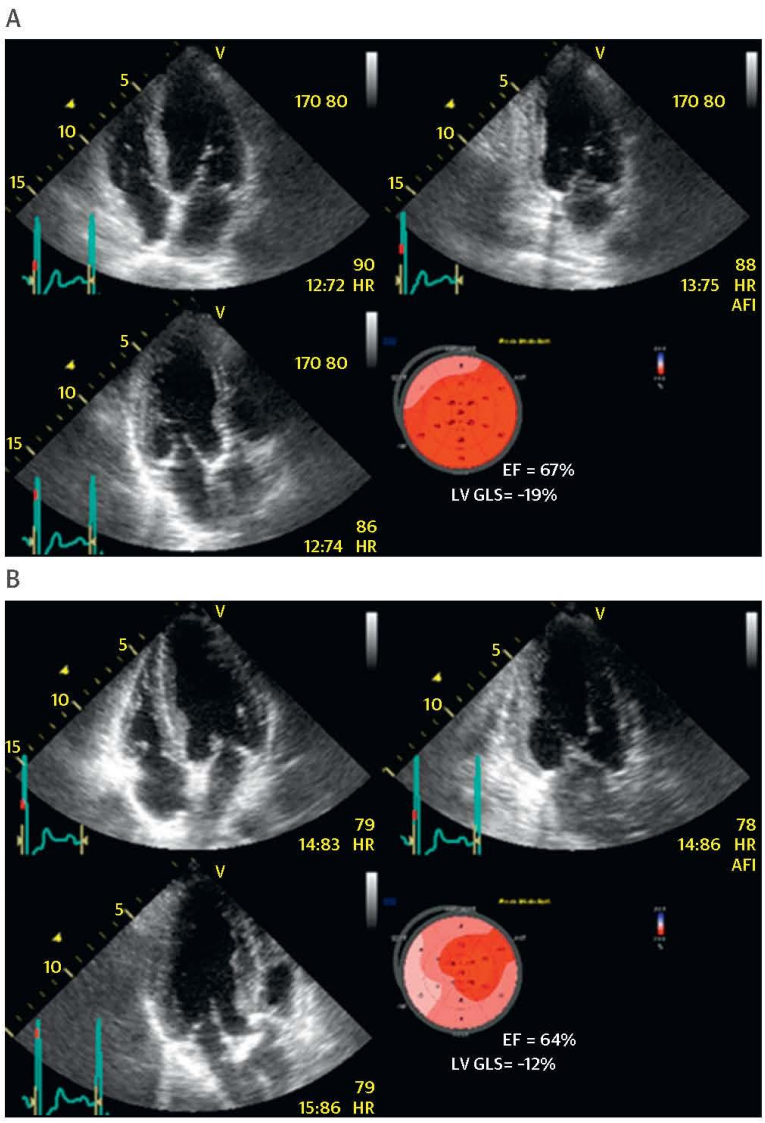
and it has a low negative predictive value to detect LV myocardial damage. However, many other parameters have been identified as useful for the risk stratification both before and after intervention, including LV morphological and functional parameters other than LVEF (29). Indeed, the presence of concentric remodeling, increased LV mass, and LVH are powerful markers of poor outcome, and even residual elevation of LV mass after intervention leads to reduced post-operative survival (30). These considerations support the contention that focus on an LVEF <50% is overly simplistic in an era when the management of AS has evolved toward more complex decision-making and preservation of LV function.

The era of tissue characterization with cardiac magnetic resonance (CMR) has provided new insights into LV responses to AS. Late gadolinium enhancement (LGE) has been identified in patients with various degrees of AS severity, despite normal LVEF (31–33). In addition, the use of myocardial longitudinal magnetization relaxation time (native T_1 time) allows more accurate assessment of diffuse changes in the interstitial space (34). A graded relationship between AS severity and longer T_1 time has been shown to be independent of CMR-derived LVEF (32,35), and good correlations have been shown between native T_1 values and collagen volume fraction obtained by myocardial biopsies (35). A large proportion of patients with significant degrees of LV LGE or with markedly elevated T_1 values still have preserved LVEF. Furthermore, both LGE and T_1 values have been associated with outcome in patients with AS (31,33). These studies suggest that: 1) preserved LVEF does not mean preserved LV function and normal morphology; and 2) the use of LVEF <50% as a trigger for intervention very likely leads to operation in patients with LV myocardial abnormalities. The current published data demonstrate that LVEF does not effectively differentiate diffuse from focal fibrosis and therefore does not provide appropriate assessment of LV morphological and functional changes. As CMR tissue characterization is not a feasible option for the increasing numbers of patients with AS, a feasible and lower cost alternative is needed.

In this regard, the use of LVGLS, derived from speckle tracking echocardiography (36), provides a semiautomated quantification of myocardial deformation (strain and strain rate) and may be an appropriate early marker of subclinical LV dysfunction. A complete evaluation of LV mechanics would include measurement of deformation in the 3 planes (longitudinal, radial, and circumferential) as well as rotation and torsion (37). Of these parameters, the feasibility of LVGLS calculation from standard 2-, 3-, and 4-chamber apical views has made this parameter the most common application of speckle tracking. GLS provides additional diagnostic and prognostic value in a wide range of conditions including valvular heart disease (38). Its interobserver and intraobserver variability (5% to 8% relative difference) compares favorably with 8% to 10% for LVEF (39,40).

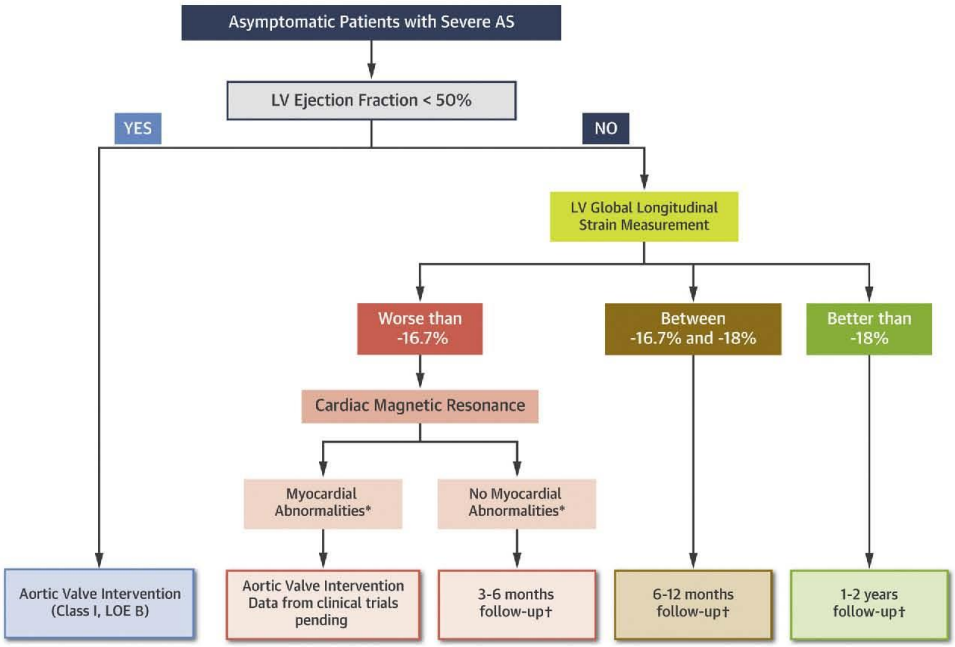
The association of deformation indexes with invasive markers of LV contractility as dp/dt (41) and the end-systolic pressure-volume relationship (42) has led to the belief that GLS might be used as a surrogate of LV contractility. However, recent studies have demonstrated that GLS, similar to LVEF, also has important load dependency (43,44) and thus is also affected by AS severity (45,46). The inability of LVEF and GLS to reflect LV contractility emphasizes one of the principal challenges of cardiac imaging. Imaging measures events occurring during the ejection phase, while contractility is the consequence of degradation/activation of actin myosin bonds that lead to building of systemic pressures in the LV and occurs during isovolumic contraction, a phase not easily measured with imaging. Newer methods of assessing myocardial stiffness may facilitate the assessment of cardiac function in AS but require further study (47).

FIGURE 3 Asymptomatic Patients With Similar LVEF and Markedly Different GLS



In both cases, the most impaired longitudinal strain is located in basal segments (bull's eye) underlining the typical gradient between base and apex in decreasing longitudinal function. **(A)** A 78-year-old woman with mean pressure gradient 56 mm Hg, aortic valve area 0.75 cm^2, left ventricular (LV) ejection fraction (EF) 67%, and LV global longitudinal strain (GLS) −19%. **(B)** A 75-year-old woman with mean pressure gradient 59 mm Hg, aortic valve area 0.71 cm^2, LVEF 64%, and LVGLS −12%.

CENTRAL ILLUSTRATION **Proposed Algorithm for the Management of Patients With Asymptomatic Severe Aortic Stenosis**



Dahl, J.S. et al. J Am Coll Cardiol Img. 2019;12(1):163–71.

This approach integrates the use of left ventricular (LV) global longitudinal strain derived from speckle tracking echocardiography. *The presence of important late gadolinium enhancement, delayed native T_1, or elevated extracellular volume in cardiac magnetic resonance. †Only if there is no other current guidelines indication for aortic valve intervention. LOE = Level of Evidence.

Depression of LVGLS in patients with AS and preserved LVEF (Figure 3) is an early sign of LV dysfunction and is attributed to the susceptibility of longitudinal subendocardial fibers to myocardial damage and interstitial collagen deposition. Furthermore, the gradient of decreasing myocardial fibrosis from the base to the apex of the LV, evidenced by amount of LGE during CMR, is inversely correlated with peak systolic longitudinal strain (48), which may show a pattern of apical sparing (Figure 3).

The degree of impairment of LVGLS worsens as AS becomes more severe (46), in contrast to the deterioration of LVEF at a later stage in the progression of AS. Ng et al. (46) showed that LVGLS worsened significantly from sclerosis to severe AS (from 20% to 15%), whereas LVEF remained preserved and did not change (from 62% to 61%). Furthermore, impaired LVGLS is strongly associated with requirement of aortic valve intervention, post-operative cardiac events, and survival in patients with AS, irrespective of LVEF and symptoms. In a recent individual participant data meta-analysis of asymptomatic AS patients with preserved LVEF (49), the median LVGLS was −16.2% (interquartile range: −18.4% to −13.5%). These results confirm that LVGLS is a powerful marker of mortality in asymptomatic patients with AS and preserved LVEF (area under the curve: 0.68) with homogeneity between studies. Patients with LVGLS above the best cutoff value for prediction of death in the meta-analysis (GLS −14.7%) had a >2.5-fold increment of mortality. However, driven by the remaining small variability of GLS between vendors

and the recognition that outcome of patients with AS is driven by a combination of factors including AS severity, abnormalities of the aorta (e.g., reduced compliance), and upstream consequences of AS (i.e., on LV, left atrium, and right ventricular size and function), it is unlikely that a specific number will be key.

Aortic valve intervention allows regression of diffuse fibrosis and myocardial cellular hypertrophy, and this improvement is accompanied by structural, functional, and biomarker changes (50). The value of GLS is not limited to pre-operative patients. About 20% of patients who survive >1 year after AVR have abnormal postoperative LVGLS, despite preserved LVEF. This finding is independently associated with adverse events, and its presence despite LV mass regression suggests that it reflects an interstitial change. Experimental studies show that focal fibrosis and cardiomyocyte loss persists after AVR, suggesting the importance of intervention before the occurrence of irreversible myocardial damage.

Paradoxical low-flow low-gradient severe AS is a well-known distinct entity of AS (51) in which preserved LVEF masks LV dysfunction. LGE has been frequently identified in this subgroup of patients (52), and impaired LV longitudinal function and reduced GLS are also frequently observed—to a similar extent to their manifestation in patients with depressed LVEF (53). Consequently, LVGLS seems able to unmask occult longitudinal systolic dysfunction, not revealed by LVEF, and may be useful to explain the "paradox" (i.e., resolve the discrepancy of reduced LV flow despite preserved LVEF).

The most recent American College of Cardiology/American Heart Association and European Society of Cardiology valvular heart disease guidelines do not include a role for GLS assessment. However, the cumulative evidence demonstrating its powerful prognostic value may promote its incorporation in the next recommendation. In the meanwhile, however, a proposed algorithm could be used in asymptomatic patients with preserved LVEF (**Central Illustration**). In the absence of other current guideline indications for aortic valve intervention or exercise stress echocardiography abnormalities, the measurement of impaired LVGLS worse than <14.7% may be one of many features to guide a decision to intervene. If the optimal management is still unclear, patients with impaired GLS could be further studied using CMR; midwall LGE, abnormal native T_1, or increased extracellular volume all provide evidence of LV impairment that could prompt surgery. In the absence of such CMR findings, close follow-up could be recommended (i.e., 3 to 6 months) to detect any changes in symptoms or LV function.

TAKE-HOME MESSAGES

Consistent with the modern view of AS as a disease of the LV as well as the valve, the authors of this review emphasize the importance of LV dysfunction in decision-making about AS. At issue is how best to measure LV function:

- The current guideline use of LVEF <50% is clearly wrong in an era where the measurement guidelines reference normal cutoffs of 52% in men and 54% in women (11).
- An EF <60% is associated with increased risk (3,7,17).
- A "preserved" EF in the presence of a small LV cavity equates to a low stroke volume—the primary problem in LFLG AS. The fundamental problem that a change of EF threshold cannot address is that it is difficult to assess the status of the LV without knowing the size of the LV cavity.
- LVGLS is a more reliable parameter than standard 2-dimensional LVEF. Despite its influence by preload and afterload, it is sensitive enough to unmask patients with structural and functional myocardial damage that LVEF cannot reveal.
- A reduced LVGLS corresponds to the presence of myocardial structural alterations by CMR and may promote early intervention in asymptomatic patients with severe AS.
- An impaired LVGLS despite preserved LVEF is a powerful predictor of outcome.

CONCLUSIONS

The central place of LVEF <50% in the assessment of LV function in patients with AS may be responsible for delays in aortic valve intervention in patients who could benefit and probably contributes to suboptimal postoperative clinical outcome in some patients. The current published data provide evidence to support the implementation of LVGLS in future recommendations.

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REFERENCES

1. Bartunek J, Weinberg EO, Tajima M, et al. Chronic N(G)-nitro-L-arginine methyl ester-induced hypertension: novel molecular adaptation to systolic load in absence of hypertrophy. Circulation 2000;101:423–9.

2. Bache RJ, Zhang J, Murakami Y, et al. Myocardial oxygenation at high workstates in hearts with left ventricular hypertrophy. Cardiovasc Res 1999; 42:616–26.

3. Dahl J, Eleid M, Michelena H, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. Circ Cardiovasc Imaging 2015;8:e002917.

4. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

5. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

6. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. J Am Coll Cardiol 1990;15:1012–7.

7. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. J Am Coll Cardiol 2018;71:1313–21.

8. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged > or =80 years. Eur J Cardiothorac Surg 2006;30:722–7.

9. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:372–92.

10. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol 2014;63:2438–88.

11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

12. O'Toole JD, Geiser EA, Reddy PS, Curtiss EI, Landfair RM. Effect of preoperative ejection fraction on survival and hemodynamic improvement following aortic valve replacement. Circulation 1978;58:1175–84.

13. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. Circulation 1980;62:42–8.

14. Vaquette B, Corbineau H, Laurent M, et al. Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. Heart 2005;91:1324–9.

15. Henkel D, Maalouf J, Connolly H, et al. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: characteristics and outcomes. J Am Coll Cardiol 2012;60: 2355–9.

16. Pellikka P, Sarano M, Nishimura R, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111: 3290–5.

17. Capoulade R, Le Ven F, Clavel MA, et al. Echocardiographic predictors of outcomes in adults with aortic stenosis. Heart 2016;102: 934–42.

18. Dahl J, Eleid M, Pislaru S, Scott C, Connolly H, Pellikka P. Development of paradoxical low-flow, low-gradient severe aortic stenosis. Heart 2015; 101:1015–23.

19. Pellikka PS, Holly TA, Lin G, et al. Variability in ejection fraction measured by echocardiography, gated single-photon emission computed tomography and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. JAMA 2018;1(4):e181456.

20. Merillon JP, Neukirch F, Motte G, et al. The left ventricular end-systolic pressure-volume ratio. Studies during changes in load and inotropism in the human. Eur Heart J 1981;2:41–8.

21. Merillon JP, Ennezat PV, Guiomard A, Masquet-Gourgon C, Aumont MC, Gourgon R. Left ventricular performance is closely related to the physical properties of the arterial system: landmark clinical investigations in the 1970s and 1980s. Arch Cardiovasc Dis 2014;107:554–62.

22. Starling EH, Visscher MB. The regulation of the energy output of the heart. J Physiol 1927;62: 243–61.

23. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol 2004;44:1030–5.

24. Dumesnil JG, Shoucri RM. Effect of the geometry of the left ventricle on the calculation of ejection fraction. Circulation 1982;65:91–8.

25. Krayenbuehl HP, Hess OM, Ritter M, Monrad ES, Hoppeler H. Left ventricular systolic function in aortic stenosis. Eur Heart J 1988;9 Suppl E:19–23.

26. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195–202.

27. Ross J Jr. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976; 18:255–64.

28. Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. Circulation 1979;59:679–88.

29. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. J Am Coll Cardiol Img 2018;11: 260–74.

30. Gavina C, Falcao-Pires I, Pinho P, et al. Relevance of residual left ventricular hypertrophy after surgery for isolated aortic stenosis. Eur J Cardiothorac Surg 2016;49:952–9.

31. Barone-Rochette G, Pierard S, De Meester de Ravenstein C, et al. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. J Am Coll Cardiol 2014;64: 144–54.

32. Chin CWL, Everett RJ, Kwiecinski J, et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. J Am Coll Cardiol Img 2017;10: 1320–33.

33. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271–9.

34. Podlesnikar T, Delgado V, Bax JJ. Cardiovascular magnetic resonance imaging to assess myocardial fibrosis in valvular heart disease. Int J Cardiovasc Imaging 2018;34:97–112.

35. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932–7.

36. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011; 24:277–313.

37. D'Hooge J, Heimdal A, Jamal F, et al. Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr 2000;1:154–70.

38. Galli E, Lancellotti P, Sengupta PP, Donal E. LV mechanics in mitral and aortic valve diseases: value of functional assessment beyond ejection fraction. J Am Coll Cardiol Img 2014;7:1151–66.

39. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE inter-vendor comparison study. J Am Soc Echocardiogr 2015;28:1171–81.e2.

40. Mirea O, Pagourelias ED, Duchenne J, et al. Variability and reproducibility of segmental longitudinal strain measurement: a report from the EACVI-ASE Strain Standardization Task Force. J Am Coll Cardiol Img 2018;11:15–24.

41. Weidemann F, Jamal F, Kowalski M, et al. Can strain rate and strain quantify changes in regional systolic function during dobutamine infusion,

B-blockade, and atrial pacing—implications for quantitative stress echocardiography. J Am Soc Echocardiogr 2002;15:416–24.

42. Greenberg NL, Firstenberg MS, Castro PL, et al. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. Circulation 2002;105:99–105.

43. Yotti R, Bermejo J, Benito Y, et al. Validation of noninvasive indices of global systolic function in patients with normal and abnormal loading conditions: a simultaneous echocardiography pressure-volume catheterization study. Circ Cardiovasc Imaging 2014;7:164–72.

44. Reant P, Metras A, Detaille D, et al. Impact of afterload increase on left ventricular myocardial deformation indices. J Am Soc Echocardiogr 2016; 29:1217–28.

45. Kowalski M, Herbots L, Weidemann F, et al. One-dimensional ultrasonic strain and strain rate imaging: a new approach to the quantitation of regional myocardial function in patients with aortic stenosis. Ultrasound Med Biol 2003;29: 1085–92.

46. Ng AC, Delgado V, Bertini M, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J 2011;32:1542–50.

47. Pislaru C, Alashry MM, Thaden JJ, Pellikka PA, Enriquez-Sarano M, Pislaru SV. Intrinsic wave propagation of myocardial stretch, a new tool to evaluate myocardial stiffness: a pilot study in patients with aortic stenosis and mitral regurgitation. J Am Soc Echocardiogr 2017;30:1070–80.

48. Hoffmann R, Altiok E, Friedman Z, Becker M, Frick M. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography in comparison to late gadolinium enhancement cardiac magnetic resonance for analysis of myocardial fibrosis in severe aortic stenosis. Am J Cardiol 2014;114:1083–8.

49. Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. Eur Heart J Cardiovasc Imaging 2016;ii:225.

50. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. J Am Coll Cardiol 2018;71:860–71.

51. Magne J, Mohty D. Paradoxical low-flow, low-gradient severe aortic stenosis: a distinct disease entity. Heart 2015;101:993–5.

52. Herrmann S, Stork S, Niemann M, et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J Am Coll Cardiol 2011;58:402–12.

53. Adda J, Mielot C, Giorgi R, et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 2012;5:27–35.

KEY WORDS aortic stenosis, ejection fraction, LV function, strain

Annexes 4: First-phase LV Ejection Fraction: a Small Step for Myocardial Assessment, a Big Leap for Aortic Stenosis.

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EDITORIAL

First-phase left ventricular ejection fraction: a small step for myocardial assessment, a big leap for aortic stenosis

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This editorial refers to 'Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis', by E Einarsen *et al.*, pp. 650–7.

The quest of the most appropriate surrogate echocardiographic marker of left ventricular (LV) systolic function able to assess accurately the impact of LV global afterload on LV myocardium in patients with aortic stenosis (AS) is still in progress. Optimally, this marker should have good sensitivity and specificity, be easy and rapid to measure, with good reproducibility, cheap, well correlated with AS severity (and its chronicity) in addition to arterial afterload, and finally to patient's prognosis. Some of these characteristics are not fulfilled by LV ejection fraction (LVEF), whereas we still continue to use it as the only recommended parameter for the assessment of LV function and decision for intervention in patients with AS. Consequently, many research efforts are done overtime to find better parameters than LVEF.

Recently, the concept of first-phase LVEF ($LVEF_1$) has been studied in patients with increased LV afterload, initially in hypertensive patients, and then in those with AS. The biophysics of cardiac myocyte contraction stipulates that shortening deactivation[1] could participate to early (i.e. close to the first peak of LV pressure) and rapid decrease in myocardial wall stress, thus facilitating LV relaxation during diastole. In the presence of increased afterload and subsequent diastolic abnormalities, shortening deactivation and delayed peak shortening velocity of myocytes may occur in order to maintain elevated myocardial wall stress and preserved global LVEF.[2] This phenomenon may also protect the myocardium against wave reflections. The measurement of $LVEF_1$ allows the assessment of these pathophysiologic compensatory mechanisms and enables to unmask early LV myocardial morphological and functional alteration. Bing *et al.*[3] reported good relationship between increased AS severity or LV global haemodynamic afterload and reduced $LVEF_1$. They also find that $LVEF_1$ is associated with cardiac magnetic resonance (CMR) markers of LV myocardial fibrosis, such as late-gadolinium enhancement or indexed extra-cellular volume. Furthermore, Gu *et al.*[4] have shown that $LVEF_1$ <25% is associated with markedly reduced event-free survival or even all-cause mortality in patients with AS. Of interest, none of these studies found any significant correlation between global LVEF and $LVEF_1$, despite the use of LV end-diastolic volume in the calculation of both parameters. In addition to classical Simpson's rule, the quantification of $LVEF_1$ requires accurate measurement of time-to-peak aortic flow velocity from continuous-wave Doppler. Therefore, this delay needs to be replicated in bi-dimensional four- and two-chamber views in order to measure the LV volume at peak aortic flow.

Einarsen *et al.*[5] extended the knowledge's about $LVEF_1$ by studying a prospective series of 114 patients with at least mild AS and preserved LVEF (>50%). Of note, patients with arrhythmias, prior pacemaker, or known coronary artery disease were excluded. In other words, all patients with AS were free from any LV functional abnormalities despite few morphological changes (LV concentric remodelling or hypertrophy). Furthermore, the exclusion of patients with arrhythmias may ensure global suitable reproducibility of the measurements. Using transthoracic echocardiography, they quantified $LVEF_1$ and assessed its relationship with LV myocardial contractility and both LV and arterial haemodynamic load.

The first results of interest from this study is the graded relationship between increase AS severity and decrease in $LVEF_1$, where $LVEF_1$ appears modestly reduced in moderate AS but much more in severe AS. In addition, the majority of patients with abnormal $LVEF_1$ has severe AS. This is crucial since $LVEF_1$ may reflect the pathophysiological continuum of AS and they consequences on LV myocardium. Of note, this relationship was also reported with LV global longitudinal strain (GLS)[6] or other modern parameters of LV function but not with LVEF in contemporary series.

Secondly, the reproducibility of $LVEF_1$, even derived from limited number of patients ($n = 18$), seems acceptable. This point is also fundamental for any new candidate parameter within the armamentarium of daily clinical practice LV function assessment. Although the

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quantification of $LVEF_1$ is not technically challenging, several small errors measurement may have major impact on the final results and in this regard, a large-scale independent reproducibility study is still required.

Third, regardless AS severity, the authors found that $LVEF_1$ is independently associated with LV global myocardial deformation, as assessed using strain rate. More interestingly, they also identify a strong association between $LVEF_1$ and arterial stiffness, as assessed using PP/SVi. This suggest that $LVEF_1$ may be used as a global parameter able to provide key findings on the real consequences of global LV haemodynamic afterload (i.e. both valvular and arterial) on LV myocardial function. The impact of such findings may be of importance since improving our assessment of LV systolic function in these patients. This may be helpful for the management of patients with AS since evidences in favour of early intervention (i.e. in the absence of symptoms or impaired LVEF) is growing.[7] Despite preserved global LVEF, asymptomatic patients with $LVEF_1$ <25% could be considered for aortic valve intervention and discussed within dedicated Heart Team. Complementary LV function parameters, such as LV GLS or even CMR markers may also be used to corroborate early subclinical LV dysfunction.

The present data elegantly strengthen the body of evidences suggesting the usefulness of $LVEF_1$ in patients with AS. Nevertheless, several points require clarification through further research.

From a mechanistic standpoint, the delayed peak aortic flow velocity and LV shortening related to increased AS severity and global afterload lead to slower LV ejection and emptying. This is the rationale for $LVEF_1$ quantification in these patients. Nonetheless, such delay will automatically modify the emptying of LV, more particularly when LVEF is still preserved. Such pattern needs to be studied in patients with AS and modern multi-modalities imaging may be helpful.

Despite a lack of data, serial measurement of $LVEF_1$ during the conservative follow-up phase of the management of patients with AS may be of interest. Following intervention, encouraging results have been reported regarding the improvement of $LVEF_1$. These data suggested that around two-thirds of patients may markedly improve $LVEF_1$ when AS-related afterload is released and that patients remaining with reduced $LVEF_1$ frequently have myocardial irreversible sequela, such as infarct-like late-gadolinium enhancement.

In patients with paradoxical low-flow severe AS, the poor prognosis may appear out of proportion regarding AS severity and even LV function since LVEF is preserved. The use of $LVEF_1$ in these patients may participate to explain the paradox but also to better assess LV function and thus stratify the risk of patients. Nevertheless, the high prevalence of arrhythmias and atrial fibrillation in these patients may limit the application of $LVEF_1$.

The load-dependency of $LVEF_1$ is obvious and already well studied.[2,4] This could be an issue since $LVEF_1$ may only reflect the global LV hemodynamic increased afterload, as demonstrated by the present data, rather than the LV dysfunction. However, the relationship between $LVEF_1$ and outcome is independent from AS severity, underlining the usefulness of this parameter in the management of AS patients. Furthermore, the load-dependency of $LVEF_1$ strongly promote careful measurement and interpretation during echocardiographic exam. Concomitant assessment of blood pressure is mandatory and serial quantification of $LVEF_1$ during the exam may be recommended. The influence of white-coat effect on $LVEF_1$ also requires to be studied.

All these points require further research in order to better understand and support the role of $LVEF_1$ measurement in the management of patients with AS. Meanwhile, $LVEF_1$ could be systematically quantified in these patients. A substantial learning curve is expected and this should encourage to start its quantification in daily practice as soon as possible in order to rapidly improve reproducibility. Although promising, implementation of $LVEF_1$ in next guidelines may be premature, similarly than others echocardiographic parameters assessing LV function. Hence, randomized clinical trial comparing strategy's management based on the use of global LVEF vs. $LVEF_1$ (or LV GLS or LV dispersion) may be encouraged in order to provide stronger evidences.

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References

1. Ezzaher A, Ouazzani T el, Crozatier B. Timing and velocity of ejection as major determinants of end-systolic pressure in isolated rabbit hearts. *Circulation* 1994;**90**:3055–62.
2. Gu H, Li Y, Fok H, Simpson J, Kentish JC, Shah AM *et al.* Manifestation of impaired shortening deactivation that links systolic to diastolic dysfunction and preserves systolic ejection fraction. *Hypertension* 2017;**69**:633–40.
3. Bing R, Gu H, Chin C, Fang L, White A, Everett RJ *et al.* Determinants and prognostic value of echocardiographic first-phase ejection fraction in aortic stenosis. *Heart* 2020;**106**:1236–43.
4. Gu H, Saeed S, Bogusławskyi A, Carr-White G, Chambers JB, Chowienczyk P. First-phase ejection fraction is a powerful predictor of adverse events in asymptomatic patients with aortic stenosis and preserved total ejection fraction. *JACC Cardiovasc Imaging* 2019;**12**:52–63.
5. Einarsen E, Hjertaas J, Gu H, Matre K, Chowienczyk P, Gerdts E *et al.* Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis. *Eur Heart J Cardiovasc Imaging* 202;**22**:650–7.
6. Ng AC, Delgado V, Bertini M, Antoni ML, Bommel RJ, van Rijnsoever EP, van der Kley F *et al.* Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. *Eur Heart J* 2011;**32**:1542–50.
7. Kang D-H, Park S-J, Lee S-A, Lee S, Kim D-H, Kim H-K *et al.* Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–9.

Annexes 5: Mechanical LV Dispersion in Aortic Stenosis: Another Parameter within Dispersed Surrogates of Myocardial Function?

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EDITORIAL

Mechanical left ventricular dispersion in aortic stenosis: another parameter within dispersed surrogates of myocardial function?

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This editorial refers to 'Determinants and prognostic implications of left ventricular mechanical dispersion in aortic stenosis', by E.A. Prihadi *et al.*, doi:10.1093/ehjci/jez004.

In patients with aortic stenosis (AS), the presence of left ventricular (LV) systolic dysfunction, defined as a LV ejection fraction <50%, is a Class I indication for valve intervention, regardless symptomatic status. Based on this definition, the prevalence of LV systolic dysfunction in strictly asymptomatic patients with severe AS is particularly rare. In addition, LV ejection fraction may remain normal for long in patients with severe AS and can mask structural and functional myocardial alteration. The use of LV ejection fraction and the cut-off of 50% in AS patients' is increasingly debated in the literature.[1] According to Starling and Laplace laws, LV ejection fraction is load dependent and is mechanically increased when LV concentric remodelling progresses, i.e. relative wall thickness increase leading to normal or supra-normal value of LV ejection fraction. These phenomena, combined with the concept of LV preload reserve, participate to maintain LV ejection fraction in a normal range in patients with AS without coronary disease. By opposition, even in the absence of reduced contractility, LV ejection fraction may be decreased due to afterload mismatch. Furthermore, its reproducibility is limited.[2] Altogether, these points underline that LV ejection fraction is not the most appropriate surrogate marker for LV systolic function and contractility in patients with AS.[1] Consequently, many efforts have been recently made to develop and validate bio-imaging markers allowing identification of subclinical myocardial damage related to LV increased haemodynamic afterload. Cardiac magnetic resonance provides gold standard parameters for LV structure and function assessment but its cost, availability, and processing time limit its daily use and, thus, could be mostly reserved to patients with poor acoustic windows and/or inconclusive echocardiography. Several echocardiography-derived indices have been already studied, and some of them are close to be routinely implemented in clinical practice (*Table 1*).

Prihadi *et al.*[3] studied the determinants and prognostic value of LV mechanical dispersion in patients with AS. This speckle tracking-derived parameter, well studied by Haugaa *et al.*,[4] reflects inhomogeneous LV myocardial contraction, is known to be independent of LV ejection fraction, and associated with subclinical dyssynchrony, ventricular arrhythmias, and LV fibrosis in several cardiomyopathies.[5] Prihadi *et al.*[6] retrospectively assessed LV mechanical dispersion in 630 patients from their previously published cohort of various degrees of native AS without other significant valve disease. They first reported a close relationship between LV mechanical dispersion and AS grade with markedly higher dispersion in patients with severe AS. Second, the authors identified older age, LV ejection fraction and mass, AS severity, and QRS duration as correlates of LV mechanical dispersion. These results confirm that correlates of LV fibrosis in patients with AS are independent determinants of LV mechanical dispersion, even after adjustment for QRS duration. Third, the authors confirmed the results of Klaeboe *et al.*[7] showing the prognostic value of LV mechanical dispersion. Indeed after robust adjustment for cofounders including age, hypertension, QRS duration, aortic valve replacement, AS severity, and classical parameters of LV function and morphology, they found the extent of LV mechanical dispersion as predictive of increased risk of mortality.

As compared to LV ejection fraction, the LV mechanical dispersion has several advantages and, from a pathophysiological standpoint, appears as a better marker of consequences of LV haemodynamic afterload on ventricular myocardial structure and function. It is associated with AS severity, their determinants are related to LV fibrosis in non-ischaemic pressure overload diseases, and its use could have incremental prognostic values as compared to LV ejection fraction. The present study obviously highlights all these benefits and suggests it's wide used in clinical practice, although promoting further larger studies and trials based on this parameter. Indeed, some limitations in this study should be addressed in the future. First, the cut-off value requires to be defined and validated. Second, the comparison of LV mechanical dispersion with LV ejection fraction is fair but many recent parameters also demonstrated added value as compared to LV ejection fraction (*Table 1*). Among them, the usefulness of LV global longitudinal strain in patients with AS could be compared with LV

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Table 1 **Main parameters of left ventricular systolic function developed in patients with aortic stenosis**

LV parameters	Cut-off value	Predictive in asymptomatic patients	Severity of AS for the validation	References
Echocardiographic				
Ejection fraction	50%	Yes[a]	Various	8
First-phase ejection fraction	25%	Yes	Moderate/severe AS	9
Global longitudinal strain	-14.7%	Yes	Significant AS	10
Basal strain	-13%	Yes	Moderate/severe AS	11
Indexed stroke volume	35 mL/m^2	No	Severe AS	12
Cardiac magnetic resonance				
Late gadolinium enhancement		No	Severe AS	13
Native T1		Yes	Moderate/severe AS	14
Extra cellular volume	Tertile	No	Severe AS	15

AS, aortic stenosis; LV, left ventricular.
[a]Asymptomatic patients with LV ejection fraction <50% are rare. Cut-off could be increased at 55–60%.

mechanical dispersion. Whether LV global longitudinal strain and mechanical dispersion provides similar or complementary information in the assessment of systolic function remains unknown in AS. A direct comparison also with myocardial biomarkers such as brain natriuretic peptides, high-sensitive troponin I, or ST2 are also necessary. Third, to improve the management of AS, the prognostic value of LV mechanical dispersion should be studied in asymptomatic patients, i.e. with normal exercise test. Fourth, its reversibility following aortic valve intervention or under treatment targeting LV remodelling needs also to be addressed. Finally, cardiac magnetic resonance and histological studies will be also required in the future to distinguish whether LV mechanical dispersion is a direct surrogate marker of LV fibrosis or, more largely, a surrogate of LV electrical conduction abnormalities related to LV morphological changes, including fibrosis, apoptosis, or other mechanisms. Meanwhile, the data reported by Prihadi *et al.* are convincing, and support the implementation of LV mechanical dispersion within the catalogue of echocardiographic LV function related parameters.

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References

1. Dahl JS, Magne J, Pellikka PA, Donal E, Marwick TH. Assessment of subclinical left ventricular dysfunction in aortic stenosis. *JACC Cardiovasc Imaging* 2019;**12**:163–71.
2. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2004;**44**:1030–5.
3. Prihadi EA, Vollema EM, Ng ACT, Marsan NA, Bax JJ, Delgado V. Determinants and prognostic implications of left ventricular mechanical dispersion in aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2019;doi:10.1093/ehjci/jez004.
4. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A *et al.* Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. *J Am Soc Echocardiogr* 2012;**25**:667–73.
5. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O *et al.* Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy—an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:237–53.
6. Ng ACT, Prihadi EA, Antoni ML, Bertini M, Ewe SH, Ajmone Marsan N *et al.* Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. *Eur Heart J Cardiovasc Imaging* 2018;**19**:859–67.
7. Klaeboe LG, Haland TF, Leren IS, Ter Bekke RMA, Brekke PH, Røsjø H *et al.* Prognostic value of left ventricular deformation parameters in patients with severe aortic stenosis: a pilot study of the usefulness of strain echocardiography. *J Am Soc Echocardiogr* 2017;**30**:727–35.e1.
8. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al.*; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.
9. Gu H, Saeed S, Boguslavskyi A, Carr-White G, Chambers JB, Chowienczyk P. First-phase ejection fraction is a powerful predictor of adverse events in asymptomatic patients with aortic stenosis and preserved total ejection fraction. *JACC Cardiovasc Imaging* 2019;**12**:52–63.
10. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY *et al.* Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92.
11. Carstensen HG, Larsen LH, Hassager C, Kofoed KF, Jensen JS, Mogelvang R. Basal longitudinal strain predicts future aortic valve replacement in asymptomatic patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2016;**17**:283–92.
12. Magne J, Mohty D, Boulogne C, Boubadara FE, Deltreuil M, Echahidi N *et al.* Prognosis importance of low flow in aortic stenosis with preserved LVEF. *Heart* 2015;**101**:781–7.
13. Barone-Rochette G, Pierard S, Meester de RC. D, Seldrum S, Melchior J, Maes F *et al.* Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J Am Coll Cardiol* 2014;**64**:144–54.
14. Lee S-P, Lee W, Lee JM, Park E-A, Kim H-K, Kim Y-J *et al.* Assessment of diffuse myocardial fibrosis by using MR imaging in asymptomatic patients with aortic stenosis. *Radiology* 2015;**274**:359–69.
15. Park S-J, Cho SW, Kim SM, Ahn J, Carriere K, Jeong DS *et al.* Assessment of myocardial fibrosis using multimodality imaging in severe aortic stenosis: comparison with histologic fibrosis. *JACC Cardiovasc Imaging* 2019;**12**:109–19.

Annexes 6: Great Debate: all Patients with Asymptomatic Severe Aortic Stenosis need Valve Replacement.

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GREAT DEBATE
Valvular heart disease

Great debate: all patients with asymptomatic severe aortic stenosis need valve replacement

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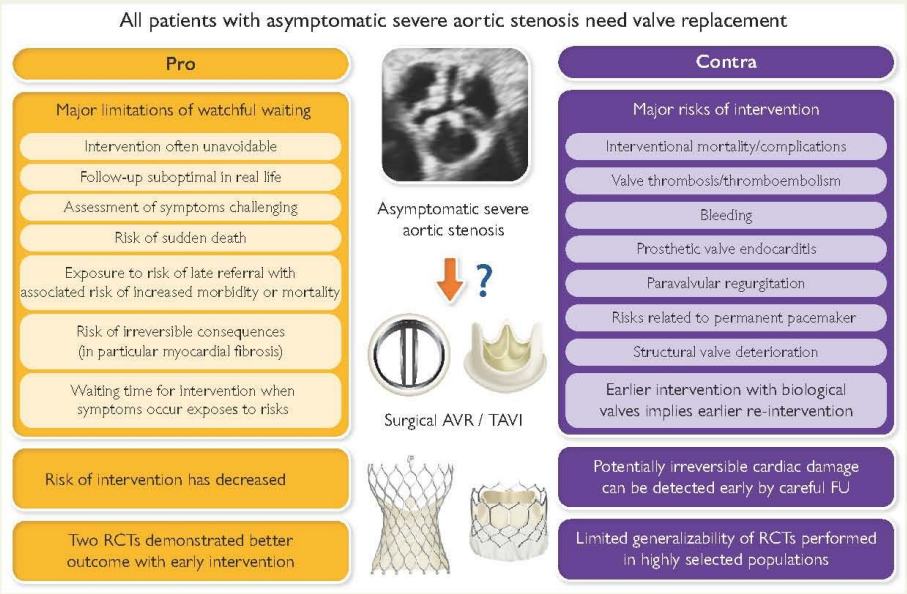
Graphical Abstract



AVR = aortic valve replacement, TAVI = transcatheter aortic valve implantation, FU = follow-up, RCT = randomized controlled trial.

Keywords Aortic stenosis • Early intervention • Watchful waiting

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Introduction

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Aortic stenosis (AS) has become a significant health burden affecting 2%–6% of the population older than 65 years.[1–3] A recent study[4] estimated for 2017 globally 12.6 million patients with calcific AS—the most common etiology of AS—causing 102 700 deaths and a rapid increase in prevalence is observed with the aging population, particularly in Europe and North America.[4,5] Since calcific AS can easily be detected by echocardiography at a very early stage—when no or only mild hemodynamic consequences are present—develops slowly, and is an active process sharing pathophysiologic similarities with atherosclerosis,[6] there is hope to find medical treatment that interferes with its progression. Unfortunately, all attempts to develop effective medical treatment over the last decades—in particular addressing cholesterol lowering and statin therapy[7] but also other innovative approaches[8,9]—were so far unsuccessful and the only treatment option currently remains aortic valve replacement (AVR) by a prosthetic valve when the stenosis has become severe. While studies reported a relatively good outcome for asymptomatic severe AS,[10,11] the prognosis becomes dismal as soon as the patients develop symptoms.[12,13] AVR has been shown to dramatically improve symptoms and survival at this stage of the disease.[13,14] Therefore, the strong indication for AVR in symptomatic severe AS is generally accepted.[15,16] Whether and when to intervene in asymptomatic severe AS to improve outcome remains, however, controversial.[15–17] In a recent survey, asymptomatic patients accounted for 19% of patients with severe AS[18] and 17% of patients with severe high gradient AS[19] referred to the participating centers, but the percentage in the general population must be expected to be much higher. Thus, the question of how to manage these patients is of critical importance. The potential rationale for intervening in asymptomatic severe valvular heart disease has recently been summarized.[17] Arguments include in particular the risk of life-threatening events and irreversible end-organ damage as well as practical limitations of a watchful waiting strategy in guaranteeing optimal timing of intervention.[17]

The potential benefits of intervening in an asymptomatic patient must, however, be weighed against the operative/catheter interventional risk and the long-term risks associated with a valve substitute.[15–17]

Over the years, a number of predictors of worse outcome in asymptomatic AS have been identified.[15] These include clinical characteristics such as older age, atherosclerotic risk factors, and echocardiographic parameters such as degree of valve calcification, peak velocity and its progression,[11,20] ejection fraction, increase in mean gradient > 20 mmHg with exercise,[21,22] severe left ventricular hypertrophy,[23] indexed stroke volume,[24] left atrial volume,[25] left ventricular global longitudinal strain,[26–28] pulmonary hypertension,[29–33] and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A).[34–37] While these risk factors could be demonstrated to predict event-free survival, it must be kept in mind that in most studies, the predominating event was the development of symptoms requiring intervention. It still remains to be shown whether, in the presence of such risk factors, patients benefit indeed from early intervention when they are still asymptomatic.

Based on observational data, current guidelines recommend by expert consensus rather than by strong evidence to intervene in the following groups of asymptomatic patients with severe AS[15] (the references cited after each recommendation are the ones provided in the guideline document to support the respective recommendation):

- Patients with systolic left ventricular dysfunction defined by ejection fraction <50% when no other causes are present (IB)[38–40]
- When exercise testing reveals symptoms attributable to AS (IC)

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

- Patients with systolic left ventricular dysfunction defined by ejection fraction <55% when no other causes are present (IIaB)[38,41,42]
- Patients with a sustained fall in blood pressure > 20 mmHg during exercise testing (IIaC)
- Patients with ejection fraction >55% and a normal exercise test who are at low procedural risk and present with one of the following parameters (IIaB):
  - Mean gradient ≥ 60 mmHg or peak velocity >5 m/s[38,43]
  - Severe valve calcification and peak velocity progression ≥0.3 m/s/year[11,44,45]
  - B-type natriuretic peptide levels >3 × age- and sex-corrected normal range confirmed by repeated measurements and without other explanations[34,35]

Current guidelines admit, however, that the management of patients with asymptomatic AS (including a normal exercise test) and normal left ventricular function remains controversial. Decision-making requires careful weighing of risk and benefit. In this regard, the fact that catheter interventional treatment of AS is rapidly evolving and recent data demonstrate that the risk of both, surgical AVR and transcatheter aortic valve implantation (TAVI) have markedly decreased over the years[46] has an obvious impact as this may change the threshold to intervene in asymptomatic patients when weighing risk vs. potential benefit. On the other hand, the complexity of long-term planning considering the consequences for later re-interventions, access to coronary arteries after TAVI, and other aspects have been recognized.[47] New important data including randomized controlled trials comparing watchful waiting vs. early surgery in asymptomatic AS have also been provided.[48] Thus, it appears timely to revisit the pro and cons of whether all patients with asymptomatic severe AS need a valve replacement.

Declarations

Disclosure of Interest

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References

1. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, *et al.* Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;**29**:630–634. https://doi.org/10.1016/s0735-1097(96)00563-3
2. Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993;**21**:1220–1225. https://doi.org/10.1016/0735-1097(93)90249-z
3. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011. https://doi.org/10.1016/S0140-6736(06)69208-8
4. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, *et al.* Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990–2017. *Circulation* 2020;**141**:1670–1680. https://doi.org/10.1161/CIRCULATIONAHA.119.043391
5. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, *et al.* European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* 2022;**43**:716–799. https://doi.org/10.1093/eurheartj/ehab892
6. Mohler ER, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation* 2001;**103**:1522–1528. https://doi.org/10.1161/01.cir.103.11.1522
7. Zhao Y, Nicoll R, He YH, Henein MY. The effect of statins therapy in aortic stenosis: meta-analysis comparison data of RCTs and observationals. *Data Brief* 2016;**7**:357–361. https://doi.org/10.1016/j.dib.2016.02.045
8. Pawade TA, Doris MK, Bing R, White AC, Forsyth L, Evans E, *et al.* Effect of denosumab or alendronic acid on the progression of aortic stenosis: a double-blind randomized controlled trial. *Circulation* 2021;**143**:2418–2427. https://doi.org/10.1161/CIRCULATIONAHA.121.053708
9. Diederichsen ACP, Lindholt JS, Möller S, Øvrehus KA, Auscher S, Lambrechtsen J, *et al.* Vitamin K2 and D in patients with aortic valve calcification: a randomized double-blinded clinical trial. *Circulation* 2022;**145**:1387–1397. https://doi.org/10.1161/CIRCULATIONAHA.121.057008
10. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, *et al.* Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005;**111**:3290–3295. https://doi.org/10.1161/CIRCULATIONAHA.104.495903
11. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, *et al.* Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;**343**:611–617. https://doi.org/10.1056/NEJM200008313430903
12. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968;**38**:61–67. https://doi.org/10.1161/01.cir.38.1s5.v-61
13. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607. https://doi.org/10.1056/NEJMoa1008232
14. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J* 1988;**9**:57–64. https://doi.org/10.1093/eurheartj/9.suppl_e.57
15. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.* 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395
16. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint committee on clinical practice guidelines. *Circulation* 2020;**143**:e72–e227. https://doi.org/10.1161/CIR.0000000000000923
17. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J* 2020;**41**:4349–4356. https://doi.org/10.1093/eurheartj/ehaa485
18. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, *et al.* Contemporary presentation and management of valvular heart disease: the EURObservational research programme valvular heart disease II survey. *Circulation* 2019;**140**:1156–1169. https://doi.org/10.1161/CIRCULATIONAHA.119.041080
19. Eugène M, Duchnowski P, Prendergast B, Wendler O, Laroche C, Monin JL, *et al.* Contemporary management of severe symptomatic aortic stenosis. *J Am Coll Cardiol* 2021;**78**:2131–2143. https://doi.org/10.1016/j.jacc.2021.09.864
20. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, *et al.* Natural history of very severe aortic stenosis. *Circulation* 2010;**121**:151–156. https://doi.org/10.1161/CIRCULATIONAHA.109.894170
21. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. *Am J Cardiol* 2009;**104**:972–977. https://doi.org/10.1016/j.amjcard.2009.05.044
22. Maréchaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, *et al.* Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J* 2010;**31**:1390–1397. https://doi.org/10.1093/eurheartj/ehq076
23. Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E, *et al.* Prognostic value of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart* 2011;**97**:301–307. https://doi.org/10.1136/hrt.2010.192997
24. Rusinaru D, Bohbot Y, Ringle A, Maréchaux S, Diouf M, Tribouilloy C. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *Eur Heart J* 2018;**39**:1992–1999. https://doi.org/10.1093/eurheartj/ehy123
25. Rusinaru D, Bohbot Y, Kowalski C, Ringle A, Maréchaux S, Tribouilloy C. Left atrial volume and mortality in patients with aortic stenosis. *J Am Heart Assoc* 2017;**6**:e006615. https://doi.org/10.1161/JAHA.117.006615
26. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, *et al.* Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92. https://doi.org/10.1016/j.jcmg.2018.11.005
27. Vollema EM, Sugimoto T, Shen M, Tastet L, Ng ACT, Abou R, *et al.* Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis: natural course and prognostic value. *JAMA Cardiol* 2018;**3**:839–847. https://doi.org/10.1001/jamacardio.2018.2288
28. Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. *Circ Cardiovasc Imaging* 2012;**5**:613–620. https://doi.org/10.1161/CIRCIMAGING.112.973834
29. Zuern CS, Eick C, Rizas K, Stoleriu C, Woernle B, Wildhirt S, *et al.* Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement. *Clin Res Cardiol* 2012;**101**:81–88. https://doi.org/10.1007/s00392-011-0367-3
30. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, *et al.* Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. *Circulation* 2012;**126**:851–859. https://doi.org/10.1161/CIRCULATIONAHA.111.088427
31. Mutlak D, Aronson D, Carasso S, Lessick J, Reisner SA, Agmon Y. Frequency, determinants and outcome of pulmonary hypertension in patients with aortic valve stenosis. *Am J Med Sci* 2012;**343**:397–401. https://doi.org/10.1097/MAJ.0b013e3182309431
32. Zlotnick DM, Ouellette ML, Malenka DJ, DeSimone JP, Leavitt BJ, Helm RE, *et al.* Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. *Am J Cardiol* 2013;**112**:1635–1640. https://doi.org/10.1016/j.amjcard.2013.07.025
33. Miceli A, Varone E, Gilmanov D, Murzi M, Simeoni S, Concistrè G, *et al.* Impact of pulmonary hypertension on mortality after operation for isolated aortic valve stenosis. *Int J Cardiol* 2013;**168**:3556–3559. https://doi.org/10.1016/j.ijcard.2013.05.001
34. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, *et al.* Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;**109**:2302–2308. https://doi.org/10.1161/01.CIR.0000126825.50903.18
35. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, *et al.* B-type natriuretic peptide clinical activation in aortic stenosis—impact on long-term survival. *J Am Coll Cardiol* 2014;**63**:2016–2025. https://doi.org/10.1016/j.jacc.2014.02.581
36. Chin CW, Shah AS, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, *et al.* High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;**35**:2312–2321. https://doi.org/10.1093/eurheartj/ehu189
37. Koos R, Brandenburg V, Mahnken AH, Mühlenbruch G, Stanzel S, Günther RW, *et al.* Association of fetuin-A levels with the progression of aortic valve calcification in non-dialyzed patients. *Eur Heart J* 2009;**30**:2054–2061. https://doi.org/10.1093/eurheartj/ehp158
38. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, *et al.* Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol* 2018;**3**:1060–1068. https://doi.org/10.1001/jamacardio.2018.3152
39. Dahl JS, Eleid MF, Michelena HI, Scott CG, Suri RM, Schaff HV, *et al.* Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circ Cardiovasc Imaging* 2015;**8**:e002917. https://doi.org/10.1161/CIRCIMAGING.114.002917
40. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, *et al.* Prognostic impact of left ventricular ejection fraction in patients with severe aortic stenosis. *JACC Cardiovasc Interv* 2018;**11**:145–157. https://doi.org/10.1016/j.jcin.2017.08.036
41. Bohbot Y, de Meester de Ravenstein C, Chadha G, Rusinaru D, Belkhir K, Trouillet C, *et al.* Relationship between left ventricular ejection fraction and mortality in asymptomatic and minimally symptomatic patients with severe aortic stenosis. *JACC Cardiovasc Imaging* 2019;**12**:38–48. https://doi.org/10.1016/j.jcmg.2018.07.029
42. Capoulade R, Le Ven F, Clavel MA, Dumesnil JG, Dahou A, Thébault C, *et al.* Echocardiographic predictors of outcomes in adults with aortic stenosis. *Heart* 2016;**102**:934–942. https://doi.org/10.1136/heartjnl-2015-308742
43. Bohbot Y, Kowalski C, Rusinaru D, Ringle A, Marechaux S, Tribouilloy C. Impact of mean transaortic pressure gradient on long-term outcome in patients with severe aortic

stenosis and preserved left ventricular ejection fraction. *J Am Heart Assoc* 2017;**6**: e005850. https://doi.org/10.1161/JAHA.117.005850
44. Pawade T, Clavel MA, Tribouilloy C, Dreyfus J, Mathieu T, Tastet L, *et al.* Computed tomography aortic valve calcium scoring in patients with aortic stenosis. *Circ Cardiovasc Imaging* 2018;**11**:e007146. https://doi.org/10.1161/CIRCIMAGING.117.007146
45. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–2270. https://doi.org/10.1161/01.cir.95.9.2262
46. Baumgartner H. Aortic stenosis management in 2021: better teaming up than fighting between specialties. *Eur Heart J* 2022;**43**:680–682. https://doi.org/10.1093/eurheartj/ehab778
47. Windecker S, Okuno T, Unbehaun A, Mack M, Kapadia S, Falk V. Which patients with aortic stenosis should be referred to surgery rather than transcatheter aortic valve implantation? *Eur Heart J* 2022;**43**:2729–2750. https://doi.org/10.1093/eurheartj/ehac105
48. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation* 2022;**145**:648–658. https://doi.org/10.1161/CIRCULATIONAHA.121.057639

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The consequence of restricted indications for intervention in asymptomatic patients with severe aortic stenosis (AS) is that the majority of patients are managed according to the so-called "watchful waiting" strategy, i.e. waiting for symptom onset. However, the rationale supporting the safety of watchful waiting is challenged in clinical practice by a number of considerations derived from observational findings and recent trials.

Watchful waiting strategy in practice

Intervention is often unavoidable

Cardiac events, most often symptom onset requiring an intervention, will occur in as many as 80% of asymptomatic patients with severe AS within 3 years and in more than 20% within one year.[1] The likelihood of remaining asymptomatic further decreases with AS severity and is very low among the subset of patients classified as very severe AS for whom an intervention is now recommended.[2]

Follow-up is suboptimal in real life

Close follow-up is thus needed, at least twice a year to detect symptom onset. However, the watchful waiting strategy relies on two major principles that are often unsatisfactory in clinical practice: first, the patient immediately reports the occurrence of symptoms (patient compliance), and, second, a close follow-up could always be achieved (optimal follow-up). Thus, it has been shown that a third of asymptomatic patients with known severe AS are followed less than once a year and experience higher mortality.[3] Although patients are informed to promptly report any change in symptoms, this is frequently not done in clinical practice.

Assessment of symptoms is challenging in the AS population

Symptoms are subjective and may develop insidiously and patients adapt to symptoms, which accounts for an underestimation of symptoms by both patients and practitioners.[4] Since AS frequently occurs in the elderly, impaired functional capacity may be attributed to ageing and/or comorbidities. Difficulties in symptom interpretation highlight the usefulness of exercise testing for an objective evaluation of exercise tolerance. However, in the recent valvular heart disease (VHD) II survey which included 2152 patients referred to the hospital for severe AS, stress tests were used in only 6% of asymptomatic patients with severe AS.[5] Although exercise testing is now recommended in guidelines for asymptomatic severe AS, it was not performed more frequently in VHD II than in the Euro Heart Survey in 2001. In addition, in the elderly AS population, a stress test may not be feasible in a significant proportion of patients.

Risk of sudden death

Sudden death rates are low in asymptomatic patients but higher than in the general population, and this very low risk of mortality is generally achieved in patients having strict follow-up in the context of heart valve clinics.[6] Although the rate of sudden death is low in true-asymptomatic patients, it significantly raises in those who developed symptoms during follow-up, especially if not reported and/or not recognized as shown in the RECOVERY trial.[7]

Delaying intervention exposes to the risk of late referral with associated increased mortality and morbidity risk

A recent meta-analysis has shown that the risk of death under conservative management is high, that deaths are mostly of cardiac cause, and that sudden death only accounts for a part of it.[8] The VHD II survey attests to the late referral of patients with severe AS. More than a third of patients with severe AS were referred to hospital in outpatient clinics or in hospitalization in NYHA class III or IV and 16% had been hospitalized for heart failure during the preceding year.[5] These findings combine patients with undiagnosed AS and patients with known AS but in whom symptom onset has not been interpreted in due time. Late referral is also observed in patients followed in dedicated heart valve clinics. In a series of 103 asymptomatic patients

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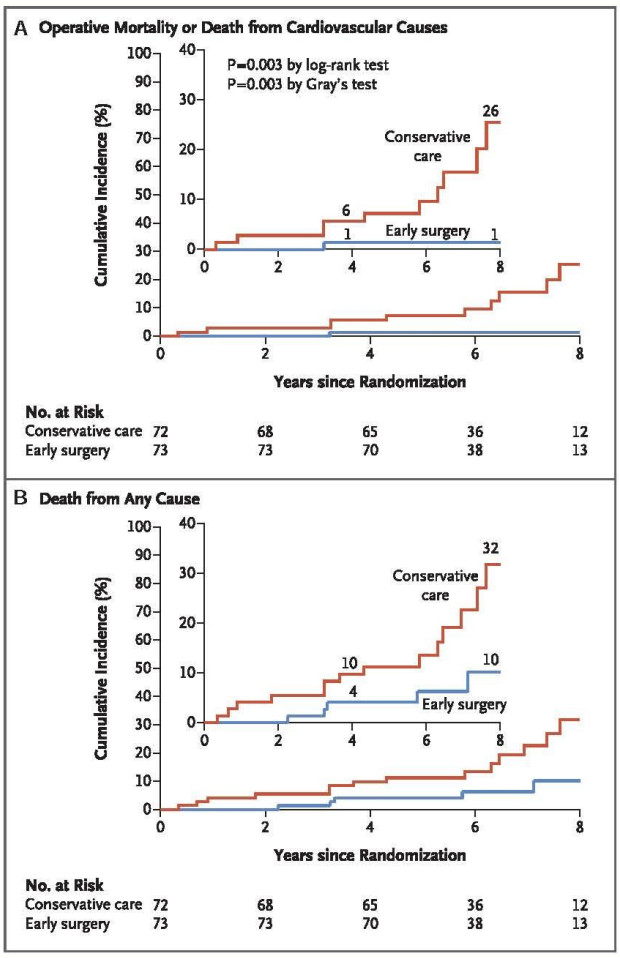

Figure 1 Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized RECOVERY trial. Reproduced with permission from Kang *et al.*[7].

aged ≥ 70 years with severe AS who were followed every 6 months in a heart valve clinic, an indication of aortic valve replacement occurred in 82 of them during a mean follow-up of only 19 months and 32 patients had severe symptoms at the time of aortic valve replacement, as defined by NYHA class ≥ III or CCS class ≥ 3.[9] A total of 30 patients had impaired mobility due to comorbidities and this contributed probably to defer the identification of symptom onset. Severe symptoms or prior heart failure are associated with an increased risk of early morbidity and mortality after surgical AVR or TAVI, as compared with interventions performed in patients with few or no symptoms.[10–12] Indications for intervention based only on the severity of AS appear as an effective approach to reduce late referral by avoiding delays in the interpretation of symptom onset.

Risk of irreversible consequences

Advanced left ventricular remodelling due to AS may compromise the quality of late results of aortic valve intervention. In contrast to ejection fraction, strain analysis detects subtle impairment of left ventricular function, and abnormal strain rate is associated with decreased event-free survival.[13] Left ventricular remodelling in AS is also related to the presence of ventricular fibrosis which has an incremental negative prognostic value.[14,15] Beyond the left ventricle, more than half of asymptomatic patients with moderate-to-severe AS present markers of left atrial or mitral valve damage, pulmonary hypertension, or right heart failure which are associated with impaired outcome.[16] Not all these features are direct consequences of AS; however, it is likely that they would be less frequent if intervention is performed early.

Waiting time and increased mortality

Excessive time delays in the identification of symptom onset and inherent late referral cumulate with time delays on the waiting list for intervention, which are associated with an increased risk of hospitalizations for heart failure and death before intervention.[17,18]

Risk of intervention is now lower

The last decade has seen a marked decrease in the operative mortality and morbidity, in particular with transcatheter valve interventions in the elderly population. The risk of intervention increases with age and severity of the clinical presentation and the watchful waiting strategy is therefore intrinsically associated with an increased operative mortality.

Association between early intervention and outcome

Observational series

These have been used to compare the strategies of early intervention and watchful waiting. Their interpretation is hampered by inherent sources of bias which affect the comparability of therapeutic groups. Large series allow for adjusting on potential confounders, and this approach was used in the CURRENT AS registry which included 1808 consecutive asymptomatic patients with severe AS, of whom 291 underwent early AVR and 1517 were managed conservatively.[19] In a comparison of two propensity-matched subgroups of 291 patients, there was a significant decrease in the incidence of hospitalization for heart failure and, more importantly, of all-cause mortality in asymptomatic patients who underwent early surgery as compared with conservative management.

Randomized controlled trials

Randomized trials are the only valid method to compare therapeutic strategies without bias due to measured and unmeasured confounders, although one should not forget their limitations due to open-label (and not double-blind) design and, as for all clinical trials, concerns on the generalizability of the findings. Two randomized trials comparing surgical AVR in asymptomatic patients with severe AS with a conventional conservative strategy have been published over the last two years, formally proving the benefit of an early intervention. The first randomized trial (RECOVERY) was conducted in four Korean centres and randomized 73 patients to early surgery and 72 patients to conservative strategy.[7] Inclusion criteria corresponded to a more severe degree of AS than usual criteria and were defined by valve area ≤ 0.75 cm^2 and ($V_{max} \geq 4.5$ m/s or mean gradient ≥ 50 mmHg). The absence of symptoms was based on case history and exercise testing was performed only in case of doubtful symptoms. The mean age was 64 years, and the mean EuroSCORE II was 0.9%. Outcome according to the primary endpoint of operative mortality or post-operative cardiovascular mortality was markedly better after early surgery as compared with conservative management [hazard ratio (HR) 0.09; 95% confidence interval (CI) 0.01–0.67] (*Figure 1*). The benefit of early surgery was also consistent across the different secondary endpoints, even for all-cause mortality (HR 0.33; 95% CI 0.12–0.90).

More recently, the AVATAR trial included patients with commonly used definitions of severe aortic stenosis (valve area ≤ 1.0 cm^2 and $V_{max} \geq 4.0$ m/s or mean gradient ≥ 40 mmHg).[20] Exercise testing was mandatory to confirm the absence of symptoms, thereby corresponding to current guidelines. The mean age was 67 years, and the mean STS score was 1.7%; 78 patients were randomized to early surgery, and 79 patients to conservative strategy. The incidence of the primary endpoint combining all-cause death or major adverse cardiac events was significantly reduced in the early surgery group as compared with

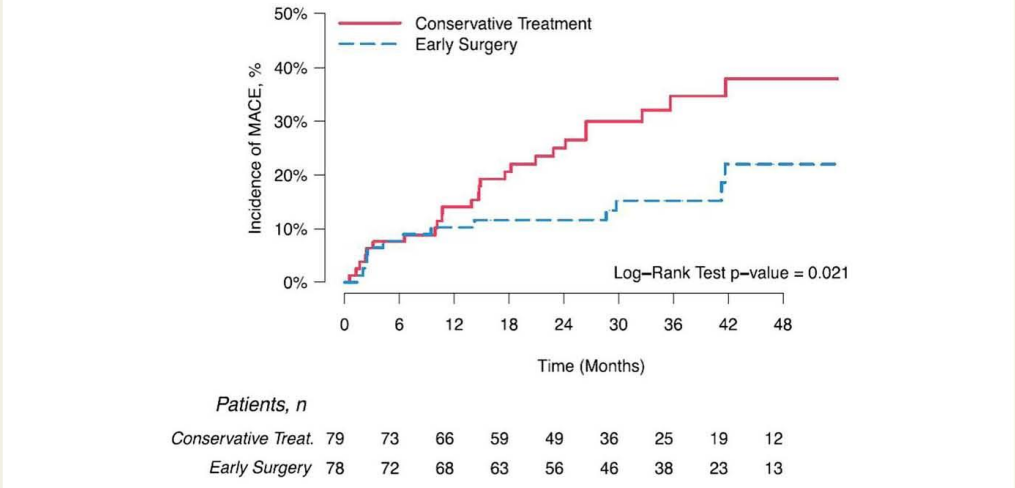

Figure 2 Comparison of incidence rates of the primary endpoint of all-cause mortality and major adverse cardiac events between early surgery and conservative treatment in the randomized AVATAR trial. Reproduced with permission from Banovic *et al.*[20].

conservative management (HR 0.46; 95% CI 0.23–0.90, $P = 0.02$) (*Figure 2*). Although not reaching statistical significance, the trend for all-cause mortality (HR 0.56; 95% CI 0.24–1.27, $P = 0.16$) and heart failure hospitalization were also in favour of the early surgery group (HR 0.32; 95% CI 0.08–1.19, $P = 0.075$). The absence of difference in cardiovascular mortality may seem paradoxical. However, of the 16 deaths which occurred in the conservative strategy group, four were caused by pneumonia, including three due to COVID-19. Severe AS may have contributed to worse outcome and highlighted the difficulties related to an accurate identification of the cause of death.

A meta-analysis combing 10 observational series (two prospective and eight retrospective) and the two randomized trials included 4130 patients and showed a significant association between early surgery and significantly lower all-cause mortality as compared with conservative management (pooled odds ratio 0.40; 95% CI 0.35–0.45, $P < 0.01$).[8] The restriction of the analysis to the two randomized trials showed also a lower all-cause mortality after early surgery (pooled odds ratio 0.45; 95% CI 0.25–0.82, $P < 0.01$) with no heterogeneity. Ongoing randomized controlled trials comparing the watchful waiting strategy and an early intervention using either surgical AVR or TAVI will formally demonstrate the superiority of one strategy vs. the other.

Implications on AS detection

Early intervention in asymptomatic patients as soon as AS becomes severe will require an increased awareness towards the diagnosis of AS. The underdiagnosis of heart valve disease in the community was first reported by Nkomo *et al.* in 2006[21] and confirmed more recently in the OxVALVE study.[22] In the OxVALVE cohort, systematic echocardiographic screening in the general practice of patients aged ≥ 65 years detected a prevalence of 6.4% of undiagnosed moderate or severe valvular disease (0.7% for AS), higher than the 4.9% prevalence of previously diagnosed valvular disease of the same severity.[22]

Conclusion

In conclusion, although the watchful waiting strategy seems sound, its routine implementation is hampered by different issues, in particular, the considerable underuse of exercise testing and the frequent delay in the identification of symptom onset. This contributes to late referral, thereby compromising the safety and quality of the results of the valvular intervention. The results of the two recent randomized trials now provide evidence that early surgical aortic valve replacement in asymptomatic patients with severe AS is a valuable alternative to watchful waiting.

Declarations

Disclosure of Interest

Dr. Iung has nothing to declare. Dr. Messika-Zeitoun received a research grant from Edwards Lifesciences.

References

1. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–2270. https://doi.org/10.1161/01.cir.95.9.2262
2. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, *et al.* Natural history of very severe aortic stenosis. *Circulation* 2010;**121**:151–156. https://doi.org/10.1161/CIRCULATIONAHA.109.894170
3. Ahmed A, Sorajja P, Garberich RF, Farivar RS, Harris KM, Gössl M. Association of guideline adherence for serial evaluations with survival and adverse clinical events in patients with asymptomatic severe aortic stenosis. *JAMA Cardiol* 2017;**2**:1141–1146. https://doi.org/10.1001/jamacardio.2017.2952
4. Arnold SV, Manandhar P, Vemulapalli S, Vekstein AM, Kosinski AS, Spertus JA, *et al.* Patient-reported vs. Physician-estimated symptoms before and after transcatheter aortic valve replacement. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:161–168. https://doi.org/10.1093/ehjqcco/qcab078
5. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, *et al.* Contemporary presentation and management of valvular heart disease: the EURObservational research programme valvular heart disease II survey. *Circulation* 2019;**140**:1156–1169. https://doi.org/10.1161/CIRCULATIONAHA.119.041080
6. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, *et al.* Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol* 2018;**3**:1060–1068. https://doi.org/10.1001/jamacardio.2018.3152
7. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, *et al.* Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–119. https://doi.org/10.1056/NEJMoa1912846
8. Costa GNF, Cardoso JFL, Oliveiros B, Goncalves L, Texeira R. Early surgical intervention versus conservative management of asymptomatic severe aortic stenosis: a systematic review and meta-analysis. *Heart* 2023;**109**:314–321. https://doi.org/10.1136/heartjnl-2022-321411
9. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic severe aortic stenosis in the elderly. *JACC Cardiovasc Imaging* 2017;**10**:43–50. https://doi.org/10.1016/j.jcmg.2016.05.015
10. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, *et al.* The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2–isolated valve surgery. *Ann Thorac Surg* 2009;**88**:S23–S42. https://doi.org/10.1016/j.athoracsur.2009.05.056
11. Iung B, Laouénan C, Himbert D, Eltchaninoff H, Chevreul K, Donzeau-Gouge P, *et al.* Predictive factors of early mortality after transcatheter aortic valve implantation: individual risk assessment using a simple score. *Heart* 2014;**100**:1016–1023. https://doi.org/10.1136/heartjnl-2013-305314
12. Edwards FH, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, *et al.* Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. *JAMA Cardiol* 2016;**1**:46–52. https://doi.org/10.1001/jamacardio.2015.0326
13. Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, *et al.* Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92. https://doi.org/10.1016/j.jcmg.2018.11.005
14. Musa TA, Treibel TA, Vassiliou VS, Captur G, Singh A, Chin C, *et al.* Myocardial scar and mortality in severe aortic stenosis. *Circulation* 2018;**138**:1935–1947. https://doi.org/10.1161/CIRCULATIONAHA.117.032839
15. Kwak S, Everett RJ, Treibel TA, Yang S, Hwang D, Ko T, *et al.* Markers of myocardial damage predict mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2021;**78**:545–558. https://doi.org/10.1016/j.jacc.2021.05.047
16. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, *et al.* Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:550–563. https://doi.org/10.1016/j.jacc.2019.04.065
17. Elbaz-Greener G, Masih S, Fang J, Ko DT, Lauck SB, Webb JG, *et al.* Temporal trends and clinical consequences of wait times for transcatheter aortic valve replacement: a population-based study. *Circulation* 2018;**138**:483–493. https://doi.org/10.1161/CIRCULATIONAHA.117.033432
18. Albassam O, Henning KA, Qiu F, Cram P, Sheth TN, Ko DT, *et al.* Increasing wait-time mortality for severe aortic stenosis: a population-level study of the transition in practice from surgical aortic valve replacement to transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2020;**13**:e009297. https://doi.org/10.1161/CIRCINTERVENTIONS.120.009297
19. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, *et al.* Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol* 2015;**66**:2827–2838. https://doi.org/10.1016/j.jacc.2015.10.001
20. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation* 2022;**145**:648–658. https://doi.org/10.1161/CIRCULATIONAHA.121.057639
21. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011. https://doi.org/10.1016/S0140-6736(06)69208-8
22. D'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, *et al.* Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE population cohort study. *Eur Heart J* 2016;**37**:3515–3522. https://doi.org/10.1093/eurheartj/ehw229

Contra

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Aortic stenosis (AS) is the most frequent valvular heart disease.[1] Both European and American guidelines recommend aortic valve replacement (AVR) (Class I or IIa) in patients with severe AS exhibiting symptoms and/or left ventricular ejection fraction (LVEF) < 50%.[2,3] However, for asymptomatic patients with severe AS and preserved LVEF, the management and, in particular, the timing of intervention remains highly controversial and challenging and is still based on a relatively lower level of evidence.

What are the current guideline recommendations for the management of asymptomatic severe AS?

Current guidelines recommend that asymptomatic patients with severe AS be followed closely in a heart valve clinic and be referred to a comprehensive heart valve center for confirmation of the indication of AVR and the selection of the type of AVR: i.e. surgical AVR (SAVR) with a mechanical or bioprosthetic valve or transcatheter aortic valve implantation (TAVI) with a balloon-expandable or self-expanding valve.[2,3] This should be a shared decision-making process with particular emphasis on patient preferences. Until now, AVR is not recommended for all patients with asymptomatic severe AS. Indeed, according to the guidelines, AVR is indicated (Class I) if the patient has a LVEF <50% or an indication for another cardiac surgery (Class I) or if symptoms can be demonstrated on exercise testing. However, specifically in such cases, the patient should not be considered as truly asymptomatic. Furthermore, AVR (SAVR or TAVI) may be considered (Class IIa) in the presence of specific risk markers (*Table 1*). Several studies[4–10] lend support to this recommendation of early AVR in the presence of these risk markers. Nevertheless, these studies are only observational and cannot lead to a high level of evidence. In addition, these studies also show that the majority of asymptomatic patients with severe AS do not present with any of these risk markers and can be safely managed with conservative management.

In light of the current evidence,[9,11] we believe that early 'prophylactic' AVR strategy, i.e. in patients without current indication according to most recent guidelines, should not be applied to all asymptomatic patients but should be individualized by taking into account the patient's risk profile and personal preferences (*Figure 3*) and by addressing the four following key questions: (i) Is the patient really asymptomatic?; (ii) is the stenosis really severe?; (iii) does the risk of conservative management exceed the risk of early AVR?; (iv) does the proven durability of the prosthetic valve match the expected life expectancy of the patient?

Is the patient really asymptomatic?

Many patients with asymptomatic severe AS may have progressively reduced their level of activity to avoid symptoms or may deny or not report their symptoms. This issue is more important in older vs. younger patients and in women vs. men.[12] An exercise test is recommended to unmask symptoms and identify true asymptomatic patients.[11,13] Regrettably, only a minority (6.1%) of asymptomatic patients are submitted to an exercise test as shown in the EURObservational VHD II survey.[14] Previous studies reported that at least one-third of patients claiming to be asymptomatic and submitted to an exercise test actually develop exercise-limiting symptoms.[15] These falsely asymptomatic patients have an increased risk of adverse events in the short term and have a Class I indication for AVR according to current guidelines. Das *et al.* reported that the positive predictive value of exercise testing was good (79%) in patients younger than 70 years but only 57% for the older population.[15] These findings underline the limitations of exercise test in the elderly population and provide an argument for the utilization of other tools to identify the asymptomatic patients who are at higher risk for adverse events and who may benefit from early AVR.

Is aortic stenosis really severe?

AS is considered severe when peak aortic velocity is ≥4 m/s, mean transvalvular pressure gradient is ≥40 mmHg, and aortic valve area (AVA) is <1.0 cm^2 (or <0.6 cm^2/m^2). However, AVA may be underestimated and thus AS severity may be overestimated because of the underestimation of left ventricular outflow tract diameter by echocardiography, which is squared in the continuity equation. Furthermore, Doppler echocardiography may overestimate pressure gradient and thus AS severity because of the pressure recovery phenomenon. Peak aortic jet velocity and pressure gradients and thus severity may also be underestimated if meticulous multiwindow interrogation with continuous-wave Doppler is not performed. Indeed, the exclusion of non-apical windows may result in the misclassification of AS severity in a significant proportion of patients. Hence, in asymptomatic patients with apparently severe AS, it is first essential to rule out measurements errors and to use additional parameters of AS severity to confirm the presence of true severe AS, particularly in patients with discordant grading at echocardiography (i.e. severe AVA but non-severe gradient). These parameters include Doppler velocity index < 0.25 to corroborate AVA, energy loss index < 0.55 cm^2/m^2 to account for pressure recovery, and computed tomography aortic valve calcium score >1200 AU in women and >2000 AU in men to assess the anatomic severity of AS.

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Table 1 Indications for intervention in asymptomatic severe AS according to European guidelines

Criteria	Class of indication and LOE	Comments
LVEF <50%	I, B	Applicable to very few (<2%) asymptomatic patients with severe AS and no CAD
Symptoms during exercise	I, C	If not, patients should be considered as truly asymptomatic
LVEF <55%[a]	IIa, B	Recommendation only based on retrospective studies
Sustained fall in blood pressure >20 mmHg during exercise	IIa, C	Despite being supported by pathophysiologic mechanisms, limited data are available. Recommendation requiring further investigation
LVEF >55% and: Very severe AS (mean gradient ≥60 mmHg or V_{max} >5 m/s) - Severe valve calcification and V_{max} progression ≥0.3 m/s/year - Elevated BNP levels (>three-fold higher than age- and sex-corrected normal range)	IIa, B	– Supported by strong evidence but true asymptomatic patients rarely have very severe AS. - CT is the gold standard for aortic calcium score measurement. V_{max} progression is limited by measurement inter- intra-variability that may exceed the proposed cut-off. - Need to be cautiously interpreted in the context of patients with comorbidities

[a] < 60% in US guidelines when a progressive decrease in LVEF is observed in at least three serial imaging studies.
LOE, level of evidence; LVEF, left ventricular ejection fraction; AS, aortic stenosis; CAD, coronary artery disease; BNP, brain natriuretic peptide; CT, computed tomography.

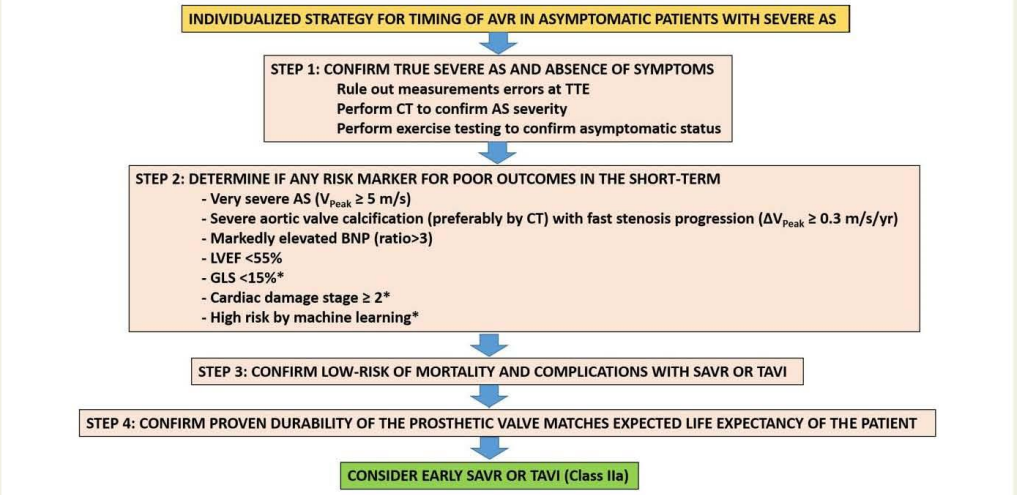

Figure 3 Individualized strategy for the management of asymptomatic severe aortic stenosis. *These are risk markers that are not presented in the guidelines and that will thus require further validation to be adopted in clinical practice. AVR, aortic valve replacement; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; V_{Peak}, peak aortic jet velocity; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Does the risk of conservative management exceed the risk of early AVR?

AVR consists in replacing a severe native aortic valve disease with another hopefully milder disease, which is the prosthetic valve. Early intervention is associated with a substantial risk of procedural mortality and complications including bleeding, coronary obstruction and myocardial infarction, stroke, permanent pacemaker implantation, and non-structural valve dysfunction (paravalvular regurgitation and prosthesis-patient mismatch). Furthermore, an earlier intervention will expose the patients, sooner in their life, to the long-term risk of complications related to the prosthetic valve including valve thrombosis,

Table 2 Summary of the design and results of the ongoing randomized trials in asymptomatic severe aortic stenosis

Trial	Location	Design	*n*	Primary outcome	Main inclusion criteria	Main non-inclusion criteria	Sponsor	Comments
Early TAVR—evaluation of TAVR compared to surveillance for patients with asymptomatic severe aortic stenosis. https://clinicaltrials.gov/ct2/show/study/NCT03042104	US and Canada	Randomized (TAVR vs. clinical surveillance). Open label	901	2-year combined all-cause death, all stroke, and unplanned cardiovascular hospitalization.	≥ 65 years old. Severe asymptomatic AS. LVEF ≥50%. Low risk (STS score ≤10).	>3 + mitral and/or aortic regurgitation. Patients unsuitable for TAVI.	Edwards lifesciences	Patients with class IIa indication can be randomized. Highly selected patients. Estimated primary completion date March 2024
EVOLVED—early valve replacement guided by biomarkers of LV decompensation in asymptomatic patients with severe AS. https://clinicaltrials.gov/ct2/show/study/NCT03094143	UK	Randomized (4 arms according to results of cardiac MRI: mid-wall fibrosis or not). Open label.	400	Composite of all-cause mortality or unplanned AS-related hospitalization (mean follow-up of 2.75 years).	Severe asymptomatic AS.	LVEF <50%. Severe aortic or mitral regurgitation. Mild mitral stenosis. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis. Advanced renal impairment.	Academic	Patients with class IIa indication can be randomized. Randomization based on MRI results and not echocardiography. Patients with mid-wall fibrosis despite LVEF >50% will be randomized in no intervention group whereas their prognosis is already known to be reduced in absence of intervention.
EASY-AS—the early valve replacement in severe asymptomatic aortic stenosis study https://clinicaltrials.gov/ct2/show/NCT04204915	UK, Australia and NZ	Randomized (surgery vs. expectant management). Open label.	2844	3-year combined measure of cardiovascular death and hospitalization for heart failure	Severe asymptomatic AS.	Additional severe valvular heart disease. LVEF <50%. Other pre-inclusion cardiac surgery. Co-morbid condition that, in the opinion of the treating cardiologist, limits life expectancy to <2 years	Academic	Patients with class IIa indication can be randomized. No TAVI in the intervention arm.

thromboembolism, haemolysis, structural valve deterioration, valve failure, valve-related reintervention, or death. Furthermore, the risk of sudden cardiac death in asymptomatic patients with severe AS is low (<1% per year) and is actually lower than the risk of operative mortality with SAVR. When considering early AVR in a true asymptomatic patient, it is important to emphasize that AVR has no or minimal potential to improve the patient because he or she is not suffering from any symptom or side effect of the disease prior to AVR. In this context, it is crucial to not deteriorate the symptomatic status and quality of life of the patient with the intervention and to avoid any complication. Hence, early AVR can only be considered in these patients if the risk of procedural mortality and complications is very low.

Adopting a delayed intervention strategy in asymptomatic patients with severe AS may lead to the development of more advanced and potentially irreversible damage and dysfunction of the left ventricle and other cardiac chambers. Using a multi-echocardiographic parameter integrative approach for staging extra-valvular cardiac damage, Tastet *et al.* reported that 61% of patients with asymptomatic severe AS have advanced cardiac damage (i.e. Stage ≥ 2) and these patients display a higher risk of mortality in the short-term and may thus benefit from early intervention.[7] However, in a substantial proportion of these patients, the advanced cardiac damage was likely not related to the AS *per se* but to other comorbidities, therefore undermining the potential benefit of early AVR in these patients. Moreover, close to 40% of the patients in this series were in Stage 0 or 1 (left ventricular damage only), and these patients harbored an excellent mid-term outcome with the management strategy currently recommended in the guidelines, i.e. intervention when symptoms or left ventricular systolic dysfunction develop or when one of the risk markers mentioned above occur.

Does the proven durability of the bioprosthetic valve match the expected life expectancy of the patient?

When selecting a type of AVR and valve substitute, it is essential to match the proven durability of the prosthetic valve vs. the expected life expectancy in order to reduce the risk of reintervention and ensuing complications.[16] Asymptomatic patients with severe AS are generally younger and have longer life expectancy and considering early AVR in these patients inherently raises the requirements in terms of long-term durability of the prosthetic valve. Hence, in most of these patients, the prosthetic valve should have a minimum durability of at least 10, if not 15, years. Few SAVR valves and no TAVI valves have such proven long-term durability, thus further limiting the consideration of early AVR in all asymptomatic patients with severe AS.

Current randomized trials of early AVR vs. conservative management in asymptomatic severe AS

Two small controlled randomized trials have been published until now. Kang et al. randomized 145 patients to early SAVR (within 2 months) vs. conservative management.[17] The primary endpoint, which was the composite of death within 30 days or cardiovascular death during the entire follow-up, occurred in only one patient in the early surgery group vs. 11 of 72 (15.2%) patients in the conservative group. In this group, the incidence of sudden death was 4% at 4 years and 14% at 8 years. There was no operative mortality in both the surgical group and the conservative group (17% submitted to surgery because of acute decompensation). Such outstanding results may be difficult to achieve in real-life practice and in all cardiac surgery centers. There are severe other limitations to this study. First, it included predominantly young patients (average: 64 years) with bicuspid valve disease, and all of them had very severe AS (peak aortic jet velocity > 5 m/s). Furthermore, several patients who developed symptoms did not undergo AVR and were thus not treated according to the guidelines.

The second trial, AVATAR (aortic valve replacement vs. conservative treatment in asymptomatic severe aortic stenosis), randomized 157 patients (mean age 67 years; severe AS using the classical criteria; normal left ventricular function and negative exercise test) SAVR vs. conservative management.[18] The incidence of the primary endpoint, i.e. the composite of all-cause death, acute myocardial infarction, stroke, and unplanned hospitalization for heart failure, was lower in the SAVR vs. conservative management group (hazard ratio 0.46), and operative mortality in the SAVR arm was 1.4%. The sample size was, however, small, and although this was a multicenter trial, 73% of patients were recruited in one center. The study was prematurely stopped because of early superiority in the SAVR arm. There was no difference in cardiovascular death: 9.54% in the early SAVR group vs. 9.09% in the conservative group. The event curves diverged only after 18 months for both all-cause death and heart failure and the indications for delayed surgery in the conservative group were symptom onset (60%), AS progression (16%), and a decrease in LVEF (4%), which can all be identified during appropriate close (every 6 months) follow-up.

These two trials are interesting but do not provide any definitive answer regarding the timing of intervention in asymptomatic severe AS. We must wait for the results of large controlled trials (*Table 2*), such as ESTIMATE (early surgery for patients with asymptomatic aortic stenosis—NCT02627391), early TAVR (evaluation of trans-catheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis—NCT03042104), EVOLVED (early valve replacement guided by biomarkers of left ventricular decompensation in patients with asymptomatic severe aortic stenosis—NCT03094143), and EASY-AS (early valve replacement in severe, asymptomatic aortic stenosis study—NCT04204915). These trials plan to include 360, 901, 1000, and 2844 patients, respectively.

The use of TAVI rather than SAVR in some of these trials may reduce the risk of short-term complications, but there are not yet any large studies on the potential benefits and more importantly the long-term valve durability and outcomes of TAVI in asymptomatic patients with severe AS.

In the event that these trials are positive and demonstrate the superiority of early AVR over conservative management, this would not necessarily imply that the results of these trials apply to all asymptomatic patients with severe AS and that early AVR is the best option for all patients.

Individualized strategy rather than early AVR for all asymptomatic patients with severe AS

The incidence of severe AS is expected to increase markedly in the next decades due to the aging of the population and rise of the prevalence of

cardiometabolic risk factors involved in the initiation and progression of AS.[19] Furthermore, AS is currently under-detected and under-diagnosed[20,21] and the anticipated improvement in screening due to the implementation of digital tools and artificial intelligence may also contribute to the rise in the prevalence of asymptomatic severe AS. In the last 10 years, the number of AS-related interventions (mainly TAVI) has grown exponentially in both the US[22] and European countries.[23]

Currently, these issues may exceed the capacity of interventional cardiology and cardiovascular surgery departments to treat all patients with TAVI or SAVR. As a consequence, the waiting lists for AVR may increase. In the future, the diminished incidence of coronary artery disease due to better prevention may allow the healthcare systems to re-allocate more resources to structural heart diseases. Furthermore, TAVI happened to be futile in a substantial number of patients.[24–26] And finally, it is estimated that about one-third of patients with symptomatic severe AS and Class I indication for AVR ultimately do not receive SAVR or TAVI because of various reasons. Hence, expanding AVR indication to all patients with asymptomatic severe AS may be questionable from both an ethical and healthcare resource standpoint.

Given that current evidence as well as current guidelines do not support the application of an early AVR strategy for all asymptomatic patients with severe AS and the results of the ongoing trials will likely not refute this statement, we would strongly favor the adoption of an individualized strategy including the following steps (*Figure 3*): **Step 1:** Confirm that the patient has true severe AS and is really asymptomatic. **Step 2:** Determine if the patients have any risk marker included in the guidelines (i.e. very severe AS, severe aortic valve calcification with fast stenosis progression, markedly elevated B-type natriuretic peptide, LVEF <55%) as well as other emerging risk markers (i.e. cardiac damage stage ≥ 2; global longitudinal strain <15%, etc.) pending further validation.[7,27] In the future, machine learning algorithm using clinical, imaging, and/or blood biomarker data may help to identify the patients who are at higher risk of poor outcomes in the short term and who may thus benefit from earlier intervention.[28] **Step 3:** Ascertain that the patient has a low risk for mortality and procedural complications with SAVR or TAVI. **Step 4:** Ascertain that the proven durability of the prosthetic valve selected for early AVR matches or exceeds the expected life expectancy of the patient.

If the patients do not meet the criteria described in these four steps, they should probably be managed conservatively. However, this conservative management should not be a passive, i.e. 'wait for symptoms' strategy but rather an active clinical surveillance with regular (every 3 to 6 months) clinical, echocardiographic, and blood biomarkers follow-up, ideally conducted in the context of a dedicated heart valve clinic.[4,10,29]

In conclusion, early AVR is likely not the optimal strategy for all patients with asymptomatic severe AS. We rather advocate for an individualized strategy that would determine the best management for the given patient according to his or her risk profile, preferences, and life expectancy.

Declarations

Disclosure of Interest

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References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al.* Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;**76**:2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010
2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.* 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:563–632. https://doi.org/10.1093/eurheartj/ehab395
3. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol* 2021;**77**:450–500. https://doi.org/10.1016/j.jacc.2020.11.035
4. Zilberszac R, Lancellotti P, Gilon D, Gabriel H, Schemper M, Maurer G, *et al.* Role of a heart valve clinic programme in the management of patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2017;**18**:138–144. https://doi.org/10.1016/j.jcmg.2016.05.015
5. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, *et al.* Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;**343**:611–617. https://doi.org/10.1056/NEJM200008313430903
6. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–2270. https://doi.org/10.1161/01.cir.95.9.2262
7. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, *et al.* Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:550–563. https://doi.org/10.1016/j.jacc.2019.04.065
8. Sá MPBO, Cavalcanti LRP, Neto ACAE, Perazzo AM, Simonato M, Clavel MA, *et al.* Early aortic valve replacement versus watchful waiting in asymptomatic severe aortic stenosis: a study-level meta-analysis. *Structural Heart* 2019;**3**:483–490. https://doi.org/10.1080/24748706.2019.1652946
9. Lindman BR, Dweck MR, Lancellotti P, Généreux P, Piérard LA, O'Gara PT, *et al.* Management of asymptomatic severe aortic stenosis: evolving concepts in timing of valve replacement. *JACC Cardiovasc Imaging* 2020;**13**:481–493. https://doi.org/10.1016/j.jcmg.2019.01.036
10. Lancellotti P, Magne J, Dulgheru R, Clavel M-A, Donal E, Vannan MA, *et al.* Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol* 2018;**3**:1060–1068. https://doi.org/10.1001/jamacardio.2018.3152
11. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, *et al.* Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol* 2016;**67**:2263–2288. https://doi.org/10.1016/j.jacc.2016.02.057
12. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex differences and similarities in valvular heart disease. *Circ Res* 2022;**130**:455–473. https://doi.org/10.1161/CIRCRESAHA.121.319914
13. Redfors B, Pibarot P, Gillam LD, Burkhoff D, Bax JJ, Lindman BR, *et al.* Stress testing in asymptomatic aortic stenosis. *Circulation* 2017;**135**:1956–1976. https://doi.org/10.1161/CIRCULATIONAHA.116.025457
14. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, *et al.* EORP VHD II investigators. Contemporary presentation and management of valvular heart disease: the EURObservational research programme valvular heart disease II survey. *Circulation* 2019;**140**:1156–1165. https://doi.org/10.1161/CIRCULATIONAHA.119.041080
15. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J* 2005;**26**:1309–1313. https://doi.org/10.1093/eurheartj/ehi250
16. Pibarot P, Herrmann HC, Wu C, Hahn RT, Otto CM, Abbas AE, *et al.* Standardized definitions for bioprosthetic valve dysfunction following aortic or mitral valve replacement: jACC state-of-the-art review. *J Am Coll Cardiol* 2022;**80**:545–561. https://doi.org/10.1016/j.jacc.2022.06.00
17. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK Y, *et al.* Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–119. https://doi.org/10.1056/NEJMoa1912846
18. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. *Circulation* 2022;**145**:648–658. https://doi.org/10.1161/CIRCULATIONAHA.121.057639
19. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, *et al.* Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;**62**:1002–1012. https://doi.org/10.1016/j.jacc.2013.05.015
20. Gaede L, Di Bartolomeo R, van der Kley F, Elsässer A, Iung B, Möllmann H. Aortic valve stenosis: what do people know? A heart valve disease awareness survey of over 8,800 people aged 60 or over. *EuroIntervention* 2016;**12**:883–889. https://doi.org/10.4244/EIJY16M06_02
21. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, *et al.* Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE population cohort study. *Eur Heart J* 2016;**37**:3515–3522. https://doi.org/10.1093/eurheartj/ehw229
22. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, *et al.* STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;**76**:2492–2516. https://doi.org/10.1016/j.jacc.2020.09.595

23. Nguyen V, Willner N, Eltchaninoff H, Burwash IG, Michel M, Durand E, *et al.* Trends in aortic valve replacement for aortic stenosis: a French nationwide study. *Eur Heart J* 2022; **43**:666–679. https://doi.org/10.1093/eurheartj/ehab773
24. Puri R, Iung B, Cohen DJ, Rodés-Cabau J. TAVI or no TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225. https://doi.org/10.1093/eurheartj/ehv756
25. Parikh PB. Predicting futility in aortic stenosis: what's the holdup? *J Am Coll Cardiol* 2022; **80**:801–803. https://doi.org/10.1016/j.jacc.2022.06.011
26. Minha S, Marcus G. Can we truly predict futility for TAVR based on pre-procedural indices? *Cardiovasc Revasc Med* 2021;**23**:77–78. https://doi.org/10.1016/j.carrev.2020.11.009
27. `Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, *et al.* Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovasc Imaging* 2019;**12**:84–92. https://doi.org/10.1016/j.jcmg.2018.11.005
28. Sengupta PP, Shrestha S, Kagiyama N, Hamirani Y, Kulkarni H, Yanamala N, *et al.* Artificial intelligence for aortic stenosis at risk international consortium. A machine-learning framework to identify distinct phenotypes of aortic stenosis severity. *JACC Cardiovasc Imaging* 2021;**14**:1707–1720. https://doi.org/10.1016/j.jcmg.2021.03.020
29. Chambers JB, Ray S, Prendergast B, Taggart D, Westaby S, Grothier L, *et al.* Specialist valve clinics: recommendations from the British Heart Valve Society working group on improving quality in the delivery of care for patients with heart valve disease. *Heart* 2013;**99**:1714–1716. https://doi.org/10.1136/heartjnl-2013-303754

Imaging Markers of Left Ventricular Function in Patients with Aortic Stenosis: A Clinical Epidemiology Perspective

Imaging Markers of Left Ventricular Function in Patients with Aortic Stenosis: A Clinical Epidemiology Perspective

La sténose aortique (SA) est la valvulopathie la plus fréquente dans le monde et sa prévalence augmente avec l'âge. L'échocardiographie est l'outil d'imagerie de première ligne pour le diagnostic de la SA et de ses répercussions sur le ventricule gauche (VG). En revanche, les marqueurs d'imagerie permettant une évaluation fine de la fonction VG reste discutés dans ce contexte. L'objectif général de ce travail était, dans une perspective d'épidémiologie clinique, d'identifier des marqueurs d'imagerie de la fonction ventriculaire gauche permettant une meilleure stratification du risque chez les patients atteints de SA, afin, à terme, d'améliorer leur prise en charge et leur devenir. Nous avons démontré, à travers une méta-analyse sur données individuelles, que la mesure de la déformation longitudinale globale du VG permettait de stratifier le risque de mortalité des patients, même en l'absence de symptôme ou lorsque la fraction d'éjection VG était préservée. Nos travaux ont également souligné l'intérêt, pour l'évaluation et la stratification du risque des patients avec SA, d'autres marqueurs d'imagerie tel que la fraction d'éjection de première phase et la dispersion mécanique. S'opposant à la stratégie consistant à proposer une intervention précoce à tous patients asymptomatiques avec SA serrée, l'utilisation de ces marqueurs d'imagerie permettent de mieux caractériser l'impact réel de la SA sur la fonction VG et d'identifier des sous-groupes de patients à plus haut risque d'évènements cardiovasculaires. Nous pourrions ainsi mieux individualiser la prise en charge et optimiser le moment de l'intervention sur la valve. Néanmoins cette approche doit être testée et validée afin de s'assurer de son efficacité et de sa sécurité.

Mots-clés : Epidémiologie, sténose aortique, échocardiographie, marqueurs pronostiques, fonction ventriculaire gauche.

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Aortic stenosis (AS) is the most common valvular heart disease worldwide, and its prevalence increases with age. Echocardiography is the first-line imaging tool for diagnosing AS and its impact on the left ventricle (LV). However, imaging markers for accurate assessment of LV function remain debated in this context. The overall aim of this study was to identify, from a clinical epidemiological perspective, imaging markers of left ventricular function that would enable better risk stratification in patients with AS, with a view to ultimately improving their management and outcome. In a meta-analysis of individual data, we demonstrated that measurement of LV global longitudinal strain can stratify the risk of patient mortality, even in the absence of symptoms or when the LV ejection fraction is preserved. Our work also highlighted the value of other imaging markers, such as first-phase ejection fraction and mechanical dispersion, in assessing and stratifying the risk of patients with AS. In contrast to the strategy of offering early intervention to all asymptomatic patients with tight AS, the use of these imaging markers will enable us to better characterize the true impact of AS on LV function, and identify subgroups of patients at higher risk of cardiovascular events. We could thus better individualize management and optimize the timing of valve intervention. Nevertheless, this approach needs to be tested and validated to ensure its efficacy and safety.

Keywords: Epidemiology, aortic stenosis, echocardiography, prognostic markers, left ventricular function