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STATE-OF-THE-ART PAPER

Management of Asymptomatic Severe Aortic Stenosis

Evolving Concepts in Timing of Valve Replacement

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ABSTRACT

New insights into the pathophysiology and natural history of patients with aortic stenosis, coupled with advances in diagnostic imaging and the dramatic evolution of transcatheter aortic valve replacement, are fueling intense interest in the management of asymptomatic patients with severe aortic stenosis. An intervention that is less invasive than surgery could conceivably justify pre-emptive transcatheter aortic valve replacement in subsets of patients, rather than waiting for the emergence of early symptoms to trigger valve intervention. Clinical experience has shown that symptoms can be challenging to ascertain in many sedentary, deconditioned, and/or elderly patients. Evolving data based on imaging and biomarker evidence of adverse ventricular remodeling, hypertrophy, inflammation, or fibrosis may radically transform existing clinical decision paradigms. Clinical trials currently enrolling asymptomatic patients have the potential to change practice patterns and lower the threshold for intervention. (J Am Coll Cardiol Img 2019;■:■-■)

Aortic stenosis (AS) is the most common heart valve lesion encountered in clinical practice and affects 2% to 5% of older adults (1). Statistical modeling has suggested an incidence rate of severe AS of ~4% to 7% per year among persons ≥65 years of age (2). These estimates, coupled with an expanding older population, have significant implications for both resource allocation and public health. In addition, there is concern that many patients with AS are either not recognized or not referred for evaluation and treatment (3), emphasizing the need for both broad-scale educational programming and health system redesign.

The etiology of AS is largely accounted for by congenital, degenerative, and rheumatic processes. The common pathways of progressive valvular fibrosis and calcification lead to gradual orifice obstruction and left ventricular (LV) pressure

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CAD = coronary artery disease

CMR = cardiac magnetic resonance

EACTS = European Association for Cardio-Thoracic Surgery

EF = ejection fraction

ESC = European Society of Cardiology

GLS = global longitudinal strain

hsTnI = high-sensitivity troponin I

LGE = late gadolinium enhancement

LV = left ventricular

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

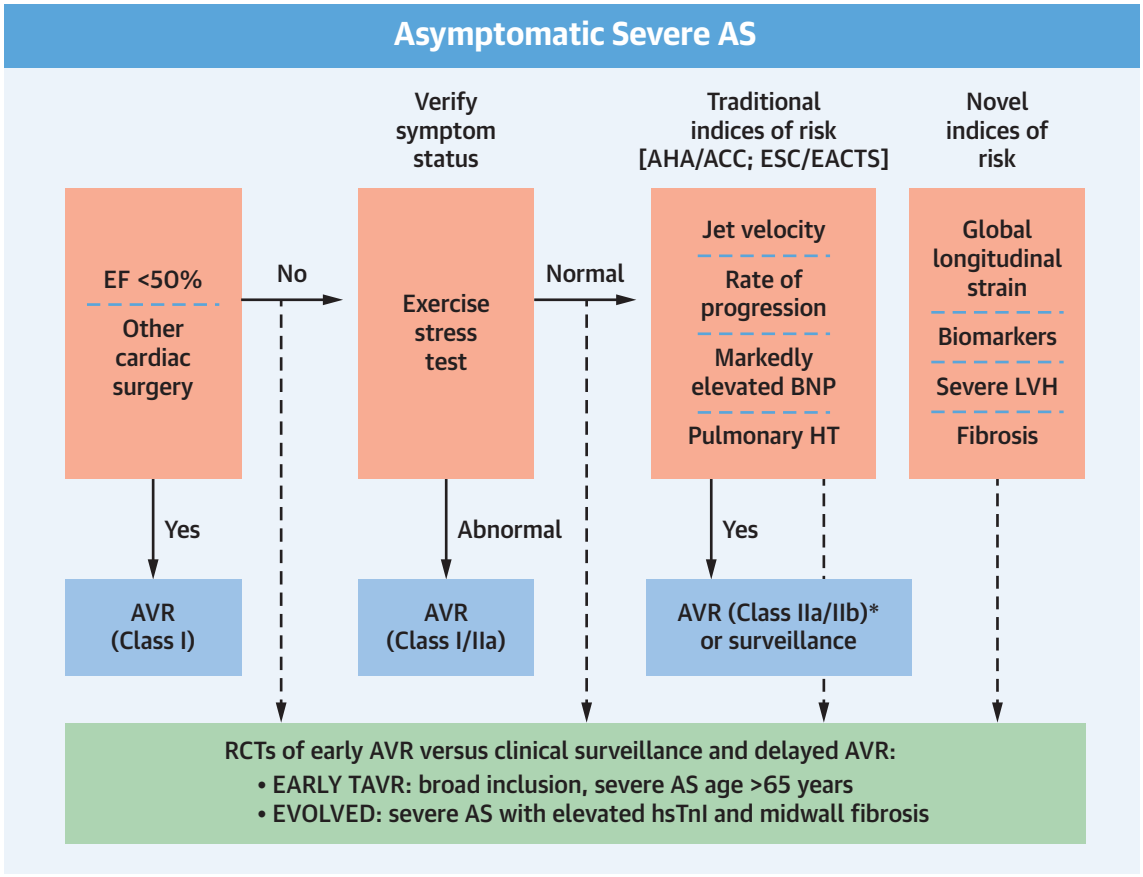
overload and eventually symptoms, the onset of which herald a fatal course over 2 to 3 years if not corrected with aortic valve replacement (AVR). To date, there is no medical therapy available to either retard or correct these processes.

The foundational principles of managing patients with AS derive from the seminal natural history study of a relatively small cohort of younger patients published by Ross and Braunwald (4) a half-century ago and validated subsequently by more recent reports (5). Patients at risk of AS, such as those with a congenitally bicuspid valve or childhood rheumatic fever, experience a long, latent phase during which progressive valve obstruction occurs but clinical events, including sudden cardiac death (estimated annual risk ~1.0%), are infrequent, such that the mortality risk of intervention (i.e., AVR) during this asymptomatic period is believed to exceed that associated with active surveillance. A strategy of expectant but vigilant management in which intervention is triggered by the development of symptoms or LV systolic dysfunction has heretofore appeared safe even for patients with severe or very severe AS followed up longitudinally with clinical and echocardiographic monitoring (6–8). The Class I recommendations for AVR in patients with severe AS from the updated American Heart Association/American College of Cardiology (ACC/AHA) and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) clinical practice guidelines (9,10) are predicated on these fundamental observations.

However, the treatment paradigm has become more nuanced over time with the recognition that conservatively managed asymptomatic patients with severe AS in other observational series have fared less well (11,12) and that outcomes after AVR have improved significantly over time. Analyses comparing early surgical AVR (SAVR) (i.e., within 3 months of recognition of severe AS) with an expectant approach, including delayed intervention following the emergence of traditional Class I triggers, have suggested a survival advantage for early SAVR (13,14). A study-level meta-analysis of 4 such investigations comprising 2,486 patients reported a pooled unadjusted all-cause mortality risk ratio of 0.29 (95% confidence interval: 0.17 to 0.51) for early SAVR compared with a conservative strategy (15). It is fair to ask whether waiting for symptoms to occur or LV function to decline may endanger patients in ways not previously appreciated. This challenge is especially poignant if patients cannot be followed up closely and at frequent intervals. Identification of asymptomatic AS patients at higher risk for death or the imminent need for AVR during follow-up has been the subject of intense investigation and has led to several Class II guideline recommendations by which pre-emptive AVR is believed reasonable or could be considered in patients at low surgical risk (9,10). Important risk features include hemodynamic and echocardiographic responses to exercise, AS severity by jet velocity, rate of AS progression, pulmonary hypertension not explained by another cause, and markedly elevated brain natriuretic peptide levels. There is also widespread interest in the potential for indices of global longitudinal strain (GLS) and cardiac magnetic resonance (CMR)-detected myocardial fibrosis to aid in AS risk stratification (16,17) (**Central Illustration**). Application of several Class II recommendations for AVR in asymptomatic AS patients has become more commonplace in practice. A more in-depth discussion of the evaluation and use of early risk features to inform management of the asymptomatic AS patient is the subject of the current review.

It is recognized that the renaissance engendered by the development and explosive growth of transcatheter AVR (TAVR) over the past decade, enabled by the iterative improvements in devices, catheters, multimodality imaging, patient selection and outcomes, has fueled increasing interest in revisiting traditional treatment paradigms for patients with severe AS. Indeed, a level of clinical equipoise regarding the management of patients with severe asymptomatic AS has been reached that would not previously have been anticipated and now finds itself expressed in strategy trials comparing immediate AVR versus clinical surveillance with deferred AVR when symptoms develop. Some of these trials are more broadly inclusive, most notably the randomized trial of Edwards Sapien 3 TAVR versus active surveillance in the EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104) trial. The trial protocol mandates the use of exercise testing in most patients, performance on which must be considered normal before randomization. Other strategy trials enrolling patients with severe asymptomatic AS will restrict enrollment to patients with high-risk

CENTRAL ILLUSTRATION **Current and Evolving Management Strategies for Patients With Asymptomatic AS**



Lindman, B.R. et al. J Am Coll Cardiol Img. 2019;■(■):■–■.

Evaluation and treatment of patients with asymptomatic severe aortic stenosis (AS). Beyond determination of left ventricular ejection fraction (EF) and verification of asymptomatic status with exercise testing, there are several established indices of disease severity supported by the American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines as well as evolving novel indices. These are now being testing in randomized controlled trials (RCTs) to determine if early aortic valve replacement (AVR) results in better outcomes than traditional clinical surveillance until onset of symptoms. BNP = brain natriuretic peptide; EARLY TAVR = Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; EVOLVED = The Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; HT = hypertension; LVH = left ventricular hypertrophy. *AVR is recommended using these criteria only if asymptomatic patients are considered low-risk candidates for surgical AVR.

features, such as EVOLVED (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143) trial, which will enroll asymptomatic patients with evidence of myocardial fibrosis. These randomized strategy trials and ongoing and future research on particular high-risk features are anticipated to have a significant influence on the clinical management of patients with severe asymptomatic AS.

THE CASE FOR ECHOCARDIOGRAPHY AND EXERCISE TESTING

DISEASE SEVERITY AND PROGRESSION. Echocardiography remains a widely used imaging modality for initial and serial assessment of asymptomatic patients with AS (Figure 1). Numerous studies indicate that several echocardiographic criteria, including stenosis severity, degree of calcification, and disease progression, are associated with clinical

outcomes (18). Peak aortic jet velocity (V_{max}) is a robust prognostic parameter in AS, with increasing event rates as patients progress from mild (<3 m/s) to moderate (3 to 4 m/s), severe (>4 m/s), and very severe (>5 m/s) stenosis (6,8,19). Although the majority of "events" in previous studies have been the development of symptoms warranting AVR, the recent HAVEC (Heart Valve Clinic International Database) registry, reporting the natural history in 1,375 asymptomatic patients with AS (20), confirmed that very severe AS (peak velocity >5 m/s) is predictive of all-cause mortality during the natural history of AS without AVR (4-year survival: 83 ± 6% vs. 20 ± 17% in those with peak velocities <5 m/s vs. >5 m/s, respectively; $p < 0.05$) and also in those who undergo AVR (4-year post-operative survival: 78 ± 4% vs. 65 ± 10%; $p < 0.05$). Although current guidelines recommend consideration of AVR in patients with V_{max} >5 to 5.5 m/s if the estimated surgical risk is low (Class IIa, Level of Evidence: C) (9,10), these hard endpoints from the HAVEC registry may justify consideration of a stronger recommendation.

Patients with rapid progression of AS severity (peak jet velocity increase >0.3 m/s/year) and moderate or severe valve calcification have a rate of symptom development or mortality of 79% at 2 years (7). Although this observation derived from a single limited observational study (and despite the high variability in the serial measurement of peak velocity in practice), it is classified as a Class IIa recommendation for AVR (9,10).

An increase in global (valvular and vascular) afterload, as assessed by the valvulo-arterial impedance (>5 mm Hg/ml/m^2) is also a marker of poor clinical outcome and poor hemodynamic capacity, although data are limited in asymptomatic patients (18,21).

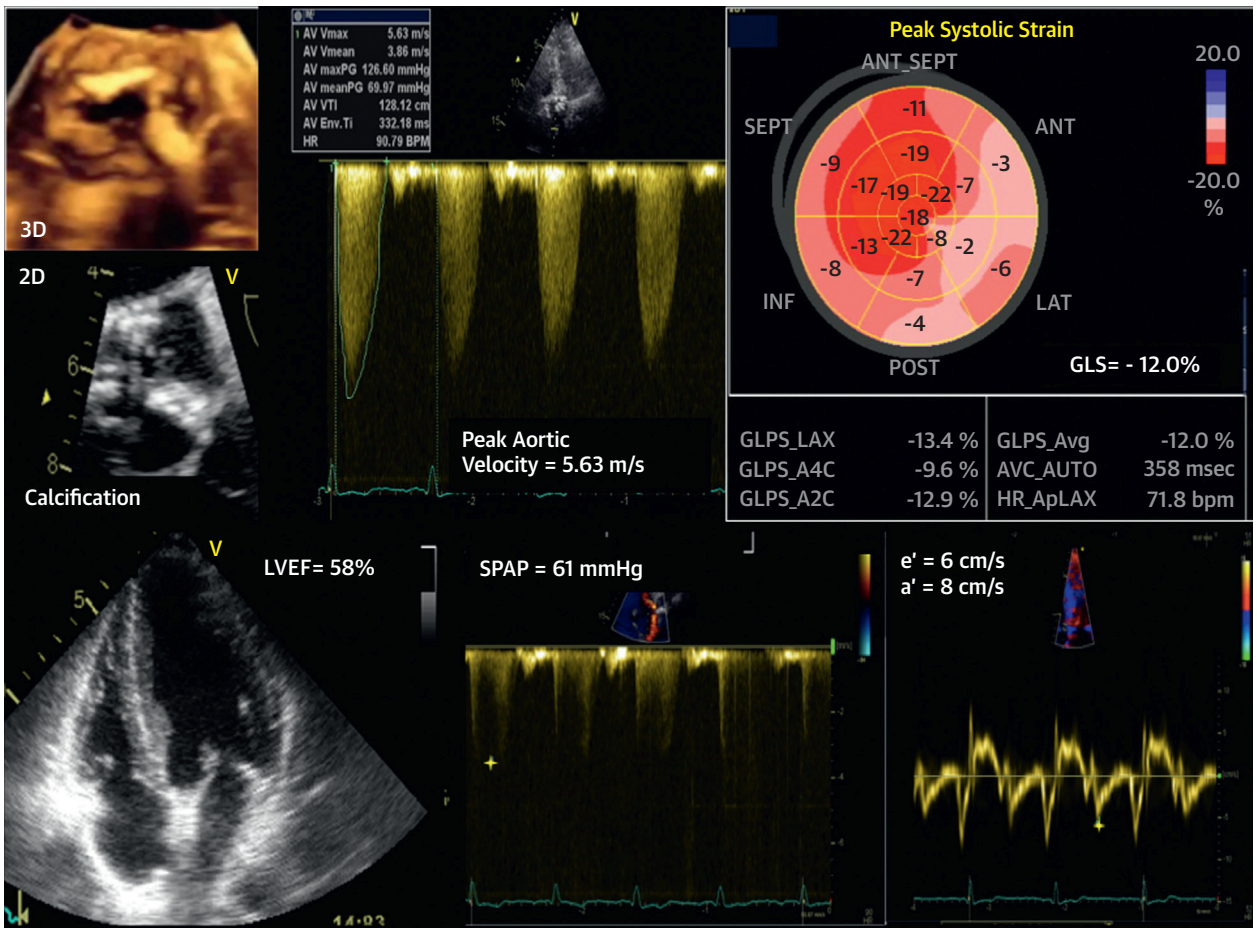
LV FUNCTION, REMODELING, AND STRAIN. The chronic increase in global afterload inevitably leads to cardiac remodeling, most often in the form of hypertrophy and associated myocardial fibrosis (22,23). Initially, the LV ejection fraction (EF) tends to increase and, as such, supranormal values of LVEF (>60%) are common. However, if untreated, progressive impairment of LV systolic function is indicative of the afterload mismatch and, at some degree, of the presence of myocardial fibrosis, which may be irreversible (23,24). In ~25% of patients, LVEF does not improve after AVR, which is associated with adverse long-term outcomes (25,26). Currently, LVEF <50% is considered the appropriate threshold for defining LV systolic dysfunction and referring asymptomatic AS patients to AVR (9,10). In the HAVEC registry, patients with EF between 50% and 59% had less favorable outcomes and experienced more heart failure-related deaths than those with EF >60% (4-year survival: 68 ± 4% vs. 87 ± 2% in those with EF <60% vs. ≥60%, respectively; $p < 0.05$), even after AVR (20). These data reinforce observations from previous retrospective studies (27,28) and provide support for a threshold of LVEF <60% instead of <50% to define dysfunction.

Although the finding of excessive LV hypertrophy in the absence of hypertension was removed from guidelines for AVR indication (9,10), inappropriate high LV mass (>110% of that expected for body size, sex, and wall stress) heralds a significant increased risk of mortality independent of other known risk factors (29).

Reduced LV GLS is an early marker of impaired contractile function when EF is still preserved and is also associated with the presence of myocardial fibrosis (30–32). Emerging data indicate that GLS may have important prognostic potential in patients with preserved EF, although the majority of patients studied to date have been symptomatic, including those undergoing AVR (16,33,34). Small series in asymptomatic patient have also linked GLS with subsequent cardiac events (18,35) and worsening of strain abnormalities as AS progresses despite the lack of a simultaneous fall in EF (36). The risk of death for patients with an absolute GLS <14.7% has been shown to be 2.5-fold higher in a recent individual participant data meta-analysis (37). Although the precise role and threshold used for clinical decision-making require further study, evidence is accumulating for the prognostic significance of impaired GLS in patients with significant AS and preserved EF.

LEFT ATRIAL SIZE AND PULMONARY HYPERTENSION. Left atrial size increases with worsening diastolic dysfunction, reflects the magnitude and the chronicity of increased LV filling pressure, and is associated with cardiac events in patients with AS (18). Although conventional diastolic parameters (E/A, E/e′) are not related to symptomatic deterioration, reduced mitral annulus systolic and late diastolic velocity (s′ <4.5 cm/s, a′ <9 cm/s) are associated with cardiac events, including AVR (38). Pulmonary hypertension is a sign of advanced disease stage and is a robust prognostic parameter in AS (39–41). European guidelines recommend consideration for AVR (Class IIa) in patients with pulmonary artery systolic pressure >60 mm Hg at rest confirmed by invasive measurement (without other explanation) and if the risk of intervention is low (10).

FIGURE 1 **Echocardiography in an Asymptomatic Patient With Severe Aortic Stenosis**



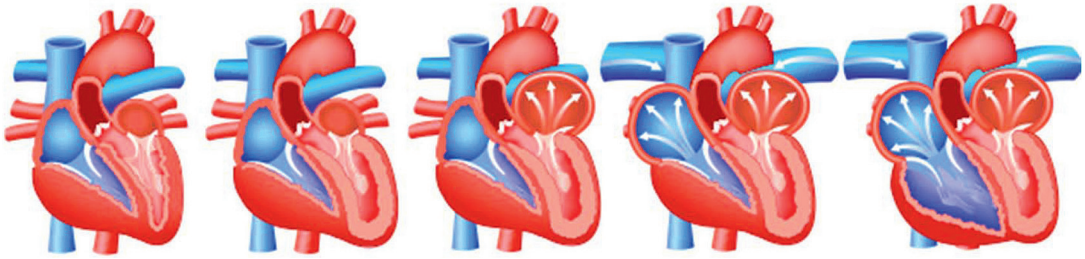
Echocardiography in an asymptomatic patient with severe aortic valve calcification (two- and three-dimensional short-axis views), very severe aortic stenosis (AS) (peak velocity >5 m/s), preserved left ventricular ejection fraction (LVEF) (but LVEF <60%), reduced global longitudinal strain (GLS) (<14.7%), pulmonary hypertension (systolic pulmonary hypertension [SPAP] >60 mm Hg), and impaired left atrial function (a′: peak late diastolic velocity by tissue <9 cm/s). All these parameters are associated with poor outcomes.

EXERCISE TESTING. Exercise testing is contraindicated in patients with severe AS and symptoms related to the valve disease. In contrast, exercise testing should be considered in asymptomatic patients with severe AS after a careful history (9,10) as this method may unmask symptoms or abnormal blood pressure responses (42-44). However, there are challenges in interpreting exercise test results, particularly in patients with baseline electrocardiogram abnormalities (6). Up to 20% of patients with AS are unable to perform a stress test due to poor mobility, and impaired exercise capacity and exertional dyspnea may be related to physical deconditioning independent of AS severity. Although a negative exercise test result is a reassuring finding in younger patients, the predictive value of the test is lower in older adults and may be further improved when combined with echocardiographic assessment of LV function, transvalvular pressure gradients, and pulmonary arterial pressure (39,43-47). However, current guidelines do not recommend exercise echocardiography in asymptomatic patients with AS, and its role in patient management requires further investigation.

THE CASE FOR STAGING OF AS SEVERITY

Stratification and recommendations for AVR in patients presenting with AS rely mainly on 2 criteria: 1) the demonstration of severe stenosis based on valvular criteria, including V_{max}, mean gradient, and aortic valve area (AVA) or aortic valve area index; and

FIGURE 2 **Risk Stratification of Aortic Stenosis Based on the Extent of Cardiac Damage**



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

Reproduced with permission of European Society of Cardiology from Genereux et al. (48). LV = left ventricular; RV = right ventricular.

2) the presence or absence of symptoms related to AS (9,10). In addition, risk stratification of patients being considered for AVR is currently based on surgical risk scores (e.g., the Society of Thoracic Surgeons [STS] Predicted Risk of Mortality Score) and the presence of additional comorbidities (e.g., frailty, chronic obstructive pulmonary disease, renal failure). The current AVR decision algorithm does not take into consideration the importance of anatomical or functional cardiac consequences of AS with the exception of reduced LV systolic function, defined as an LVEF <50%.

NOVEL STAGING CLASSIFICATION BASED ON THE EXTENT OF CARDIAC DAMAGE. Recently, a novel anatomic and functional cardiac staging classification was described for patients with severe AS undergoing AVR that was based on the extent of extravalvular cardiac "damage" (48). In this study, 1,661 patients with severe AS undergoing TAVR or SAVR in the PARTNER 2 (Placement of Aortic Transcatheter Valves 2) trials were pooled and classified in different stages according to the presence or absence of cardiac damage as detected by pre-AVR: no extravalvular cardiac damage (stage 0), LV damage (stage 1), left atrial or mitral valve damage (stage 2), pulmonary vasculature or tricuspid valve damage (stage 3), or right ventricular damage (stage 4) (**Figure 2**). At 1 year, all-cause death and cardiac death significantly increased with each stage of worsening cardiac damage. Furthermore, after multivariable analysis and when tested in multiple models, stage of cardiac damage was shown to be significantly associated with 1-year death, with an adjusted mortality hazard ratio of ~1.45 with each increase in stage, even after adjusting for frailty and STS score. This new multiparametric staging classification objectively characterized the extent of anatomical and functional cardiac damage associated with AS before AVR and illustrated the important prognostic implications after AVR.

Admittedly, this staging system was derived in symptomatic patients at intermediate surgical risk (48). The components of each stage are not specific for AS alone, and higher stages could reflect the effect of cumulative cardiac and noncardiac comorbid factors that contribute to poor outcomes after AVR, including concomitant coronary artery disease (CAD), hypertension, atrial fibrillation, and chronic lung disease. Further studies are needed to prospectively validate this classification across different AS severities (i.e., mild, moderate, and severe) and to define whether it could be integrated with the existing

algorithms in guiding the timing of AVR for asymptomatic patients with AS.

THE CASE FOR BLOOD BIOMARKERS

Blood biomarkers offer the promise of a simple, accessible way to gather additional information that might refine or clarify patient risk and optimize recommendations regarding the timing of AVR. Although all patients with severe AS might not benefit from AVR before symptoms occur, circulating biomarkers could conceivably identify a subgroup of patients who may benefit from earlier AVR.

Biomarkers may refine assessment of the relative adaptive versus maladaptive nature of the hypertrophic remodeling that occurs in response to progressive valve obstruction and pressure overload (**Figure 3**). Several studies have now documented that increased LV hypertrophic remodeling is associated with worse systolic function, worse heart failure symptoms, and increased mortality, but cardiac hypertrophy in response to pressure overload is not simply all good or all bad; both adaptive and maladaptive processes are involved (49-54). LV mass and geometry are only part of the story; the composition and energetics of the myocardium are also important (54). For example, it is now clear that cardiac fibrosis is associated with impaired symptomatic improvement and increased mortality after AVR, but the amount of fibrosis is not strongly related to the degree of hypertrophic remodeling (30). Accordingly, simplistic cut-points to trigger surgical referral based on the LV mass or geometry will likely be too insensitive and nonspecific.

The ability to characterize the myocardial tissue in patients with LV hypertrophy could be helpful as a complement to measures of mass and geometry, offering more insight into the health of the hypertrophic remodeling response. Results of myocardial biopsy could provide this information, but it is an expensive, invasive procedure with sampling bias. CMR can detect myocardial fibrosis via late gadolinium enhancement (LGE) or measurement of extracellular volume with T1 mapping, but these methods are expensive and not widely available. Circulating biomarkers offer a simple, accessible alternative, albeit more indirect, to gain insight into the health of the hypertrophic remodeling response in patients with AS. For example, preclinical studies have shown the role that markers such as sST2, GDF15, and high-sensitivity troponin play in the biology of hypertrophic remodeling, and studies in non-AS and AS populations have reported their association with prognosis (22,55-61).

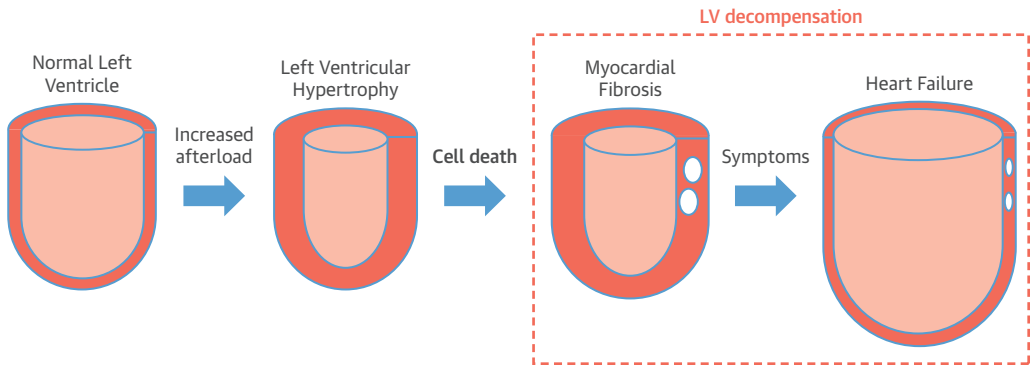
To date, most biomarker studies involving patients with valvular heart disease in general and AS in particular have focused on the natriuretic peptides (62-65). Collectively, these studies show an association between natriuretic peptide levels and symptom/event-free survival and post-operative symptoms, LV function, and mortality. However, the biology of the hypertrophic remodeling response to pressure overload is more complex than altered myocardial stretch and strain. More recent studies have evaluated the association between other biomarkers, including multiple biomarkers in combination, and outcomes in patients with AS (60,61,65-68).

Despite these studies, the AHA/ACC and ESC/EACTS guidelines do not offer a clear role for biomarkers in the management of patients with AS (9,10). The AHA/ACC guidelines make no mention of biomarkers, whereas the ESC/EACTS guidelines currently indicate that valve replacement is reasonable (Class IIa) in an asymptomatic patient with a "markedly elevated natriuretic peptide level" defined as levels 3-fold greater than the age- and sex-corrected normal range, confirmed by repeated measurements without other explanations (10).

Further investigation is needed to show an adverse association between increased levels of certain biomarkers and clinical outcomes before they can be incorporated into the clinical management of patients with asymptomatic AS. Although data suggest the possibility that asymptomatic patients with elevated natriuretic peptide levels or other biomarkers of cardiovascular stress may benefit from earlier AVR (60-62,64,65,68), this theory has not been tested. The same could be said about other threshold values included in the guidelines (e.g., EF, peak aortic jet velocity, mean gradient), but these are well imbedded in clinical decision-making. Adding or comparing a biomarker risk score to existing clinical risk scores should not be the goal, although it may be an intermediate step in providing proof of concept data. Rather, the most likely utility for biomarkers in optimizing the timing of SAVR or TAVR is to identify patients with progressively maladaptive hypertrophic remodeling and subclinical dysfunction that place them at risk for LV impairment and heart failure after AVR if intervention is delayed until development of symptoms or overt evidence of LV systolic function.

Simple dichotomous biomarker cut-points are unlikely to be helpful, as biomarker levels will require accounting for age, sex, race/ethnicity, body size, renal function, and other factors (68). Furthermore, given the complexity of the biology, and as studies in non-AS populations have shown, it is likely that multiple biomarkers will have greater utility than a

FIGURE 3 Left Ventricular Decompensation in Aortic Stenosis



The transition from hypertrophy to heart failure is driven by both progressive myocyte cell death and by myocardial fibrosis. LV = left ventricular.

single biomarker in identifying patients who may benefit from earlier AVR (69). Change versus stability of longitudinal measurements of biomarkers may be more informative than isolated assessments.

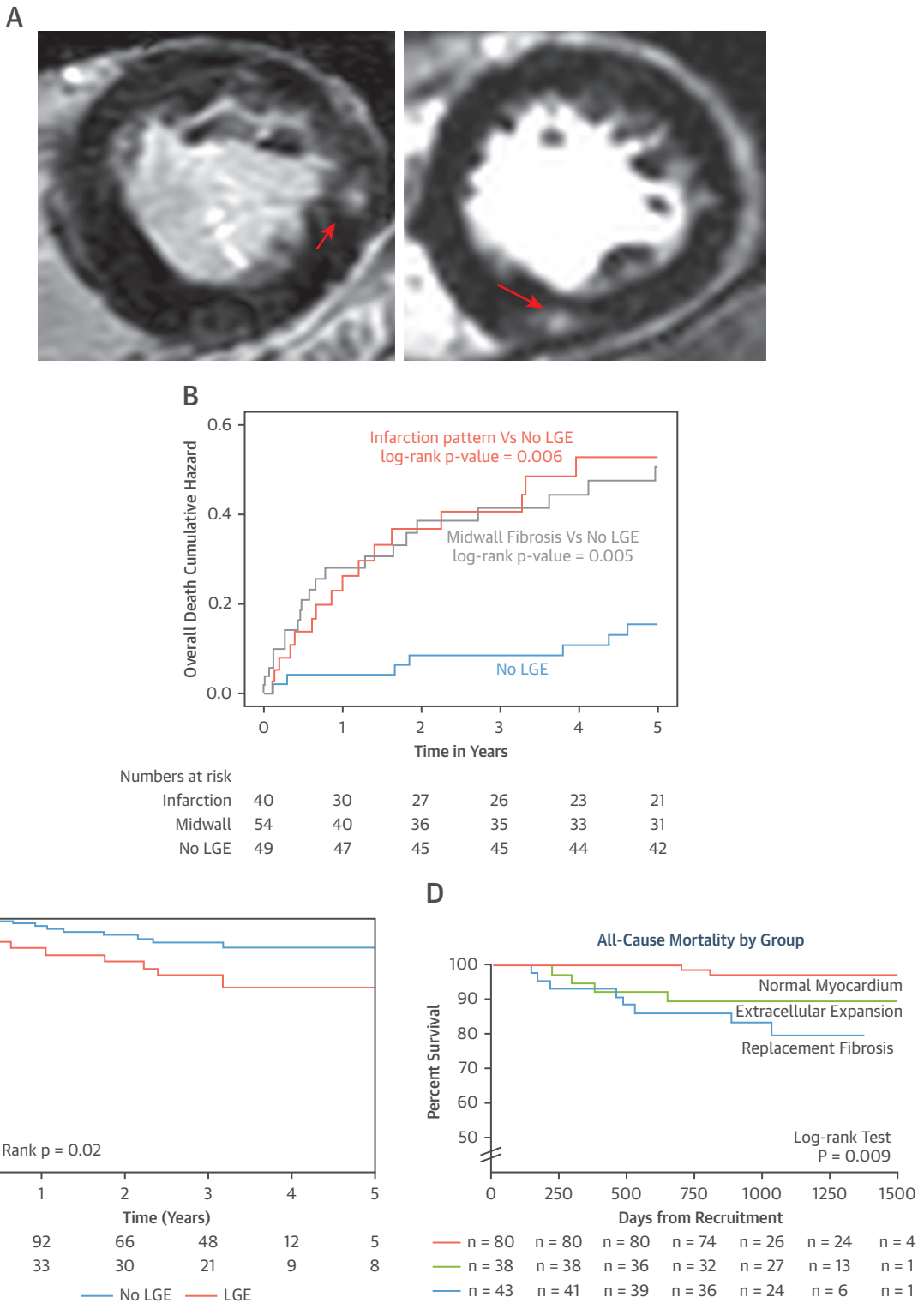
The EARLY TAVR Trial will include a biobank, which should facilitate greater understanding of the role of biomarkers in risk stratification of asymptomatic patients with severe AS. Similarly, high-sensitivity troponin I (hsTnI) is being used in the EVOLVED trial (described in a later section) as a method for selecting high-risk asymptomatic patients most likely to benefit from early AVR.

THE RATIONALE FOR THE EARLY TAVR TRIAL

Although current guidelines recommend AVR for selected patients with asymptomatic severe AS (9,10), in practice, an active surveillance strategy is adopted for the majority of asymptomatic patients, with intervention considered only when symptoms emerge or LV systolic dysfunction develops. This strategy has some well-appreciated practical challenges. It is often challenging for patients and clinicians to interpret symptoms or the lack thereof, particularly in sedentary elderly patients. Delayed reporting of symptoms can result in irreversible myocardial damage with suboptimal outcome after AVR. Given that AS progression is highly variable and unpredictable, rapid deterioration may occur. Operative risk increases with patient age and LV dysfunction. The risk of sudden death in patients with severe AS without classic symptoms has been estimated between 1% and 3% per year, depending on the patient population studied (15,70). Finally, a well-defined and validated algorithm for active surveillance is lacking.

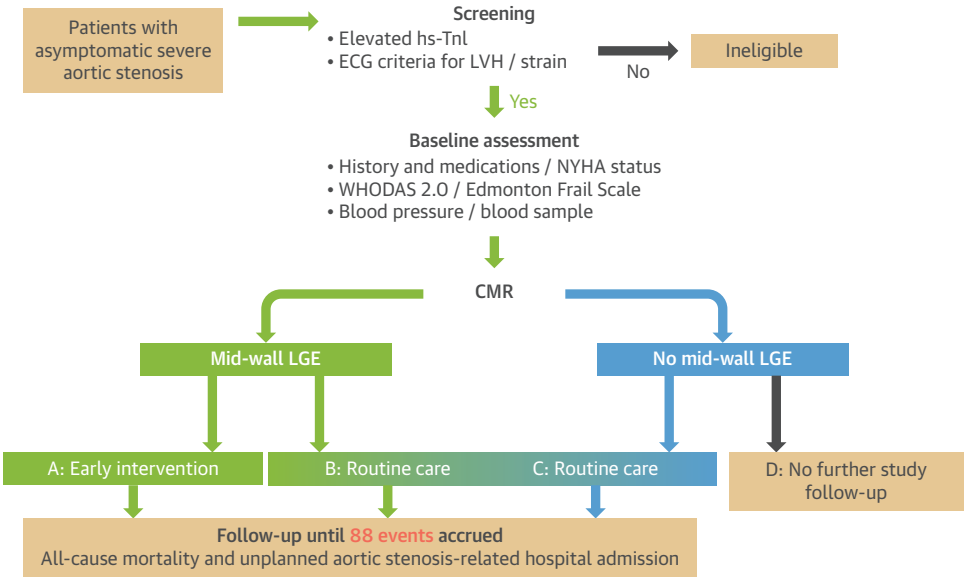
Given the low periprocedural mortality and morbidity rates for isolated AVR in contemporary practice, especially for TAVR, earlier intervention has been increasingly advocated. However, early referral to AVR has never been tested against a conservative strategy of surveillance in patients with asymptomatic severe AS in a randomized trial. The lack of robust data to support guideline recommendations for asymptomatic patients, paired with the emergence of TAVR as a viable and less invasive alternative to SAVR, has led to the conception of the EARLY TAVR trial as cited earlier. This trial is a prospective, randomized controlled, multicenter study, enrolling a total of 1,109 patients. Patients included in this trial must be ≥65 years of age, asymptomatic, and diagnosed with severe AS (defined as AVA ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2 and V_{max} ≥4.0 m/s or mean gradient ≥40 mm Hg). Major exclusion criteria include: STS scores >10%; LVEF <50%; any concomitant valvular, aortic, or CAD requiring surgery; and unsuitability for transfemoral TAVR. Before enrollment, most patients will undergo a low-level treadmill stress test to confirm their asymptomatic status. Patients who cannot safely perform a treadmill stress test (i.e., those with orthopedic issues, frailty, or limited mobility) may also be considered for enrollment in the trial, pending review by a dedicated executive committee. The primary endpoint at 2 years is a composite of all-cause death, all stroke, and unplanned cardiovascular hospitalization, powered for superiority. To complement the EARLY TAVR trial, the pre-defined biomarker substudy (with blood

FIGURE 4 **Midwall LGE in Aortic Stenosis Is Associated With Adverse Long-Term Clinical Outcomes**



Areas of replacement fibrosis can be detected using magnetic resonance imaging and the late gadolinium enhancement (LGE) technique in a midwall distribution **(red arrows)** in patients with aortic stenosis **(A)**. Midwall LGE is associated with an adverse prognosis. Kaplan-Meier curves for all-cause mortality are shown from patient cohorts in **(B)** London (78), **(C)** Brussels (77), and **(D)** Edinburgh (24) and illustrate the poor prognosis associated with midwall LGE compared with patients with no LGE.

FIGURE 5 Summary of Protocol for the EVOLVED Trial



Asymptomatic patients with severe aortic stenosis are first screened for left ventricular decompensation by using high-sensitivity troponin I (hs-TnI) and electrocardiogram (ECG). A total of 1,000 patients at higher risk for left ventricular decompensation (e.g., troponin levels >6.0 ng/l) then proceed to magnetic resonance imaging. Patients with midwall LGE are considered to have objective evidence of left ventricular decompensation and are randomized 1:1 to undergo early surgical aortic valve replacement/transcatheter aortic valve replacement versus routine care. Patients without fibrosis are also randomized to receive treatment. This method will ensure that blinding is maintained among patients undergoing routine care and follow-up who have an equal chance of having or not having midwall fibrosis. CMR = cardiac magnetic resonance; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0.

collected in both randomization arms, at baseline, and pre- and post-TAVR) will provide meaningful biological insight to evaluate the potential benefit of a biomarker-driven early intervention strategy. The results of the EARLY TAVR trial have the potential to substantially influence the future management paradigms for patients with severe asymptomatic AS.

THE CASE FOR MIDWALL FIBROSIS AND THE EVOLVED TRIAL

Histopathological studies have shown that the 2 key processes driving LV decompensation and the transition from hypertrophy to heart failure are progressive myocyte death and myocardial fibrosis (71). Both are therefore important potential biomarkers of LV decompensation. They are believed to develop as a consequence of supply-demand ischemia in a hypertrophied left ventricle that has outgrown its blood supply (72).

Levels of hsTnI now allow detection of low-level myocyte cell death and injury due to a range of different cardiovascular conditions beyond myocardial infarction. In patients with AS, hsTnI levels relate not to the burden of CAD but instead to the magnitude of the hypertrophic response and the presence or absence of myocardial fibrosis (60).

Myocardial fibrosis is also detectable with the use of modern noninvasive imaging techniques. Indeed, CMR can detect areas of replacement fibrosis in patients with AS by using the widely applied LGE technique (73). A midwall pattern of LGE is observed that can be differentiated from scarring due to other causes (e.g., myocardial infarction, cardiac amyloidosis) and that is associated with multiple other markers of LV decompensation such as advanced LV hypertrophy, reductions in diastolic and systolic function, increased symptomatic status, and reduced exercise capacity (**Figure 4**) (23,24,30). Once it first develops, further midwall LGE accumulates rapidly in the ventricle and is irreversible even after AVR (74). As a consequence, the myocardial scarring that patients develop while waiting for AVR persists into the long term, potentially governing myocardial health and adverse events well beyond valve intervention. Consistent with this hypothesis, midwall LGE has

been confirmed as a powerful long-term prognostic marker in several independent studies (23,24,75-78). This occurs in a dose dependent manner, with the more LGE, the higher the rates of adverse cardiovascular events (23). A rationale is therefore evolving to consider whether AVR should be performed when midwall LGE is first identified to prevent further progression of fibrosis and to improve long-term clinical outcomes.

RATIONALE FOR THE EVOLVED TRIAL: TARGETING EARLY AORTIC VALVE INTERVENTION TO PATIENTS WITH OBJECTIVE EVIDENCE OF LV DECOMPENSATION. The EVOLVED study is a multicenter, randomized controlled trial investigating such a strategy and whether objective markers of LV decompensation can be used to optimize the timing of AVR (**Figure 5**). Asymptomatic patients with severe AS will initially be screened for LV decompensation by using hsTnI and electrocardiography. Those patients with a normal level (<6 ng/l) on this simple inexpensive blood marker will be considered to have healthy myocardium and continue to undergo routine clinical follow-up. Patients with an elevated troponin level or an electrocardiographic strain pattern (a marker of myocardial fibrosis) (79) will proceed to CMR to confirm whether they have LV decompensation due to AS. Patients in whom midwall LGE is identified will then be randomized to receive either early AVR (TAVR or SAVR at the discretion of the clinical care team) or the standard watchful waiting approach. The primary endpoint is a composite of all-cause death or unplanned AS-related hospital admission (unplanned admission with syncope, heart failure, chest pain, ventricular arrhythmia, or high-degree atrioventricular block). The study is powered on the basis of 88 events across the patient population.

The aim of this novel approach is to identify both the high-risk patients who will benefit most from early valve intervention and the asymptomatic patients with a healthy myocardium in whom major heart intervention can be safely delayed. EVOLVED will investigate whether this personalized medicine approach can optimize the timing of AVR, improve long-term patient outcomes, and therefore justify the costs of this stratified biomarker/imaging approach.

CONCLUSIONS

As treatment options for managing symptomatic patients with AS expand at an astounding rate, fueled by the TAVR revolution, the diagnostic armamentarium with which to evaluate asymptomatic patients with this condition has also continued to evolve rapidly. Echocardiography will continue to be the clinical workhorse for initial diagnosis and routine re-evaluation. However, echocardiography is also expanding its diagnostic horizons, principally through advances in strain imaging. The coupling of these newer echocardiographic modalities with advanced CMR imaging of myocardial fibrosis and the use of multiple serum biomarkers hold promise for the earlier identification of patients with AS who can be treated effectively before the onset of irreversible structural and functional myocardial changes that would otherwise impair long-term outcomes. Several ongoing strategy trials are enrolling patients with severe asymptomatic AS with or without additional high-risk markers and randomizing them to receive early intervention or clinical surveillance with delayed AVR when symptoms occur. These trials are anticipated to provide long-awaited, important evidence to guide clinical decision-making on the timing of valve replacement for the growing number of patients with asymptomatic AS.

HIGHLIGHTS

- Although AS is the most common heart valve lesion encountered in clinical practice, affecting 2% to 5% of older adults, determining its severity in asymptomatic patients remains problematic.
- New methods of risk stratification for asymptomatic patients with AS are emerging, including circulating biomarkers, Doppler-derived global longitudinal strain, and magnetic resonance assessment of left ventricular myocardial fibrosis.
- Prospective randomized trials are underway for asymptomatic patients with AS to assess timing of aortic valve replacement and determinants of clinical outcomes.

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