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REVIEW

STATE-OF-THE-ART PAPER

Moderate Aortic Stenosis and Heart Failure With Reduced Ejection Fraction

Can Imaging Guide Us to Therapy?

Philippe Pibarot, DVM, PhD,[a] David Messika-Zeitoun, MD,[b] Ori Ben-Yehuda, MD,[c,d] Rebecca T. Hahn, MD,[c,d] Ian G. Burwash, MD,[b] Nicolas M. Van Mieghem, MD, PhD,[e] Ernest Spitzer, MD,[e,f] Martin B. Leon, MD,[c] Jeroen Bax, MD,[g] Catherine M. Otto, MD[h]

ABSTRACT

Clinical management of patients with only moderate aortic stenosis (AS) but symptoms of heart failure with a reduced left ventricular ejection fraction (HFrEF) is challenging. Current guidelines recommend clinical surveillance with multimodality imaging; aortic valve replacement (AVR) is deferred until the stenosis becomes severe. Given the known benefits of afterload reduction in management of patients with HFrEF, it has been hypothesized that AVR may be beneficial in patients with only moderate AS who present with HFrEF. In this article, we first review the current approach for management of patients with moderate AS and HFrEF based on close clinical and imaging surveillance with AVR delayed until AS is severe. We then discuss the case for transcatheter AVR (TAVR) earlier in the disease course, when AS is moderate, based on stress echocardiographic data. We conclude with a detailed summary of the TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure) trial, in which patients with moderate AS and HFrEF are randomized to guideline-directed heart failure therapy alone versus guideline-directed heart failure therapy plus TAVR. (J Am Coll Cardiol Img 2019;12:172–84)

Valvular aortic stenosis (AS) imposes a systolic pressure load on the left ventricle, often exacerbated by concurrent hypertension. Most adults with symptoms resulting from severe AS present with a high velocity (≥4 m/s) and gradient (≥40 mm Hg) across the valve, a small valve area (typically, ≤1.0 cm^2) and a normal left ventricular ejection fraction (LVEF). These patients are classified as high-gradient severe AS (Stage D1) with aortic valve replacement (AVR), either surgical or transcatheter (TAVR), recommended to relieve symptoms and reduce mortality.

Some patients with AS present with LV systolic dysfunction, defined as a LVEF <50%. In these patients, it can be challenging to distinguish severe AS with pressure overload resulting in LV dysfunction

From the [a]Institut Universitaire de Cardiologie et de Pneumologie de Québec/Québec Heart & Lung Institute, Université Laval, Québec, Canada; [b]University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [c]Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York; [d]Cardiovascular Research Foundation, New York, New York; [e]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; [f]Cardialysis, Rotterdam, the Netherlands; [g]Department of Cardiology Leiden University Medical Centre, Leiden, the Netherlands; and the [h]Division of Cardiology, University of Washington School of Medicine, Seattle, Washington. Dr. Pibarot has received funding from Edwards Lifesciences and Medtronic for echocardiography core laboratory analyses in transcatheter heart valves with no personal compensation. Dr. Hahn has received funding from Edwards Lifesciences for echocardiography core laboratory analyses with no personal compensation. Dr. Spitzer has received speaker fees from Edwards Lifesciences. Dr. Messika-Zeitoun is a consultant for Edwards Lifesciences, Mardil, Abbott, and Cardiawave. Dr. Van Mieghem has received research grants from Medtronic, Abbott, Boston Scientific, and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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from moderate AS with concurrent LV dysfunction resulting from primary myocardial disease (1). These patients present with symptoms including a calcified aortic valve with reduced systolic opening, LVEF <50%, resting aortic valve area (AVA) <1.0 cm^2, and a transvalvular velocity (or gradient) between 3 and 4 m/s (mean gradient: 20 to 40 mm Hg). In patients with a low LVEF, severe AS (Stage D2) is defined as an aortic velocity of 4 m/s or higher without an increase in valve area to >1.0 cm^2 on low-dose dobutamine stress echocardiography. In effect, these patients have heart failure with reduced ejection fraction (HFrEF) resulting from severe AS. Both European and American guidelines recommend AVR in these patients to improve symptoms and reduce mortality (2,3). In fact, guidelines recommend AVR for severe AS with low LVEF even in asymptomatic patients. Many of these patients have a dramatic improvement in LVEF after relief of valve obstruction.

Currently, guidelines do not recommend AVR in adults with AS and LV systolic dysfunction when AS severity is moderate at rest and/or on low-dose dobutamine stress echocardiogram. It is obvious, however, that both AS severity and LV systolic dysfunction are continuous variables with conventional definitions of "severe" and "abnormal" based on observational clinical studies (1,4). Given that each incremental increase in AS severity does impose an (albeit small) pressure load on the left ventricle, it has been hypothesized that relief of AS earlier in the disease course might be beneficial, particularly in patients with HFrEF (**Central Illustration**). Even if concurrent primary myocardial disease or secondary myocardial changes are present, afterload reduction might improve LV function and cardiac output, perhaps to even a greater extent than in patients with HFrEF and a normal aortic valve. There is some evidence to support the hypothesis that patients with moderate AS and HFrEF may benefit from AVR (5,6).

This hypothesis is currently being tested in the TAVR UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure) trial, in which patients with moderate AS and HFrEF are randomized to guideline-directed heart failure (HF) therapy alone versus guideline-directed HF therapy plus TAVR (NCT02661451) (7). This trial will provide data to address whether patients with HFrEF, moderate AS, and LVEF <50% will have:

- Improved LV systolic function after AVR;
- Reduced symptoms and improved functional status or exercise capacity;
- Fewer HF hospitalizations; and/or
- Improved long-term survival.

Most important, will the benefits outweigh the risks? Patients randomized to TAVR will be exposed to the morbidity and mortality of this procedure earlier in the disease course than if intervention was delayed until symptom onset. In addition, although TAVR valve durability is excellent at 5 years, we do not yet have robust data on longer-term valve durability; patients randomized to TAVR are likely to experience more incident valve dysfunction than those who delay TAVR until later in life.

In this article, we first review the current approach for management of patients with moderate AS and HFrEF based on close clinical and imaging surveillance with AVR delayed until AS is severe. Next, we discuss the case for TAVR earlier in the disease course, when AS is moderate, based on stress echocardiographic data. We conclude with a detailed summary of the TAVR UNLOAD trial, the results of which will be eagerly awaited.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVA = aortic valve area
AVR = aortic valve replacement
CI = confidence interval
CT = computed tomography
DSE = dobutamine stress echocardiography
HFrEF = heart failure with a reduced left ventricular ejection fraction
HR = hazard ratio
LVEF = left ventricular ejection fraction
LVOT = left ventricular outflow tract
MG = mean pressure gradient
SV = stroke volume
TAVR = transcatheter aortic valve replacement
Z_{va} = valvulo-arterial impedance

CLINICAL SURVEILLANCE USING MULTIMODALITY IMAGING WITH AVR PERFORMED WHEN STENOSIS BECOMES SEVERE

Although the guidelines define LV systolic dysfunction as an LVEF <50%, the exact LVEF threshold and measurement method are debated. Some have proposed using an ejection fraction threshold of 60% (8–11), whereas others highlight the limitation of LVEF as an accurate marker of contractility when associated with concentric LV hypertrophy and suggest that speckle tracking with strain imaging may be a superior method (12,13). Over the past decade, several conceptual issues have emerged that complicate indications for intervention for AS, especially with the availability of TAVR. A more precise definition of severe AS, the recognition of patients with discordant grading of severity (AVA <1 cm^2, but mean pressure gradient [MG] <40 mm Hg), evidence for a low-flow state both in patients with reduced and preserved LVEF, and the concepts of global LV afterload and valvuloarterial impedance have led investigators to consider the potential benefit of AVR in patients with moderate AS (**Central Illustration**). Addressing the management of patients with so-called moderate AS and HFrEF, however, requires answering 2 questions:

1. Is the AS truly moderate?
2. Can HF be explained by a reason other than AS?

In this section, we summarize the safeguards that need to be applied to confirm AS severity and the eventual relationship between AS and HF, and present current data on the prognosis and management of patients with moderate AS and HFrEF.

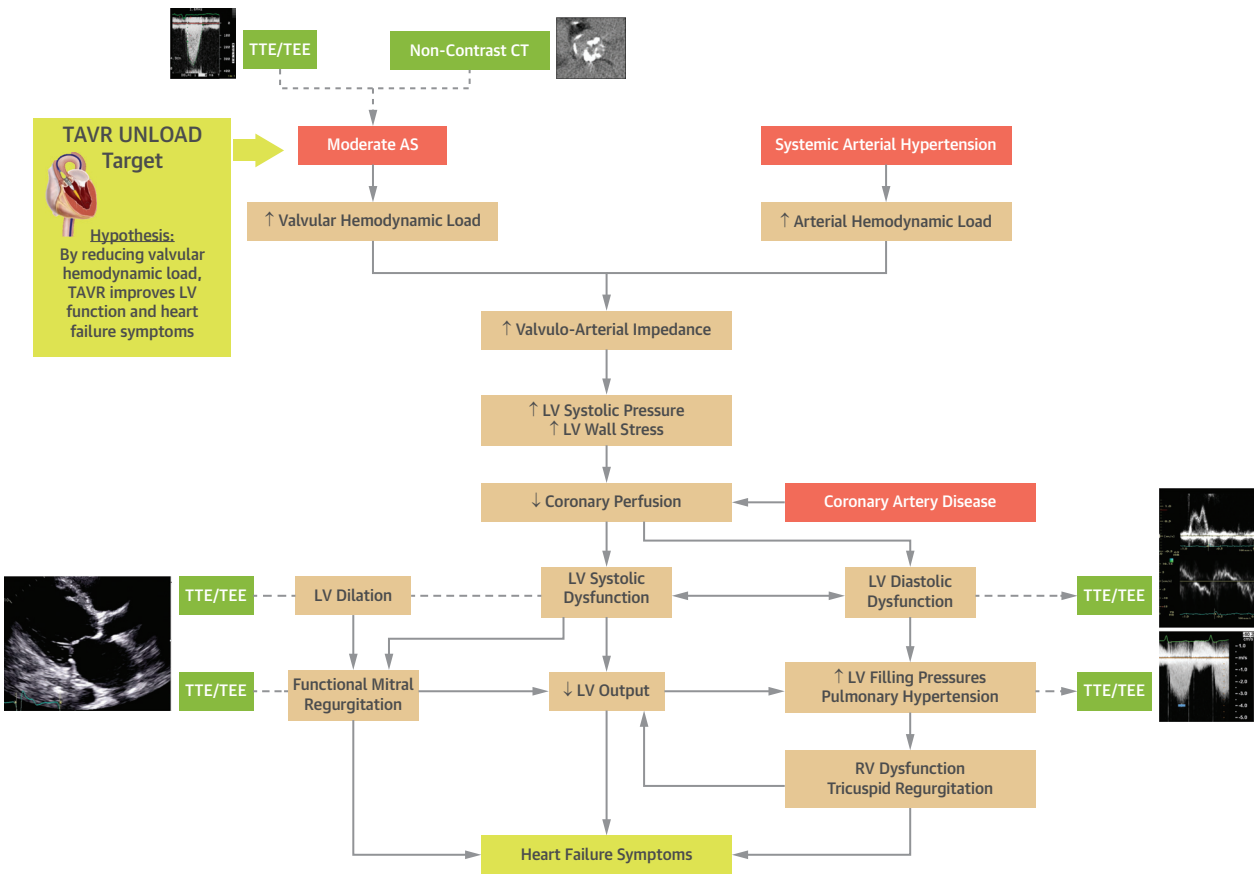
CONFIRMING THE ASSESSMENT OF AS SEVERITY. AS severity relies on 3 main parameters: AVA, maximum velocity, and MG, with the latter 2 being highly correlated. Calculation of AVA by a Doppler-echocardiography continuity equation requires a measurement of LV outflow tract (LVOT) area as well as LVOT/aortic valve time-velocity integrals, with each parameter being a potential source for error. Conventionally, the LVOT area is estimated from the diameter measurement using a circular assumption; however, the LVOT and aortic valve annulus often are more elliptical rather than circular in shape (14). The distance from the aortic valve for measuring the LVOT diameter is debated, but we recommend the level of leaflet insertion ("annulus"). Although an underestimation of the LVOT diameter is more common, overestimation can occur when the LVOT view is oblique and the insertion of the third cusp is included in the image plane (15). In this circumstance, severe AS may be falsely concluded to be moderate. LVOT time-velocity integrals may also be overestimated if measured "too close" to the valve in the region of flow acceleration, or if the outside "envelope" rather than the modal velocity is traced. The importance of this measure is often underemphasized. Finally, obtaining the highest gradient and aortic time-velocity integrals requires interrogating the valve from multiple windows, ideally using a dedicated continuous wave Doppler probe. Failure to interrogate from the right parasternal view may lead to an underestimation of AS severity in 20% of patients and the incorrect classification of severe AS as moderate severity only (16).

After excluding measurement errors, approximately one-third of patients have discordant grading, in which 1 parameter suggests severe AS (usually AVA <1 cm^2), whereas the other suggests moderate AS (MG <40 mm Hg) (17,18). To resolve these discrepant cases, some authors propose an AVA cutoff value <0.8 cm^2 for severe AS rather than 1.0 cm^2 because in theory this value better matches an MG >40 mm Hg (19–21). Recent studies reducing the AVA cutoff value for severe AS from 1.0 to 0.8 cm^2 did not improve risk stratification in patients with low-gradient AS, however. Indeed, patients in the 0.8 to 1.0 cm^2 stratum were at higher risk of adverse events compared with those with AVA >1.0 cm^2, even with a normal volume flow rate (22). In light of these findings, we conclude it is preferable to maintain the status quo with utilization of both AVA <1.0 cm^2 as a sensitive marker and MG ≥ 40 mm Hg as a specific marker of severe AS. In the presence of discordant grading, additional tests should be considered to confirm AS severity.

In patients with a reduced LVEF, the combination of a small AVA and a low transaortic gradient may be the consequence of reduced flow secondary to poor LV contractility. Dobutamine stress echocardiography (DSE) may help in differentiating patients with severe AS ("true severe AS") from moderate AS ("pseudo-severe") using the peak dobutamine MG, AVA, and/or projected AVA (23,24). Interpretation of the DSE can be challenging, however, because the results can be ambiguous, and misclassification has been reported in up to 30% of patients when compared with surgical findings or other imaging techniques (9). Complementary imaging with measurement of the aortic valve calcium score by computed tomography (CT) is desirable in these patients. The diagnostic value of aortic valve calcium scoring is well established, and a multicenter study has shown excellent reproducibility (25–27). Thresholds of $\geq$1,200 AU in women and $\geq$2,000 AU in men are highly suggestive of severe AS (3). On the other hand, if the aortic valve calcium score is $<$800 AU in women or $<$1,600 AU in men, the presence of severe stenosis is less likely. Valve leaflet fibrosis also contributes to AS but, as opposed to calcification, is not captured by noncontrast CT so that CT calcium score may underestimate AS severity in patients with predominant valvular fibrosis. Thus, a low calcium score does not exclude moderate AS, particularly if the valve leaflets appear thickened and hyperechogenic on TTE. The integration of the 2 methods, DSE and CT calcium scoring, can provide a more robust evaluation of AS severity and categorization of severe versus moderate AS.

Another proposed approach to improve classification of AS severity is hybrid imaging, in which the LVOT area is measured by contrast CT, 3-dimensional transesophageal echocardiography, or cardiac magnetic resonance is used in the Doppler-echocardiography continuity equation (28–31). This methodology does not consistently reconcile discordant AS grading, but rather may increase the prevalence of concordant moderate AS while increasing the prevalence of discordant high gradient AS (AVA >1 cm^2, MG >40 mm Hg) (32). For hybrid imaging, the AVA threshold for excess mortality is larger at 1.2 cm^2 and does not improve on the prediction of prognosis compared to an AVA of 1.0 cm^2 derived using the standard continuity equation (33).

CENTRAL ILLUSTRATION **Moderate Aortic Stenosis and Heart Failure With Reduced Ejection Fraction: Pathophysiology and Role of Imaging**



Pibarot, P. et al. J Am Coll Cardiol Img. 2019;12(1):172–84.

Aortic regurgitation often coexists with AS; however, there are few data on the outcome of patients with mixed AS and regurgitation in the setting of a low LVEF. The coexistence of aortic regurgitation in a patient with moderate AS may further increase LV afterload and thus negatively affect LV systolic function. Several studies have reported that moderate AS plus moderate aortic regurgitation is equivalent to isolated severe AS in terms of prognosis (34–37). It is therefore reasonable to hypothesize that patients with moderate AS plus moderate aortic regurgitation and reduced LVEF would benefit from TAVR to a larger extent than those with isolated moderate AS and reduced LVEF, although there currently are no data to support this hypothesis.

IDENTIFY NONVALVULAR CAUSES OF CONGESTIVE HF. It is also important to identify nonvalvular causes of HF and ascertain that dyspnea is, at least in part, related to AS. Valvular AS is primarily a disease of the elderly population in whom comorbidities are common. Chronic obstructive pulmonary disease is present in 10% to 15% of patients with severe AS and dyspnea from respiratory disease might be falsely attributed to moderate AS. Coronary artery disease coexists in up to 50% of AS patients and can cause ischemic symptoms such as dyspnea or LV dysfunction. Hypertension may lead to LV concentric hypertrophy, diastolic dysfunction, and HF independent of AS. Cardiac amyloidosis has been reported in 1 of 7 patients with severe AS (38,39). Atrial fibrillation commonly causes dyspnea and HF.

In AS, HF is a manifestation of the interaction among myocardial function, valvular load, and arterial load. The degree to which each plays a part in the development of HF is a frequent challenge to clinicians. Valvulo-arterial impedance (Z_{va}), a measure of global LV afterload accounting for both the valvular and arterial loads, has been shown to provide important prognostic information in AS patients (40). In patients with a combination of moderate AS and

reduced arterial compliance, global LV afterload or Z_{va} may be equivalent to patients with severe AS, with similar adverse effects on the left ventricle (**Central Illustration**) (41). Z_{va} does not distinguish the magnitude of the loads attributable to the individual components, however, limiting its utility to guide therapeutic intervention. New indices, such as the Relative Valve Load, which describe the relative contribution of the valvular load to the global LV load, deserve further evaluation in the specific population of moderate AS and HF (42).

MANAGEMENT OF PATIENTS WITH MODERATE AS AND HF. Current guidelines do not recommend AVR in patients with moderate AS unless cardiac surgery is required for other reasons (i.e., ascending aorta or coronary artery bypass grafting). Although the hypothesis that relieving part of the afterload burden, especially in patients with LV dysfunction, appears attractive, supporting evidence is weak and AVR should be discouraged until proven in high-quality studies. In patients with moderate AS and a reduced LVEF, either at rest or after DSE (pseudo-severe AS), the main problem appears to be poor LV systolic function. Fougères et al (43) have shown that patients with pseudo-severe AS have a prognosis similar to patients with systolic HF in the absence of AS, with a mortality rate of 50% at 5 years. In another study, the survival of symptomatic AS patients with an AVA > 1.0 cm^2 who were managed medically was similar to that of an age and sex matched population at 4-year follow up (44).

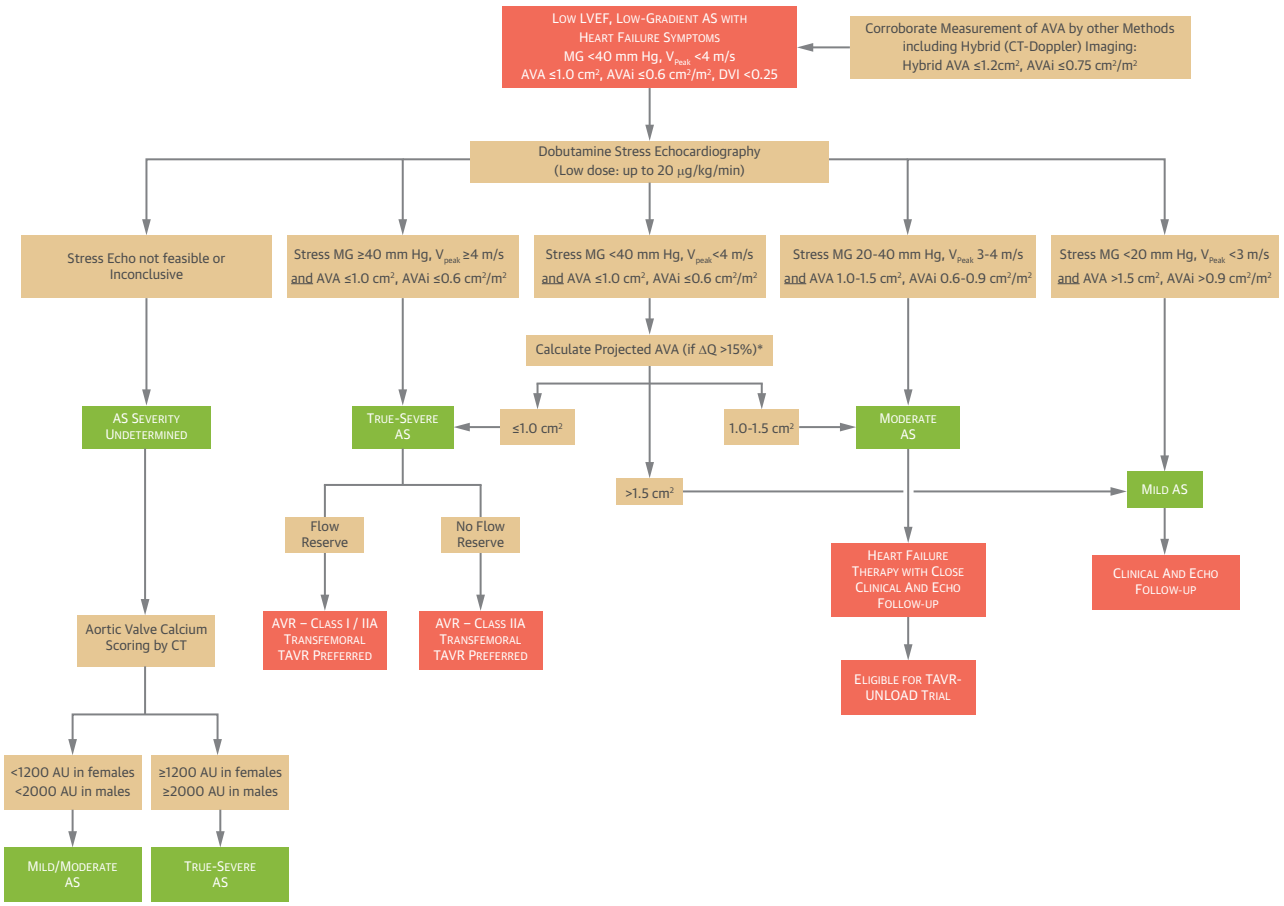
The relatively benign nature of moderate AS in the presence of LV systolic dysfunction has been questioned in a recent multicenter study (6). In 305 patients with moderate AS (AVA: 1.0 to 1.5 cm^2) and an LVEF <50%, the mortality rate was 36% at 4 years. Unfortunately, no comparative population with HF was included and the observed mortality rate was similar to the data reported by Fougères et al. (45) and contemporary HF patients. Results from the Duke Echocardiographic Database have also been advanced to support AVR in patients with moderate AS and LV dysfunction (5). In this study, 1,634 patients with moderate (n = 1,090) or severe AS (n = 544) and LVEF <50% were identified. AVR was associated with a mortality benefit in patients with both moderate and severe AS, with a hazard ratio of 0.59 in the moderate AS group; however, the rate of AVR was remarkably low despite a 5-year follow-up (severe AS: 50%; moderate AS: 26%). Given that the study period was, in large part, prior the introduction of TAVR, the lower rate of AVR presumably is related to exclusion of patients with a prohibitive operative risk. Furthermore, AVA indexed to body surface area was not provided, and only 1.4% of the population underwent DSE, precluding any conclusion as to whether these patients truly had moderate or severe AS. More than one-half of the moderate AS patients undergoing AVR also had concomitant coronary artery bypass graft; another 12% had associated significant valve diseases. Importantly, AS progression may act as a confounding factor. Patients may progress from moderate to severe AS (as observed in 10% of cases in the Duke study), but the benefit of AVR may be falsely attributed to patients with moderate AS.

STRESS ECHOCARDIOGRAPHY IN HF PATIENTS WITH AS AND LOW LVEF. Patients with AS and HFrEF often harbor a low-flow, low-gradient pattern (i.e., a stroke volume index <35 ml/m^2, AVA <1.0 cm^2, and MG <40 mm Hg) (46). In these patients with discordant grading of AS severity (i.e., small AVA with low gradient) at resting echocardiography, additional tests such as stress echocardiography or aortic valve calcium scoring by CT are required to confirm AS severity (**Figure 1**) (3,17,18,47).

A low-dose (up to 20 μg/kg/min) dobutamine stress echocardiography is particularly useful in patients with low LVEF, low-flow, low-gradient (1) to assess the presence of LV flow reserve, which is defined as a >20% increase in stroke volume (SV) and (2) to differentiate severe versus moderate versus mild AS (**Figures 1 and 2**) (17,47). Dobutamine infusion is started at 5 μg/kg/min and increased by 5 μg/kg/min increments every 5 to 8 min up to a maximum dose of 20 μg/kg/min. Measurements of LVOT and aortic flow jet velocities are performed at rest and at each stage of DSE after a steady state (i.e., stable heart rate and flow velocities) has been reached (**Figure 2**). The LV outflow diameter is measured at rest and assumed to remain constant during DSE. Measurement of SV, mean flow rate (SV divided by LV ejection time), AVA, and Doppler velocity index should be obtained at each stage of the DSE to avoid missing the maximum values of SV, AVA, and MG and allow calculations of the projected AVA.

If the maximum velocity increases to at least 4 m/s or the MG increases to at least 40 mm Hg and the AVA remains <1.0 cm^2 during DSE, stenosis is considered fixed and severe and AVR is indicated according to current guidelines: Class IIa in ACC/AHA guidelines (2,3,48); Class I in ESC/EACTS guidelines if LV flow reserve is present or Class IIa in the absence of flow reserve (**Figures 1 and 2**). On the other hand, if the maximum stress MG is between 20 and 39 mm Hg and the maximum stress AVA between 1.0 and 1.5 cm^2

FIGURE 1 Proposed Approach to Use of Stress Echocardiography and Aortic Valve Calcium Scoring by CT in the Management of Low Gradient AS, Low LVEF, and Heart Failure Symptoms



The proposed management approach is based on the authors' experience and review of the literature and is not included in current guidelines. *The calculation of the projected AVA at normal transvalvular flow rate is not included in the guidelines (2) to confirm AS severity and indication of AVR in patients with low LVEF and low gradient AS. Recent studies suggest however that this parameter may be useful in patients with persistent discordant grading at DSE (24,50). AS = aortic stenosis; AVA = aortic valve area; AVAi = indexed AVA; AVR = aortic valve replacement; DSE = dobutamine stress echocardiography; DVI = Doppler velocity index; MG = mean pressure gradient; ΔQ = percent increase in mean transvalvular flow rate during DSE; LVEF = left ventricular ejection fraction; V_{Peak} = peak aortic jet velocity.

(indexed AVA between 0.6 and 0.9 cm^2/m^2), stenosis is graded moderate (49).

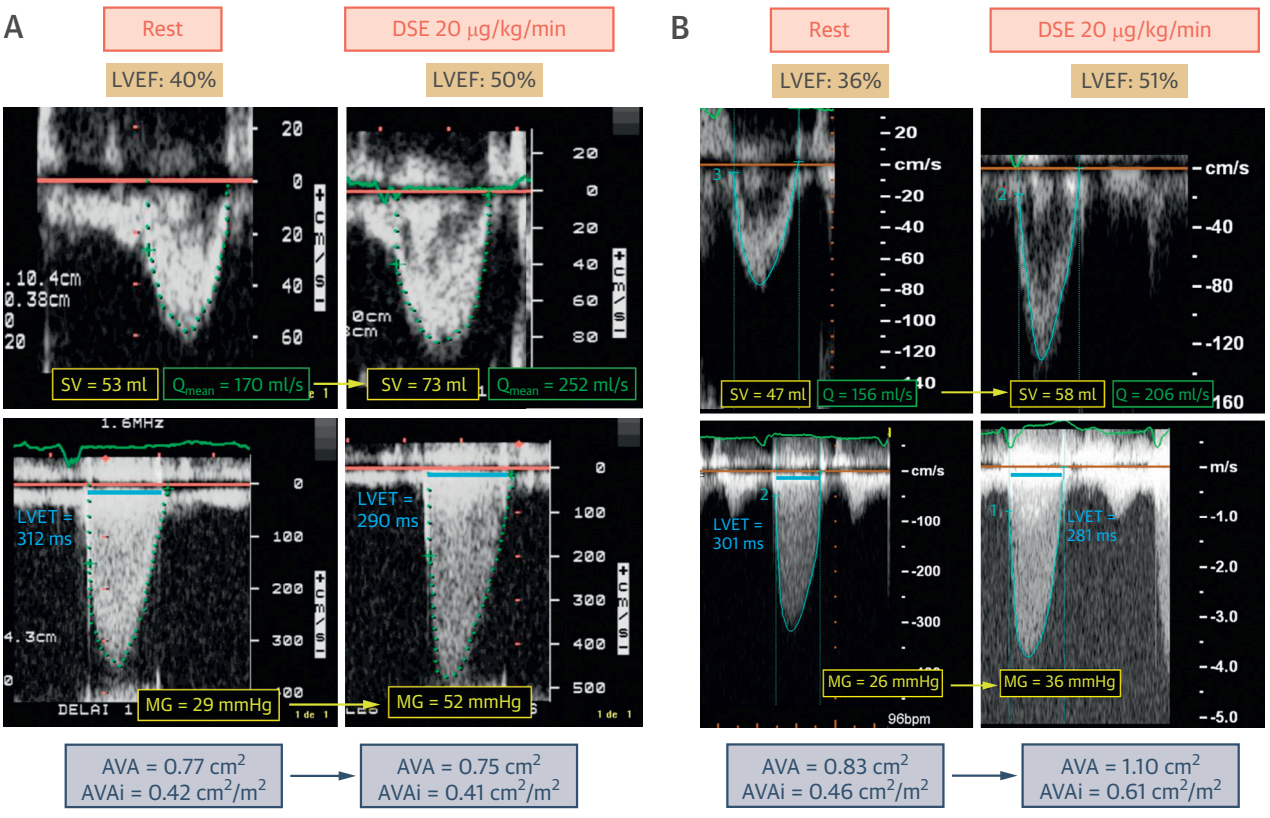
However, a significant number of patients still exhibit a discordant grading pattern, with a small AVA and low gradient, at the end of DSE (24), most often due to failure to achieve a normal stroke volume (>35 ml/m^2) and transvalvular flow rate (i.e., >200 ml/s). Thus, MG may not cross the 40 mm Hg cutpoint during DSE despite the presence of true-severe AS (2,3). In patients with persisting discordant grading at the end of DSE, calculation of the projected AVA at a normal flow rate of 250 ml/s, may be helpful to confirm AS severity (**Figures 1 and 2**) (47,50). The flow rate of 250 ml/s represents the median value of the normal flow range and not the lower limit, which is closer to 200 ml/s. This projected AVA estimates the expected AVA if flow rate had actually reached the normal range and is calculated as (**Figure 2**):

$$AVA_{Proj} = AVA_{Rest} + [(\Delta AVA/\Delta Q) \times (250 - Q_{Rest})]$$

where AVA_{Rest} and Q_{Rest} are the AVA and mean transvalvular flow rate (Q) at rest and ΔAVA and ΔQ are the absolute increases in AVA and Q during DSE. The value of 250 ml/s included in the formula corresponds to the median value of the normal flow range.

With an AVA_{Proj} ≤1.0 cm^2 and indexed AVA_{Proj} <0.6 cm^2/m^2, the valve stenosis is most likely severe

FIGURE 2 Utility of Dobutamine Stress Echocardiography to Confirm Stenosis Severity in Low Gradient AS



(A) Discordant grading of AS severity at resting echocardiography: small AVA consistent with severe AS but low MG consistent with moderate AS. With DSE, the SV, Q, and MG increase, whereas AVA remains unchanged; both the AVA and MG are now within the severe range, confirming the presence of severe AS. Q is calculated by dividing the SV by the LVET, which is measured on the continuous-wave Doppler signal of transvalvular flow velocity (blue lines). **(B)** Discordant grading at resting echocardiography: AVA consistent with severe AS but low MG consistent with moderate AS. With DSE, the SV and mean Q increase and both the AVA and MG are now within the moderate range, confirming the presence of moderate AS. **(C)** Discordant grading at rest (similar to case in panel A) but that persists at the end of DSE. Indeed, although the SV and Q increase significantly with DSE, the Q at peak DSE remains below normal (<200 ml/s). The gradient increases but remains in the moderate range and the AVA increases but remains in the severe range. In such case, the calculation of the projected AVA at normal flow rate (250 ml/s) may be useful to confirm stenosis severity: $AVA_{Proj} = AVA_{Rest} + \Delta AVA/\Delta Q \times (250 - QRest) = 0.69 + 0.19/44 \times (250 - 141) = 1.17\ cm^2$. The projected AVA confirms the presence of moderate AS in this case. **(D)** Discordant grading with AVA in the moderate range but MG in the mild range. With DSE, the MG increases but remains in the mild range and the AVA increases to the mild range. In this case, DSE confirms that the stenosis is mild. LVET = left ventricular ejection time; Q = mean transvalvular flow rate; other abbreviations as in Figure 1.

Continued on the next page

and AVR may be reasonable (48). In contrast, a projected AVA between 1.0 and 1.5 cm^2 is consistent with moderate AS (Figure 1). Of note, a ≥15% increase in flow rate is required to obtain a reliable estimate of AVA_{Proj} (50). The majority of patients with no flow reserve (i.e., increase in SV<20%) actually achieve this minimum requirement because the shortening of LV ejection time compensates for the absent or minimal increase in SV. In the recent report of the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study (24), 44% of the patients with classical low-flow, low-gradient AS had no evidence of flow reserve on DSE, but only 11% had <15% increase in mean flow rate, thus precluding the determination of AVA_{Proj}. In the same study (24), the percentage of correct classification of true versus pseudo-severe AS was 48% for stress MG ≥40 mm Hg, 60% for stress AVA ≤1.0 cm^2, and 70% for AVA_{Proj} ≤1.0 cm^2.

If DSE results are consistent with severe AS, AVR is indicated (2,3). Transfemoral TAVR may be the preferred intervention in many elderly patients with low-flow, low-gradient AS and HFrEF, especially if they have no flow reserve on DSE, although guidelines do not specifically address the choice of surgical

FIGURE 2 Continued

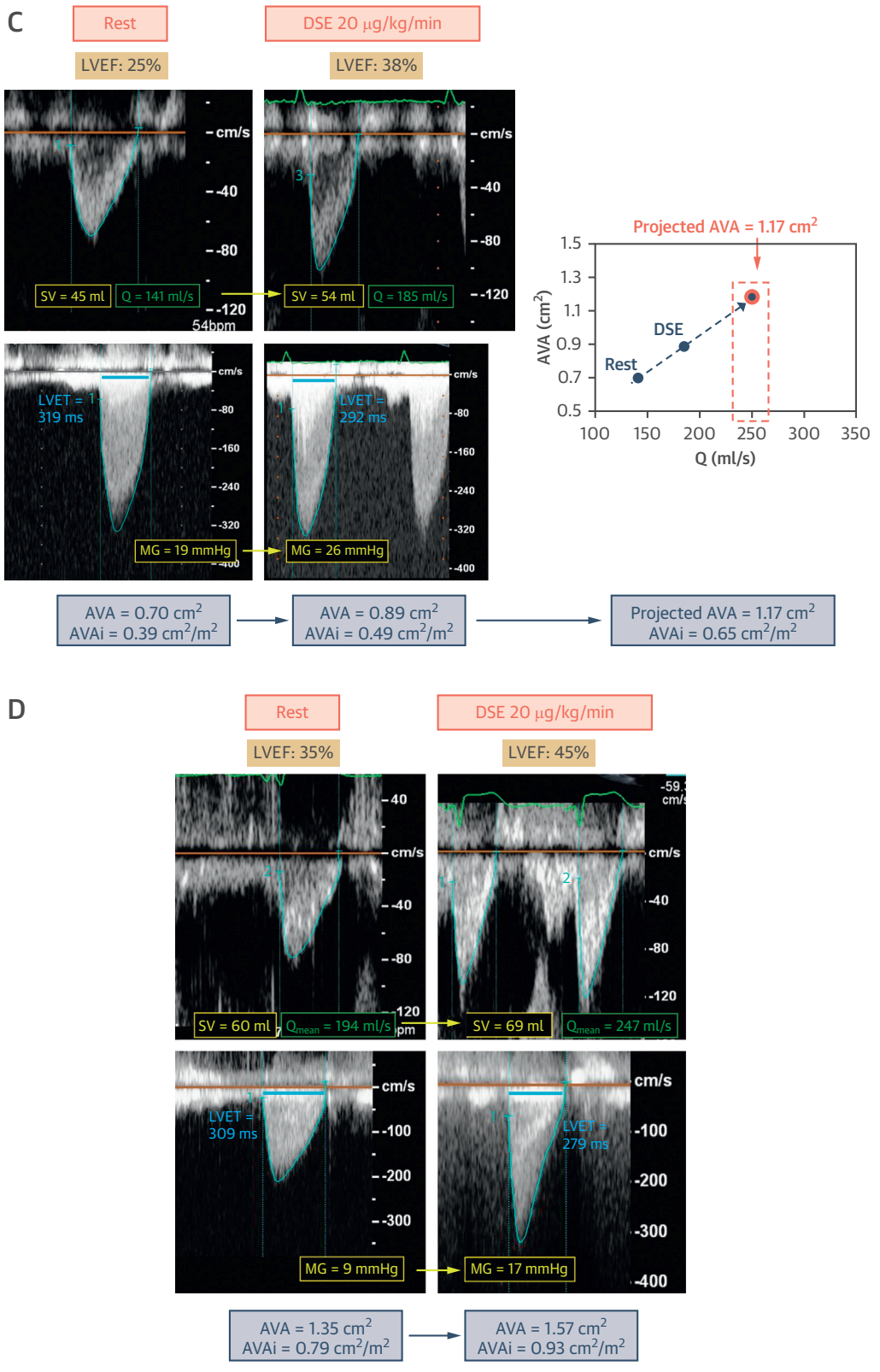
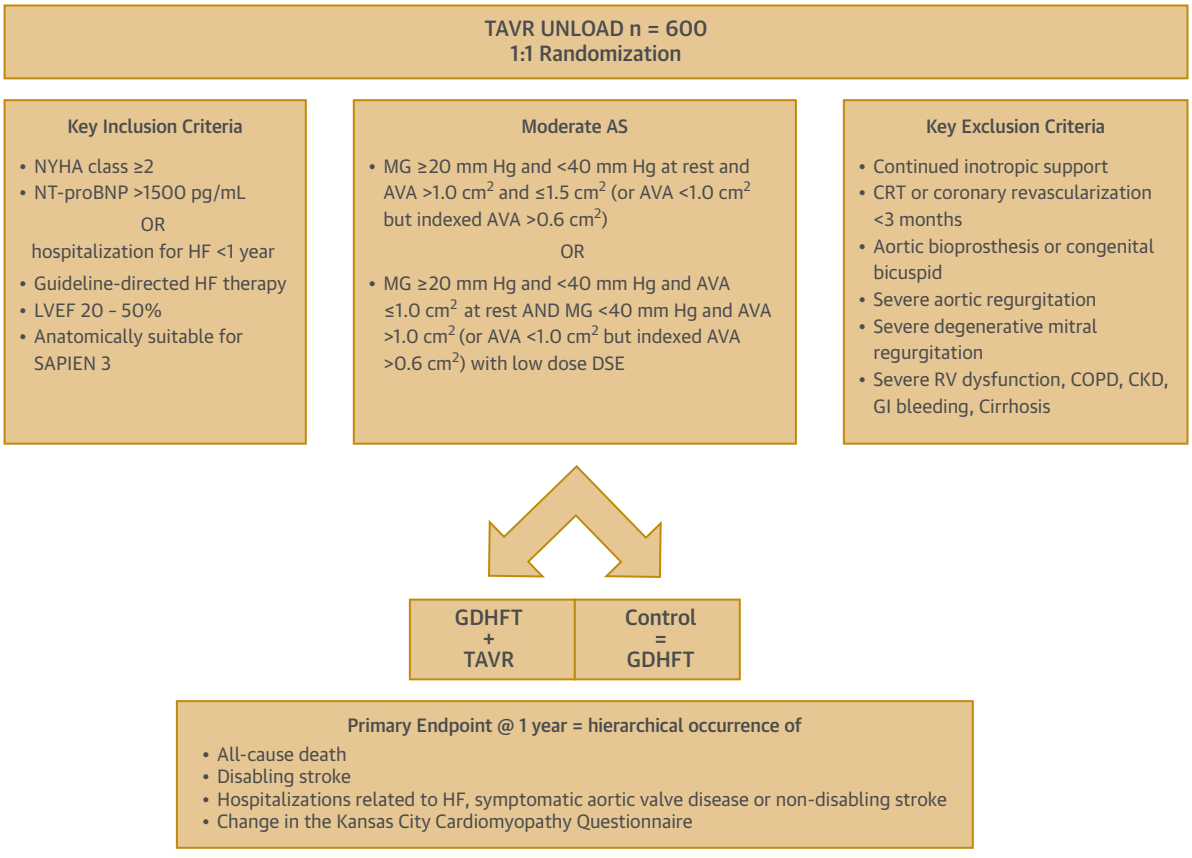


FIGURE 3 Design of the TAVR-UNLOAD Trial



CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; HF = heart failure; GDHFT = guideline-directed heart failure therapy; GI = gastrointestinal; NYHA = New York Heart Association; RV = right ventricular; TAVR UNLOAD = Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure; other abbreviations as in Figure 1.

versus transcatheter AVR in this subset of patients (Figure 1). A lack of flow reserve is associated with a marked increase in 30-day mortality following surgical AVR (51), whereas TAVR was associated with good outcomes regardless of the presence or absence of flow reserve in the TOPAS-TAVI registry (52). The magnitude of improvement of both symptoms and LVEF was similar in patients with versus without flow reserve following surgical or transcatheter AVR (52,53).

THE NEED FOR A TRIAL: TAVR UNLOAD. The development and clinical maturation of TAVR is changing the risk-benefit ratio of AVR in favor of earlier intervention. The increasing focus and understanding of ventricular function in HF in general and in HF with AS in particular, has led to the hypothesis that moderate AS with a low LVEF may be equivalent to severe AS with a normal LVEF and thus could warrant early intervention (Central Illustration). Several lines of evidence support this hypothesis:

1. LV systolic function and clinical HF progression in patients with a reduced LVEF is influenced by LV afterload. In the elderly, afterload typically is increased due to age-related arterial stiffness. Valve obstruction, in series with increased arterial stiffness, imposes an additional load on the LV; often called the “double-loaded ventricle” (41). Zva reflects global LV afterload, as determined by the aortic valve and the arterial resistance. Conceivably, in HF patients with moderate AS, a progressive increase in arterial stiffness will limit options to reduce the arterial component, leaving moderate valve obstruction as a potential target to reduce Zva and lower total LV afterload (54).

2. What is considered a normal LVEF in the absence of AS may not be optimal in the setting of any degree of AS. Mortality is higher in AS patients with an LVEF of 50% to 60% compared with those with an LVEF >60%, whether assessed pre-operatively (55) or post-operatively (56).
3. LV systolic function may be adversely affected by moderate AS even in the presence of an ostensibly normal LVEF; this degree of LV systolic dysfunction can be detected by more sensitive techniques such as strain imaging (11,57).
4. Patients with moderate AS and HF have a high rate of progression to severe AS requiring AVR and have high rates of HF hospitalization and death. In a recent retrospective analysis of patients from 4 academic institutions, 305 patients with moderate AS and HF (74% symptomatic in New York Heart Association functional class II to IV) were followed for up to 4 years. Death, AVR, or HF hospitalization occurred in 61%, death or HF hospitalization in 48%, and death in 36%, with a 27% rate of HF hospitalization (6).

Although there is a sound physiologic basis for advocating AVR in patients with moderate AS and LV systolic dysfunction, particularly in the setting of overt HF, there is no randomized clinical trial data to support either SAVR or TAVR for these patients (**Central Illustration**). A retrospective study identified patients with LV dysfunction and AS, both moderate and severe (5). Those who underwent prompt surgical AVR had a better prognosis compared with those treated with medical therapy. AVR compared with medical therapy was associated with lower mortality with a hazard ratio (HR) of 0.49 (95% confidence interval [CI]: 0.38 to 0.62; $p < 0.0001$). The difference in outcomes was greater in patients with severe AS (HR: 0.35; 95% CI: 0.26 to 0.48) but was still significant in the patients with moderate AS (HR: 0.59; 95% CI: 0.44 to 0.78) as defined by MG, with similar results when defined by AVA (5).

TAVR is associated with shorter recovery times and clinical outcomes are at least noninferior compared with surgical AVR in patients at intermediate surgical risk, making TAVR a particularly attractive option for patients with moderate AS, HF, and a reduced LVEF. In addition, TAVR has been shown to result in greater improvement in LVEF in patients with reduced LVEF compared with SAVR (58).

To assess the efficacy and safety of TAVR in patients with moderate AS and a low LVEF, the TAVR-UNLOAD trial will randomize 600 patients (age ≥18 years) with moderate AS, HF, and an LVEF between 20% and 50% to TAVR plus appropriate HF therapy versus continued appropriate HF therapy alone. HF is defined as previous HF hospitalization(s) or elevated serum BNP/NT-proBNP levels (**Figure 3**). AS severity and LVEF will be assessed in an echocardiography core laboratory.

The primary endpoint for TAVR-UNLOAD is a hierarchal composite endpoint of: 1) all-cause death; 2) disabling stroke; 3) hospitalizations related to HF, symptomatic aortic valve disease, or nondisabling stroke; and 4) change in Kansas City Cardiomyopathy Questionnaire relative to baseline.

The primary composite endpoint will be assessed by the Finkelstein-Schoenfeld methodology (59), which compares pairs of patients and declares a win, loss, or tie in a sequential hierarchal approach. The number of wins in the TAVR group versus the medical therapy only group determines the primary efficacy endpoint. The Finkelstein-Schoenfeld approach allows for a single composite endpoint that includes disparate components such as death, HF hospitalizations, functional capacity, and quality of life. The related Win Ratio (60) then allows computation of an effect size, which will give clinicians greater insight to the potential benefit of the intervention.

The primary endpoint will be analyzed when all patients have reached at least 1 year of follow-up, with a sweep performed for those patients between yearly visits. The Finkelstein-Schoenfeld methodology allows for the analysis of longitudinally collected parameters because each subject will be compared at the same follow-up period for any given parameter. In any pairwise comparison, therefore, the subject with the longer follow-up will be censored at the follow-up time of the subject with the shorter follow-up and only the data available for both subjects for the same period will be compared.

The patient population targeted for inclusion in the TAVR-UNLOAD trial is not without challenges. Technical aspects and varying methodologies for determining AVA (e.g., continuity equation vs. planimetry) may yield divergent results. Patients with reduced LVEF may have low-flow, low-gradient AS, making the assessment of degree of AS more problematic. Patients with ostensibly severe AS may be found on low-dose DSE to have moderate AS (i.e., pseudo-severe AS) and therefore eligible for the trial; conversely, patients with moderate AS on baseline echocardiography may be found to have mild AS (pseudo-moderate AS) and will be ineligible (**Figures 2 and 3**). In some patients, the lack of contractile reserve renders the DSE inconclusive, in which case the degree of calcification of the valve as

determined by computed tomography may be used to guide the determination (17). The influence of obesity, and increased as well as decreased body surface area, may also affect the determination of stenosis severity. Identifying eligible patients is also challenging because, unlike severe AS patients, they may not be referred to a valve clinic.

Although the theoretical basis for benefit with AVR and TAVR, particularly for moderate AS and HF, is supported by the pathophysiology and retrospective data highlighted previously, the clinical utility of this approach will ultimately depend on the balance between any mid- and long-term benefit and both early and late complications of the TAVR procedure. Nonrandomized data, particularly if retrospective, can only be considered hypothesis-generating. A randomized clinical trial is needed to overcome possible selection and ascertainment bias and provide a definitive answer.

CONCLUSIONS

Patients with symptoms of AS may present with classical high-gradient severe AS, low-gradient severe AS with low LVEF, or low-gradient severe AS with normal LVEF. AVR is recommended for relief of outflow obstruction for all groups of patients with symptomatic severe AS in addition to asymptomatic patients with severe high-gradient AS and a low LVEF. Clinical management is challenging for patients with only moderate AS but with symptoms of HF and reduced LVEF. Current guidelines recommend clinical surveillance with multimodality imaging; AVR is deferred until stenosis becomes severe. Stress echocardiography and CT-based aortic valve calcification scoring help guide decision making in these patients by determining with certainty whether AS in fact is severe, in which case the patient would benefit from prompt AVR.

At this time, our understanding of AS is undergoing an important paradigm shift, with a greater emphasis on the ventricle and the interaction of the diseased valve, the ventricle, and the arterial circulation. Given the known benefits of afterload reduction in management of patients with HFrEF, it has been hypothesized that AVR may be beneficial in patients with only moderate AS who present with HFrEF. The TAVR-UNLOAD trial will not only assess the potential benefit of TAVR in this population, but also will provide invaluable insights into the complex interaction among the valve, the ventricle, and the vasculature. Pending results of that trial, we should continue to assess patients with AS and HFrEF carefully with multimodality imaging and stress testing as appropriate and follow current guidelines for timing of AVR.

ADDRESS FOR CORRESPONDENCE: Dr. Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec City, Québec G1V 4G5, Canada. E-mail: philippe.pibarot@med.ulaval.ca.

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