American Heart Association | American Stroke Association

# Transcatheter Aortic Valve Replacement in Low-Flow Aortic Stenosis: Treat the Flow or Treat the Patient?

Sasan Ryan Raissi, MD; James D. Thomas, MD; Robert O. Bonow, MD, MS

Aortic valve calcification and mechanical stenosis is a common finding in advanced age and has a progressive course. Myocardial dysfunction and remodeling, on the other hand, is a common entity in advanced age and could be caused by a wide variety of sources (from a mechanical sequel of valvular diseases, to coronary artery disease, hypertension, diastolic dysfunction, and a host of cardiomyopathies). The overlap of these 2 interdependent entities, in the growing population of elderly patients, is a source of complexity in our daily practice as their presenting symptoms, namely dyspnea, are very nonspecific. Unfortunately, our knowledge of these mechanical/hemodynamic enigmas appears to exceed our insight into the molecular science of myocardial cells.

Over the past 10 years, with improvement in interventional skills, prosthetic valve fabrication, and multimodality imaging, transcatheter aortic valve replacement (TAVR) has evolved to become almost a routine procedure in our daily clinical practice. Indeed, one might note that never in the history of cardiology has a procedure gone from "gee whiz" to "ho hum" so quickly! A myriad of high-quality randomized clinical trials have targeted patients with decreasing operative risk, from inoperable to high-risk to intermediate risk, with current trials seeking to extend the safety profile essentially to all patients with trileaflet calcific aortic stenosis (AS). Guidelines from American and European Societies have recognized the utility of TAVR in growing segments of patients with AS.[1,2]

Severity of AS must be viewed as a continuum: from aortic sclerosis to hemodynamically severe valve obstruction. The 2017 focused update on the echocardiographic assessment of AS by the European Association of Cardiovascular Imaging and the American Society of Echocardiography[3] provided new insights into the difficult subgroup with low-gradient AS, and recommended a systematic stepwise approach for accurate AS evaluation.

AS grading can be straightforward when the maximum velocity, mean pressure gradient (MPG), and aortic valve area (AVA) are all concordant. When these parameters are discordant, it is important to integrate these criteria with additional imaging findings plus clinical data to determine the final diagnosis. This is especially important when the MPG suggests only moderate AS and the AVA by continuity equation falls in the severe range (Figure).

A systematic approach must be adopted, with special attention to any confounding factors that could distort the patient's underlying hemodynamic condition; these include the volume status and blood pressure at the time of study, presence of severe anemia, fever, or high-flow states such as aortic insufficiency and thyrotoxicosis. Accurate Doppler interrogation of maximum velocity and MPG along with detailed measurement of left ventricular (LV) outflow tract diameter is necessary for calculating AVA by continuity equation. This underscores the need for an accredited echocardiography laboratory for daily clinical practice and core laboratories for clinical trials.

It should also be noted that current thresholds for AVA and velocity/gradient for defining severe AS are not consistent. Based on fluid dynamics principles, to generate a mean gradient of 40 mm Hg at a normal flow rate in a standard-sized human, the projected valve area must be closer to 0.8 than to 1.0 $cm^2$.[4–6] On the other hand, determination of the flow status by stroke volume index (SVI) has intrinsic limitations. With increasing severity of AS the ejection time may prolong, and even patients with a normal SVI may have reduced transvalvular flow.[7] These caveats must be taken into account when measures of AS severity are conflicting.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Mangner and colleagues investigate the impact of SVI, MPG, and LV ejection fraction (LVEF) on mortality and functional capacity in a single-center cohort of 1600 patients who underwent TAVR from 2006 to 2014.[8]

Patients undergoing TAVR in this study were all symptomatic and considered to have severe AS, although it is not

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

*From the Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL.*

**Correspondence to:** Robert O. Bonow, MD, MS, Department of Medicine, Northwestern University Feinberg School of Medicine, 251 East Huron St, Galter 3-150, Chicago, IL 60611. E-mail: r-bonow@northwestern.edu

*J Am Heart Assoc.* 2018;7:e008932. DOI: 10.1161/JAHA.118.008932.

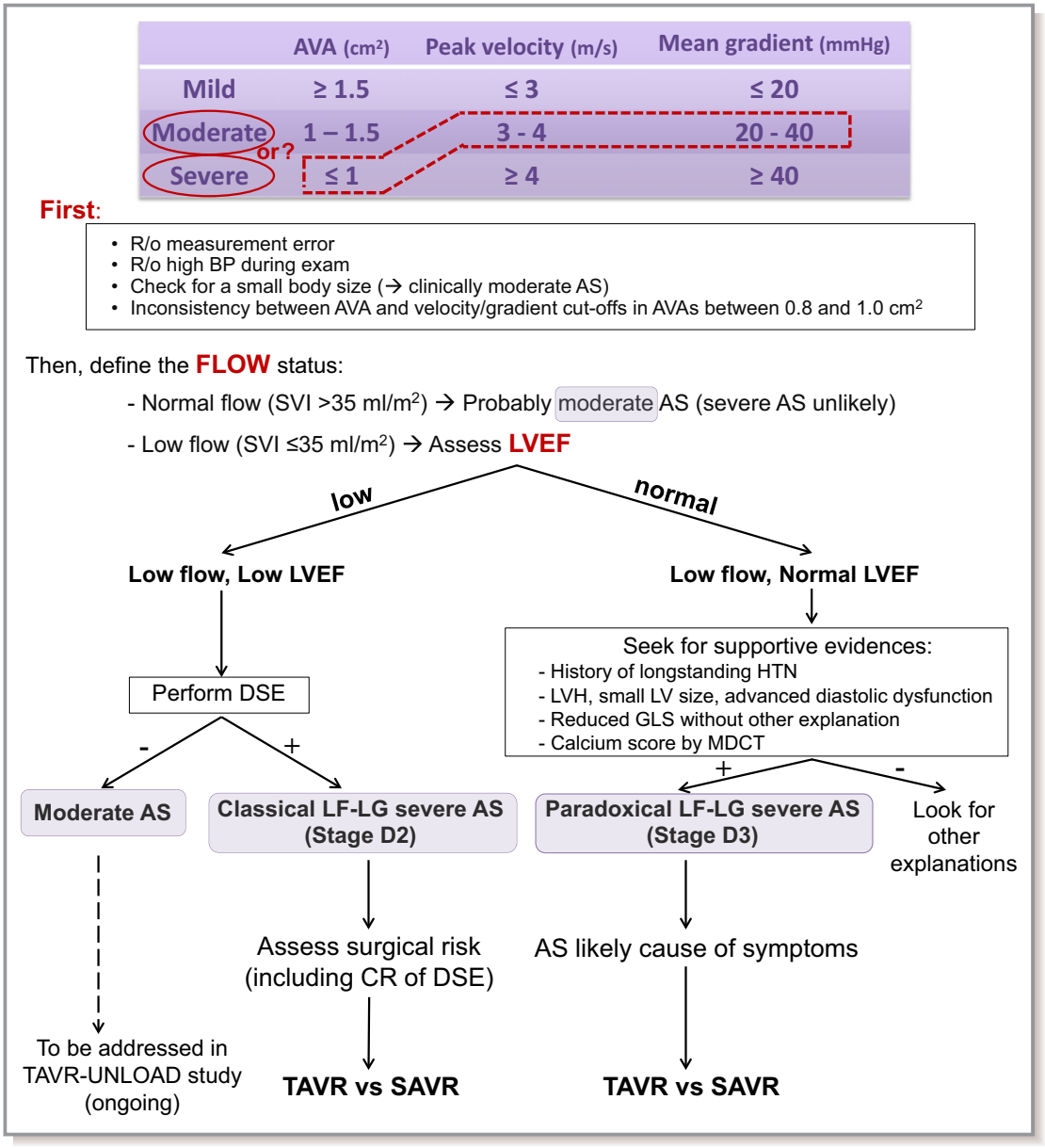


**Figure.** Stepwise approach to the complex subgroup of low gradient aortic stenosis (AS). Top panel: Disconnect between aortic valve area (AVA) and peak velocity and mean gradient in current guidelines definitions of severe AS. Fluid dynamic principles indicate that a mean gradient of 40 mm Hg or greater would be associated with an AVA of 0.8 $cm^2$. The threshold of 1.0 $cm^2$ is more aligned with moderate AS. Bottom panel: Decision tree for management decisions based on flow status determined by stroke volume index (SVI). BP indicates blood pressure; LFLG, low-flow low-gradient; CR, contractile reserve; DSE, dobutamine stress echocardiography; GLS, global longitudinal strain; HTN, hypertension; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MDCT, multidetector computed tomography; R/o, rule out; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TAVR-UNLOAD, transcatheter aortic valve replacement to unload the left ventricle in patients with advanced heart failure.

clear whether this was based on AVA or MPG or a combination of both. Approximately half of the patients had normal flow (NF) using a threshold of SVI >35 $mL/m^2$. Patients were subgrouped according to NF versus low-flow (LF) and high versus low MPG (high gradient >40 mm Hg). Patients with LF and low gradient (LG) were further subdivided into those with classical LF-LG AS (LVEF ≤50%) and paradoxical LF-LG AS (LVEF >50%). The authors noted that patients with LF AS (comprising ≈50% of patients) had higher 30-day and 3-year all-cause mortality rates, independent of MPG and LVEF. These are important observations. It is noteworthy, however, that patients in the 3 LF groups had a greater

burden of comorbid conditions than those with NF AS, with higher Society of Thoracic Surgeons scores and logistic EuroScores, greater New York Heart Association functional class, and higher levels of N-terminal pro-brain natriuretic peptide. As the patients with LF were clearly a sicker group than those with NF, there is undoubtedly the potential for unmeasured confounding that would contribute to the worse outcomes in the LF groups.

It is also worth noting that not all patients in this series may have had truly severe AS. First, those with NF-LG and normal LVEF (18% of all patients) may not have had severe AS if an AVA threshold of 1.0 $cm^2$ was used rather than 0.8 $cm^2$, as noted above. The 2017 focused guideline update[1] emphasized that these patients should *not* be categorized as severe AS (Figure), a recommendation supported by studies demonstrating similar outcome of such patients and those with moderate AS.[9,10]

Second, among patients in the classical LF-LG group (14% of the total), the absence of dobutamine stress data, as noted by the authors, leaves open the possibility that some may have had only moderate AS[11] and symptoms could have been driven by primary LV dysfunction. Whether TAVR improves outcomes in such patients is being tested in the ongoing TAVR-UNLOAD randomized trial (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure; NCT02661451).

Third, the patients with paradoxical LF-LG AS with normal LVEF (11% of patients) represent an enigmatic group in which the confirmation of severe AS remains elusive.[12] In the absence of confirmatory data, such as aortic valve calcification determined by computed tomography, it is possible that several of these patients may have had a phenotype of heart failure with preserved EF more so than severe AS, which might explain lack of benefit of TAVR.

Numerous large clinical trials and registry cohort studies have reported the influence of MPG,[13] LVEF,[14] and flow,[15–17] and some a combination of 2 or all 3 factors, on outcomes of patients after TAVR, but with no consistent unifying results. A common message of these studies appears to be that LVEF is a strong predictor of outcomes in patients undergoing surgical valve replacement, while MPG and flow are powerful risk factors for mortality in patients undergoing TAVR.[18–20]

One very salutary aspect of the study of Mangner et al is the independent assessment of the optimal cut point for SVI that is associated with mortality,[8] which they determined to be 34.4 $mL/m^2$, gratifyingly close to the traditionally used value of 35 $mL/m^2$. Their observation that LF status, itself, rather than the mechanism leading to LF, is significantly associated with short-term and long-term mortality after TAVR is an important take-home message, but one that is tempered by the likelihood of residual confounding noted previously.

These data should stimulate further research to unravel the complex inter-relationships between LV function, pressure gradient, and flow in patients with AS and how these hemodynamic factors relate to prognosis. Conceivably such information could in the future inform decisions regarding whether TAVR or other interventions will be efficacious or futile. However, these factors should never be considered in isolation of the full clinical presentation of individual patients and need to be integrated with clinical factors that are more difficult to measure, such as symptoms and the impact of comorbid conditions and frailty. As we refine our diagnostic tools to identify those with truly severe AS, we must also improve our knowledge of the clinical characteristics that identify patients in whom TAVR will lead to improved survival and enhanced quality of life.

## Disclosures

Dr Thomas reports honoraria and consulting for Abbott, Edwards, General Electric, and Bay Labs, and spouse employment for Bay Labs. The remaining authors have no disclosures to report.

## References


1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin V, Sundt TM III, Thompson A. 2017 ACC/AHA focused update on the management of patients with valvular heart disease. An update of the 2014 AHA/ACC guideline on 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. *Circulation*. 2017;135:e1159–e1195.
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Munoz DR, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler T, Windecker S, Zamorano JL. 2017 ESC/EACTS guidelines for the management of valvular heart disease. The Task Force for 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*. 2017;38:2739–2791.
3. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. 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;30:372–392.
4. Carabello BA. Aortic stenosis. *N Engl J Med*. 2002;346:677–682.
5. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart*. 2010;96:1463–1468.
6. Michelena HI, Margaryan E, Miller FA, Eleid M, Maalouf J, Suri R, Messika-Zeitoun D, Pellikka P, Enriquez-Sarano M. Inconsistent echocardiographic grading of aortic stenosis: is the left ventricular outflow tract important? *Heart*. 2013;99:921–931.
7. Chahal NS, Drakopoulou M, Gonzalez-Gonzalez AM, Manivarmane R, Khattar R, Senior R. Resting aortic valve area at normal transaortic flow rate reflects true valve area in suspected low-gradient severe aortic stenosis. *JACC Cardiovasc Imaging*. 2015;8:1133–1139.
8. Mangner N, Stachel G, Woitek F, Haussig S, Schlotter F, Höllriegel R, Adam J, Lindner A, Mohr FW, Schuler G, Kiefer P, Leontyev S, Borger MA, Thiele H, Holzhey D, Linke A. Predictors of mortality and symptomatic outcome of patients with low-flow severe aortic stenosis undergoing transcatheter aortic

valve replacement. *J Am Heart Assoc*. 2018;7:e007977. DOI: 10.1161/JAHA.117.007977.

9. Mehrotra P, Jansen K, Flynn AW, Tan TC, Elmariah S, Picard MH, Hung J. Differential left ventricular remodeling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low gradient severe aortic stenosis. *Eur Heart J*. 2013;34:1906–1914.
10. Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: clinical characteristics and predictors of survival. *Circulation*. 2013;128:1781–1789.
11. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, Baumgartner H, Beanlands RS, Chayer B, Kadem L, Garcia D, Durand LG, Pibarot P. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. *Circulation*. 2006;113:711–721.
12. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;15:2856–2864.
13. Baron SJ, Arnold SV, Herrmann HC, Holmes DR Jr, Szeto WY, Allen KB, Chhatriwalla AK, Vemulapali S, O'Brien S, Dai D, Cohen DJ. Impact of ejection fraction and aortic valve gradient on outcomes of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67:2349–2358.
14. Tribouilloy C, Levy F, Rusinaru D, Guéret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Quéré JP, Monin JL. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol*. 2009;53:1865–1873.
15. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low flow severe aortic stenosis: a PARTNER trial analysis. *Circulation*. 2013;127:2316–2326.
16. Clavel MA, Berthelot-Richer M, Le Ven F, Capoulade R, Dahou A, Dumesnil JG, Mathieu P, Pibaro P. Impact of classic and paradoxical low flow on survival after aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol*. 2015;65:645–653.
17. LeVen F, Freeman M, Webb J, Clavel MA, Wheeler M, Dumont E, Thompson C, De Larochellière R, Moss R, Doyle D, Ribeiro HB, Urena M, Nombela-Franco L, Rodés-Cabau J, Pibarot P. Impact of low flow on the outcome of high risk patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2013;62:782–788.
18. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, Petit-Eisenmann H, Gori M, Jobic Y, Bauer F, Chauvel C, Leguerrier A, Tribouilloy C. Aortic valve replacement for low-flow/low-gradient aortic stenosis: operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol*. 2008;51:1466–1472.
19. O'Sullivan CJ, Stortecky S, Heg D, Pilgrim T, Hosek N, Buellesfeld L, Khattab AA, Nietlispach F, Moschovitis A, Zanchin T, Meier B, Windecker S, Wenaweser P. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013;34:3437–3450.
20. Dayan V, Vignolo G, Magne J, Clavel MA, Mohty D, Pibarot P. Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *J Am Coll Cardiol*. 2015;66:2594–2603.

**Key Words:** Editorials • aortic valve stenosis • transcatheter aortic valve replacement