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Bioprosthetic Aortic Valve Hemodynamics: Definitions, Outcomes, and Evidence Gaps

JACC State-of-the-Art Review

Howard C. Herrmann, MD,[a] Philippe Pibarot, DVM, PHD,[b] Changfu Wu, PHD,[c,*] Rebecca T. Hahn, MD,[d] Gilbert H.L. Tang, MD, MSC, MBA,[e] Amr E. Abbas, MD,[f] David Playford, MBBS, PHD,[g] Marc Ruel, MD, PHD,[h] Hasan Jilaihawi, MD,[i] Janarthanan Sathananthan, MBCHB, MPH,[j] David A. Wood, MD,[j] Ruggero De Paulis, MD,[k] Jeroen J. Bax, MD, PHD,[l] Josep Rodes-Cabau, MD,[b] Duke E. Cameron, MD,[m] Tiffany Chen, MD,[a] Pedro J. Del Nido, MD,[n] Marc R. Dweck, MD,[o] Tsuyoshi Kaneko, MD,[p] Azeem Latib, MD,[q] Neil Moat, MD,[r] Thomas Modine, MD, PHD,[s] Jeffrey J. Popma, MD,[t] Jamie Raben, PHD,[c,*] Robert L. Smith, MD,[u] Didier Tchetche, MD,[v] Martyn R. Thomas, MD,[w] Flavien Vincent, MD, PHD,[x] Ajit Yoganathan, PHD,[y] Bram Zuckerman, MD,[c,*] Michael J. Mack, MD,[u] Martin B. Leon, MD,[d] on behalf of the Heart Valve Collaboratory†

ABSTRACT

A virtual workshop was organized by the Heart Valve Collaboratory to identify areas of expert consensus, areas of disagreement, and evidence gaps related to bioprosthetic aortic valve hemodynamics. Impaired functional performance of bioprosthetic aortic valve replacement is associated with adverse patient outcomes; however, this assessment is complicated by the lack of standardization for labelling, definitions, and measurement techniques, both after surgical and transcatheter valve replacement. Echocardiography remains the standard assessment methodology because of its ease of performance, widespread availability, ability to do serial measurements over time, and correlation with outcomes. Management of a high gradient after replacement requires integration of the patient's clinical status, physical examination, and multimodality imaging in addition to shared patient decisions regarding treatment options. Future priorities that are underway include efforts to standardize prosthesis sizing and labelling for both surgical and transcatheter valves as well as trials to characterize the consequences of adverse hemodynamics. (J Am Coll Cardiol 2022;80:527–544)

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From the [a]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [b]Department of Medicine, Québec Heart and Lung Institute, Laval University, Québec City, Quebec, Canada; [c]U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [d]Columbia University Medical Center, New York, New York, USA; [e]Mount Sinai Health System, New York, New York, USA; [f]Beaumont Hospital Royal Oak, Royal Oak, Michigan, USA; [g]The University of Notre Dame, Fremantle, Western Australia, Australia; [h]University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [i]Heart Valve Center, NYU Langone Health, New York, New York, USA; [j]Centre for Cardiovascular Innovation, University of British Columbia, Vancouver, British Columbia, Canada; [k]European Hospital, Unicamillus University, Rome, Italy; [l]Leiden University Medical Centre, Leiden, the Netherlands; [m]Massachusetts General Hospital, Boston, Massachusetts, USA; [n]Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [o]BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom; [p]Division of Thoracic and Cardiac Surgery, Brigham and Women's Hospital, Boston, Massachusetts, USA; [q]Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA; [r]Abbott Structural Heart, Santa Clara, California, USA; [s]Hopital Cardiologique de Haut Leveque, Bordeaux, France; [t]Medtronic Inc, Minneapolis, Minnesota, USA; [u]Baylor Scott and White, The Heart Hospital, Plano, Texas, USA; [v]Clinique Pasteur, Toulouse, France; [w]Edwards Lifesciences, Irvine, California, USA; [x]University Lille, Lille, France; and the [y]Georgia Institute of Technology and Emory University, Atlanta, Georgia, USA. *This paper reflects the views of the authors and does not necessarily represent the practices, policies, requirements, or recommendations of the U.S. Food and Drug Administration. The mention of commercial products, their sources,

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ABBREVIATIONS AND ACRONYMS

EOAi = effective orifice area indexed

ISO = International Organization for Standardization

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

SHV = surgical heart valve

SVD = structural valve degeneration

TAVR = transcatheter aortic valve replacement

Bioprosthetic valve hemodynamic performance is predictive of intermediate and long-term clinical outcomes after aortic valve replacement (AVR).[1-12] Transcatheter prostheses may have better systolic hemodynamic performance than surgical bioprostheses, but important differences exist between types of surgical and transcatheter valves.[13-20] In addition, assessment of valve function is complicated by the lack of standardization in device sizing, labelling, definitions, and measurement.[21] A recent virtual workshop organized by the Heart Valve Collaboratory[22] was convened to discuss and address these issues to identify areas of consensus, areas of disagreement, and those with evidence gaps for which more information is needed. This report summarizes the results of that workshop.

HIGHLIGHTS

- Impaired functional performance of aortic valve bioprostheses is associated with adverse outcomes.
- Assessment of valve performance is complicated by lack of standardized labeling, definitions, and measurement techniques after either surgical or transcatheter valve replacement.
- Management of patients with high transvalvular bioprosthetic aortic valve gradients requires integration of clinical status, clinical and multimodality imaging findings, and shared decision-making.

ASSESSMENT OF VALVE HEMODYNAMICS POST-AVR

The hemodynamic performance of a prosthetic aortic valve is dependent on several structural and flow characteristics that may differ between devices and the methods of assessment. Current guidelines recommend echocardiography for the initial postoperative evaluation of prosthetic valves to establish baseline function and repeat echocardiography for the evaluation of suspected prosthetic valve dysfunction, a change in clinical status or examination, and when findings would change management or guide therapy.[23-26] However, recent studies demonstrating discordance between echocardiographic and invasive measures of pressure gradients immediately following prosthetic valve implantation have raised questions about the utility of some noninvasive measurements of valve hemodynamic function.[27,28]

ADVANTAGES OF ECHOCARDIOGRAPHIC MEASUREMENT. There are multiple advantages to the use of echocardiography for diagnosis and follow-up (Table 1). First, the test is known to be safe and widely accessible. Because it is performed awake, without fasting or change in medications, hemodynamics can be assessed both during the patients' baseline loading conditions, and if needed during stress.[29] Second, echocardiographic measurements can provide multiple confirmatory parameters to improve diagnostic accuracy: flow velocities and pressure gradients, valve area, and Doppler velocity index.[30] Third, echocardiography allows assessment of the morphology of valve leaflets and thus can identify structural changes to the prosthetic valve, distinguish paravalvular from central bioprosthetic regurgitation, and accurately measure severe prosthetic stenosis.[31] Finally, noninvasive testing, such as echocardiography, can be used to exclude thrombosis or endocarditis when invasive studies may be contraindicated.[6] Perhaps most importantly, hemodynamically significant valve dysfunction of surgically implanted and transcatheter bioprosthetic valves identified by echocardiography correlates with the composite outcome of death from any cause or aortic reintervention.[4-8]

ADVANTAGES OF INVASIVE HEMODYNAMIC MEASUREMENT. Despite the listed advantages of echocardiography, there are also limitations (Table 1).

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Echocardiography calculates a velocity-derived transvalvular gradient through application of a simplified version of the Bernoulli equation.[32] This equation omits the contribution of flow acceleration, viscous forces, proximal left ventricular (LV) velocity, and pressure recovery on the derived gradient.[33] Conversely, invasive measurement provides a direct assessment of transvalvular gradients and is the net pressure gradient across the aortic valve that accounts for valvular, flow, and fluid hemodynamic considerations. Immediately after transcatheter aortic valve replacement (TAVR), pressure gradient differences between echocardiography and invasive measurements suggest that these modalities are not interchangeable.[27] Invasive measurements, however, can also be limited by methodological considerations, including the lack of end-hole catheters to capture the maximal gradient and correction of sheath pressures for time delay and systolic augmentation caused by reflected waves.[34]

TABLE 1 Advantages and Limitations of Echocardiographic and Hemodynamic Measurements of Bioprosthetic Aortic Valve Replacement Prostheses

Echocardiography	Hemodynamic Assessment
Advantages	
Safe, noninvasive	Recording incorporates contributions of all valve, flow, and fluid components
Widely accessible	Independent of incidence angle of ultrasound beam
Assessment during normal loading conditions	
Ability to do serial, repeat, and exercise measurements	
Can obtain multiple, confirmatory parameters to improve diagnostic accuracy	
Can differentiate between stenosis and regurgitant contributions to measures	
Measures correlate with outcomes	
Limitations	
Fails to account for flow acceleration, viscous forces	Invasive
May not account for proximal LV pressure, pressure loss recovery	Immediate post-TAVR measures not reflective of normal flow state and subsequent valve adaption
Requires alignment of Doppler probe to flow to record maximal gradient	Lack of outcome data
	Fluid-filled catheters may introduce error caused by inaccurate zeroing or catheter calibration
	Catheters with multiple side-holes may not capture the maximal gradient
	Cardiac output measures not validated in elderly and post-AVR

AVR = aortic valve replacement; LV = left ventricle/ventricular; TAVR = transcatheter aortic valve replacement.

REASONS FOR DISCORDANCE OF ECHOCARDIOGRAPHIC AND HEMODYNAMIC MEASUREMENTS. The discordance between echocardiographic and invasive gradients occurs following both TAVR and surgical aortic valve replacement (SAVR).[27,28,35-37] There are a number of reasons why echocardiographic measures of mean transvalvular gradients may be higher than invasive measurements immediately following valve replacement in the setting of normal bioprosthetic valve function (Table 2). These can be classified into several major categories: 1) principles of fluid mechanics and pitfalls of the modified Bernoulli equation; 2) variability of the contraction coefficient (ratio of effective to anatomic valve orifice area) depending on the shape of the orifice; 3) pressure recovery distal to the vena contracta in a tubular structure; and 4) technical aspects of measurement, including temporal and hemodynamic variability.

PITFALLS OF THE MODIFIED BERNOULLI EQUATION. The Bernoulli equation was designed to derive transstenotic gradients from velocity in the presence of laminar, steady flow with a single level of stenosis. The stenotic pressure gradient is related to 3 forces: *convective acceleration*, which is the increase in blood-flow velocity when traversing a reduced aortic valve area; *flow acceleration* (different from flow convergence), which is the increase in blood-flow velocity with ventricular contraction; and *viscous forces* from blood viscosity and friction forces among blood layers and against the aorta.[32,33] In the modified (simplified) Bernoulli equation, the velocity-derived gradient accounts only for convective acceleration. Additional fundamental assumptions include no additional loss of pressure from viscous effects (friction), a small contribution of flow acceleration at any specified time point, and that the proximal velocity is significantly smaller than the distal velocity. Although the first assumption is for the most part true, the second and third assumptions may not be true in the setting of a nonrestrictive bioprosthetic valve.[33] Flow acceleration in a normal valve increases because of the relatively large volume of blood and may play a significant role in the overall pressure gradient. Additionally, the proximal and distal velocities are closer in magnitude, and thus, the proximal LV velocity should be subtracted from the distal velocity to calculate the true pressure gradient.[30] This is not often performed clinically, and thus the pressure gradient reported following prosthetic valve implantation is likely an overestimate of the true transvalvular gradient.

The vena contracta is the point at which a jet has its minimal effective area. When the fluid jet passes through a sharp-edged orifice, the jet continues to constrict for a certain length before expanding radially. This contraction of the jet or contraction coefficient is defined as the minimal area of the jet (ie, effective orifice area [EOA]) divided by the anatomic

TABLE 2 Summary of Reasons for Discordance Between Echocardiographic and Invasive Hemodynamic Measurement of Bioprosthetic Valve Function

Echocardiographic
Failure to align Doppler sector parallel to maximal velocity
Simplified Bernoulli equation fails to account for a. Laminar/average flow with lower velocity adjacent to vessel wall b. Proximal LV velocity c. Variability of contraction coefficient d. Nonconvective forces of flow acceleration, viscosity, and convective acceleration
Not corrected for pressure recovery
Invasive hemodynamic
Inaccuracies introduced by a. Fluid-filled catheters b. Use of pigtail instead of end-hole catheters c. Improper positioning within LV and aorta
Timing of measurements immediately post-TAVR

Abbreviations as in Table 1.

area of the orifice; ranges from 0.6 (abruptly narrowed orifice) to 1.0 (gradually narrowed orifice); is affected by the geometry of the orifice, flow rate, and flow eccentricity; and likely differs based on the bioprosthetic valve design.[35]

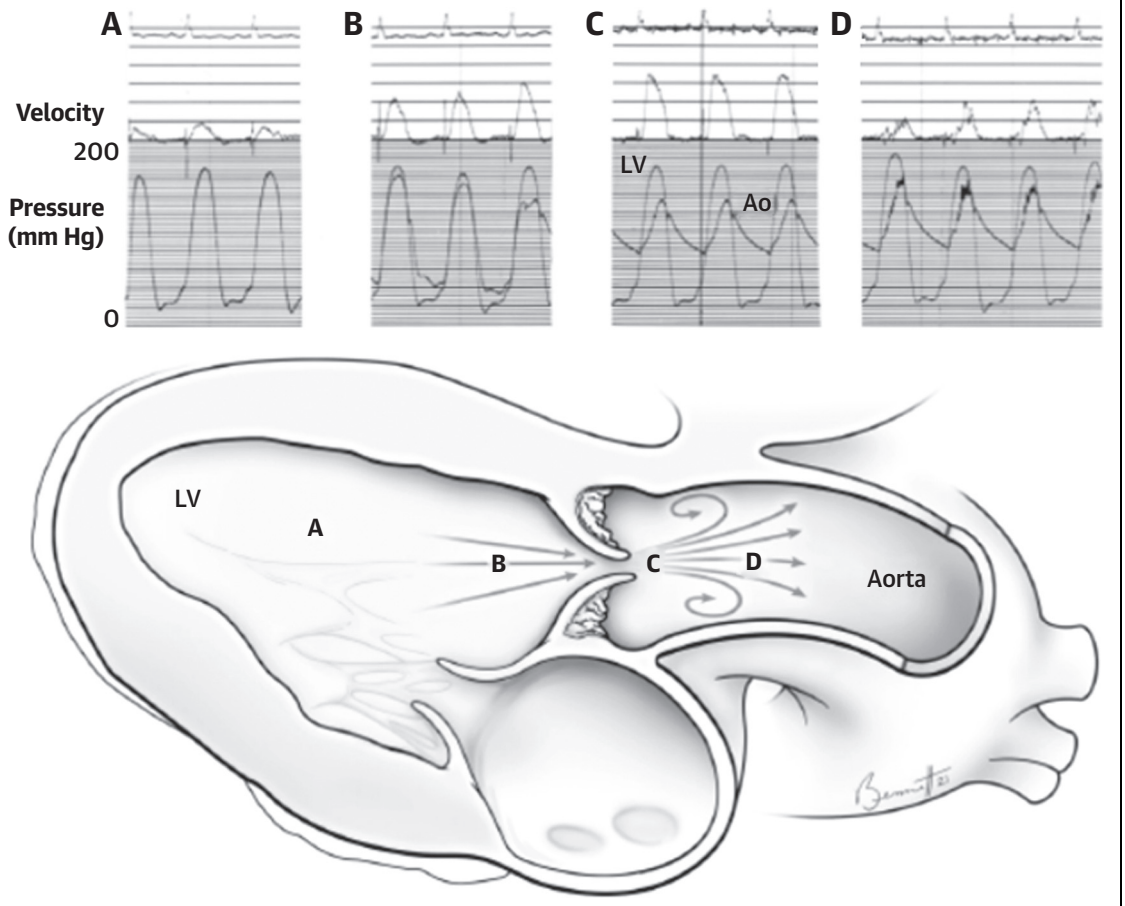
PRESSURE RECOVERY DISTAL TO THE VENA CONTRACTA. Pressure loss recovery is a hydrodynamic phenomenon that occurs whenever blood encounters and exits from a narrowed conduit (Figure 1). The maximal velocity of blood flow and the calculated gradient occurs at the vena contracta. Because of irrecoverable loss from viscous effects, the pressure downstream from the vena contract does not reach the original static level pressure. Invasive measurements at the site of the recovered pressure will be lower than the Doppler measurement of the vena contracta pressure gradient.[38]

Pressure loss recovery causes especially significant differences between Doppler and catheter gradients in the setting of high flow rates, small ascending aorta diameter (<30 mm), highly eccentric jets, and larger orifice size.[4,36,39-41] In these settings, it is likely that some discordance between Doppler and invasive measurements of pressure gradient may be related to pressure loss recovery. However, in aortic stenosis, several studies have demonstrated that the recovered pressure in absolute terms is small and is not clinically relevant in patients with low gradients (<25 mm Hg), normal flow, and aortas larger than 3 cm diameter.[40-42] Two in vitro studies of TAVR prostheses compared echocardiographic gradients with hemodynamics recorded with a micromanometer-tip pressure catheter at different flow rates and demonstrated that the gradients measured by catheterization were lower than those measured echocardiographically and were directly related to flow, and that the contribution of pressure recovery to the measured gradient is small.[43,44]

TECHNICAL ASPECTS OF MEASUREMENT. Inherent in this discussion is the assumption of technically accurate and appropriate methodology. Hahn et al[17] from 3 echocardiographic core laboratories involved in TAVR studies described the assessment of the normal function of multiple iterations of TAVR prostheses and provided tables of expected valve hemodynamics. Key technical aspects are specifically delineated, including measurements of the neo-LV outflow tract and pulsed wave Doppler velocity at 2 locations of the stent frame and standardized calculations for stroke volume for both the balloon-expandable and self-expanding prostheses. Hemodynamic measurements must also be performed with specific protocols. As frequently performed, post-TAVR measurements with a pigtail catheter in the left ventricle and aortic pressure from the side-arm of a distal aortic sheath must include corrections for time delay and systolic augmentation caused by reflected waves. In addition, fluid-filled catheters generally lack the fidelity and frequency response required to detect small differences in gradient, including pressure recovery, over small distances along the flow stream. The pressure gradient along the LV outflow tract and pressure recovery in the aorta occur over a limited zone, making the use of pigtail catheters with multiple side-holes, which average the pressure in and around these zones, less suitable.[38] One protocol for assessment of late post-TAVR larger gradients with careful hemodynamics as part of a clinical trial (NCT04827238) has been proposed. Key elements of this protocol include an intravenous infusion of normal saline to minimize the effects of hypovolemia, careful levelling and zeroing of 2 transducers, and the use of 2 pigtail catheters (1 catheter deep in the left ventricle and a second one sampling multiple positions in the ascending aorta).

TIMING OF MEASUREMENTS. Differences in intraprocedural transvalvular gradients and follow-up gradients may be partly related to the hemodynamic effects of anesthesia with lower echocardiographic-derived transaortic gradients under anesthesia than in nonsedated patients.[45] This phenomenon has also been observed immediately after TAVR.[27,46] It may be related to resolution of the effects of sedation/anesthesia, rapid pacing-induced ischemia with subsequent improvement in transaortic stroke volume and flow, hypovolemia caused by the fasting state, as well as improvement in systolic blood pressure and

FIGURE 1 Heart Diagram Illustrating Pressure Loss Recovery in Aortic Stenosis



(A to D) Aortic flow velocity and left ventricular (LV) and aortic pressure (Ao) recordings during a pull back with a high-fidelity catheter with 2 laterally mounted manometer transducers spaced 5 cm apart and a velocity sensor located at the proximal transducer site in a patient with severe aortic stenosis. Velocity increases and a pressure gradient appears as the catheter is withdrawn from the LV cavity **(A)** toward the outflow tract **(B and C)**. Maximal LV-aorta gradient coincides with the maximal velocity at the vena contracta **(C)**. Further withdrawal of the catheter **(C to D)** illustrates pressure recovery: the difference in peak systolic pressures recorded from the proximal sensor while lodged in the vena contracta **(C)** and that recorded from the same sensor withdrawn further into the aortic root **(D)**—in this case, a "recovery" of 20 mm Hg. Reproduced with permission from Herrmann and Laskey.[38]

systemic vascular resistance.[27,41,46] This increase in transvalvular gradients from immediately post-procedure to discharge appears to affect patients with smaller prostheses and with balloon-expandable valves to a larger extent than self-expanding valves.[27,46] Although changes in flow may account for some of the differences in gradients over time, the rise in transvalvular gradients appears to be disproportionate to the increase in stroke volume, and low-flow state alone may not account for the lower gradients immediately post-TAVR. There may also be hemodynamic adaptation early postimplant (between immediately postprocedure and postprocedure day 1) that could differ depending on transcatheter heart valve size or structure.[46]

In summary, the simplicity and availability of echocardiography and the ability to obtain serial measurements over time coupled with natural history data confirming the correlation of echocardiographic gradients with clinical outcomes support the continued use of echocardiography for routine assessment of valve function, while reserving invasive measurements to settings before consideration of interventions. Despite rigorous acquisition protocols, there may be differences in echocardiographic and invasive measurements of gradients among valve

types, sizes, and hemodynamics at the time of measurement.[27,28,46] The pitfalls of the Bernoulli equation, a greater contraction coefficient for the balloon-expandable valve, and other technical and timing differences may explain some of these differences.

ISSUES RELATING TO SURGICAL VS TRANSCATHETER BIOPROSTHESES AND THE SMALL AORTIC ANNULUS

The choice of surgical heart valve (SHV) is a key determinant of successful SAVR and postoperative outcomes. For each valve, cardiac surgeons require appropriate sizing information and guidance on intended implant position to allow for optimal prosthesis choice. In addition, the aortic annulus is rarely a perfect circle. Some biological SHVs feature an inherent degree of sewing ring flexibility, whereas other bioprostheses and all mechanical SHVs do not, adding to the complexity required to maximize the size of the prosthesis. The physical dimensions of SHVs are related to their performance, but manufacturers often use nonuniform terminology to describe the physical dimensions of their SHVs.[9] The proper interpretation of labeled valve size, defined in the International Organization for Standardization (ISO) standard as the "manufacturer's designation of a surgical heart valve substitute which indicates the intended patient annulus diameter," remains one of the most challenging issues surrounding the labelling and use of SHVs.[47-49]

Practically, labeled valve sizes represent tissue annulus diameter ranges with the lower margin of this range determined by the diameter of the largest valve specific tubular sizer that fits the annulus. The upper margin of this range is indirectly bordered by the diameter of the largest sizer that does not fit. However, as the margins of these tissue annulus ranges were not defined in the corresponding ISO standards, they can vary for different SHV models having the same labeled valve size.[21]

The presence of a small aortic annulus represents a particular clinical challenge in patients with aortic stenosis, including in women who account for up to 90% of these patients.[10,11,50,51] Prosthesis-patient mismatch (PPM) occurs more often in these patients.[2,5] In SAVR, severe PPM is associated with decreased survival, worse quality of life, and early structural valve degeneration.[1,2,52] In surgical series, a small annulus has been commonly defined as one that would not accommodate a prosthesis size ≥21 mm or an aortic annulus ≤23 mm measured either by echocardiography or intraoperatively by direct sizing.[50] More recently, an annular area defined by 3-dimensional computed tomography (CT) of <400 mm^2 [51] or <430 mm^2 [53] has been proposed for defining a small annulus.

A small aortic annulus is associated with poorer outcomes after surgical aortic valve replacement, with increased mortality, ischemic cardiovascular events, and stroke.[10,11] Surgical strategies to improve valve hemodynamics and clinical outcomes include aortic root enlargement, stented prostheses implanted in a supra-annular position, stentless and sutureless bioprostheses, and the Ross procedure (autograft replacement).[50] Supra-annular positioning can improve hemodynamics compared with intra-annular prostheses, but in surgical series, this has not translated into significant benefits in long-term survival or the prevention of major adverse valve-related events. Similar comparisons between transcatheter valves are limited by differing non-hemodynamic competing risks for mortality, such as paravalvular aortic regurgitation and permanent pacemakers.[19,54] Finally, different implantation techniques (ie, U-stitches reinforced with or without pledgets, single interrupted stitches without pledgets, hemi-continuous sutures) have been suggested to improve hemodynamic performance.[55]

Sutureless aortic valve implantation has received recent interest, because of the rapid development of transcatheter valve technology. Two such devices, the Sutureless Perceval-S (LivaNova) and rapid-deployment Intuity (Edwards Lifesciences) bioprosthesis, provide good and similar early clinical and hemodynamic outcomes. The Perceval-S valve implantation leads to shorter cross-clamp and cardiopulmonary bypass times, whereas the Intuity valve implantation may provide lower transaortic gradients.[56]

Root enlargement can also increase the size of a surgical bioprosthesis implanted in a small annulus[57,58]; however, the results have been contradictory.[59-61] The Ontario study utilizing administrative data showed that aortic root enlargement was not associated with short-term mortality,[60] whereas the STS Adult Cardiac Surgery Database study showed that root enlargement was associated with increased 30-day mortality.[61] The risks of root enlargement include longer cardiopulmonary bypass time, bleeding from the suture line, and potential for mitral regurgitation. In the STS study, the root was enlarged in only 2.9% of all SAVR performed.

In younger and particularly active patients with long life expectancies, the Ross procedure, which involves an aortic root replacement with a pulmonary autograft, has demonstrated excellent long-term outcomes and durability in experienced centers.[62,63]

TABLE 3 Definitions for Prosthesis-Patient Mismatch

	Severe, cm^2/m^2	Moderate, cm^2/m^2
ASE guidelines[26]	<0.65	0.65-0.85
VARC-2[105]	<0.65	0.65-0.85
BMI ≥30 kg/m^2	<0.60	0.60-0.70
EACVI recommendations[80]	<0.65	0.65-0.85
BMI ≥30 kg/m^2	<0.55	0.55-0.70
VARC 3[6]	≤0.65	0.66-0.85
BMI ≥30 kg/m^2	<0.55	0.55-0.70

ASE = American Society of Echocardiography; BMI = body mass index; EACVI = European Association of Cardiovascular Imaging; VARC = Valve Academic Research Consortium.

The Ross procedure is ideal in young and active patients with small annulus, since the aortic valve prosthesis is a living substitute, with lower risk of structural valve degeneration and endocarditis than a xenograft or homograft bioprosthesis.

The lack of a sewing ring in transcatheter valve prostheses may allow for slightly better hemodynamics with TAVR compared with SAVR.[51,64-67] In the most recent PARTNER 3 trial in patients with severe aortic stenosis and low surgical risk, transvalvular gradients, valve areas, percentage of severe PPM, regression of LV hypertrophy, and evolution of LV systolic function were similar with all sizes of balloon-expandable transcatheter valves compared with SAVR in short-term follow-up.[68] In contrast, TAVR using a self-expanding valve resulted in better hemodynamics and a reduced incidence of PPM compared with surgery for annuli with diameter smaller than 26 mm.[65] In a propensity-matched analysis from the German Aortic Valve Registry, valve hemodynamics of SAVR with current-generation rapid-deployment valves (Intuity and Perceval) were compared with TAVR. The authors observed a hemodynamic advantage of the Intuity prosthesis, with less residual gradients and less aortic regurgitation compared with Sapien 3. In contrast, the Perceval prosthesis had the highest residual gradients, whereas the Evolut TAVR prosthesis was associated with the lowest gradients of all analyzed valves.[69]

DEFINITIONAL ISSUES OF BIOPROSTHETIC VALVE STRUCTURAL DETERIORATION, DYSFUNCTION, AND FAILURE

Bioprosthetic valve dysfunction and failure may be caused by structural valve dysfunction (SVD) or non-SVD and may have an impact on LV recovery, symptoms and quality of life, valve durability, cardiac rehospitalization, and mortality following AVR.[6,12,70] Non-SVD includes PPM and paravalvular aortic regurgitation. The durability of bioprosthetic valves may be limited because of SVD. Midterm (5-8 years) durability of the new generation of transcatheter valves appears to be similar to that of surgical valves. However, it is still unknown whether transcatheter valves will have similar long-term durability as surgical valves.

Recent expert consensus statements redefined SVD based on identification of structural and hemodynamic valve deterioration at echocardiographic follow-up.[6,71,72] The definitions of bioprosthetic valve dysfunction and failure are presented in detail in a companion paper.[73] Key points regarding these definitions include the following:

1. Definitions of SVD based on valve-related reintervention or death underestimate the true incidence of SVD.[4]
2. Definitions solely based on the presence of a high transprosthetic gradient (>20 mm Hg) at a given echocardiogram during follow-up overestimate the incidence of SVD. A high gradient may occur in the case of a patient with a normally functioning bioprosthetic valve and severe PPM.
3. Definitions of SVD should therefore include permanent structural changes to the leaflets (or stent) and irreversible hemodynamic valve deterioration, including as a result of valve thrombosis or endocarditis.[73]

PROSTHESIS-PATIENT MISMATCH

CONCEPT AND DEFINITION OF PPM. PPM was first described by Rahimtoola[74] in 1978. It is defined by an EOA of the prosthetic valve that is too small in relation to a patient's body size, resulting in a high residual transvalvular pressure gradient and/or insufficient cardiac output, particularly with exercise.[75] A high residual gradient (mean gradient ≥20 mm Hg) on transthoracic echocardiography is a red flag for PPM. However, a high transprosthetic gradient may also be related to a high flow state, aortic regurgitation, or acquired prosthetic valve stenosis caused by valve thrombosis or SVD. Similarly, because the transvalvular gradient is flow dependent, a low gradient does not necessarily exclude the presence of PPM, and the gradient may be low even in the presence of PPM.

PPM is generally defined and categorized on the basis of the indexed effective orifice area (EOAi), ie, the EOA divided by the patient's body surface area. Initially, the cutoff values of EOAi that were recommended to define PPM in the aortic position were <0.85 cm^2/m^2 for moderate and <0.65 cm^2/m^2 for severe PPM[25] (Table 3). However, it has been

TABLE 4 Summary of Reasons for Discrepancy in Effects of Severe PPM on Outcomes

Reasons why the reported incidence of PPM varies after AVR
Method of EOA calculation (measured vs predicted)
Correction or not for obesity
Timing of measurement (immediate vs later)
Effect of underlying flow state
Method of gradient determination (echocardiographic vs hemodynamic)
Reasons why the effects of severe PPM on outcomes are conflicting
Measurements and calculations differ as above
Incomplete correction for confounding and competing outcome variables
Paravalvular aortic regurgitation
Low flow state
Older patients or other survival limitations
Underpowered analyses
Limited follow-up (1 year may not be sufficient)

AVR = aortic valve replacement; EOA = effective orifice area; PPM = prosthesis-patient mismatch.

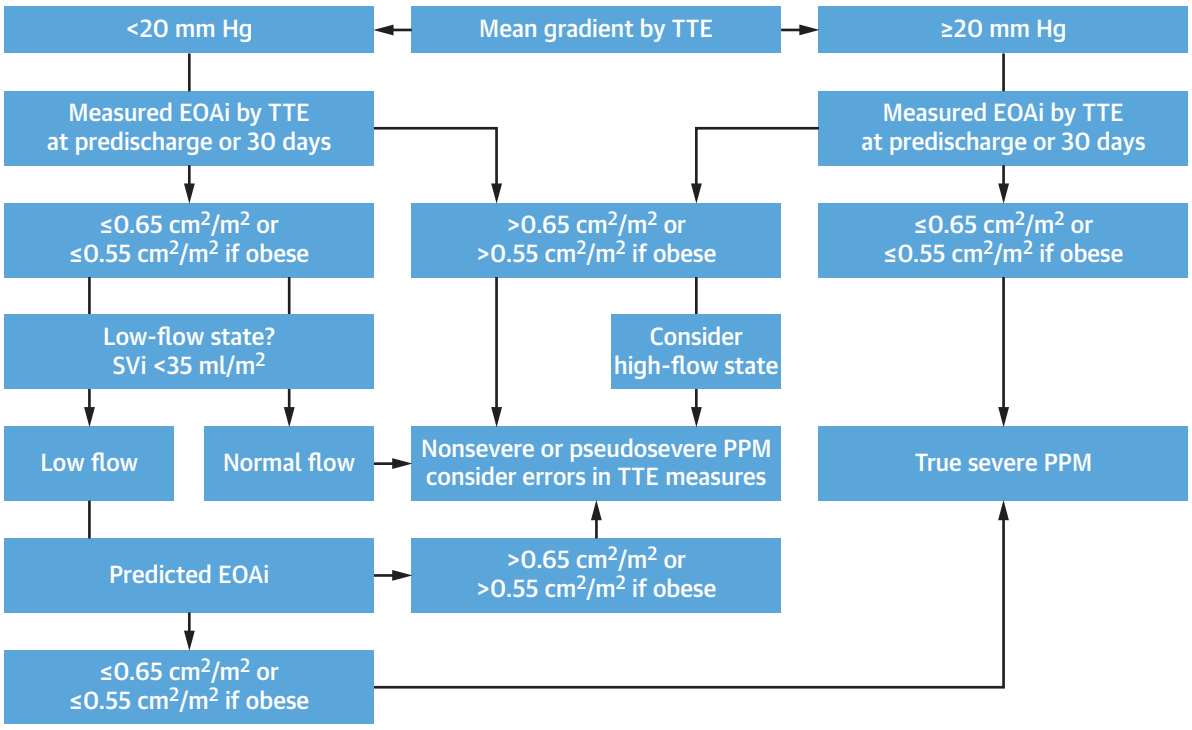
suggested that in obese patients (ie, body mass index ≥30 kg/m^2), the use of these EOAi cutpoints may result in an overestimation of the incidence and severity of PPM.[6,76] Although the cardiac output requirements in obese patients may be greater, they exercise less, and cardiac output does not increase linearly with size and may depend on age as well as the ratio of fat-free muscle mass to fat mass.[77] Outcome data in surgery have shown an increased effect of severe PPM on mortality both with a higher[78] and lower[79] body mass index and no interaction of severe PPM and body mass index was observed in the largest TAVR study to date[5] (Table 4). Thus, the use of an obesity correction for severe PPM remains an area of controversy, despite recent recommendations for the application of a lower cutoff value of EOAIs in these patients: <0.70 cm^2/m^2 for moderate and <0.55 cm^2/m^2 for severe PPM[6,80] (Table 3).

CALCULATION AND MEASUREMENT OF PPM. In addition to the definitional issues described in the previous text, different methodologies for the calculation of PPM have been suggested: 1) the measured method using the EOAi calculated at predischarge or 30-day transthoracic echocardiogram using the continuity equation; and 2) the predicted method using the EOAi obtained from the published normal reference values of EOA for each model and size of prosthetic valve.[74,76,80] The measured EOAi may overestimate the incidence and severity of PPM because it also includes "pseudo-severe" PPM caused by low-flow state.[81] In this case, the EOAi measured by echocardiography may be "pseudo-severe," leading to an erroneous conclusion that severe PPM is present (Figure 2). An important issue is whether a low EOAi in this situation, not necessarily because of physical valve characteristics, has the same implications for patient outcomes because low-flow pre- and post-TAVR has been independently associated with adverse outcomes.[82,83] To overcome this issue of pseudo-severe PPM, it is suggested to perform EOA measurements at 30 days post-AVR when the highly prevalent low-flow state during and early after the procedure has resolved or to use the predicted EOAi instead.[76,80] In normal flow conditions, the measured and predicted indexed EOAi should be consistent and yield concordant grading of PPM severity. Transthoracic echocardiography may also underestimate LV outflow tract diameter and area and thus overestimate the incidence and severity of PPM. For this reason, the aortic annulus area measured by CT before or after the procedure may be used to calculate a "hybrid" (ie, CT-Doppler) EOAi. This method systematically yields a lower incidence of PPM, but has not been shown to provide a better association with clinical outcomes vs PPM measured by echocardiography.[84]

To obtain an accurate predicted EOAi, it is essential to know the exact model and label size of the bioprosthetic valve and to use reliable sources for the normal reference values of EOA for both SAVR[79] and TAVR[17] valves. However, the application of predicted values in a general population to measured values in an individual patient may also introduce errors caused by specific characteristics, such as the actual valve size after deployment (under and over expansion), effects of noncircularity, and paravalvular regurgitation. Patient factors that have been associated with severe PPM include a small aortic annulus, women, valve-in-valve procedures, small valve prostheses, older age, lower ejection fraction, non-White and Hispanic, and atrial fibrillation.[2,5,34,85] To enhance the definition, prediction, and prevention of PPM following AVR, a task force led by ISO and the Heart Valve Collaboratory has been launched to establish accurate and reliable normal reference values of EOAs for each given model and size of surgical or transcatheter bioprosthesis using a robust and standardized methodology as described in the following text.

INCIDENCE AND IMPACT ON OUTCOMES OF PPM FOLLOWING SAVR. The incidence of PPM ranges from 20% to 70% and that of severe PPM from 2% to 20% following SAVR.[2,78,85] Patients with severe aortic PPM have poorer functional class and worse exercise capacity, reduced regression of LV hypertrophy, more adverse cardiac events, more cardiac

FIGURE 2 Algorithm for the Diagnosis and Classification of PPM



The figure depicts a proposed algorithm for differentiating between true severe prosthesis-patient mismatch (PPM) defined by the effective orifice area indexed to body surface area (EOAi) with a measured mean echocardiographic gradient >20 mm Hg and nonsevere or pseudosevere PPM caused by the presence of a low gradient and/or a low flow state. In the latter case of low flow that is often present early after transcatheter and surgical aortic valve replacement, use of the predicted EOAi may be more suitable. SVI = stroke volume index; TTE = transthoracic echocardiogram.

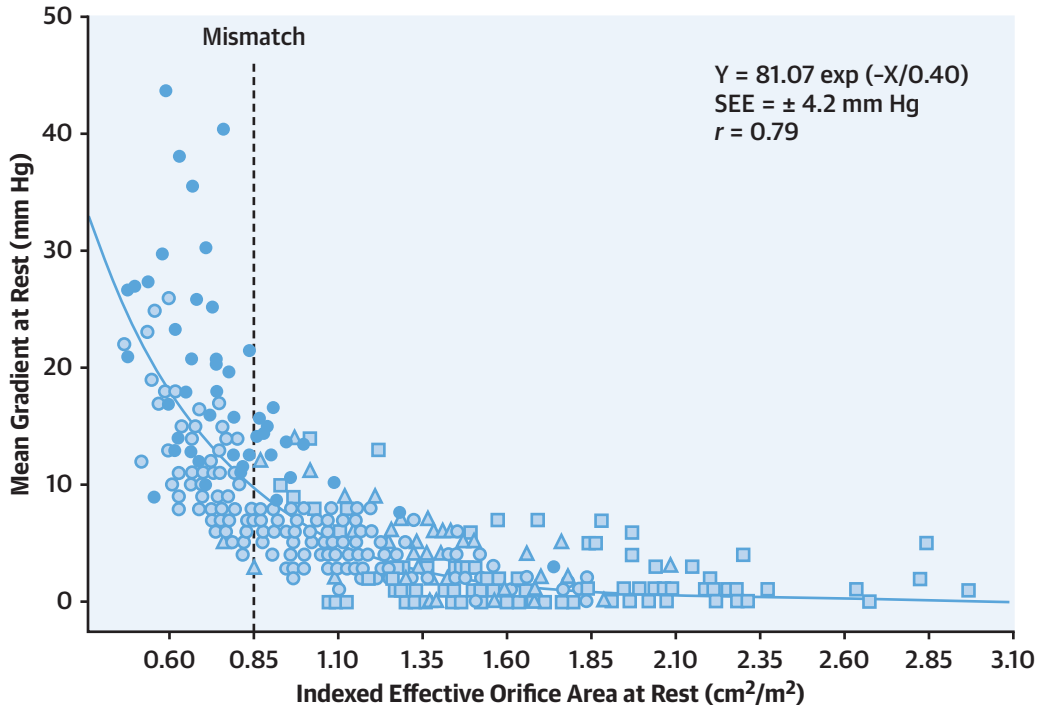
rehospitalizations, increased risk of structural valve deterioration, shorter valve durability, and increased risk of both perioperative and late mortality after SAVR when compared with patients who do not have PPM[1,2,52,78,85] (Supplemental Table 1). Greater clinical impact of severe and even moderate PPM is observed in specific groups of patients such as those with pre-existing LV dysfunction or hypertrophy, those with concomitant mitral regurgitation, and in those <65-70 years of age.[2,78,85]

INCIDENCE AND IMPACT ON OUTCOMES OF PPM IN TAVR VS SAVR. PPM is less frequent with TAVR compared with SAVR.[3,66,86] The vast majority of SAVR studies have used the predicted EOAi to examine the incidence and impact of PPM on clinical outcomes,[2,78] whereas TAVR studies have used both predicted and measured EOAi.[5,76] Although some TAVR prostheses may have a more favorable hemodynamic profile than surgical prostheses, the difference in the method used to identify and grade PPM may also explain the discrepancies in PPM incidence and impact reported between TAVR and SAVR series (Table 4). In most trials, the incidence of severe PPM was lower with TAVR compared with SAVR. The association of severe PPM with clinical outcomes occurs after SAVR and TAVR,[5,34,87] but was generally more significant with SAVR (Supplemental Table 1). This may be related, in part, to the fact that in TAVR series, the use of the measured EOAi may have resulted in an overestimation of incidence and severity of PPM in patients with a low-flow state. Alternatively, the different effects on outcomes may be caused by the low incidence of severe PPM in small studies, competing and confounding factors that affect outcomes, short length of follow-up, and underpowering for outcome events (Table 4).

HIGH RESIDUAL GRADIENTS AFTER AVR

ASSESSMENT. After SAVR or TAVR, comprehensive transthoracic echocardiography should be undertaken early after hospital discharge to assess valve hemodynamics.[23,26,29] LV ejection fraction and global longitudinal strain, along with any regional areas of LV systolic dysfunction, should be reported along

FIGURE 3 Correlation Between Mean Transvalvular Aortic Gradient and Indexed Orifice Area



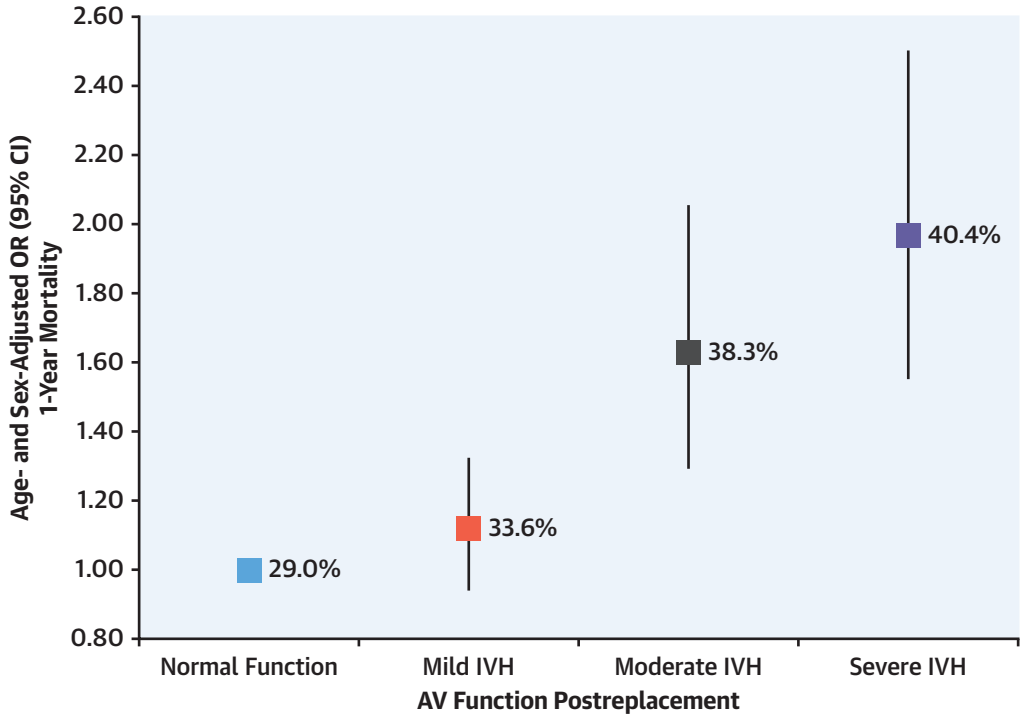
Patients shown with a stented prosthesis (n = 51) **(solid circles)**, a stentless bioprosthesis (n = 194) **(open circles)** an aortic homograft (n = 55) **(triangles)** and a pulmonary autograft (n = 96) **(squares)**. Several points overlap. Reproduced with permission from Pibarot and Dumesnil.[91]

with LV mass calculation.[88] Diastolic function assessment is challenging post-AVR because of tethering of the basal ventricular septum by the aortic valve prosthesis, along with other limitations such as bundle branch blocks, atrial arrhythmias, and atrioventricular block (ventricular pacing), all of which are more likely post-AVR.

Echocardiographic measures post-AVR should include 4 key components: motion of the AVR leaflets, peak aortic valve velocity, mean gradient, and EOA.[89] Each component should be assessed in the context of LV systolic function, transvalvular flow, ascending aortic dimensions, and arterial blood pressure. The presence and severity of PPM should be systematically assessed. In PPM, the peak aortic valve velocity and mean aortic valve gradient are generally high immediately after implantation (**Figure 3**) and remain abnormally elevated, whereas structural valve deterioration is associated with rising gradients over time. The pathophysiology of PPM and structural valve deterioration behave similarly to native aortic stenosis, with persisting LV hypertrophy and diastolic dysfunction and increased risk of heart failure hospitalization and mortality.[8,90] In this regard and as described in the previous text, understanding the relationship between gradient, flow, and the calculation of severe vs pseudo-PPM as well as the consequences of high gradient and low flow on outcomes is essential (**Figure 2, Table 3**).

EFFECT OF IMPAIRED VALVULAR HEMODYNAMICS POST-AVR. Impaired valvular hemodynamics refers to consistently elevated transvalvular gradients, a hemodynamic state that may be caused by obstruction at the level of the valve or PPM.[8,74,91] Valve obstruction may occur in the setting of SVD, characterized by restricted leaflet motion and progressively worsening gradients, or valve design-related (eg, some stented prostheses).[71-73] Impaired valve hemodynamics post-AVR may behave like native aortic stenosis and may worsen over time, with clinical consequences including persistent LV hypertrophy, impaired coronary flow reserve, diastolic dysfunction, and symptomatic heart failure with a higher risk of hospitalization and subsequent mortality.[4,91,92]

FIGURE 4 **Outcomes With IVH Following Aortic Valve Replacement**



Effect shown are age and sex-adjusted ORs for 1-year mortality relative to normal function and actual mortality as a percentage with 95% CI. Reproduced with permission from Playford et al.[8] IVH = impaired valvular hemodynamics.

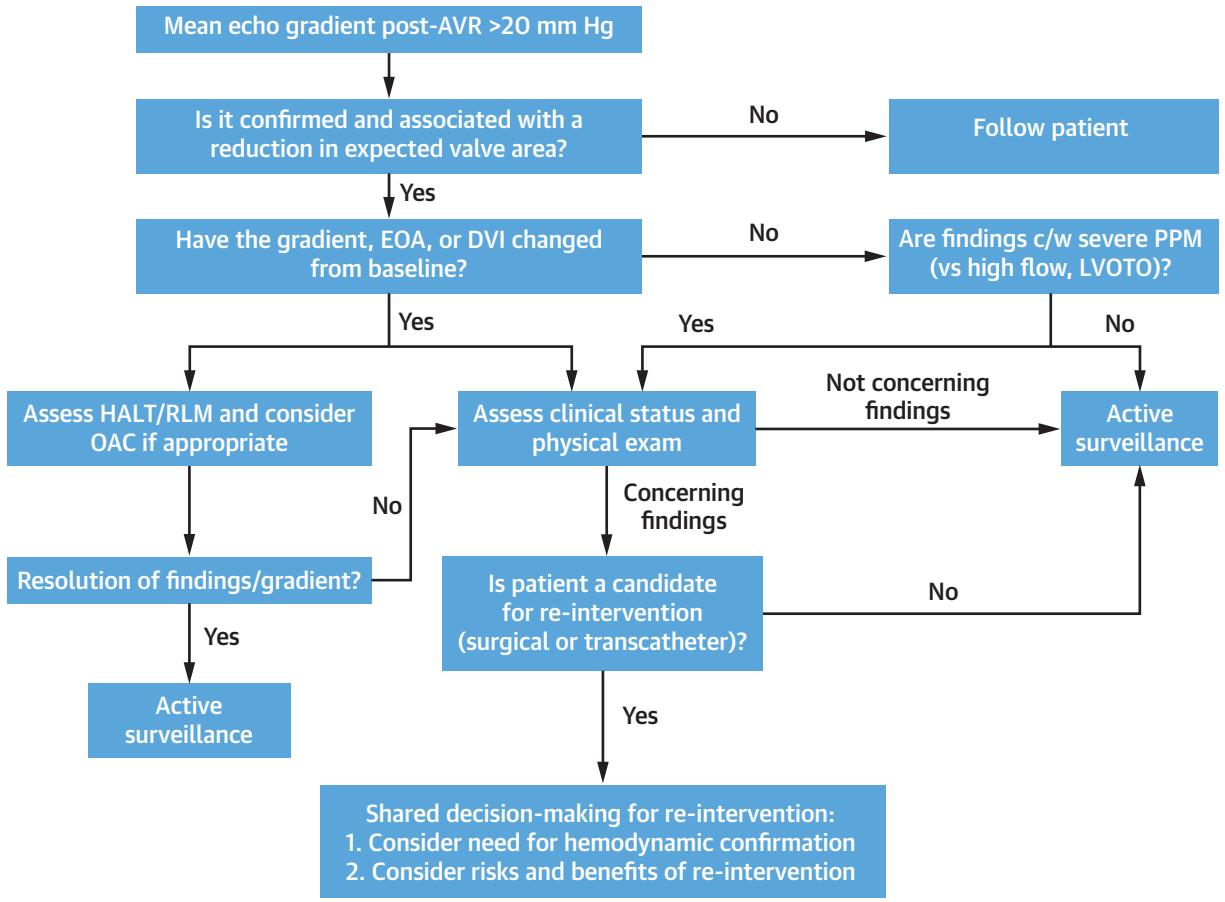
Studies of native and post-AVR stenosis have confirmed a strong relationship with mortality for a smaller EOA as well as a higher transvalvular gradient (Figure 4). Progression of elevated gradients over time depends on the underlying cause, with bioprosthetic valve degeneration tending to deteriorate more quickly than PPM. Native valve aortic stenosis follows a steep age gradient, with progressive LV hypertrophy, diastolic dysfunction, and pulmonary hypertension occurring in parallel with increased mortality risk.[93-95] Impaired valve hemodynamics following AVR follows a similar trajectory, with the gradient threshold at which mortality rises being above 20 mm Hg.[8] This mortality threshold is remarkably similar to native valve aortic stenosis and persisted after correction for EOA (Figure 4).

CONSEQUENCES AND CLINICAL APPROACH TO ADVERSE HEMODYNAMICS POST-AVR. Adverse valve hemodynamics with elevated residual gradients after aortic valve replacement are associated with mortality primarily after SAVR, with conflicting data after TAVR, as described in the previous text, as well as with early structural valve degeneration.[8,96] Residual physiological stenosis is particularly relevant in physically active, often younger, individuals as well as those with large body mass indexes needing to maintain a certain level of metabolic demands. Anatomically, patients with a small aortic root/annulus and smaller implanted bioprotheses have the highest risk of residual elevated gradients. Randomized trials have demonstrated larger EOAs and lower mean echocardiographic gradients for supra-annular self-expanding prostheses compared with balloon-expandable, mechanically expandable, and intra-annular self-expanding prostheses.[54,97-99]

Clinically, these patients may have less improvement after aortic valve replacement. Echocardiography would typically show a normally functioning bioprosthesis with no evidence of leaflet thrombosis, thickening, or degeneration, but elevated transvalvular gradients. Such patients must be differentiated from those with residual diastolic function abnormalities and normal valve gradients and those with other comorbidities.

In patients with increased gradients by echocardiography on mid- and long-term follow-up, additional imaging is recommended to evaluate for valve leaflet

CENTRAL ILLUSTRATION **Approach to the Patient With a High Gradient Post-Aortic Valve Replacement**



Herrmann HC, et al. J Am Coll Cardiol. 2022;80(5):527–544.

AVR = aortic valve replacement; c/w = consistent with; echo = echocardiographic; EOA = effective orifice area; DVI = Doppler velocity index; HALT = hypoattenuated leaflet thickening; LVOTO = left ventricular outflow tract obstruction; PPM = prosthesis-patient mismatch; RLM = reduced leaflet motion.

structural change or thrombus. In a small study of patients with increasing echocardiographic gradients to ≥20 mm Hg at midterm follow-up following TAVR and with no evidence of structural valve changes on CT angiography, concomitant echocardiographic and invasive aortic valve assessment have demonstrated invasive gradients <20 mm Hg in many patients.[100] This finding suggests a role for invasive confirmation before consideration for aortic valve reinterventions. As such, echocardiography and catheterization should be viewed as complimentary and not competitive modalities following TAVR.

The approach to the patient post-AVR with a high mean echocardiographic gradient (eg, ≥20 mm Hg) requires integration of clinical assessment, physical examination, and the echocardiographic and/or additional imaging findings (**Central Illustration**). First, the echocardiographic gradient should be confirmed, and the quality of the measurement assessed to ensure that it is reproducible. In addition, the EOA or Doppler velocity index should be measured to confirm that the gradient is associated with a reduced expected valve area. If the mean gradient, EOA, or Doppler velocity index have changed from baseline measures, the patient should be assessed for leaflet thrombosis and reduced leaflet motion with additional imaging modalities (eg, transesophageal echocardiography, 4-dimensional CT angiography), and if this diagnosis is confirmed, consideration should be given for anticoagulation therapy. The patient's clinical status, including signs or symptoms of heart failure, should guide the need for further investigation or intervention. Although studies have correlated a high residual gradient with

increased mortality,[4,6-8] it should be recognized that the gradient should be considered in the context of flow measurement, the potential need for invasive hemodynamic confirmation, and other causes for high flow. Finally, the potential options for reintervention (including both surgical and transcatheter ones) and the risks of reintervention should be discussed along with the patient's preferences with shared-decision making (**Central Illustration**).

EVIDENCE GAPS AND STEPS FORWARD

INTERNATIONAL EFFORTS ON SURGICAL VALVE LABELING AND SIZING. Suboptimal selection of a valve prosthesis for a given patient could be a contributing factor to high gradients and PPM post-AVR. To explore solutions to various controversies surrounding the sizing and labeling of surgical heart valves and to facilitate intraoperative and postoperative comparison of different valves, a valve labeling task force with representatives from multiple surgical societies, cardiologists, engineers, regulatory bodies, the ISO Cardiac Valves Working Group, and major valve manufacturers was convened in 2018.[21] Subsequently, in a consensus document, the task force recommended the use of standardized valve charts by the manufacturers to present essential information on surgical heart valve characteristics, including the physical dimensions, implant position, and hemodynamic performance of an SHV.[9]

In parallel to the work by the valve labeling task force, the ISO Cardiac Valves Working Group started to develop recommendations on surgical valve sizing and labeling. This ISO group comprises representatives of the heart valve device manufacturers, independent subject matter experts (clinicians, veterinarians, and engineers), and regulatory bodies and is tasked with developing and updating international standards on the evaluation of heart valve devices, which are widely followed by industry and global regulators.[47-49] This group ultimately recommended that the outer container for an SHV include a label in diagrammatic and/or tabular form with the following items:

- Intended valve to be replaced;
- Inflow orifice diameter;
- Effective orifice diameter (a virtual diameter derived from benchtop steady forward flow EOA that serves as an indicator of size of the flow passage is inside a replacement heart valve device);
- Valve housing external diameter.

Once implemented, these valve charts will make information on the valve characteristics more readily available to the implanting surgeons and facilitate intraoperative and postoperative comparison of different valves. Importantly, no such valve standards for sizing and labeling have been proposed for transcatheter heart valves, which represents a reasonable and necessary next step, as the proliferation of new and iterative transcatheter valve designs become commercially available in the future.

ISSUES ON WHICH NEW TRIALS SHOULD FOCUS. Despite the revolutionary change in the management of severe symptomatic aortic stenosis provided by the technology advances and clinical evidence supporting TAVR use in many clinical circumstances, there remain unresolved issues that require further investigation. These include the following: 1) the lifelong journey of valvular heart disease, especially with TAVR extension to younger patients and the expectation of multiple sequential procedures; 2) management of bicuspid aortic valve disease (often in younger patients and with complex valve and aorta anatomies); 3) avoidance of important procedure-related complications affecting clinical outcomes (stroke, paravalvular regurgitation, conduction abnormalities, and vascular events); and 4) considerations that may have late consequences, such as valve leaflet thickening and/or thrombosis, coronary obstruction, and commissural alignment. Herein, we have limited our discussion to hemodynamics and valve durability.

As described in the previous text, patients with a small native annulus and those with a failing small surgical valve receiving a small bioprosthesis are at the highest risk for residual gradients and PPM. These patients are typically female, often underrepresented in clinical trials, and infrequently offered surgical solutions, such as aortic root enlargement. There are several ongoing and planned clinical trials aimed at addressing these issues.

The ongoing VIVA (Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement for Treating Elderly Patients with Severe Aortic Stenosis and small Aortic Annuli; NCT03383445) randomized trial compares SAVR and TAVR in 300 patients with severe aortic stenosis and a small annulus, defined as mean aortic annulus diameter $<$22 mm. The primary endpoint of this trial is valve hemodynamics (severe PPM and/or $\geq$ moderate aortic regurgitation) as evaluated by echocardiography at 2-month follow-up.

A recent small randomized multicenter study compared balloon-expandable and self-expanding TAVR prostheses for patients with failed small ($\leq$23 mm) surgical valves (NCT03520101).[101] A total of

98 patients were randomized with no differences in clinical outcomes at 30 days. The mean echocardiographic gradient was significantly lower with self-expanding valves compared with balloon-expanded valves (15 mm Hg vs 28 mm Hg), with a trend toward a lower rate of severe PPM. Longer follow-up will be needed to determine the potential clinical impact of the observed differences in valve hemodynamics.

The SMART (Small Annuli Randomized To Evolut or SAPIEN Trial; NCT04722250) was designed to compare the performance of the 2 most widely available commercial TAVR devices in patients with symptomatic severe native aortic stenosis with a small aortic valve annulus undergoing transfemoral TAVR.[53] Planned enrollment is approximately 700 patients at 90 international sites, and the primary composite clinical endpoint includes mortality, disabling stroke, or heart failure hospitalization at 12 months. A coprimary valve function composite endpoint is defined as bioprosthetic valve dysfunction (hemodynamic structural and nonstructural valve dysfunction (severe PPM, ≥ moderate aortic regurgitation, thrombosis, endocarditis, and aortic valve reintervention) at 12 months. An exercise substudy as well as long-term follow-up to assess durability is planned.

Pilot data for the DISCORDANCE TAVR trial (NCT04827238) comparing echocardiographic and hemodynamic gradients between 2 months and 4 years post-TAVR was recently published.[100] An extension of this valve gradient study to include simultaneous assessments immediately after balloon-expandable TAVR and in follow-up for patients with echocardiographic mean gradients >20 mm Hg will be part of the COMPLETE TAVR study, a 4,000-patient international randomized trial exploring management alternatives of concomitant coronary artery disease after TAVR.

Finally, studies of bioprosthetic valve durability utilizing modern-era serial echocardiography assessments will be critical for management of younger patients with an extended expected lifespan and to make comparative decisions between surgical and transcatheter bioprosthetic heart valves. Currently, U.S. Food and Drug Administration–approved clinical trials of transcatheter valves in intermediate and low surgical-risk patients require at least 10 years of clinical and echocardiography follow-up, although this is not typically required for new surgical bioprostheses. The need for long-term follow-up is emphasized in the following circumstances: 1) impact of early (in the first year) valve leaflet thickening/thrombosis on subsequent structural valve deterioration; 2) importance of commissural alignment on coronary access and valve durability; 3) assessment of new polymeric, modified bioprosthetic, and regenerative leaflet materials[102]; 4) effects of novel preprocedural multimodality imaging[103] to improve the lifetime management of patients with aortic stenosis; and 5) assessment of novel pharmacotherapy approaches to delay the progression of native calcific aortic stenosis or to diminish deleterious pathologic LV remodeling.[104]

SUMMARY AND CONCLUSIONS

Impaired functional performance of bioprosthetic aortic valves is associated with adverse patient outcomes. The assessment of valve performance by hemodynamic assessment is complicated by the lack of standardization for sizing, labeling, definitions, and measurement techniques. Echocardiography remains the standard methodology because of its ease of performance, widespread availability, ability to do serial measurements over time, and correlation with outcomes. Nonetheless, both theoretical and technical limitations may require the need for invasive hemodynamic confirmation in selected cases.

Surgical bioprostheses are particularly subject to sizing and labeling disparity. In addition, their hemodynamics are influenced not only by the prosthesis design, but also by implantation techniques. Transcatheter valves generally have more favorable hemodynamic profiles, but differences among TAVR devices exist. Definitions for bioprosthetic valve deterioration, dysfunction, and failure as well as for PPM are still evolving. Nonetheless, severe PPM and high residual gradients after surgical and transcatheter AVR are associated with adverse outcomes and reduced quality of life and should be avoided when possible.

Management of high AVR gradient requires integration of the patient's clinical status, physical examination, and multimodality imaging in addition to complex shared patient decisions regarding the treatment options. Future efforts to standardize prosthesis sizing and labelling for both surgical and transcatheter valves are underway, as are clinical trials to better understand the consequences of adverse hemodynamics.

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ADDRESS FOR CORRESPONDENCE: Dr Howard C. Herrmann, Hospital of the University of Pennsylvania, PCAM South Pavilion 11-107, 3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: Howard.herrmann@pennmedicine.upenn.edu. Twitter: @howard_herrmann.

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KEY WORDS aortic stenosis, aortic valve replacement, bioprosthetic

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

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