JACC Cardiovascular Interventions

Updated September 2025

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CORRESPONDENCE FOR AMERICAN COLLEGE OF CARDIOLOGY

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Updated September 2025

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

STATE-OF-THE-ART REVIEW

Artificial Intelligence in Valvular Heart Disease

Innovations and Future Directions

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ABSTRACT

Managing valvular heart disease (VHD) requires integrating multimodal data, including demographics, symptoms, biomarkers, electrocardiogram findings, and imaging studies. However, the capacity and processing power of the human mind are limited, particularly in the current era where vast quantities of complex data require rapid processing. Integrating artificial intelligence (AI) into the management of VHD offers an opportunity to enhance diagnostic accuracy, streamline clinical workflows, optimize procedural strategies, and predict outcomes and disease progression. Subsets of AI such as machine learning and deep learning algorithms can uncover the unseen data from routine investigations (eg, electrocardiograms, echocardiography, and computed tomography), providing robust and accurate risk prediction tools to inform personalized treatment strategies. Intraprocedurally, AI-based enhancements in imaging guidance can be leveraged to improve procedural safety and success. Digital twin technology can allow case-specific disease modelling, such as simulating valve designs and predicting adverse events, fostering precision medicine. By using the full potential of AI, clinicians can provide a comprehensive, personalized management strategy for VHD patients, ultimately enhancing clinical outcomes. However, models based on AI algorithms require rigorous validation across multiple centers to ensure their reliability. Concerns about bias, data privacy, and limited transparency challenge the application of AI decision-making to digital health care. This review discusses the applications of AI in the management of patients with VHD, highlights the future directions of AI technologies, and considers the challenges of integrating AI into clinical practice. (JACC Cardiovasc Interv. 2025;18:2439–2457) © 2025 by the American College of Cardiology Foundation.

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ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2025.08.031

ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

AUROC = area under the receiver-operating characteristic curve

CT = computed tomography

DL = deep learning

ECG = electrocardiogram

LLM = large language models

LVOT = left ventricular outflow tract

ML = machine learning

TAVR = transcatheter aortic valve replacement

VHD = valvular heart disease

The management of valvular heart disease (VHD) involves the assimilation of heterogeneous information, ranging from structured data in electronic health records (eg, demographics, symptoms, and laboratory values) to unstructured data from electrocardiograms (ECGs) and imaging. As the volume and complexity of data increases, it becomes harder for human cognitive capabilities to process and analyze these data effectively. Artificial intelligence (AI) enables computers to mimic human cognitive function at magnitudes beyond human capacity.

Through machine learning (ML) and deep learning (DL) (**Figure 1**) integrating AI into the management of VHD can enhance diagnostic accuracy, predict disease progression, streamline clinical workflows, and optimize procedural strategies (**Central Illustration**). In addition, various ML techniques, for example, supervised learning and unsupervised clustering, have been applied to predict outcomes after valve intervention.[1]

Importantly, despite the potential of AI, models based on ML or DL must undergo rigorous validation across diverse patient cohorts, from multiple centers, before being applied clinically. Prospective validation is essential to ensure their reliability, akin to how clinical trials are required to establish the safety and efficacy of novel therapeutic interventions.

This review discusses the applications of AI in the management of VHD, highlights the future directions of AI technologies, and considers the challenges of integrating AI into clinical practice.

HIGHLIGHTS

- Managing VHD involves the assimilation of a large volume of heterogenous multimodal data, making it difficult for human cognitive capabilities to effectively process and analyze.
- Integrating AI in the management of VHD enables clinicians to provide robust personalized management strategies, enhances diagnostic accuracy and decision-making, streamlines clinical workflows, optimizes procedural success, and improves the accuracy of outcome prediction.
- Models based on AI algorithms require rigorous validation in multicenter studies to ensure their reliability. Further challenges for the transition to digital health care include concerns about potential bias, data privacy, and limited transparency in AI decision-making.

AI-AUGMENTED DIAGNOSIS AND SEVERITY ASSESSMENT OF VHD

VHD is underdiagnosed, with many patients being identified at advanced disease stages. Auscultation is a low-cost, first-line diagnostic tool, hence the application of well-validated ML algorithms to optimize auscultation for early diagnosis of VHD is worth pursuing. The ECG is another attractive modality for AI-augmented screening of VHD, due to its widespread availability, low-cost, and standardized digital format. Echocardiography is the main modality for evaluating VHD, but is more time-consuming, requires skilled imagers and acquisition errors lead to measurement variability, therefore AI optimized echocardiography is of interest. Ultimately, the ideal approach would be a multimodal AI and ML framework that integrates data from various AI-based models (auscultation, ECG, echocardiography, computed tomography [CT], cardiac magnetic resonance imaging) to assist in diagnosis, risk prediction and treatment of VHD.[2,3]

AUSCULTATION. Auscultation skills have diminished in recent decades.[4] Compared with echocardiography, auscultation has low sensitivity for detecting VHD, especially aortic regurgitation and mild or moderate valve disease.[5,6] Digitized acoustic

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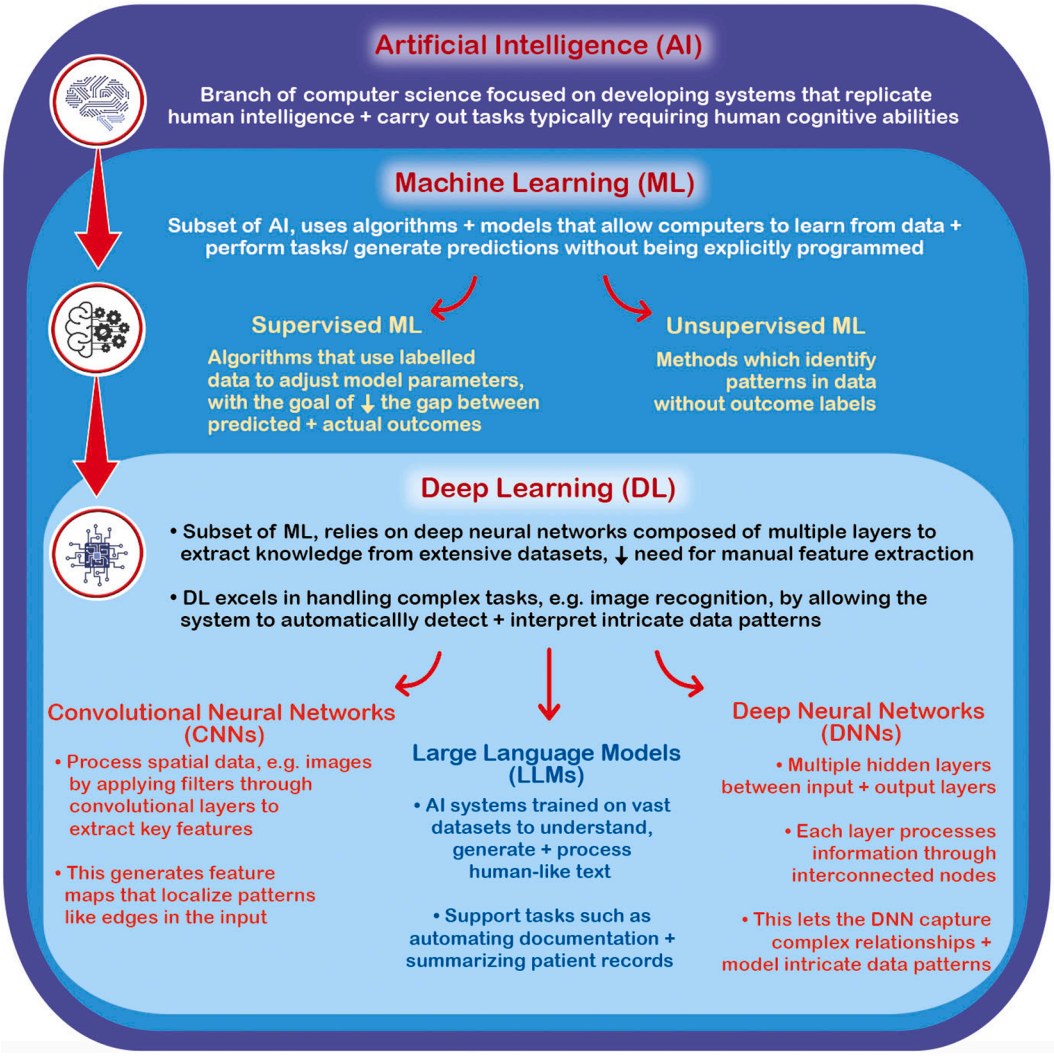
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 5, 2025; revised manuscript received August 19, 2025, accepted August 25, 2025.

FIGURE 1 **Terminologies Explained**

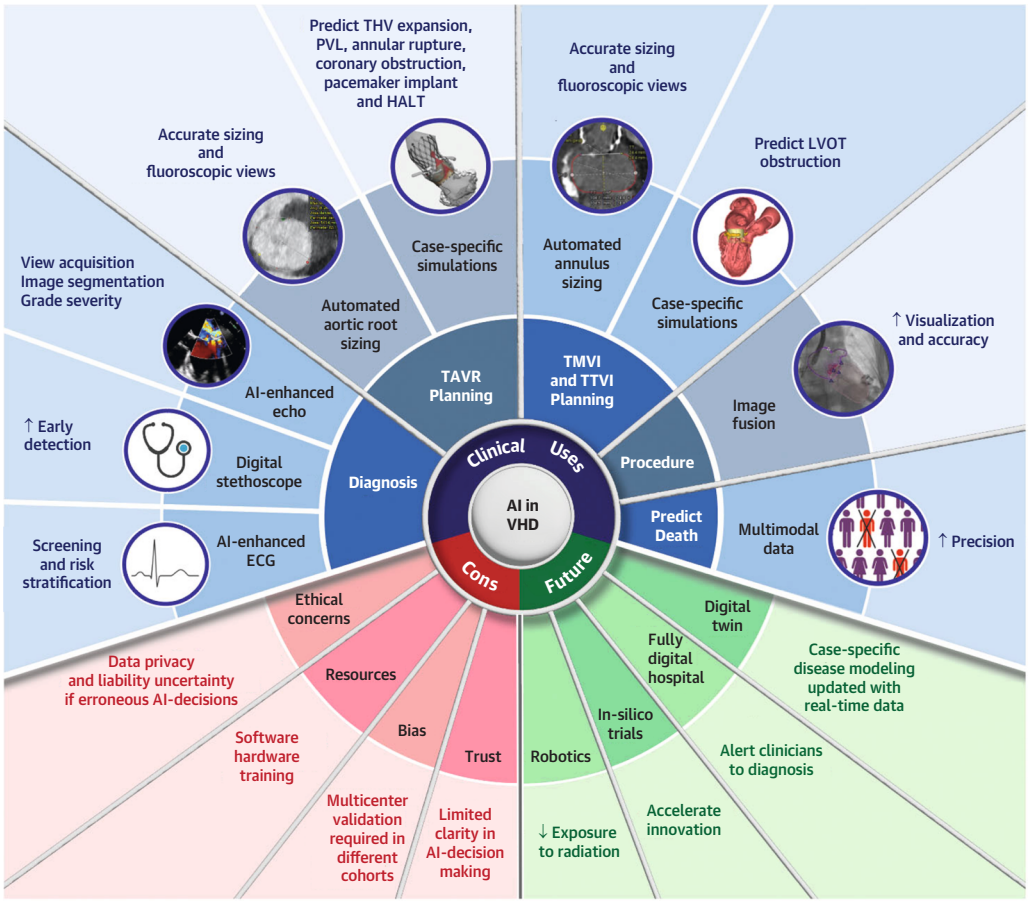


AI = artificial intelligence; CNN = convolutional neural network; DL = deep learning; DNN = deep neural network; LLM = large language model; ML = machine learning.

data can be processed for use by DL algorithms to produce output that can guide the physician toward the correct interpretation. Several AI-enabled digital stethoscopes have been developed and marketed, and are being evaluated for diagnostic accuracy.[7,8] For detecting aortic stenosis, the VoqX AI-enhanced stethoscope system (Sanolla) achieved high diagnostic accuracy (sensitivity 84%, specificity 92%).[7] By contrast, the Eko murmur analysis software performed considerably worse for detecting VHD (sensitivity 39%, specificity 82%).[8] Before adopting AI algorithms for auscultatory enhancement, they should be trained on large datasets and meticulously validated. One such validation study encouragingly detected pathologic murmurs with 86% sensitivity and 84% specificity.[9]

ELECTROCARDIOGRAM. Recent studies have demonstrated progress in applying convolutional neural networks, a type of DL, to ECG data for VHD detection.[10] The ValveNet model was developed and validated across multiple sites with over 77,000 patients

CENTRAL ILLUSTRATION Use of AI in Managing VHD



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AI = artificial intelligence; ECG = electrocardiogram; HALT = hypoattenuating leaflet thickening; LVOT = left ventricular outflow tract; PVL = paravalvular leak; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve; TMVI = transcatheter mitral valve intervention; TTVI = transcatheter tricuspid valve intervention; VHD = valvular heart disease.

and achieved a sensitivity of 78% and specificity of 73% (area under the receiver-operating characteristic curve [AUROC] of 0.84) for detecting ≥moderate aortic stenosis, aortic regurgitation, or mitral regurgitation.[11] The model performed better for aortic stenosis than for mitral or aortic regurgitation (AUROCs: 0.88, 0.83, and 0.77, respectively).[11] Similar results were observed in an analysis from the Mayo Clinic of 258,607 adults, with performance improving when incorporating age and sex data (AUROC: 0.87).[12]

Beyond improving early detection of VHD, AI-enhanced ECG analysis may predict the progression of structural heart disease, enabling more precise risk stratification. As an example, the PRESENT-SHD (practical screening using ensemble ML strategy for structural heart disease) model, validated across multiple cohorts, showed that individuals with positive AI-ECG screens had 2 to 4 times higher risk of developing new-onset structural heart disease or heart failure.[13] Successful clinical adoption of AI-guided ECG screening will depend on thorough validation across diverse health care settings, seamless integration into existing clinical workflows, and clear demonstration of improved patient outcomes.[14]

ECHOCARDIOGRAM. The main applications of AI in echocardiography are: image/view acquisition[15]; image segmentation of anatomical structures for automated analysis[16]; detection of significant VHD,[17,18] identification of high-risk phenogroups,[19,20] and live fusion with fluoroscopy. Importantly, AI may improve the detection of VHD in health care settings without access to trained sonographers, indeed with AI guidance, the percentage of evaluable images acquired by novice nurses performing echocardiograms was 92%, 96%, and 83% for the aortic, mitral, and tricuspid valves, respectively.[21] Commercial AI companies have developed the ability to accurately identify severe aortic stenosis from echocardiograms without left ventricular outflow tract (LVOT) data.[22] For detecting high-severity aortic stenosis, a ML model (trained on echocardiograms from 1,052 patients) demonstrated 99% accuracy when compared with experienced echocardiographers.[23] For quantification of mitral regurgitation, a novel DL system, which intakes a complete transthoracic echocardiogram, identifies color Doppler videos, and determines mitral regurgitation severity on a 4-step ordinal scale using the reading cardiologist as a reference standard, has shown slightly more accurate classification of mitral regurgitation using multiple transthoracic echocardiography views compared with only apical 4-chamber views (82% vs 80%).[17] AI algorithms can also correctly grade the severity of aortic regurgitation and tricuspid regurgitation,[18] for example, an AI automation pipeline, EchoNet-TR, identified cases of ≥moderate tricuspid regurgitation with an AUROC >0.93 and a negative predictive value >0.89, with strong grading concordance with cardiac magnetic resonance imaging.[24]

AI-enhanced echocardiography can also predict the progression of aortic[3,25] and mitral[18] regurgitation, with the potential to aid decision-making on the timing of intervention, and can stratify patients according to risk of periprocedural adverse events[20] and mortality.[1,19,26,27] Of note, when high-quality images are used in the training data, the algorithm can lead to errors in analysis when applied to suboptimal imaging, which can occur in real-world practice. The solution is ongoing training of algorithms with real-world data to ensure the detection and exclusion of suboptimal echocardiographic imaging and errors in echocardiographic measurements.

COMPUTED TOMOGRAPHY. AI can quantify aortic and mitral valve calcification from non-gated chest CT scans, thereby enabling opportunistic detection of VHD.[28] Furthermore, DL models provide automated aortic valve calcium quantification using contrast-enhanced CT and show excellent agreement with Agatston scores derived from noncontrast CT scans,[29] thereby facilitating the assessment of aortic stenosis severity when echocardiographic findings are equivocal.

MORTALITY PREDICTION GUIDED BY AI

AI has emerged as a powerful tool for risk stratification and mortality prediction in VHD.[30] Unlike the traditional risk scores, AI-based approaches incorporate a broader set of longitudinal and multimodal data (including multiple imaging modalities[2]), offering a more comprehensive assessment of procedural risk and disease progression.[31] In patients where clinical ambiguity persists, such as those with low-flow, low-gradient aortic stenosis, echocardiography-based ML algorithms can integrate global longitudinal strain (a marker of early subclinical myocardial dysfunction) and left ventricular remodeling metrics for a more refined risk stratification.[32] ML models using cardiac magnetic resonance or CT imaging have also been shown to predict prognosis in aortic stenosis.[33,34] By incorporating frailty markers (eg, sarcopenia, gait speed, and nutritional status) and postprocedural factors (eg, paravalvular leak severity and left ventricular remodeling), these AI-based mortality predictions may be further refined.[34,35] For predicting mortality after mitral-TEER, AI-derived risk scores (EuroSMR,[36] MitrAI,[37] and MITRALITY[38]), which integrate clinical, procedural, and echocardiographic parameters, outperformed conventional models. Overall, AI-driven models have the potential to offer superior risk stratification by integrating multimodal datasets, although potential biases, methodological transparency, and reproducibility remain concerns.

AI FOR PLANNING TRANSCATHETER AORTIC VALVE REPLACEMENT

The success of transcatheter aortic valve replacement (TAVR) relies on precise preprocedural CT assessment of the aortic root and vascular anatomy to determine patient eligibility, prosthesis sizing, and access strategy. To address the increasing demand for efficient CT analysis,[39,40] advanced semi-automated and fully automated methods have been developed, which use DL algorithms to automatically segment cardiac structures, followed by anatomical landmark detection and aortic root identification. A summary of commercial AI companies and technologies is provided in Supplemental Table 1.

3mensio Structural Heart (Pie Medical) is a widely used semiautomated TAVR planning tool, offering 2- and 3-dimensional (3D) assessments of the aortic root. However, key measurements for TAVR sizing, and risk stratification remain a manual, time-consuming process prone to observer variability. Fully automated software packages such as 4TAVR (Hi-D Imaging) and HeartNavigator (Philips Healthcare) automatically provide essential measurements for TAVR planning.[39] Exploratory data indicate that these packages provide fast, accurate segmentation and measurements. However, validation studies have excluded certain anatomical variants (eg, bicuspid morphology) limiting system robustness. To address this gap and meet practical needs, the FORSSMANN algorithm has recently been developed and validated as a fully automated tool capable of detecting and classifying valve phenotypes (bicuspid, severely calcified, etc) and anatomical risk factors (eg, horizontal aorta and calcification distribution) with high consistency and reliability.[40]

Although the aforementioned tools provide precise aortic root anatomy for geometric transcatheter heart valve sizing, they do not account for the mechanical interaction between the TAVR and surrounding tissues. Patient-specific simulation technologies such as FEops HEARTguide (FEops-Materialise) and DASI Simulations, validated against post-TAVR CT scans, incorporate the geometric and mechanical properties of both the transcatheter valve and host anatomy (**Figure 2**). FEops HEARTguide integrates finite element technology to predict TAVR frame expansion, apposition, and contact pressure on host tissue. Studies have demonstrated its ability to predict calcium displacement, frame deformation, conduction abnormalities, and paravalvular leak in patients undergoing TAVR.[41-43]

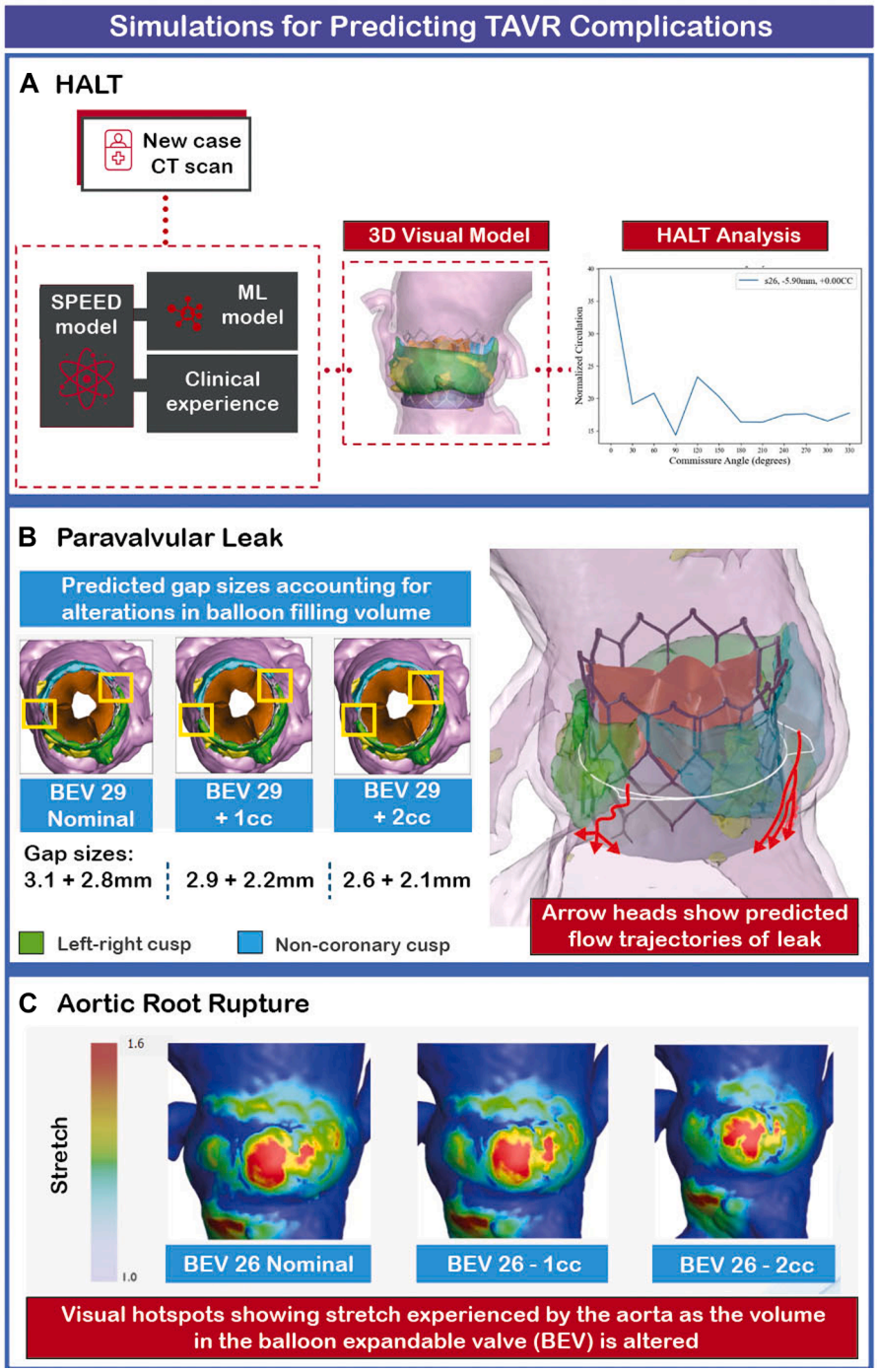
DASI Simulations use physics-based AI and reducer-order modeling to simulate TAVR deformation within patient-specific native anatomy. The resulting outputs are combined with ML algorithms to generate computationally derived quantitative biomarkers that help assess the risk of various post-procedural complications, for example, coronary obstruction, annular rupture, and hypoattenuating leaflet thickening. The accuracy of AI models for predicting hypoattenuating leaflet thickening may be increased by incorporating clinical features, for example, platelet/coagulation biomarkers and post-TAVR echocardiographic and CT features (such as valve underexpansion). DASI simulations also incorporate pre-TAVR echocardiographic data with CT imaging to predict post-TAVR transvalvular gradients, valve leaflet shear stress, and flow dynamics.[44,45] Randomized clinical trials are underway to evaluate how patient-specific simulation may add value over standard CT planning in real-world clinical practice.[46]

TAVR planning for younger patients must address the challenges of future TAVR-in-TAVR procedures and the risk of pacemaker implantation. ML models that integrate CT with clinical, ECG and echocardiographic data can robustly predict pacemaker implantation post-TAVR.[47] For TAVR-in-TAVR procedures, the upward displacement of the old valve leaflets by the new valve frame creates a neo-skirt that may impair coronary access and flow. Additionally, the risk of patient-prosthesis mismatch increases as multiple stented frame layers accumulate within the annulus, progressively reducing the residual valve area. FEops HEARTguide and DASI Simulations allows for the virtual implantation of sequential TAVRs, accounting for the mechanical and physical properties of the valve-in-valve construction and its interaction with adjacent tissue.[48] This approach offers insights into coronary accessibility and residual effective orifice areas and may guide TAVR type, size, and implantation target depth for both index and sequential TAVR procedures (**Figure 3**).

AI FOR PLANNING OF TRANSCATHETER MITRAL AND TRICUSPID VALVE INTERVENTIONS

AI is already used relatively routinely for planning transcatheter mitral and tricuspid valve interventions, particularly for valve replacements (**Figures 4, 5, and 6**). ML allows automated identification and measurement of the mitral and tricuspid annulus within seconds.[49] Patients evaluated for transcatheter mitral valve replacement tend to have challenging anatomies, for example, mitral annular calcification, or anatomies at risk for LVOT obstruction, therefore selecting eligible patients can be time-consuming. During transcatheter mitral valve replacement, the anterior mitral valve leaflet is displaced toward the LVOT, creating a confined neo-LVOT area, and AI models for CT analysis can predict the risk of LVOT obstruction.[50] This planning process involves annular segmentation, mitral valve trajectory, neo-LVOT centerline generation, and planimetric quantification of neo-LVOT size using a simulated valve frame. A similar method can be applied to 3D echocardiographic datasets with high concordance with CT analyses.[51] Most simulations assume uniform valve expansion, failing to account for patient-specific anatomical variations and the dynamic tissue-stent interactions during

FIGURE 2 **Examples of TAVR Planning and Patient-Specific Simulations Showing Prediction of HALT, Paravalvular Leak, and Aortic Root Rupture**



Schematic outline of the DASI simulation workflow, where a transcatheter aortic valve replacement (TAVR) computed tomography (CT) scan is used to create a 3-dimensional (3D) virtual model, and then a simplified force-driven particle model (SPEED) is generated where machine learning (ML) algorithms can: (A) assess the risk of subsequent hypoattenuating leaflet thickening (HALT); (B) predict the risk of paravalvular leak; and (C) predict the risk of aortic root rupture after TAVR using a computationally derived biomarker that detects the amount of stretch experienced by the aorta with balloon-expandable valve (BEV) deployment. The software can account for varying implant depths and alterations in balloon filling volume. In C, the surface area of the visual hot spots dynamically changes as the volume of the balloon is modulated.

deployment. DASI Simulation's SPEED (simplified force-driven particle model) technology can be applied to CT simulations of transcatheter mitral valve replacement to predict how the transcatheter valve frame will deform in a patient's anatomy, and can illustrate the impact of procedural modifications, such as LAMPOON (laceration of the anterior mitral valve leaflet to prevent LVOT obstruction) (Supplemental Figure 1).

At present, computational simulations for mitral transcatheter edge-to-edge repair remain largely exploratory. Previous studies have leveraged CT data to evaluate how different transcatheter edge-to-edge repair device placements affect relevant parameters including mitral annular dimensions, regurgitant orifice area, and transvalvular gradient.[52,53] However, CT imaging is not routinely performed for transcatheter edge-to-edge repair planning. A scalable methodology capable of predicting hemodynamic outcomes using only routine preprocedural patient-specific information is essential for broader clinical adoption.

As a next step, companies are developing and validating full cardiac-cycle CT-analysis software, which can generate patient-specific simulations of transcatheter mitral or tricuspid valve implantations and even mitral transcatheter edge-to-edge repair procedures.

MITRAL AND TRICUSPID VALVE INTERVENTIONS FACILITATED BY AI

The cornerstone of applying AI advances to clinical practice is to achieve procedural simplification (eg, automating tasks and standardizing workflows), and to make outcomes more reproducible. Indeed, integration of AI into cardiac structural intervention procedures has demonstrated improved procedural efficiency and consistency.[54] A particularly useful AI innovation is intraprocedural image fusion, which harnesses real-time data to support complex mitral and tricuspid valve procedures (**Figure 6**). Advanced tools such as EchoNavigator (Philips Healthcare) employ AI to generate 3D heart models based on the detection of cardiac structures on transesophageal echocardiography, complete with precise segmentation of anatomical structures such as cardiac chambers, and valvular annuli.[55] Once the segmentation of the 3D volume dataset is performed, the software must "coregister" the shape of the transesophageal echocardiography probe with the fluoroscopic tilt (caudal or cranial) and rotational angle to fuse both modalities. This allows the fused real-time echocardiographic image to change its orientation on the fluoroscopic image, based on both the location of the probe and the C-arm position, enabling dynamic intraprocedural visualization of patient anatomy. Echo-fluoro fusion improves communication between the imager and interventionalist by allowing the 2 different imaging perspectives to be visualized on a single screen. This fusion imaging system is available with the latest-generation transesophageal echocardiogram probes and is also expected to be developed for intracardiac echocardiography in the near future.

Integrating echo-CT and fluoro-CT fusion technologies can enhance intraprocedural guidance[56,57] and may enhance procedural accuracy in some situations. By combining 3D transesophageal echocardiography or fluoroscopy with preprocedural CT imaging, fusion imaging enables precise positioning of the transcatheter mitral or tricuspid valve replacement at the annular plane, may contribute to a faster and more efficient assessment of coaxiality, and could simplify a paravalvular leak closure procedure. A limitation of fused CT images is that these are static and can be subject to coregistration inaccuracies.

As mitral and tricuspid valve interventions become increasingly complex and widely adopted, AI-driven technologies may offer superior visualization and real-time navigation. The challenge for the imager is to continuously image the device throughout the procedure while showing the interventionalist the correct orientation and position of the desired target, especially during mitral transcatheter edge-to-edge repair. A novel software DeviceGuide (EchoNavigator SmartVue, Philips) facilitates this process by using AI to continuously identify both the mitral transcatheter edge-to-edge repair device and 3D transesophageal echocardiography probe face on fluoroscopic imaging. By recognizing the 3D transesophageal echocardiography probe face, the location of the 3D volume dataset can be identified on the fluoroscopic image. While the imager maintains the device within the 3D volume dataset, DeviceGuide automatically reforms the 3D volume into multiplanar reconstructed 2-dimensional images without operator interaction. Different DeviceGuide models can: 1) simultaneously display onto the multiplanar images, device trajectory, position, and orientation relative to the target; and 2) continuously track the device to maintain a stable image despite respiratory motion or probe manipulation (**Figure 7**). This novel AI software could reduce errors in interpretation of device trajectory, position, and orientation, thereby improving the accuracy of device implantation, shorten procedure

times by reducing the need for frequent multi-planar readjustment of imaging, and reduce complications by continuously imaging the device movement relative to the adjacent structures.

EDUCATION AND TRAINING SIMULATIONS USING AI

The application of AI in simulation-based training for VHD is in its early stages. Most AI advancements have focused on precision medicine, decision support, and procedural planning rather than hands-on training. AI enables more realistic simulation environments, which can allow physicians to overcome steep learning curves of low-frequency, high-complexity procedures (Figure 8).[58] Notably, AI can improve understanding of 3D cardiac navigation by visualizing the relationship between different anatomical structures, and can create algorithms for step-by-step valve intervention guidance. Furthermore, extended virtual, augmented, and mixed reality is an emerging medical imaging display platform (Figure 8),[59] which enhances training and guides complex procedures.

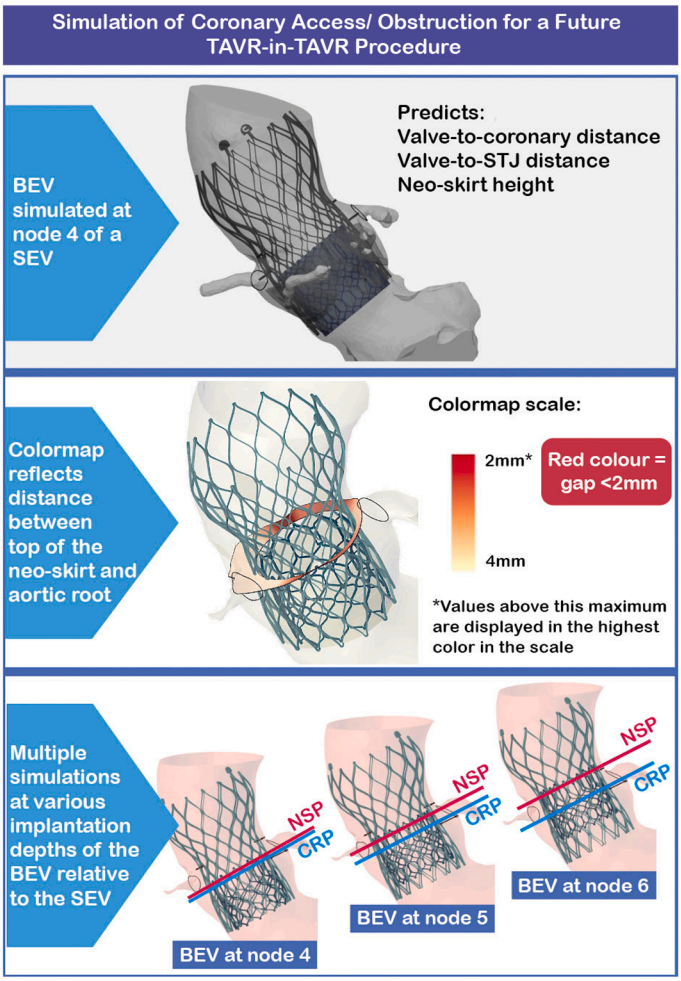
Another promising approach is the analysis of user behavior during simulations. By examining how different individuals manipulate and deploy medical devices, AI can identify patterns, detect common errors, and provide targeted feedback. Additionally, an AI-driven "proctor" could offer real-time guidance tailored to the trainee's skill level, adjusting the difficulty and support dynamically, which, once proven reliable, could guide real-life procedures. Moreover, generative AI techniques are used to create life-like fluoroscopy and ultrasound images, making training simulations more realistic.[60]

Looking toward the future, AI models could learn from real-world procedural data to refine device behavior simulations, making virtual training even more representative of actual clinical conditions. Although these applications are still under development, AI-driven training solutions could significantly improve procedural competency.

AI BEYOND THE VALVE FOR VHD

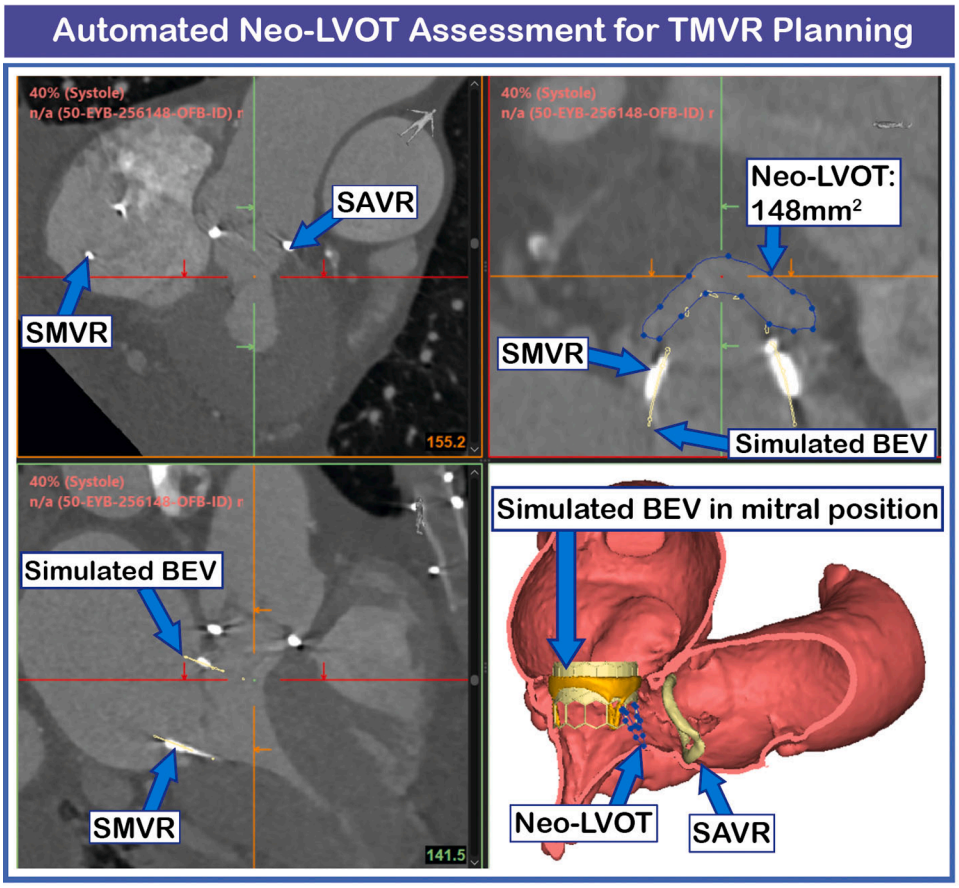
Most AI studies in VHD have centered on the direct assessment of valves; however, the potential of AI goes far beyond the valve itself. Disease progression leads to extravalvular cardiac damage, including remodeling of the atria and ventricles, myocardial dysfunction, and hemodynamic alterations that affect the pulmonary and renal circulations. Cardiac magnetic resonance and CT imaging can play a crucial role in myocardial characterization by quantifying extracellular volume expansion, which aids in the diagnosis and prognosis of amyloidosis and other cardiomyopathies superimposed on VHD.[61] These imaging modalities provide detailed tissue characterization, helping to identify early myocardial changes that may influence treatment decisions. Integrating AI algorithms enhances the accuracy and efficiency of analyzing myocardial extracellular volume on CT and magnetic resonance imaging, improving risk stratification and outcome prediction.

FIGURE 3 Patient-Specific Simulation of a TAVR-in-TAVR Procedure Based on a Preindex TAVR CT Scan



Analysis and images generated by means of FEops HEARTguide (FEops-Materialise). The patient was scheduled for a first TAVR; this patient-specific simulation aimed to assess the feasibility of a future TAVR-in-TAVR procedure, assessing the risk of coronary obstruction and/or inaccessibility. CRP = coronary risk plane (base of the lowest patent coronary ostia); NSP = neoskirt plane (top of the neoskirt); SEV = self-expanding valve; STJ = sinotubular junction; other abbreviations as in Figure 2.

FIGURE 4 Example of an Automated Neo-LVOT Assessment for TMVIV Planning, to Assess the Risk of LVOT Obstruction in a Patient With a Prior Surgical Mitral Valve Bioprosthesis



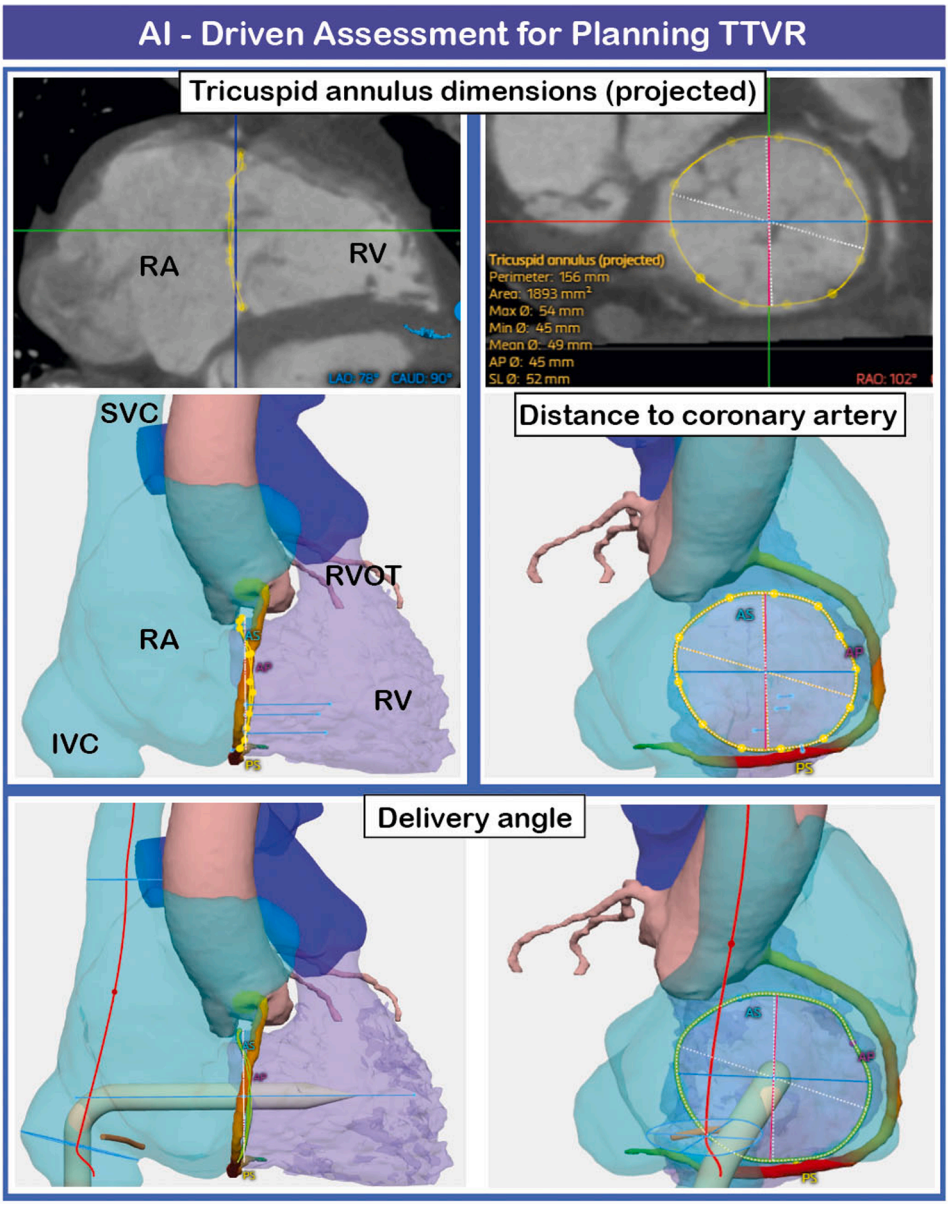
Analysis and images generated by means of Mimics (FEops-Materialise). BEV = balloon expandable valve; LVOT = left ventricular outflow tract; SAVR = surgical aortic valve replacement; SMVR = surgical mitral valve replacement; TMVIV = transcatheter mitral valve-in-valve.

This approach may be particularly valuable for patient with moderate VHD, allowing early intervention to prevent irreversible cardiac damage and improve long-term outcomes. Additionally, patient-specific factors including genetics, age, body composition, and other comorbidities add another layer of complexity, making a personalized and integrative approach essential for optimal VHD management.

AI holds promise in addressing these complexities by enabling comprehensive, automated analysis across multiple datasets and modalities. AI-driven segmentation and quantification of imaging datasets enable detailed anatomical and functional assessments, which extend from valves to cardiac structures (automated volumetric analysis of cardiac chambers, ejection fraction, strain) and the vascular system. Furthermore, AI-based body composition analysis in CT and magnetic resonance imaging can quantify fat, muscle, bone, and other organ composition to identify novel biomarkers for risk stratification, thereby capturing metabolic and structural factors that influence the outcomes of VHD patients.[62]

AI-driven approaches offer opportunities to analyze largescale databases that integrate valvular and cardiovascular structural data with genomic information through imaging-genomics methodologies.[63] This approach can help uncover genetic determinants of VHD pathophysiology for personalized treatment strategies. By using the full potential of AI, clinicians can move beyond a valve-centric approach toward a comprehensive, patient-centered management strategy, ultimately enhancing therapeutic decision-making, risk prediction, and outcomes.

FIGURE 5 Example of AI-Driven TTVR Planning to Assess the Feasibility and Procedural Risks of TTVR

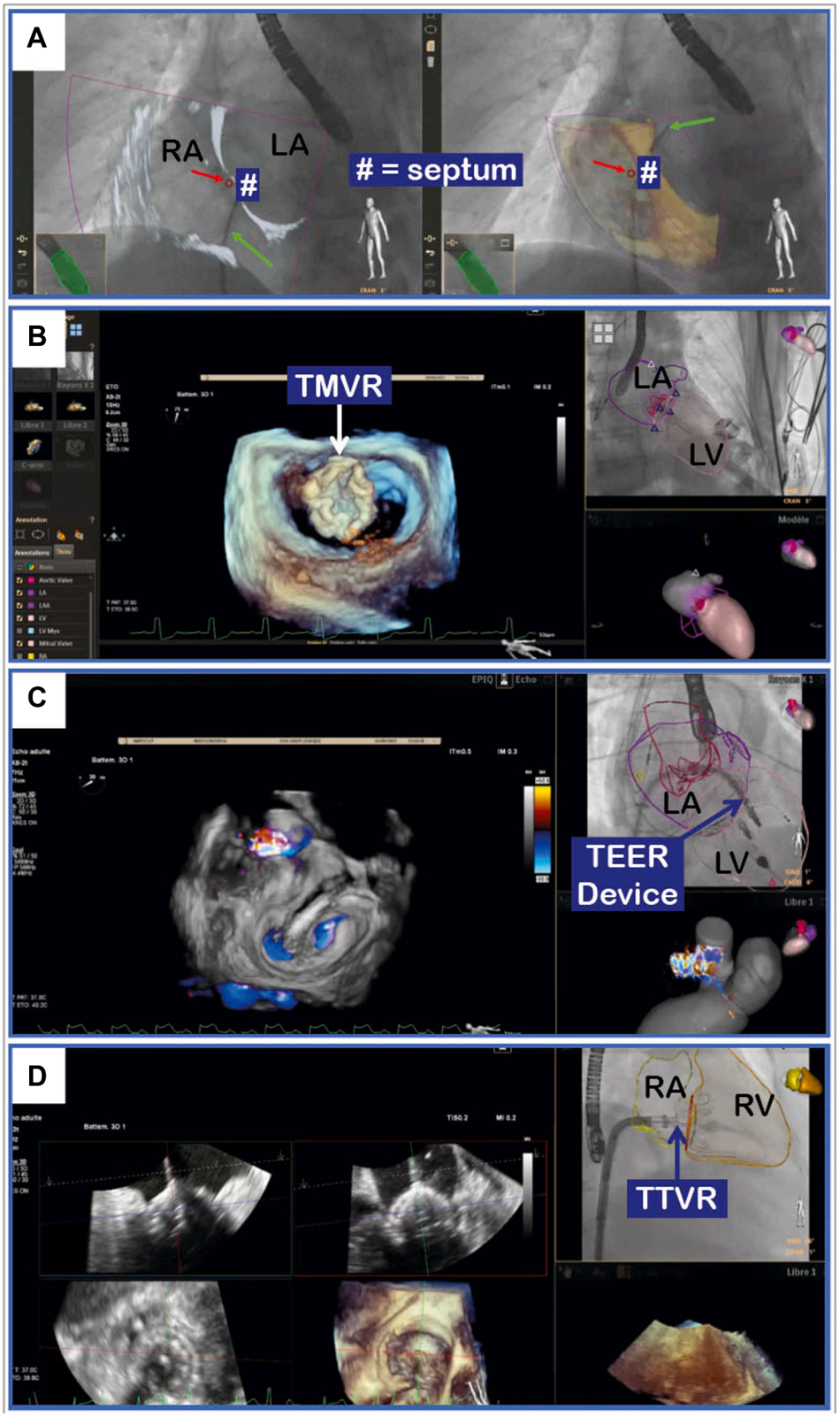


Analysis and images provided by Mimics Planner (FEops-Materialise). AI = artificial intelligence; IVC = inferior vena cava; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; SVC = superior vena cava; TTVR = transcatheter tricuspid valve replacement.

FUTURE DIRECTIONS

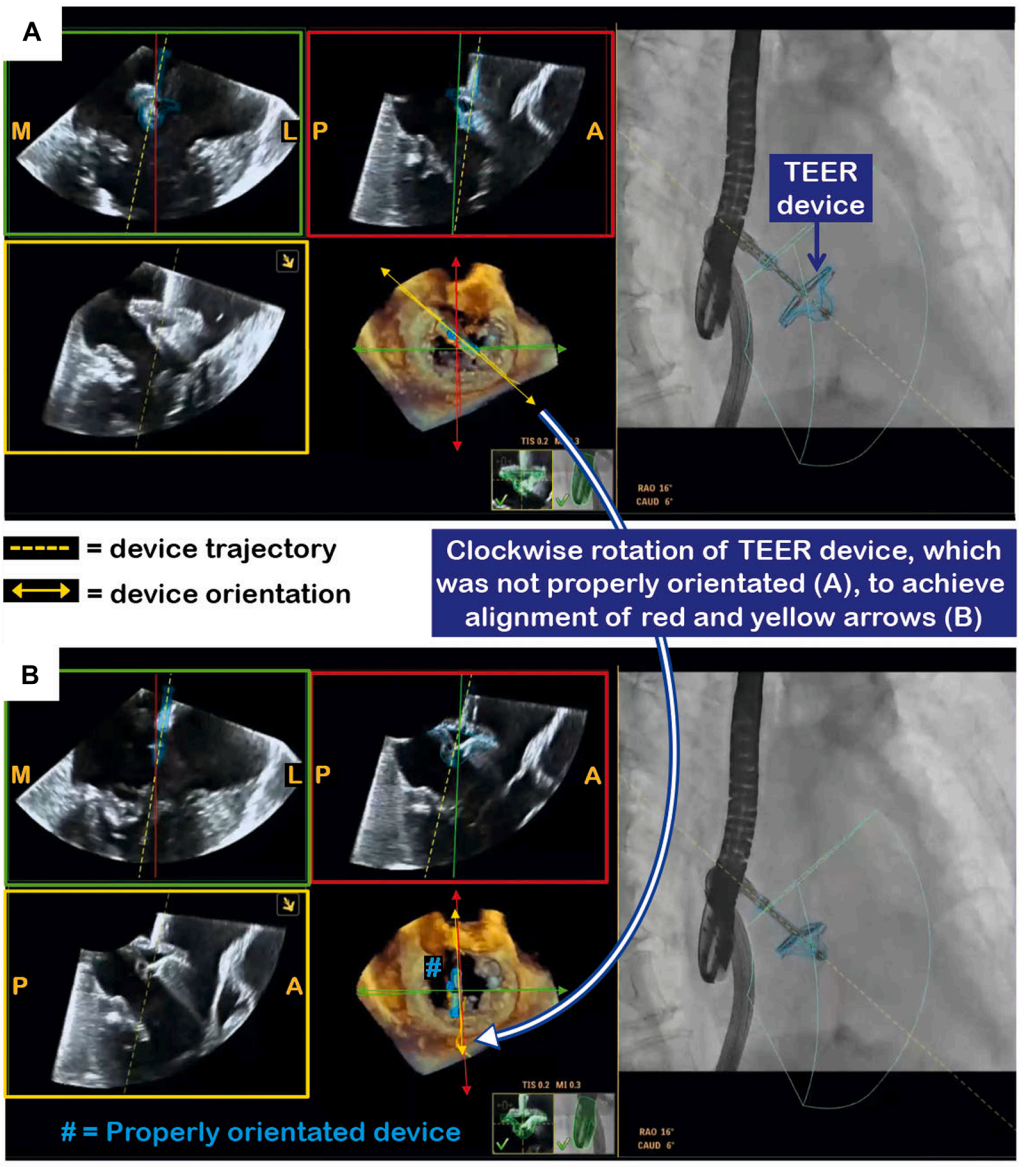
The adoption of AI technology accelerates the transition to digital health care. A future is foreseeable whereby the diagnosis and severity assessment of VHD and preprocedure planning will become fully automated. In a fully digital hospital, the use of natural language processing to extract diagnosis, symptoms, and demographic and clinical data from the electronic health record could be combined with AI-driven analysis of data from digital stethoscopes, ECGs, and echocardiography to provide a fully integrated system to alert clinicians to diagnosis and progression of VHD. In addition to the hospital setting, the widespread adoption of wearable technology offers the opportunity for continuous

FIGURE 6 Examples of Echo-Fluoroscopy Fusion Imaging to Guide Transcatheter Mitral and Tricuspid Interventions



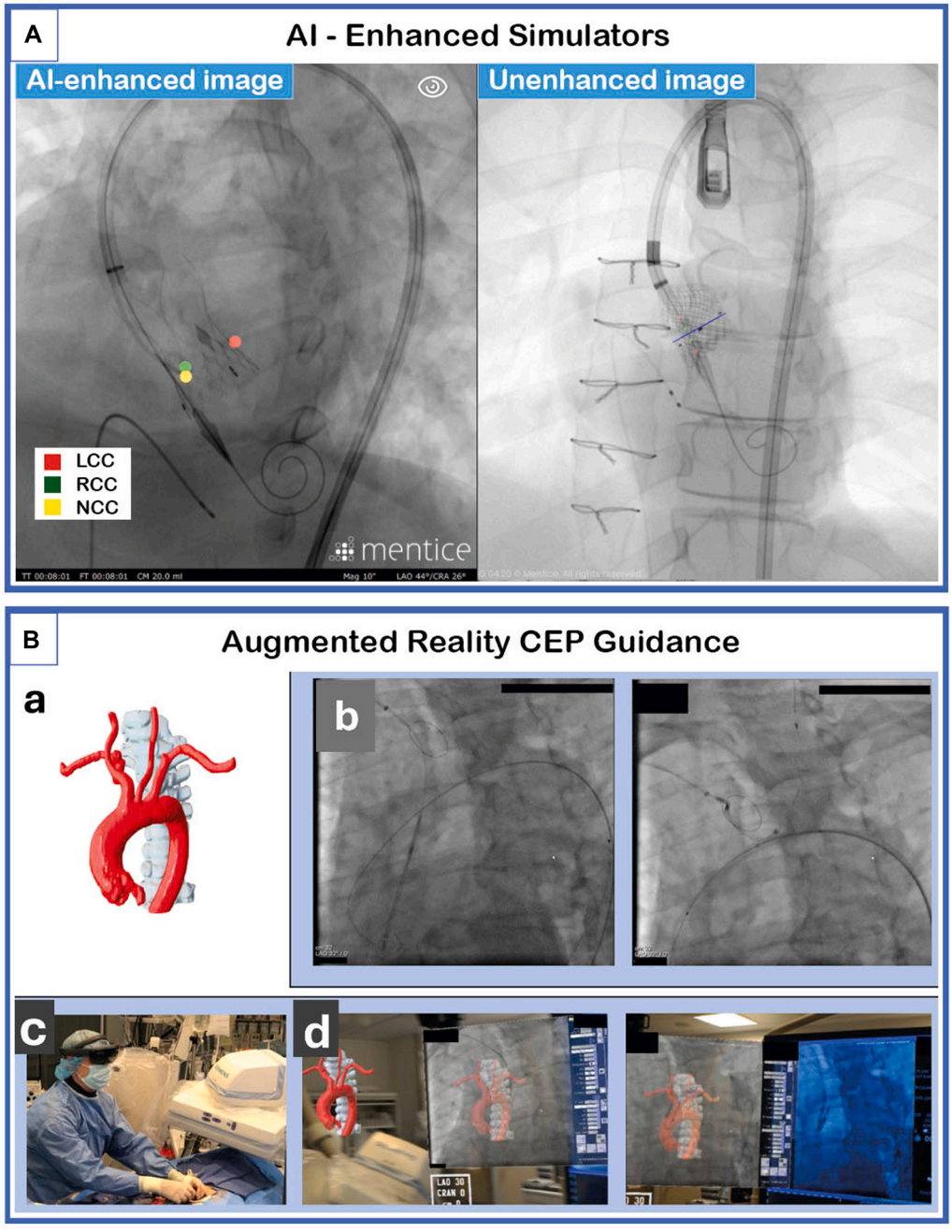
(A) Two and 3-dimensional transesophageal echocardiography combined with marker superimposition during transeptal puncture. (B) Left cardiac chambers overlay during TMVR using a transapical approach. (C) Left cardiac chambers overlay during mitral-TEER in a patient with temporary left ventricular assist. (D) Right cardiac chambers overlay during TTVR using a transfemoral approach. Images in B to D are generated by means of the Heart Model, Philips. LA = left atrium; LV = left ventricle; TEER = transcatheter edge-to-edge repair; TMVR = transcatheter mitral valve replacement; other abbreviations as in Figure 5.

FIGURE 7 **AI-Based Intraprocedural Guidance for Mitral TEER**



A novel AI-based software program identifies the device (blue overlay) and the 3-dimensional (3D) volume of the transesophageal echocardiography probe, allowing for automated generation of multiplanar images for intraprocedural guidance of mitral TEER. The medial (M)-lateral (L) (green box) and posterior (P)-anterior (A) (red box) multiplanar images are automatically generated by DeviceGuide for continuous information about device position as well as trajectory (yellow dashed lines) in these planes. The yellow box (which replaces the standard "blue box") continuously shows an on-axis image of the device. The 3D en face view shows the target (intersection of the green and red lines), as well as the orientation of the device (yellow line). In this example, the initial device orientation in the left atrium (A) requires the paddles be clockwise rotated, to align with the target red line (B). When the device is aligned with the red target line, the images in the red box and yellow box should be the same. In this example, the trajectory will require further adjustment to align with the green and red lines on the 2D images. Abbreviations as in Figures 5 and 6.

FIGURE 8 Example of an AI-Based Simulation and Intraprocedural Guidance



(A) AI-enhanced fluoroscopic imaging for TAVR on images provided by Mentice AB. (B) Virtual reality visualization and manipulation of a virtual 3D model of the patient's aortic arch (A) and a virtual copy of live fluoroscopy (B) in augmented reality while placing cerebral embolic protection (CEP) filters under fluoroscopy (C). Reproduced with permission from Sadri et al.[59] LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp; other abbreviations in Figures 5, 6, and 7.

AI-facilitated ambulatory monitoring of VHD patients beyond traditional clinical environments; for example, identifying the risk of deterioration in those with known severe aortic stenosis awaiting TAVR, or monitoring for conduction disturbances postprocedure to enable safe early discharge.[64]

It is envisaged that digital twin technology (virtual replicas of physical systems continuously updated with real-time or periodic data) will offer case-specific disease modelling,[65,66] as has already been demonstrated in cardiac electrophysiology procedures. Digital twin technology can allow clinicians to virtually test different valve types before interventions, simulate various scenarios, and select the best approach. Conventional simulations (often mislabeled as digital twins) lack adaptability, whereas a true digital twin integrates pre- and post-treatment data, continuously refining itself over time.[65,66] For a digital twin in VHD to be effective, it must go beyond static simulations and allow continuous, bidirectional interaction between the physical (patients) and digital counterparts, using real-time sensor integration. Dynamically updating digital twins with data from wearable devices (eg, continuous ECG monitors), implantable pressure sensors in prosthetic valves, and serial follow-ups enables dynamic adaptation and provides feedback for clinical decision-making (eg, identification of valve deterioration).[65,66] Of note, AI-driven analysis combined with computational fluid dynamics could help predict adverse events, such as valve thrombosis by assessing abnormal flow patterns, shear stress, and patient-specific hemodynamic changes, allowing for early intervention and personalized treatment adjustments.

During valve interventions, it is anticipated that advances in assisted and virtual reality will guide the operator in real-time, whereas robotics could reduce the need for in-room medical staff.[67] Notably, a remotely controlled robotic system for transesophageal echocardiography has already demonstrated reliable, fast, and accurate performance in preclinical tests and could reduce radiation exposure to the imager.[68] During valve deployment in TAVR, AI models can analyze invasive pressure tracings to detect early signs of valve malposition or hemodynamic instability, enabling immediate correction. During transcatheter edge-to-edge repair, AI can provide real-time anatomical tracking for enhanced procedural navigation, helping operators to precisely position the clip to maximize leaflet capture and reduce regurgitation. Moreover, with the advent of large language models (LLM), interactive copilots facilitate physician-device interaction for optimal transducer placement in echocardiography. The concept of cognitive interventional suites will further support interventionalists in their routine by automatically detecting the phase of the procedure, by analyzing key patterns of the workflow and predicting the remaining procedure time, or by providing automatic context information from the electronic health record at the right time of the procedure.

We will see a major step towards improving the realism of cardiac simulators by generative AI techniques. These methods could generate different scenarios for the trainee from a LLM input. The LLM could further instruct the trainee of the next procedural step or provide context information on its inherent difficulties. Finally, the development of in-silico clinical trials can potentially accelerate novel valve device development, by replacing animal studies and human trials with virtual models to evaluate device performance[69]; however, the virtual representation of the physical system needs to be proven to be credible.

LIMITATIONS OF AI

Despite the potential of novel AI approaches, there are limitations (**Central Illustration**). Although AI is generally superior to standard methods for estimating quantitative parameters from medical images, ML models for risk prediction might not outperform traditional models,[70] especially for rare events, or when informed by a limited number of clinical variables or a small number of patients. Furthermore, AI models developed using data that are not representative of the target population may be biased and have a detrimental impact on real-world clinical applications.[71] Ensuring that derivation, validation, and external datasets for AI models accurately represent the underlying patient populations is crucial to minimizing bias in the resulting algorithms. Of note, inputting the raw data rather than report data from investigations, for example, ECG, echocardiography, or CT, is crucial for AI to learn from the data and generate the output. To confirm that the output is correct, it needs to be validated by a core laboratory or an expert reader. At present, this approach is not standardized. Future studies must focus on inputting raw data and validating output with a core laboratory, to promote quality and accuracy. Importantly, comparing different algorithms on the same dataset is being used to validate and improve each algorithm and to minimize errors.[72,73] This approach can identify the best algorithms for the dataset and can improve the results by changing algorithm parameters. Managing

missing data and outliers is a particularly challenging aspect, which might lead to errors in data interpretation, and common approaches are to either delete patients with missing/outlier values from the analysis (complete case analysis), or replace the missing/outlier values by mean estimates based on the data (mean imputation).

Developing and updating AI models and implementation requires considerable financial resources (for software, hardware, and training), which poses challenges for their integration into health care systems. Potential cost-saving solutions include strategic adoption, cloud-based services (delivered over the Internet), and partnering with experienced AI vendors (Supplemental Figure 2). Clinical adoption may be hindered by the limited interpretability of complex AI models, which have been likened to "black boxes," and the limited transparency into AI decision-making that may undermine trust. Low-income countries face challenges in harnessing the benefits of AI, exacerbating global disparity in technology adoption. To achieve AI catch-up, low-income countries need to address challenges related to digital infrastructure, human capital, and commercialization. Organizations such as OpenAI aim to help low-income countries develop AI infrastructure. Developing countries could particularly benefit from AI-empowered auscultation, ECG, and echocardiography to improve the diagnosis of VHD despite unavailability of more advanced cardiac imaging technologies.

Ethical concerns such as data privacy and patient consent should also be considered. Increased regulations around AI hinder adaptation and data exchange for model training and testing. One option to circumvent this issue and enhance data security is federated learning, whereby the data remain in the hospital, but the algorithm is trained in a distributed way concurrently in different sites.[74] This concept has already been successfully demonstrated in a network of 8 hospitals providing more than 8,000 CTs for automated aortic valve analysis and calcification assessment before TAVR.[75] However, federated learning faces issues related to its complex implementation and cannot fully resolve privacy concerns.[76]

Another critical issue is uncertainty around liability in case of erroneous AI decision-making, especially if it affects a patient. It remains unclear whether accountability lies with the developer, physician, company, or hospital. Another limitation includes possible overreliance on AI translating into loss of expertise and inadequate handling of complex cases. Automatic generation of management decisions may seem less desirable than a human network engaging with the clinical, personal, environmental, and social aspects of each patient. Therefore, although AI can be a powerful tool to improve outcomes and reduce workflow, it should not replace human clinical insight and oversight.

CONCLUSIONS

By using the full potential of AI, clinicians can provide a robust, personalized management strategy for patients with VHD, with enhanced risk prediction, decision-making, procedural success, and outcomes. At present, challenges for fully integrating AI into clinical practice include potential biases, concerns about reproducibility and data privacy, and the considerable resources required. Addressing these concerns will ensure that AI-based technologies are used safely and responsibly in the transition to digital health care.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Maznyczka has received travel grants from Edwards Lifesciences, Abbott, Boston Scientific, and Medtronic. Dr Nuis has received research grant support from Vifor Pharma and Meril; and has received consulting fees from Edwards Lifesciences, Abbott, and Boston Scientific. Dr Ternacle is a consultant for Edwards Lifesciences, Abbott, GE, and Philips Healthcare. Dr Garot has received speaker/advisory fees from Abbott, Boston Scientific, Biosensors, Edwards Lifesciences, and Terumo; and is the medical director and shareholder of CERC (Cardiovascular European Research Center). Dr Khokhar has received speaker fees from Abbott, Boston Scientific, and Medtronic. Dr Gräni has received funding from the Swiss National Science Foundation, InnoSuisse, Center for Artificial Intelligence in Medicine University Bern, GAMBIT Foundation, Novartis Foundation for Medical-Biological Research, Swiss Heart Foundation, and the Bangerter-Rhyner-Foundation, outside of the submitted work; and serves as editor-in-chief of *The International Journal of Cardiovascular Imaging* (Springer). Dr Mortier is a cofounder of FEops. Dr Becker is a consultant for DASI Simulations and has patents pending on computational modeling. Dr Dasi is a stakeholder in DASI Simulations; and has a patent pending as coinventor of patents related to computational predictive modeling of heart valves. Dr Kofoed has received research grants from AP Møller og hustru Chastine McKinney Møllers Fond, Novo Nordisk Foundation, Novo Nordic A/S, Sygeforsikringen Danmark, Research Council of Rigshospitalet, The University of Copenhagen, Canon Medical Systems, and GE Healthcare. Dr Biaggi is a proctor for Abbott and Edwards Lifesciences; is a consultant for Philips Healthcare; and has institutional consulting contracts with Edwards Lifesciences and Philips Healthcare for which he has received no direct compensation. Dr Wang has served as a consultant for Abbott, Boston Scientific, and Edwards Lifesciences; and has received institutional research grant support from Boston Scientific. Dr Leroux has been a physician proctor for Medtronic and Abbott; and a consultant for Edwards Lifesciences. Dr Modine has served as a consultant for Abbott, Edwards Lifesciences, and Medtronic. Dr Windecker has received institutional research, travel, or educational grants from Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Braun, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Cordis Medical, CorFlow Therapeutics, CSL Behring,

Daiichi Sankyo, Edwards Lifesciences, Farapulse Inc., Fumedica, Guerbet, Idorsia, Inari Medical, InfraRedx, Janssen-Cilag, Johnson & Johnson, MedAlliance, Medicure, Medtronic, Merck Sharp & Dohme, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pharming Tech, Pfizer, Polares, Regeneron, Sanofi, Servier, Sinomed, Terumo, Vifor, and V-Wave; has served as advisory board member and/or member of the steering/executive groups for trials funded by Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, and V-Wave without personal payments; and is a member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact to his personal remuneration. Dr Hahn has received speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences, Medtronic, and Philips Healthcare; has institutional consulting contracts with Abbott Structural, Edwards Lifesciences, Medtronic, and Novartis; and is the chief scientific officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored tricuspid valve trials, for which she receives no direct industry compensation. Dr Van Mieghem has received grant support/research contracts from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Teleflex, Daiichi-Sankyo, AstraZeneca, and PulseCath BV; and has received consulting/speaker fees from Abbott Vascular, Boston Scientific Corporation, Medtronic, Daiichi Sankyo, Teleflex, PulseCath BV, JenaValve, Anteris, and Amgen. Dr De Backer has received institutional research grants and personal consulting fees from Abbott, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS artificial intelligence, digital twin, fusion imaging, multi-modality imaging, valvular heart disease

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

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

CORONARY

Performance of Large Language Models on the Acute Coronary Syndrome Guidelines Using Retrieval-Augmented Generation

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ABSTRACT

BACKGROUND Large language models (LLMs) are increasingly applied in interventional cardiology, but hallucinations limit their clinical utility.

OBJECTIVES The aim of this study was to assess whether retrieval-augmented generation (RAG), a technique that allows LLMs to access guideline content during response generation, improves accuracy when answering questions on the basis of the guidelines for acute coronary syndromes.

METHODS The accuracy of ChatGPT-4o, DeepSeek R1, and Med-PaLM 2 was compared using a set of 38 open-ended cardiology guideline-based questions and answers. ChatGPT-4o and DeepSeek R1 were evaluated with and without RAG, while Med-PaLM 2, a medicine-specific LLM, was tested without RAG. Model outputs were compared against guideline recommendations using an artificial intelligence-powered similarity score tool.

RESULTS DeepSeek R1 with RAG achieved the highest accuracy (94.7%; 95% CI: 82.7%-98.5%), followed by ChatGPT-4o with RAG (92.1%; 95% CI: 79.2%-97.3%) ($P = 0.922$). ChatGPT-4o without RAG achieved 71.1% accuracy (95% CI: 55.2%-83.0%), which significantly improved with RAG ($P = 0.017$). Among non-RAG models, DeepSeek R1 demonstrated the highest accuracy (78.9%; 95% CI: 63.7%-88.9%), followed by ChatGPT-4o without RAG (71.1%) ($P = 0.083$). Med-PaLM 2 had the lowest accuracy (68.4%; 95% CI: 52.5%-80.9%). Spearman correlation analysis revealed a strong correlation between DeepSeek R1 without RAG and Med-PaLM 2 ($r = 0.646$; 95% CI: 0.411-0.800; $P < 0.001$), indicating similar response patterns. Scatterplot analysis further revealed that RAG disproportionately improved lower scoring questions in DeepSeek R1 while improving scores more evenly in ChatGPT-4o.

CONCLUSIONS Embedding guideline content into LLM workflows via RAG can enhance LLM accuracy for clinical applications, particularly in scenarios common to interventional cardiology. These results support the potential for LLMs, when enhanced with domain-specific knowledge, to optimize clinical decision making and increase alignment with guidelines. (JACC Cardiovasc Interv. 2025;18:2458-2467) © 2025 by the American College of Cardiology Foundation.

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ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.019

Large language models (LLMs) have gained significant recognition and are rapidly becoming indispensable tools in clinical research and practice. ChatGPT, launched by Open AI in November 2022, has 300 million weekly active users and processes more than 1 billion queries per day as of December 2024.[1] The health care industry, especially cardiology, has begun exploring the potential of LLMs to enhance clinical decision making.[2] Most cardiologists believe that artificial intelligence (AI) can increase diagnostic efficiency; in a recent survey of 521 interventional cardiologists, 60.6% anticipated the implementation of AI in their personal clinical practice within 5 years.[3,4] However, challenges such as hallucinations—instances in which a model generates false or fabricated information despite sounding plausible—and factual inaccuracies remain significant barriers to wide clinical application.[2]

The role of LLMs in supporting clinical decision making in cardiology is still evolving, and physicians remain skeptical about their ability to provide up-to-date information and solutions for complex clinical scenarios.[5] One proposed way to improve LLM accuracy and maintain their relevance is retrieval-augmented generation (RAG).[6] RAG is a method that combines LLM with an external knowledge base, allowing real-time access to relevant documents during response generation.[7] RAG comprises 2 key components: a retriever that locates relevant documents and a generator that synthesizes these documents into coherent outputs.[8,9] It enhances the factual accuracy and domain specificity of model outputs, making it particularly valuable in medical contexts.[10] RAG could enhance LLM performance by retrieving relevant information from an external document library during the generation process, grounding responses in factual data to improve accuracy, and provide up-to-date, domain-specific knowledge, especially in knowledge-intensive contexts.

Beyond ChatGPT, other LLMs, such as DeepSeek R1 (DeepSeek AI) and Med-PaLM 2 (Google DeepMind), are also being explored. DeepSeek has shown promise, but current evidence is extremely limited. As of February 12, 2025, a PubMed search for "DeepSeek" provided only 7 results, of which only 2 were research papers.[11,12] The technical report for DeepSeek R1 (the latest model) demonstrated that it achieved outstanding performance, particularly on reasoning tasks, comparable with leading closed-source models, while having the major advantage of training efficiency, significantly reducing computational costs while maintaining performance stability.[13]

Open-source LLMs have the advantages of higher accessibility and customization. However, closed-source LLMs, which include ChatGPT-4o and Med-PaLM 2, have historically outperformed open-source LLMs.[14] Med-PaLM 2, developed by Google, is a medicine-specific LLM, currently available to a select group of Google Cloud customers for limited testing. Despite its restricted access, early research has shown promising results.[15]

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

AI = artificial intelligence

ESC = European Society of Cardiology

LLM = large language model

RAG = retrieval-augmented generation

METHODS

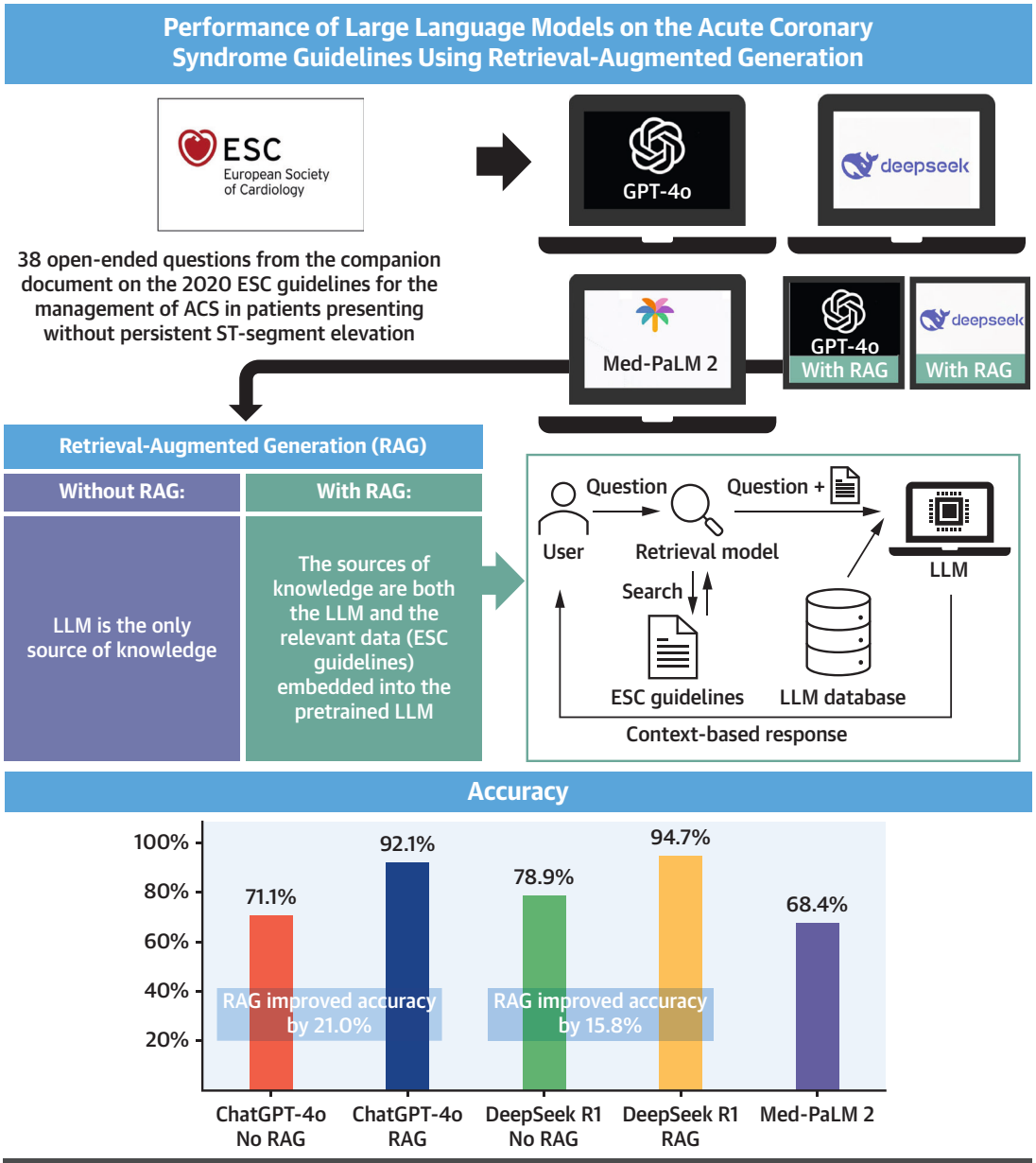
We aimed to compare the accuracy of different LLMs in answering open-ended questions on cardiology guidelines, specifically assessing the impact of RAG on performance (**Central Illustration**). We curated a set of 38 open-ended questions and answers from the companion document of the 2020 European Society of Cardiology (ESC) guidelines for managing acute coronary syndromes (ACS) in patients without persistent ST-segment elevation.[16] These questions were specifically developed to complement the guideline content and reflect core diagnostic and risk stratification principles. Their use ensures alignment with guideline recommendations and reduces the potential for subjective bias from independently generating or selecting questions not formally linked to the guidelines.

We tested ChatGPT-4o (Omni) and DeepSeek R1 by asking these questions directly from the document (without RAG) and again with the ESC guidelines embedded into a RAG model.[17,18] Additionally, we evaluated Med-PaLM 2, testing its responses without RAG, as it is medicine specific.[19] To access Med-PaLM 2, we obtained access for research purposes, as there is currently limited access to a specific group of users. To minimize variability, each model was prompted once per question, and the resulting single response was used for similarity scoring and accuracy assessment. The same prompt structure

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

Manuscript received April 19, 2025; revised manuscript received August 14, 2025, accepted August 18, 2025.

CENTRAL ILLUSTRATION **Performance of LLMs on the ACS Guidelines Using RAG**



- Embedding the guidelines in the model using RAG increased Deep Seek R1's accuracy from 78.9% to 94.7%.
- The accuracy of ChatGPT-4o increased from 71.1% to 92.1% with RAG.
- The results support the potential for LLMs, when enhanced with domain-specific knowledge, to optimize clinical decision-making and increase alignment with the guidelines.
- However, AI should augment rather than replace clinical judgment.

Alexandrou M, et al. JACC Cardiovasc Interv. 2025;18(20):2458–2467.

ACS = acute coronary syndrome(s); ESC = European Society of Cardiology; LLM = large language model; RAG = retrieval-augmented generation.

was used across all models to ensure consistency in input formatting and minimize prompt-induced variability (Supplemental Table 1).

We tried to include Meditron (Meta AI), a suite of open-source LLMs tailored to the medical field that was built on Meta Llama 3, in our comparative analysis, but it performed poorly and did not give relevant answers to the questions asked and was not included in the final analysis.[20]

For our RAG analysis, Google Colab Notebook Python 3 version 3.11 was used. All models were asked the ESC guideline questions using the method of zero-shot prompting. To create a RAG model using ChatGPT 4o, the ESC guidelines PDF was first uploaded. Using the NLTK package, text from the PDF was split into chunks of 500 tokens. Sentence transformer using the model all-MiniLM-L6-v2 was used to create embeddings from the chunked tokens.[21,22] A Facebook AI Similarity Search index was used to create vectors from the generated embeddings. In an OpenAI environment, the query vector retrieved the top 5 vectorized chunks on the basis of similarity score to give a response. The temperature of the model was set at 1, and the number of tokens generated was set at 2,048.

Similarly, to create a RAG model using DeepSeek R1, the langchain community package was installed.[13] Using the recursive character text splitter function, the text from the PDF was split into chunks of 500 tokens. Sentence transformer using the model all-MiniLM-L6-v2 was used to create embeddings from the chunked tokens. A Facebook AI Similarity Search index was used to create vectors from the generated embeddings.[23] In a HuggingFace environment, the query vector retrieved the top 5 vectorized chunks on the basis of similarity score to give a response. The temperature of the model was set at 1, and the number of tokens generated was set at 2,048.

DeepEval version 2.3.7 was used to conduct a similarity analysis among the actual output, the output provided by the LLM and the expected output, and the recommendations from the ESC guidelines. It is an open-source LLM evaluation framework. We used the GEval function using an OpenAI environment to assess outputs using the prompt "Similarity - determine if the actual output has a similar core recommendation to the expected output. Ignore structural differences and details of other options." Descriptive statistics, including accuracy percentages, were calculated to assess the overall performance of each model on the basis of the 0.5 similarity score threshold.

To evaluate the differences in similarity scores between models, we conducted a Friedman test and Wilcoxon signed rank tests, assessing statistical significance with a threshold of $P \leq 0.05$. Spearman correlation analysis was used to assess relationships between similarity scores across models. We also computed median differences to provide insight into the distribution of similarity scores. Correlation strength was categorized as very weak ($r < 0.20$), weak ($0.20 \leq r < 0.40$), moderate ($0.40 \leq r < 0.60$), strong ($0.60 \leq r < 0.80$), and very strong ($r \geq 0.80$).[24]

We performed these statistical analyses using both R version 4.4 (R Foundation for Statistical Computing) and ChatGPT-4o to verify the consistency of the results. The results generated by ChatGPT-4o were consistent with those obtained using R, confirming the reliability of AI-assisted statistical analysis.[25] P values <0.05 were considered to indicate statistical significance.

TABLE 1 Key Performance Metrics for Each Model

Model	Accuracy, %	Median Similarity (Q1-Q3)	Improvement With RAG, %
ChatGPT-4o (no RAG)	71.1	0.76 (0.43-0.90)	–
ChatGPT-4o (RAG)	92.1	0.86 (0.80-0.94)	+21.0
DeepSeek R1 (no RAG)	78.9	0.86 (0.68-0.95)	–
DeepSeek R1 (RAG)	94.7	0.88 (0.78-0.92)	+15.8
Med-PaLM 2	68.4	0.76 (0.32-0.89)	–

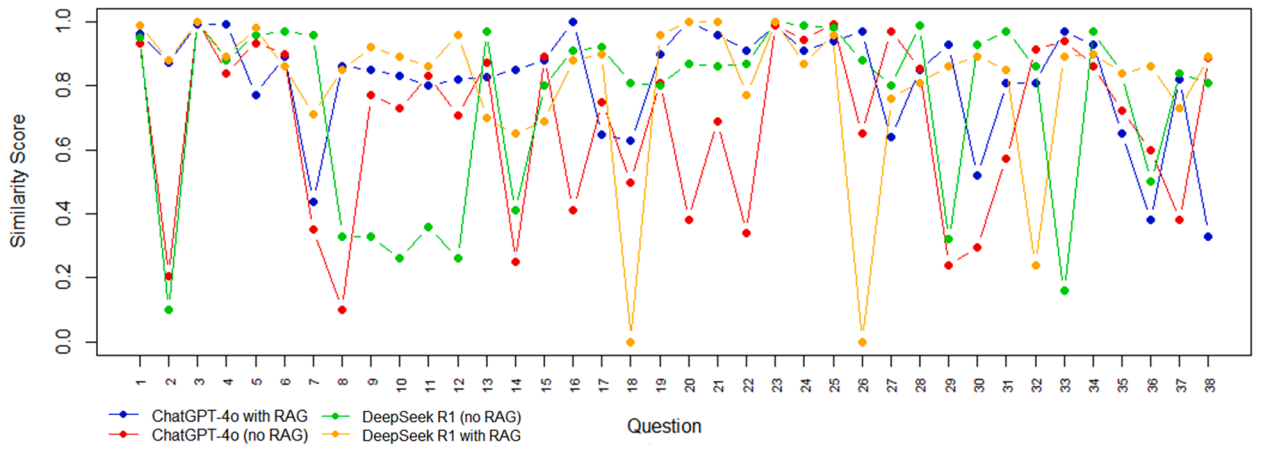
RAG = retrieval-augmented generation.

RESULTS

DeepSeek R1 achieved the highest accuracy, which increased from 78.9% (30 of 38 questions) to 94.7% (95% CI: 82.7%-98.5%; 36 of 38 questions) after embedding the guidelines in the model using RAG (Table 1). For ChatGPT-4o, accuracy was 71.1% (95% CI: 55.2%-83.0%; 27 of 38 questions) when the guidelines were not embedded (without RAG) and increased to 92.1% (95% CI: 79.2%-97.3%; 35 of 38 questions) with RAG, while Med-PaLM 2 scored the lowest (68.4%; 95% CI: 52.5%-80.9%; 26 of 38 questions).

Figure 1 presents histograms of similarity scores for each LLM, showing the distributions of similarity scores and highlighting differences in performance and consistency. Comparing the performance of ChatGPT-4o and DeepSeek R1 before the use of RAG, there was a trend toward higher accuracy for DeepSeek R1, though it did not reach statistical significance ($P = 0.083$). The median similarity score was significantly higher for ChatGPT-4o with RAG (0.86 [Q1-Q3: 0.80-0.94] vs 0.76 [Q1-Q3: 0.32-0.89];

FIGURE 1 Paired Line Plot of ChatGPT-4o and DeepSeek R1 (RAG, No RAG)

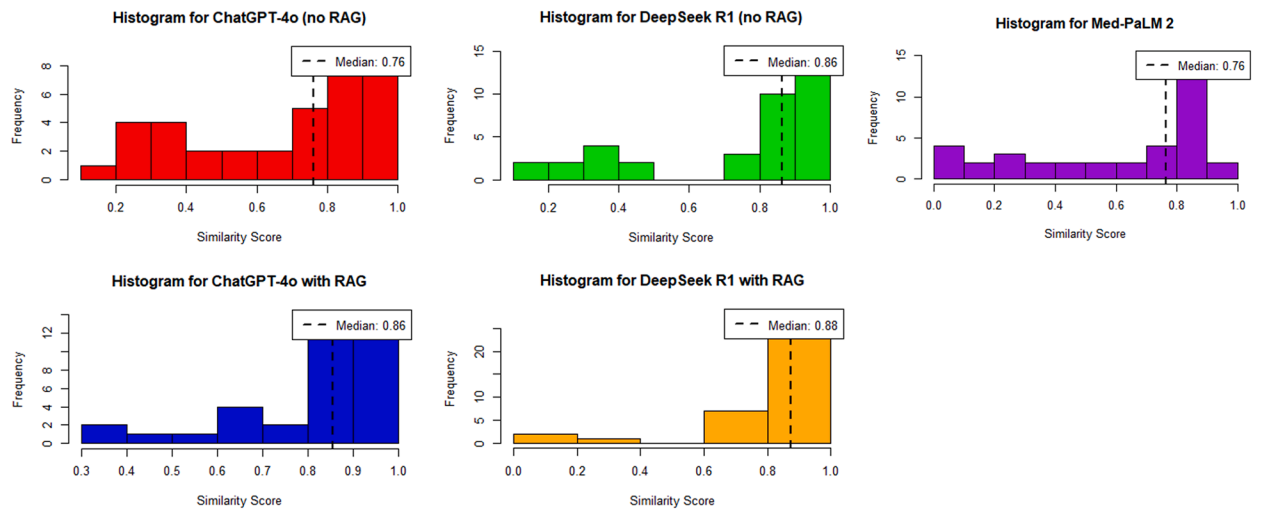


RAG = retrieval-augmented generation.

$P = 0.017$), DeepSeek R1 without RAG (0.86 [Q1-Q3: 0.68-0.95] vs 0.76 [Q1-Q3: 0.32-0.89]; $P < 0.001$), and DeepSeek R1 with RAG (0.88 [Q1-Q3: 0.78-0.92] vs 0.76 [Q1-Q3: 0.32-0.89]; $P = 0.003$) compared with Med-PaLM 2. No statistically significant differences were found when comparing the median similarity scores of ChatGPT-4o without RAG vs Med-PaLM 2 ($P = 0.437$) and ChatGPT-4o with RAG vs DeepSeek R1 without RAG ($P = 0.596$).

A paired line plot for the similarity scores of the models that were enhanced with RAG for each question is shown in **Figure 2**. No significant differences were found comparing the median similarity scores of the 2 LLMs that used RAG, ChatGPT-4o and

FIGURE 2 Histograms of Similarity Scores for Each Large Language Model



RAG = retrieval-augmented generation.

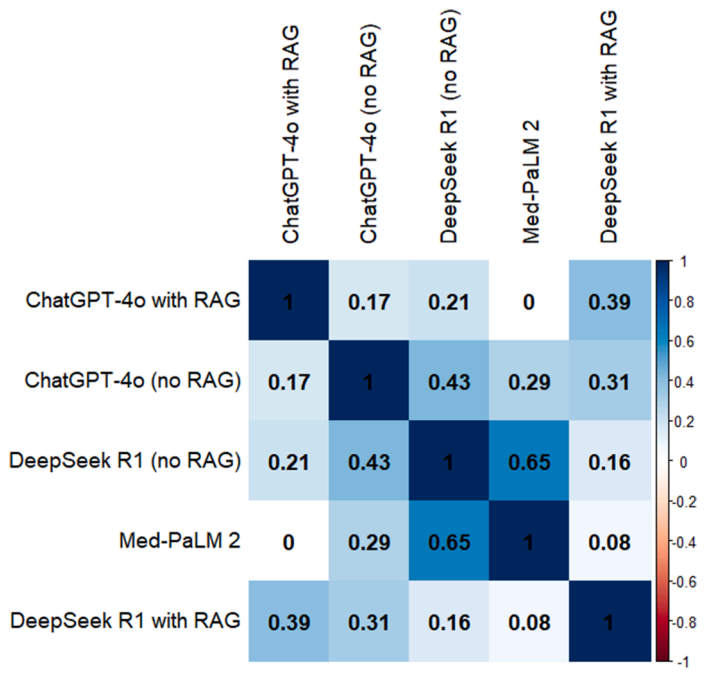
DeepSeek R1 ($P = 0.922$). The median similarity score was higher when the guidelines were embedded (RAG model) compared with when the guidelines were not embedded (0.86 [Q1-Q3: 0.80-0.94] vs 0.76 [Q1-Q3: 0.43-0.90]; $P = 0.017$) for ChatGPT-4o, while it was not statistically significant for DeepSeek R1 (0.88 [Q1-Q3: 0.78-0.92] vs 0.86 [Q1-Q3: 0.68-0.95]; $P = 0.544$).

One of the most notable differences in similarities scores when comparing the RAG vs no RAG model of ChatGPT-4o, was observed in question 2: "A 72-year-old patient with hypertension and hypercholesterolaemia as cardiovascular risk factors (CVRF) presents to the emergency department with typical chest pain of 3 h duration, palpitations, atrial fibrillation with a ventricular rate of about 120 beats per minute, ST-segment depression on electrocardiogram (ECG), and a mild elevation in cardiac troponin (cTn) (twice the upper limit of normal [ULN]). Is it correct to state that the underlying process is a rupture, ulceration, fissuring, or erosion of a coronary atherosclerotic plaque?" The guideline companion document's answer was negative, clarifying that the process could be caused by an extracoronary condition causing imbalance between myocardial oxygen supply and demand (eg, tachycardia, anemia, hypertension, hypotension). Without RAG, the LLM incorrectly stated that the process was likely plaque related. With RAG, the response aligned with the guideline, accurately emphasizing the possibility of type 2 myocardial infarction and the need for further evidence to confirm plaque rupture. Examples illustrating how RAG improved model performance are provided in Supplemental Table 2.

A Spearman correlation analysis was conducted to evaluate the relationships between the similarity scores of different LLMs (Figure 3). The strongest correlation was observed between DeepSeek R1 without RAG and Med-PaLM 2 ($r = 0.646$; 95% CI: 0.411-0.800; $P < 0.001$), indicating a high degree of similarity in their response pattern across different questions. Moderate correlation was found between ChatGPT-4o without RAG and DeepSeek R1 without RAG ($r = 0.429$; 95% CI: 0.126-0.658; $P = 0.007$) and weak between ChatGPT-4o with RAG and DeepSeek R1 with RAG ($r = 0.392$; 95% CI: 0.083-0.632; $P = 0.015$), suggesting some level of alignment between these models' outputs.

Conversely, very weak or nonsignificant correlations were identified between several models. DeepSeek R1 without RAG and DeepSeek R1 with RAG ($r = 0.157$; 95% CI: −0.171 to 0.454; $P = 0.346$) exhibited a very weak correlation. However, the scatterplot with the visual evidence indicates that RAG significantly boosted similarity scores for questions that initially had lower scores without RAG (Figure 4). Unlike DeepSeek R1, the ChatGPT-4o scatterplot suggests that RAG's influence was more balanced, with a very weak correlation between ChatGPT-4o with RAG and ChatGPT-4o without RAG ($r = 0.171$; 95% CI: −0.158 to 0.465; $P = 0.306$).

FIGURE 3 Spearman Correlation Between Similarity Scores of Differences Between the Examined Large Language Models

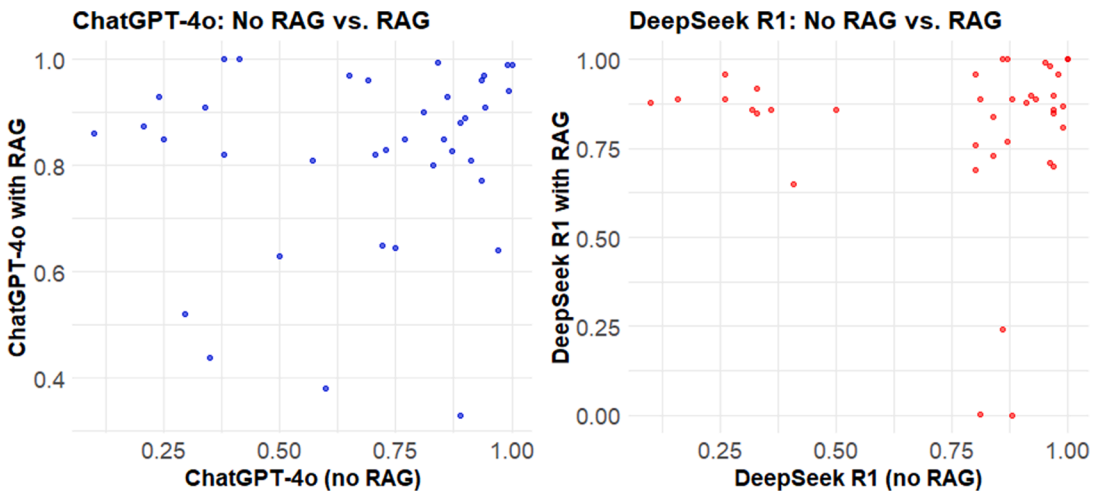


RAG = retrieval-augmented generation.

DISCUSSION

Our study demonstrated that the RAG model improved significantly the accuracy of ChatGPT-4o (from 71.1% to 92.1%), while for DeepSeek R1 (from 78.9% to 94.7%), the improvement was more apparent for questions that initially had lower scores. Among the models evaluated without RAG, DeepSeek R1 outperformed both ChatGPT-4o and Med-PaLM 2, achieving the highest accuracy (78.9%) in this setting. Although the difference between DeepSeek R1 and ChatGPT-4o without RAG was not statistically significant ($P = 0.083$), the trend suggests that DeepSeek R1 may operate better than ChatGPT-4o when no retrieval augmentation is used. In contrast, Med-PaLM 2 had the lowest accuracy (68.4%) despite being designed for medical use.

FIGURE 4 Scatterplot for Similarity Scores of ChatGPT-4o and DeepSeek R1 (RAG, No RAG)



RAG = retrieval-augmented generation.

There has been a growing literature on ChatGPT's performance in medicine and cardiology, and it has been outperforming other LLMs.[26-28] However, evidence on DeepSeek is extremely limited, making this the first study examining the performance of DeepSeek R1 on cardiology-related questions. DeepSeek uses chain-of-thought reasoning, which increases explainability, creating a "thinking aloud" sensation for the user.[29] This could be particularly useful for the clinical environment, in which the reasoning is extremely important, as it can foster a collaborative AI-human interaction and increase the trust and adoption by clinicians.[30] Additionally, DeepSeek R1 is an open-source LLM, with all the inherent advantages of such models, including the democratization of innovation and higher accessibility.[14,31]

Although DeepSeek R1 demonstrated strong accuracy, its adoption in the United States faces significant regulatory challenges. As an AI model developed by a China-based startup, it is currently subject to data security concerns and restrictions from U.S. federal and state officials, limiting its use in government, health care and other infrastructure sections.[32] In contrast, the medicine-specific LLM, Med-PaLM 2, demonstrated the lowest performance, suggesting that factors such as model architecture, training data, and optimization strategies play a more significant role in clinical question-answering accuracy.

In our study, RAG improved the performance of the LLMs examined, allowing them to achieve excellent scores. There are some early results that RAG can improve accuracy and clinical reasoning. A computational study including 7,663 questions in biomedicine demonstrated that RAG improved the accuracy of 6 different LLMs by up to 18% over chain-of-thought prompting.[33] In the field of orthopedics, RAG improved the accuracy of every LLM by an average 39.7%, when examined on the performance of 100 questions and answers based on the 2022 American Academy of Orthopaedic Surgeons anterior cruciate ligament guidelines.[34] Similar results have been observed in hepatology, ophthalmology, and oncology.[35-37] To further contextualize our findings, a recent study evaluating ChatGPT-4 on the American College of Cardiology/Society for Cardiovascular Angiography and Interventions interventional cardiology board-style examination reported an overall accuracy of 78%. In the same study, interventional cardiology fellows achieved an average accuracy of 82.2%, outperforming ChatGPT-4.[38] In contrast, our study demonstrated that when guideline content is embedded via RAG, ChatGPT-4o achieved 92.1% accuracy, and DeepSeek R1 achieved 94.7% accuracy, underscoring the importance of retrieval augmentation for high-fidelity performance in cardiology-related clinical decision making. However, the content and format of the questions differed between the 2 studies.

An additional advantage of RAG is bias reduction and disparity mitigation.[18] Ethical concerns have been repeatedly expressed by researchers regarding this inherent limitation of the LLMs.[39] They usually

lack diverse data sets, and there is evidence that this can result in selective accuracy.[40,41] In a recent study, ChatGPT exhibited gender and racial biases in ACS management; when specifying patients as female, African American, or Hispanic, the researchers observed a decrease in guideline-recommended medical management, diagnosis, and symptom management of ACS.[40] However, whether RAG meaningfully mitigates these disparities needs to be directly tested. Future research is needed to determine if embedding guideline-based content can systematically improve fairness across patient subgroups. Future research could also explore the use of counterfactual clinical scenarios to assess whether RAG-enhanced LLMs maintain fairness across patient subgroups. Such testing would be critical to understanding the role of RAG in mitigating existing biases in AI-generated clinical recommendations.

Our results suggest that developing and deploying a customized cardiology-trained LLM may help overcome some of the current LLM limitations. Pretraining LLMs on cardiology specific knowledge can optimize the use of these models in real-world settings and ensure a high level of accuracy. For clinicians, the most immediate implication of this study is the potential to use retrieval-augmented LLMs to support evidence-based decisions at the point of care, particularly in complex cases in which guideline nuances matter. For example, incorporating RAG-enhanced tools into electronic health record systems could allow physicians to ask natural language questions and receive guideline-aligned recommendations in real time. This could be especially valuable in acute settings such as the emergency department or cardiac catheterization laboratory, where time-sensitive decisions are critical.

The idea of domain-specific LLMs is not new. Future development on medical LLMs should focus of building these domain-specific LLMs on top of high-performing, general-purpose architectures, incorporating state-of-the-art reasoning, retrieval mechanisms, and training optimizations to ensure both accuracy and adaptability in real-world clinical applications. However, cardiologists must still interpret these with critical thinking, as hallucinations still occur, and accuracy is not perfect.[5,38,42] This highlights the importance of fostering collaboration between human expertise and AI systems in health care, ensuring that AI augments rather than replaces clinical judgment.

STUDY LIMITATIONS. The number of questions was limited (n = 38). Although this companion set provides a strong foundation rooted in guideline-aligned principles, we acknowledge that it may not encompass all clinical scenarios encountered in ACS care. Future work should aim to expand the test set to include additional domains.

Med-PaLM 2 was evaluated without RAG enhancement because of access restrictions not allowing integration with external document retrieval workflows. As such, its performance in this study should be interpreted cautiously and not directly compared with the RAG-enhanced ChatGPT-4o and DeepSeek R1 models. The observed differences likely reflect, at least in part, the absence of contextual augmentation rather than inherent limitations of the Med-PaLM 2 architecture. We therefore present the Med-PaLM 2 findings as exploratory.

Another limitation is the variability in responses generated by the LLM, which can affect similarity scores. As newer models are developed, the performance of these models may differ, potentially leading to improved or worse results.[5]

CONCLUSIONS

Our study shows that DeepSeek R1 and ChatGPT-4o perform better in answering open-ended cardiology questions when the relevant guidelines are embedded in a RAG system. Embedding domain-specific knowledge, such as clinical guidelines, in LLMs could address some current limitations and significantly enhance their ability to support clinical decision making. Future research should focus on optimizing LLMs for cardiology-specific applications to ensure maximum accuracy, transparency, and fairness.

ACKNOWLEDGMENTS The authors are grateful for the philanthropic support of 2 generous anonymous donors and the philanthropic support of Drs Mary Ann and Donald A. Sens; Raymond Ames and Barbara Thorndike; the Frank J. and Eleanor A. Maslowski Charitable Trust; the Joseph F. and Mary M. Fleischhacker Family Foundation; Diane and Dr Cline Hickok; Marilyn and William Ryerse; Greg and Rhoda Olsen; Wilma and Dale Johnson; the Mrs Charlotte and Mr Jerry Golinvaux Family Fund; the Roehl Family Foundation; and the Joseph Durda Foundation. The generous gifts of these donors to the Minneapolis Heart Institute Foundation's Science Center for Coronary Artery Disease helped support this research project.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Sandoval reports the following disclosures: Abbott (consultant, advisory board, speaker), CathWorks (consultant, speaker), Cleerly (speaker, research grant), GE Healthcare (consultant, advisory board), HeartFlow (consultant, speaker), Medtronic (speaker), Philips (consultant, advisory board, speaker), Roche Diagnostics (consultant, advisory board, speaker), and Zoll (advisory board); owner, Systole LLC. He is an Associate Editor for JACC Advances. He and others hold patent 20210401347. Patent 20210401347. Dr Brilakis has received consulting and speaking honoraria from Abbott Vascular, American Heart Association (associate editor, *Circulation*), Biotronik, Boston Scientific, the Cardiovascular Innovations Foundation (Board of Directors), Cordis, Cardiovascular Systems, Elsevier, GE Healthcare, Haemonetics, IMDS, Medtronic, and Teleflex; has received research support from Boston Scientific and GE Healthcare; is an owner of Hippocrates; and is a shareholder in MHI Ventures, Cleerly Health, Stallion Medical, and TrueVue. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? LLMs such as ChatGPT are being explored for medical applications but concerns about hallucinations and inaccurate responses have limited their clinical adoption.

WHAT IS NEW? This study demonstrates that integrating guideline documents into LLM workflows using RAG significantly improves the accuracy of responses to complex clinical questions in the field of interventional cardiology.

WHAT IS NEXT? Development of cardiology-specific LLMs trained on interventional data sets and decision pathways could potentially facilitate clinician decision making. Future work should focus on integrating these models into clinical environments in a safe, transparent, and regulation-compliant manner to support care teams in real time.

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KEY WORDS artificial intelligence, cardiology, guidelines, large language model

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

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

EDITORIAL COMMENT

The New Clinical Interface

Information Retrieval and Reasoning With LLMs

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Over the span of most readers' careers, the way we acquire medical information has changed dramatically. Gone are the days when, during training, we read textbooks like Braunwald cover to cover and then "kept pace" by following a few journals and attending major meetings. A strong memory was a prized asset, and few would pause midclinic to look up patient-specific information. Today, with the explosion of medical knowledge and access points, memory has given way to retrieval: answers are often just seconds away. We used to say, "Half of what you learn will be outdated in 5 years." Now, in the era of artificial intelligence (AI), depending on how we word our prompts, we might say "15% of what I access may be wrong—a hallucination." How do we best navigate this new and evolving landscape?

The answer begins with understanding how we got here. Key milestones on the path to this point include the launch of UpToDate (floppy disc version, 1992; online version, 1996), PubMed (1996), Google Scholar (2004), BMJ Best Practice (2009), and ChatGPT 3.5 (2022). This shift toward AI-powered clinical support has been propelled by remarkable, and rapid, advances in large language models (LLMs).

To illustrate the difference between traditional online clinical decision support tools and modern AI-powered platforms, consider the following example: a physician seeks guidance on managing a 60% nonculprit lesion after successful percutaneous coronary intervention of a culprit lesion in a ST-segment elevation myocardial infarction patient. Traditional tools such as UpToDate and BMJ Best Practice would direct the user to broader sections on ST-segment elevation myocardial infarction and nonculprit lesions, requiring manual synthesis across multiple text blocks. In contrast, Open Evidence delivers a focused, evidence-based summary: "For a hemodynamically stable patient, the second 60% lesion should be evaluated with FFR [fractional flow reserve] or iFR [instantaneous wave-free ratio], and only treated if physiologically significant," citing the COMPLETE trial and linking directly to the supporting data. Although all 3 platforms are carefully curated, standardized metrics on error rates or update latency are not publicly available, highlighting the ongoing need for transparency and independent validation.

For clinicians, the challenge in 2025 is no longer whether AI tools will be part of practice but how to use them wisely. A brief look at the evolution of LLMs and their defining features helps put this shift into perspective.

Just a few years ago, natural language processing systems were limited to basic keyword matching and shallow semantic understanding. A breakthrough came in 2017 with the introduction of transformer-based architectures, enabling models to process context, nuance, and reasoning at unprecedented depth. GPT-3, released in 2020, showed that machines could generate coherent, context-aware text, but it was the debut of ChatGPT 3.5 in late 2022 that brought these capabilities to the mainstream. GPT-4 followed in 2023 with marked improvements in accuracy and multimodal capabilities. GPT-4.5 and GPT-5.0, released in 2025, pushed these advances further by integrating real-time search, reducing hallucinations, and improving contextual sensitivity, solidifying its role in clinical and academic workflows. By mid-2025, progress has shifted from incremental to exponential: what once took years in

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ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.023

TABLE 1 Comparison of Leading Large Language Models Used in Medical Literature Search and Clinical Decision Support in 2025

Model	Developer	Scope	Medical Optimization	Citation Capability	Benchmark Performance	Deployment/ Access	Key Strengths	Key Limitations
ChatGPT 4.5/5	OpenAI	General purpose	No (generalist but effective)	Partial (via plugins)	Not benchmarked on MedQA; strong general reasoning	Widely available (chat.openai.com, API, plugins)	Versatile, fluent language generation, fast retrieval	Hallucination risk, citations not always verifiable
Claude 3 Opus	Anthropic	General purpose	No	Limited	Not officially benchmarked on medical datasets	Public access (claude.ai), API available	Contextual understanding; alignment and safety emphasis	Lacks structured citation, inconsistent domain-specific accuracy
Google Med-PaLM 2	Google DeepMind	Medicine specific	Yes (clinical QA fine-tuning)	Yes	MedQA, ~85% accuracy (best in class as of 2023)	Limited release (select partners, no public API)	High performance in clinical Q&A; strong evidence alignment	Restricted access, opaque update cycles
Open Evidence	Startup backed	Medicine specific	Yes (linked to guidelines and trials)	Yes (structured, real time)	Internal validation (not public); clinical trial integration ongoing	Available via web and institutional partnerships	Instant evidence synthesis with references; tailored to practice	Narrower scope (cardiology, oncology focus), proprietary
DeepSeek R1	Hangzhou DeepSeek	Open-source general plus medical	Yes	Yes (integrated external documents)	~93% diagnostic accuracy on MedQA	Open-source MIT-licensed model; widely adopted in China	Cost-effective, transparent chain-of-thought reasoning	Hallucination rate ~ 14%, higher latency, regulatory/ privacy limitations
BioGPT	Microsoft Research	Biomedical research	Yes (PubMed corpus)	No	PubMedQA, ~81% (research focused)	Open-source (Hugging Face)	Optimized for biomedical literature generation and parsing	Not interactive, lacks clinical utility out of the box
PubMedGPT	Academic (Stanford et al)	Biomedical abstracts	Yes (PubMed trained)	No	PubMedQA, ~78%; MedQA, ~70%	Research use only; not publicly deployed	Capable of summarizing biomedical abstracts	No real-time updates, no clinical interface

MedQA evaluates performance on United States Medical Licensing Examination-style multiple-choice clinical questions. PubMedQA measures accuracy in answering yes-or-no questions on the basis of biomedical abstracts.

model evolution now happens in months, accelerating both opportunity and uncertainty in clinical integration.

To appreciate how LLMs function, and their promise and limitations, it helps to understand how they work. At their core, LLMs are pattern recognition systems trained on vast data sets containing up to 10 trillion tokens (words or word fragments). They generate responses by predicting what word is most likely to come next, on the basis of statistical associations learned during training. Training on the styles most favorably rated by humans (through reinforcement learning with human feedback) enhances syntactical smoothness. Although they can follow logical sequences, especially when guided by techniques such as chain-of-thought prompting, they do not "reason" or "understand" in the human sense. Their apparent intelligence reflects statistical inference, not true comprehension. This distinction is critical in clinical contexts, in which surface-level coherence can mask important errors or omissions. As LLMs mature, meaningful differences are emerging, not just in architecture but in intended use, depth of medical tuning, and reliability. Recognizing these distinctions is critical for clinicians who must match the tool to the task. Table 1 summarizes the leading options.

- General-purpose models (eg, ChatGPT 5.0, Claude Sonnet 4, DeepSeek R1) are versatile and conversational, yet their medical citations and domain accuracy remain variable. It is important to note that even the most advanced models, updated only every few months, may sound authoritative but often reflect outdated information.
- Domain-specific models (eg, Med-PaLM 2, Open Evidence) are fine tuned on clinical data, provide structured references, and tend to align more

closely with guidelines, making them better suited to point-of-care decision support.
- Research-oriented models (eg, BioGPT, PubMedGPT) excel at synthesizing biomedical literature but lack the guards and workflows needed for real-time clinical use.

Selecting the right model, therefore, hinges on the clinical question at hand, whether broad exploration, guideline-anchored decision support, or deep literature analysis is required. Amid these differences, one cross-cutting innovation gaining momentum is retrieval-augmented generation (RAG). So what is RAG, what is it used for, and how much does it improve the models?

RAG is a hybrid framework that allows language models to retrieve and incorporate external, up-to-date information at the time of response. Instead of relying solely on what the model "remembers" from its training, RAG enables it to consult relevant sources—such as clinical guidelines, biomedical literature, and structured databases—on demand. This architecture significantly reduces hallucinations and improves factual accuracy, with studies showing performance gains of 10 to 20 percentage points on complex medical tasks.[1,2] In essence, RAG equips models with fresher facts, making them not only more accurate but also more adaptable to evolving clinical knowledge. It is important to note, however, that not all language models are equally RAG ready. Open-source platforms such as DeepSeek R1 and domain-specific systems such as Open Evidence are purpose built to support real-time retrieval, making them particularly well suited for clinical applications that require current, verifiable information. In contrast, other general-purpose models such as ChatGPT 5.0 can support RAG workflows but often rely on external tools or plugins to achieve comparable factual grounding.

In this issue of *JACC: Cardiovascular Interventions*, Alexandrou et al[3] evaluate the value of RAG in improving the accuracy of LLMs when answering questions on the basis of acute coronary syndrome guidelines. The study compares the performance of 3 LLMs—ChatGPT-4o, DeepSeek R1, and Med-PaLM 2—using a set of 38 open-ended, cardiology guideline-based questions. ChatGPT-4o and DeepSeek R1 were assessed both with and without RAG, while Med-PaLM 2, being a domain-specific model already fine tuned on medical content, was evaluated without RAG integration.

The investigators found that without RAG, overall accuracy was limited—generally in the 70% range—with DeepSeek R1 (78.9%), ChatGPT-4o (71.1%), and Med-PaLM 2 (68.4%) all falling short of optimal performance. RAG significantly improved both DeepSeek R1 and ChatGPT-4o, elevating their accuracy to >90%, with particularly notable gains in lower performing responses for DeepSeek R1.

The study had several limitations. The small question set (n = 38) limits generalizability, and Med-PaLM 2 was evaluated without RAG, making direct comparisons less reliable. Guideline selection within the RAG system was not fully detailed, and single-response sampling may not capture variability in LLM outputs. Although RAG may reduce bias, this was not formally assessed. The investigators used DeepEval version 2.3.7 to compare LLM outputs with European Society of Cardiology guidelines via automated similarity scoring (threshold ≥ 0.5) using the GEval function. Accuracy was not manually adjudicated, and the granularity of comparison (eg, overall recommendation vs level of evidence) remains unclear. Finally, model performance may shift as newer versions emerge, underscoring the need for ongoing evaluation.

Despite its limitations, this study highlights a pivotal truth: effective use of AI in medicine is not passive; it demands new competencies. Clinicians must build foundational literacies in 3 key areas: 1) understanding how different models function and where they fall short (**Table 1**); 2) crafting effective prompts; and 3) ensuring that tools incorporate mechanisms such as RAGs to ground outputs in high-quality, domain-specific data. As shown here, embedding clinical guidelines through RAG significantly improves accuracy, reminding us that model performance depends not just on how we ask but on what the model can access. Finally, the study reinforces that directly querying an LLM for clinical decisions may be unreliable. It is essential for clinicians to develop a sense of when to probe further, particularly when responses appear overly simplistic or overly confident. AI often cites secondary review sources, making it difficult to evaluate the quality of the underlying primary evidence.

Looking ahead, AI is no longer a distant promise; it is becoming the next essential instrument in the clinician's toolkit. The stethoscope amplified what we could hear; the electronic medical record captured what we could see. AI, by contrast, enhances how we think: amplifying insight, sharpening context, and

refining clinical decisions. Yet like any tool, its impact depends on the skill of the user. Mastery will require humility, curiosity, and a cultural shift from memorizing answers to shaping better questions. When thoughtfully integrated, AI in medicine offers more than technological advancement: it provides an opportunity to reexamine and refine the foundations of clinical judgment in an increasingly connected, data-driven era.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS artificial intelligence, large language models, retrieval-augmented generation

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

STRUCTURAL

Impact of Early Hemodynamic Valve Deterioration on Long-Term Outcomes Following Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND The incidence, predictors, and impact of early hemodynamic valve deterioration (HVD) after transcatheter aortic valve replacement (TAVR) are unclear.

OBJECTIVES The aim of this study was to explore the impact of early HVD on long-term clinical outcomes and bioprosthetic durability after TAVR.

METHODS Data from a prospective single-center registry including all consecutive patients undergoing TAVR between 2007 and 2023 were analyzed. Early HVD was defined as an increase of at least 10 mm Hg in the mean transaortic gradient on echocardiography performed within the first 3 months after TAVR, compared with discharge echocardiography. The primary endpoint was valve-related long-term clinical efficacy according to the Valve Academic Research Consortium 3.

RESULTS Among 1,912 patients, early HVD was observed in 68 (3.6%). Smaller annular area (OR per 10-mm^2 decrease: 1.03; 95% CI: 1.00-1.08), valve-in-valve procedure (OR: 3.86; 95% CI: 1.95-7.45), and the absence of anticoagulation at discharge (OR: 2.44; 95% CI: 1.28-5.26) were independent predictors of early HVD ($P < 0.05$ for all). After a median follow-up period of 1,107 days (Q1-Q3: 369-1,697 days), early HVD was independently associated with lower valve-related long-term clinical efficacy (subdistribution HR [sHR]: 0.43; 95% CI: 0.27-0.68; $P < 0.001$) and a higher risk for stroke (sHR: 3.03; 95% CI: 1.59-5.76; $P < 0.001$), stage 2 or 3 (sHR: 7.40; 95% CI: 4.51-12.6; $P < 0.001$) or stage 3 (sHR: 5.43; 95% CI: 2.44-12.1; $P < 0.001$) bioprosthetic valve deterioration, and bioprosthetic valve failure (sHR: 2.70; 95% CI: 1.30-5.61; $P = 0.007$). Similar results were observed in a propensity score–matched cohort including 272 patients without and 68 with early HVD.

CONCLUSIONS Early HVD was associated with worse long-term clinical and hemodynamic outcomes after TAVR. These results highlight the importance of identifying early HVD along with the need for future studies to evaluate the most appropriate treatment for this challenging group of patients.
(JACC Cardiovasc Interv. 2025;18:2472-2484) © 2025 by the American College of Cardiology Foundation.

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

Manuscript received March 27, 2025; revised manuscript received August 4, 2025, accepted August 12, 2025.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.020

The continuous advances in the field of transcatheter aortic valve replacement (TAVR) and the expansion toward the treatment of younger lower risk patients with longer life expectancy[1,2] have established this intervention as the predominant modality for aortic valve replacement in Western countries. As a result, the lifetime management of patients undergoing TAVR has become a major issue, requiring early detection of prosthetic or cardiac dysfunction and the identification of new predictors of adverse outcomes.

Current guidelines recommend lifelong clinical and echocardiographic follow-up for patients with transcatheter heart valves to monitor prosthetic function and detect early deterioration.[2,3] Transthoracic echocardiography, including transprosthetic gradient measurement, should be performed at discharge, within the first 3 months postprocedure, at 1 year, and annually thereafter. Although hemodynamic valve deterioration (HVD) has been studied after TAVR,[4,5] the long-term impact of early HVD occurring within the first few weeks post-TAVR remains unclear.

As patient-prosthesis mismatch is characterized by an elevated residual gradient immediately after the procedure, and structural valve dysfunction is unlikely to occur within such a short time frame, early HVD is likely linked to leaflet thrombosis. The latter has been reported in 5% to 15% of patients within the first month post-TAVR,[6,7] yet its relationship with clinical outcomes and long-term bioprosthetic durability remains unclear.[8] Leaflet thrombosis is often asymptomatic but can lead to alterations in prosthetic valve hemodynamic status, including increased transvalvular gradients.[9] The standard diagnostic modality for leaflet thrombosis is cardiac computed tomography, which requires contrast injection, an approach that may not be feasible for all TAVR patients and is not systematically recommended postprocedure. Therefore, early HVD could serve as a valuable surrogate marker for leaflet thrombosis. In this study, we aimed to evaluate the impact of early HVD on long-term clinical outcomes and bioprosthetic durability following TAVR.

METHODS

STUDY DESIGN AND POPULATION. This was a prospective observational study based on a single-center registry enrolling all consecutive patients undergoing TAVR at the Quebec Heart and Lung Institute between 2007 and 2023. The indications for TAVR, device type, and procedural approach were assessed by heart team on the basis of an extensive clinical and anatomical preoperative assessment. The transfemoral access was used by default, and alternative access was reserved for patients with unfavorable peripheral anatomy. The registry was approved by the local ethics committee, and all patients provided written informed consent for the procedures. The study was conducted in compliance with the Declaration of Helsinki.

Baseline, procedural, and follow-up data were prospectively collected in a dedicated TAVR data set. Clinical follow-up was performed during prescheduled outpatient clinic visits or by phone contact within 3 months, 12 months post-TAVR, and yearly thereafter. The vital status of the patient was updated after every medical contact, recording the date of the last contact for every patient. Records from referring cardiologists, general practitioners, and other hospitals were consulted whenever necessary for further information. All adverse events were prospectively collected and defined on the basis of the Valve Academic Research Consortium-3 (VARC-3) definitions.[10]

Echocardiographic follow-up was performed at discharge and within 3 months, 12 months post-TAVR, and yearly thereafter. Additional unplanned echocardiography was performed when clinically indicated. Echocardiographic data from planned and unplanned echocardiography were prospectively recorded in a web-based database using a standardized case report form.

EARLY HVD. Early HVD was defined as an increase of at least 10 mm Hg in the mean transaortic gradient on echocardiography performed within the first 3 months after TAVR, compared with discharge echocardiography.[4] Mean transaortic gradient was measured according to current recommendations.[11]

CLINICAL OUTCOMES. The primary outcome was the valve-related long-term clinical efficacy according to VARC-3 consensus.[10] Valve-related long-term clinical efficacy was defined as freedom from bioprosthetic valve failure (BVF) (defined as valve-related mortality, aortic valve reintervention, or stage 3 HVD), freedom from stroke or peripheral embolism (presumably valve related, after ruling out other nonvalvular etiologies), and freedom from VARC-3 types 2 to 4 bleeding secondary to or exacerbated by antiplatelet or anticoagulant agents, used specifically for valve-related concerns.

Secondary outcomes were the incidence of all-cause mortality, cardiovascular mortality, ischemic

ABBREVIATIONS AND ACRONYMS

aOR = adjusted OR
BMI = body mass index
BVD = bioprosthetic valve dysfunction
BVF = bioprosthetic valve failure
DASI = Duke Activity Status Index
EOA = effective orifice area
HF = heart failure
HVD = hemodynamic valve deterioration
KCCQ = Kansas City Cardiomyopathy Questionnaire
sHR = subdistribution HR
TAVR = transcatheter aortic valve replacement
VARC-3 = Valve Academic Research Consortium-3

stroke, hospitalization for heart failure (HF), myocardial infarction, types 2 to 4 bleeding, bioprosthetic valve dysfunction (BVD), and BVF during follow-up. All these events were defined according to VARC-3 consensus (Supplemental Methods).[10]

Functional capacity and quality of life were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score and the Duke Activity Status Index (DASI) score at 1 month, 1 year, 2 to 3 years, and 4 to 5 years. Changes of 5, 10, and 20 points on the KCCQ overall summary score were defined as slight, moderate, and substantial improvements in patient-level health status.

STATISTICAL ANALYSIS. Normally distributed continuous variables are presented as mean ± SD and non-normally distributed continuous variables as median (Q1-Q3). The normality of distribution was assessed using graphical methods. Categorical variables are expressed as frequency (percentage) and were compared using the chi-square test or Fisher exact test as appropriate, whereas Student's *t*-test, the Mann-Whitney *U* test, or the Wilcoxon test was used for continuous variables. Univariable and multivariable logistic regression analyses were used to identify independent factors associated with early HVD. As early HVD was considered a potential surrogate marker of leaflet thrombosis, the multivariable model included the factors previously identified as associated with leaflet thrombosis: age, sex, body mass index (BMI), chronic kidney disease, annular area, use of a balloon-expandable valve, valve-in-valve procedure, and absence of anticoagulation at discharge. Functional status and quality-of-life scores (KCCQ and DASI) were compared between patients with and those without early HVD at different time points using unpaired statistical testing (Student's *t*-test or the Wilcoxon rank sum test as appropriate).

Survival probabilities of events were estimated using the Kaplan-Meier method, and the survival curves were compared using the log-rank test. Data on patients who were lost to follow-up were censored at the time of the last contact. Cox proportional hazards methods were used to identify the predictors of events. The assumption of proportional HR was verified using Schoenfeld residuals. Multivariable Cox analyses were used to assess the association between early HVD and total death and cardiovascular death. Fine and Gray's subdistribution hazard models with all-cause death as a competing risk were used to assess the association between early HVD and valve-related long-term clinical efficacy, stroke, myocardial infarction, HF hospitalization, types 2 to 4 bleeding, stages 2 and 3 BVD, and BVF. Each model was adjusted on age, sex, BMI, chronic kidney disease, and valve-in-valve procedure.

The evolution of the mean transaortic gradient and effective orifice area (EOA) over time was assessed in patients with and without early HVD using linear mixed-effects models. In these models, the mean gradient and EOA were treated as dependent variables, and early HVD status, time, and their interaction were included as fixed effects. A random intercept for each patient was incorporated to account for within-subject correlation due to repeated measurements. Fixed effects were tested using the Satterthwaite approximation for degrees of freedom. The significance of the interaction terms was used to evaluate whether the temporal trajectories of the mean gradient and EOA differed between groups at each time point.

To reduce imbalance in baseline and procedural characteristics, the effect of early HVD on events was assessed using a strictly 1:4 propensity score-matched population (with vs without early HVD). A nearest neighbor algorithm without replacement was used to match patients with and without early HVD, with a caliper width equal to 0.2, on the following variables: sex, age category (≤74, 75-84, 85-89, and ≥90), BMI (obese vs nonobese), presence of chronic kidney disease, date of TAVR (earlier than 2015, 2015-2020, or 2021-2023), prosthesis type (self- vs balloon-expandable valve), valve-in-valve procedure, and anticoagulation at discharge (Supplemental Figure 1). To account for the matched nature of the data, multivariable Cox proportional hazards models with a robust sandwich variance estimator clustered on the matched group were used for the analysis of total and cardiovascular mortality. To account for death as a competing event to assess the association between early HVD and the other events, subdistribution hazard models were constructed using Fine and Gray's method with a robust sandwich variance estimator on the matched group. Each model was adjusted for age, sex, BMI, chronic kidney disease, and valve-in-valve procedure.

A 2-tailed *P* value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R version 4.4.2 (R Project for Statistical Computing).

RESULTS

Overall, 2,669 patients underwent TAVR and survived up to 1-month follow-up during the study period. Among them, 1,912 (72%) had available echocardiographic data at discharge and within

3 months and were included in the present analysis. The clinical characteristics of the study population are shown in Table 1. The mean age of the patients was 79 ± 8 years, with 814 women (43%), and a median Society of Thoracic Surgeons score of 3.7 (Q1-Q3: 2.5-5.8).

On echocardiography performed within 3 months after the procedure, early HVD was detected in 68 of 1,912 patients (3.6%), with an increase in mean transvalvular gradient from hospital discharge of 15 ± 5 mm Hg. There were no significant differences in age, sex, main cardiovascular risk factors, or comorbidities between patients with and those without early HVD, except for atrial fibrillation (11 of 68 patients with early HVD [16%], 537 of 1,844 patients without early HVD [29%]; $P = 0.029$), valve-in-valve procedure (24 of 68 patients with early HVD [35%], 191 of 1,844 patients without early HVD [10%]; $P < 0.001$), aortic annular area (399 ± 91 mm^2 in patients with early HVD, 443 ± 94 mm^2 in those without early HVD; $P < 0.001$), and anticoagulation at hospital discharge (10 of 68 patients with early HVD [15%], 606 of 1,844 patients without early HVD [33%]; $P = 0.003$) (Table 1). Bioprosthesis type distribution did not differ between patients with or without early HVD ($P > 0.05$).

FACTORS ASSOCIATED WITH EARLY HVD. The factors associated with early HVD are shown in Table 2. In the multivariable analysis, valve-in-valve procedures (adjusted OR [aOR]: 3.86; 95% CI: 1.95-7.45; $P < 0.001$), annular area (aOR per 10-mm^2 decrease: 1.03; 95% CI: 1.00-1.08; $P = 0.048$), and the lack of anticoagulation at discharge (aOR: 2.44; 95% CI: 1.28-5.26; $P = 0.011$) were found to be the independent predictors of early HVD.

CLINICAL OUTCOMES. The median clinical follow-up duration was 1,107 days (Q1-Q3: 369-1,697 days). The clinical outcomes of patients according to early HVD occurrence are presented in Table 3. Patients with early HVD experienced lower valve-related long-term clinical efficacy during follow-up than patients without early HVD (121 per 1,000 patient-years [95% CI: 77-182] vs 53 per 1,000 patient-years [95% CI: 47-59], respectively; log-rank $P < 0.001$) (Central Illustration). Additionally, stroke occurred more frequently during follow-up in patients with early HVD than patients without early HVD (42 per 1,000 patient-years [95% CI: 23-72] vs 16 per 1,000 patient-years [95% CI: 13-19], respectively; log-rank $P = 0.003$) (Figure 1). No difference was observed between the 2 groups in the rates of all-cause death, cardiovascular death, aortic valve reintervention, HF hospitalization, myocardial infarction and types 2 to 4 bleeding (log-rank $P > 0.05$ for all).

According to the competing risk analysis using Fine and Gray's subdistribution hazard models with all-cause death as a competing risk in the overall population, early HVD was independently associated with lower valve-related long-term clinical efficacy (subdistribution HR [sHR]: 0.43; 95% CI: 0.27-0.68; $P < 0.001$) and a higher risk for stroke (sHR: 3.03; 95% CI: 1.59-5.76; $P < 0.001$) (Table 3). The other clinical outcomes, including all-cause death, cardiovascular death, aortic valve reintervention, myocardial infarction, HF hospitalization, and types 2 to 4 bleeding, did not differ between patients with and those without early HVD ($P > 0.05$ for all). A detailed description of patients with early HVD experiencing ischemic stroke during follow-up is provided in Supplemental Table 1.

TABLE 1 Baseline Characteristics of the Study Population, Overall and According to the Presence of Early HVD

	Overall Population (N = 1,912)	Early HVD (n = 68)	No Early HVD (n = 1,844)	*P* Value
Age, y	79.3 ± 7.9	78.0 ± 8.0	79.3 ± 7.9	0.178
Female	814 (42.6)	29 (42.6)	785 (42.6)	1.000
BMI, kg/m^2	28.0 ± 5.9	28.6 ± 5.3	28.0 ± 6.0	0.304
STS score	3.7 (2.5-5.8)	3.7 (2.5-5.8)	3.6 (2.7-4.9)	0.462
Hypertension	1,718 (89.9)	66 (97.1)	1,652 (89.6)	0.073
Smoking	102 (5.4)	5 (7.4)	97 (5.3)	0.673
Dyslipidemia	1,705 (89.2)	64 (94.1)	1,641 (89.0)	0.260
Diabetes	689 (36.1)	21 (30.9)	668 (36.3)	0.430
Atrial fibrillation	548 (28.7)	11 (16.2)	537 (29.1)	0.029
Pacemaker	260 (13.6)	6 (8.2)	254 (13.8)	0.322
Coronary artery disease	1,120 (58.6)	39 (57.4)	1,081 (58.7)	0.925
Chronic kidney disease[a]	838 (43.9)	29 (42.6)	809 (44.0)	0.927
NYHA functional class III or IV	1,131 (59.2)	36 (52.9)	1,095 (59.5)	0.341
Annular area, mm^2	441 ± 94	399 ± 91	443 ± 94	<0.001
Calcium score	2,039 (1,370-2,943)	2,043 (1,375-2,942)	1,859 (1,208-2,934)	0.713
Transarterial approach	1,770 (92.6)	62 (91.2)	1,708 (92.6)	0.832
Predilatation	500 (26.3)	15 (22.1)	485 (26.4)	0.508
Postdilatation	236 (12.4)	7 (10.3)	229 (12.5)	0.727
Balloon-expandable valve	1,287 (67.3)	45 (66.2)	1,242 (67.4)	0.943
Valve-in-valve	215 (11.3)	24 (35.3)	191 (10.4)	<0.001
Moderate or severe AR at discharge	38 (2.0)	38 (2.1)	0 (0.0)	0.639
Anticoagulant at discharge	616 (32.2)	10 (14.7)	606 (32.9)	0.003

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min.

AR = aortic regurgitation; BMI = body mass index; HVD = hemodynamic valve deterioration; STS = Society of Thoracic Surgeons.

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TABLE 2 Factors Associated With Early Hemodynamic Valve Deterioration

	Univariable Analysis			Multivariable Analysis[a]		
	OR	95% CI	*P* Value	aOR	95% CI	*P* Value
Age	0.98	0.95-1.01	0.169	1.00	0.97-1.03	0.908
Female	1.00	0.61-1.63	0.990	0.94	0.51-1.71	0.828
BMI	1.02	0.98-1.06	0.348	1.02	0.98-1.07	0.264
Hypertension	3.82	1.18-23.4	0.064			
Smoking	1.39	0.48-3.26	0.488			
Dyslipidemia	1.97	0.80-6.53	0.193			
Diabetes	0.78	0.46-1.30	0.360			
Atrial fibrillation	0.47	0.23-0.87	0.023			
Pacemaker	0.61	0.23-1.30	0.246			
Coronary artery disease	0.95	0.58-1.56	0.826			
Chronic kidney disease	0.95	0.58-1.54	0.829	0.96	0.56-1.62	0.881
STS score	0.98	0.90-1.05	0.561			
Annular area (per 10-mm^2 decrease)	1.05	1.03-1.09	<0.001	1.03	1.00-1.08	0.048
Calcium score	1.00	1.00-1.00	0.695			
Predilatation	0.79	0.43-1.38	0.424			
Postdilatation	0.80	0.33-1.66	0.592			
Balloon-expandable valve	0.95	0.57-1.61	0.839			
Valve-in-valve	4.71	2.77-7.86	<0.001	3.86	1.95-7.45	<0.001
Moderate or severe AR at discharge	0.88	0.75-1.13	0.133			
Lack of anticoagulant at discharge	2.56	1.30-5.55	0.009	2.44	1.28-5.26	0.011

[a]The multivariate model includes age, sex, BMI, chronic kidney disease, annular area, balloon-expandable valve, valve-in-valve procedure, and lack of anticoagulation at discharge.

aOR = adjusted odds ratio; other abbreviations as in Table 1.

TABLE 3 Outcomes According to Early HVD in the Overall Population

	Early HVD (n = 68)	No Early HVD (n = 1,844)	aHR (95% CI)	*P* Value
Primary outcome				
Valve-related long-term clinical efficacy	121 (77-182)	53 (47-59)	0.43 (0.27-0.68)	<0.001
Secondary outcomes				
Total death	99 (65-146)	112 (104-121)	0.96 (0.64-1.43)	0.840
Cardiovascular death	46 (24-80)	34 (29-39)	1.38 (0.76-2.51)	0.294
Reintervention	11 (2-34)	6 (4-8)	1.51 (0.44-5.21)	0.521
Stroke	42 (23-72)	16 (13-19)	3.03 (1.59-5.76)	<0.001
Myocardial infarction	8 (1-28)	13 (10-16)	0.62 (0.15-2.47)	0.504
HF hospitalization	57 (51-64)	54 (28-94)	1.12 (0.61-2.07)	0.712
Type 2, 3, or 4 bleeding	16 (5-42)	24 (20-28)	0.82 (0.29-2.27)	0.698
Stage 2 or 3 BVD	126 (81-187)	14 (11-17)	7.40 (4.51-12.6)	<0.001
Stage 3 BVD	43 (20-78)	5 (3-7)	5.43 (2.44-12.1)	<0.001
Bioprosthetic valve failure	47 (24-85)	14 (11-17)	2.70 (1.30-5.61)	0.007

The incidence of each outcome is presented for each group as events per 1,000 patient-years (95% CI). Multivariable Cox analyses were used to assess the association between early HVD and total death and cardiovascular death. Fine and Gray's subdistribution hazard models with all-cause death as a competing risk were used to assess the association between early HVD and valve-related long-term clinical efficacy, reintervention, stroke, myocardial infarction, HF hospitalization, major bleeding, and stages 2 and 3 BVD. Each model was adjusted for age, sex, BMI, chronic kidney disease, and valve-in-valve procedure.

BVD = bioprosthetic valve dysfunction; HF = heart failure; other abbreviations as in Table 1.

The baseline characteristics of the propensity-matched population (n = 340; 272 patients without vs 68 with early HVD) are presented in Supplemental Table 2. Baseline demographics, main cardiovascular risk factors, comorbidities, and procedural characteristics did not differ between patients with and those without early HVD. In this population, early HVD remained independently associated with lower valve-related long-term clinical efficacy (sHR: 0.46; 95% CI: 0.27-0.77; $P = 0.003$) and a higher risk for stroke during follow-up after multiple adjustment (sHR: 3.71; 95% CI: 1.65-8.32; $P = 0.002$) (Table 4, Supplemental Figures 2 and 3).

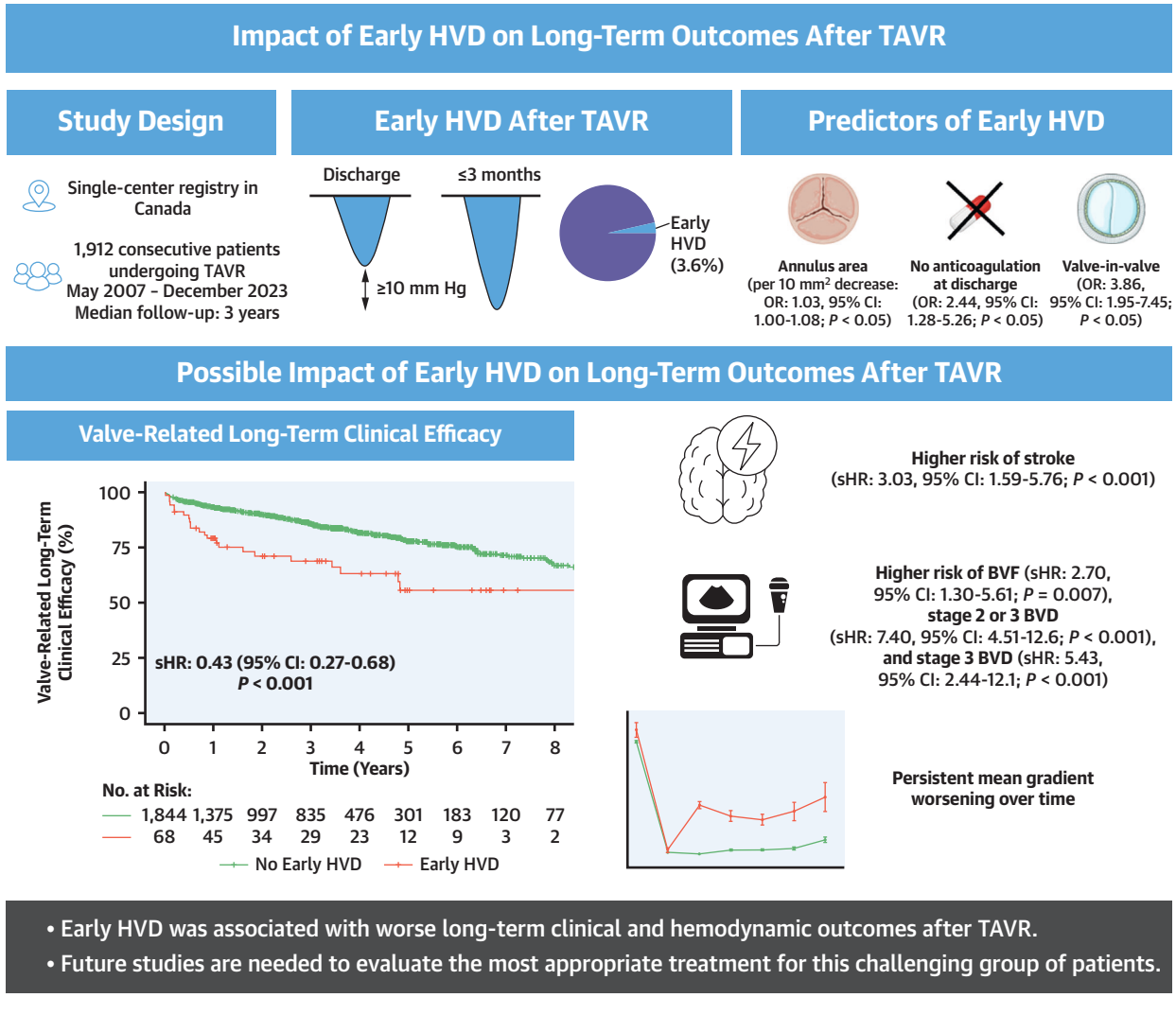
KCCQ and DASI scores at different time points according to early HVD occurrence at 1 month are presented in Supplemental Figure 4. At 1 year, KCCQ scores were lower in patients with early HVD than those without early HVD ($P = 0.012$), whereas no difference was observed at 1 month and at 2 to 3 years. No difference was observed in DASI score at each time point assessed between patients with and without early HVD.

IMPACT OF EARLY HVD ON BIOPROSTHETIC DURABILITY. The median echocardiographic follow-up was 906 days (Q1-Q3: 448-1,504 days). The proportions of patients alive with available echocardiographic data at 1, 3, and 5 years were 73% (1,110 of 1,521 patients), 70% (678 of 969 patients), and 88% (328 of 374 patients), respectively. Among the 68 patients with early HVD, 20 (29%) underwent cardiac computed tomography during the first year, and hypoattenuated leaflet thickening was identified in 15 of them (75%).

Using Kaplan-Meier analysis in the overall population, early HVD was associated with stage 2 or 3 BVD and stage 3 BVD occurrence during follow-up (log-rank $P < 0.001$ for both) (Figures 2A and 2B). In the competing risk analysis using Fine and Gray's subdistribution hazard models with all-cause death as a competing risk in the overall population, early HVD was independently associated with a higher risk for stage 2 or 3 BVD (sHR: 7.40; 95% CI: 4.51-12.6; $P < 0.001$), stage 3 BVD (sHR: 5.43; 95% CI: 2.44-12.1; $P < 0.001$), and BVF (sHR: 2.70; 95% CI: 1.30-5.61; $P = 0.007$) (Table 3).

The mean transaortic gradient in patients with early HVD remained persistently higher compared with patients without early HVD during follow-up (Figure 2C). After an initial period of stabilization, the mean gradient increased after 4 years. Similarly,

CENTRAL ILLUSTRATION Study Design and Main Findings



Trimaille A, et al. JACC Cardiovasc Interv. 2025;18(20):2472-2484.

In this single-center observational study of 1,912 consecutive patients undergoing transcatheter aortic valve replacement (TAVR), early hemodynamic valve deterioration (HVD), as defined as an increase of ≥10 mm Hg in mean transaortic gradient on echocardiography within the first 3 months post-TAVR, was observed in 3.6% of patients. The main predictors of early HVD were smaller annular area, valve-in-valve procedure, and absence of anticoagulation at discharge. Early HVD was associated with reduced long-term valve-related clinical efficacy and increased risks for stroke, stage 2 or 3 bioprosthetic valve dysfunction (BVD), and bioprosthetic valve failure (BVF). Further studies are warranted to elucidate the mechanisms underlying early HVD and to define optimal therapeutic strategies for this patient population. sHR = subdistribution HR.

EOA remained persistently lower in patients with early HVD compared with those without early HVD (**Figure 2D**) and decreased after 4 years.

In the propensity-matched population, early HVD remained independently associated with a higher rate of stage 2 or 3 BVD (sHR: 6.34; 95% CI: 3.53-11.4; $P < 0.001$), stage 3 BVD (sHR: 8.02; 95% CI: 2.81-22.1; $P < 0.001$), and BVF (sHR: 2.27; 95% CI: 1.07-4.85; $P = 0.034$) (**Table 4**, Supplemental Figure 3).

ANTICOAGULATION THERAPY CHANGES. The prescription rate of anticoagulation therapy over time in

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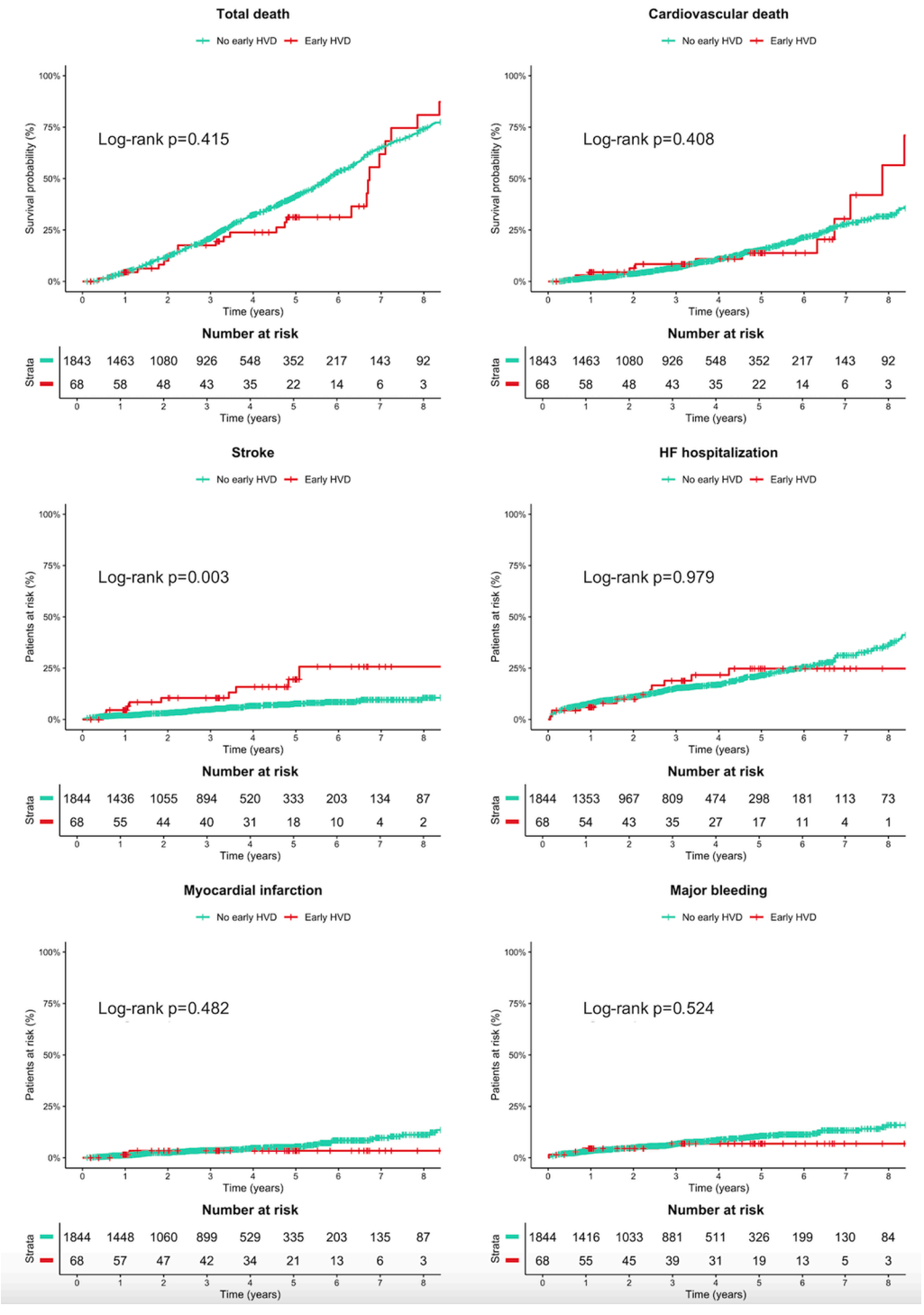
FIGURE 1 **Clinical Events According to Early HVD Occurrence in the Overall Population**



Kaplan-Meier graphs for the incidence of different clinical outcomes in the groups with and without early hemodynamic valve deterioration (HVD). Green indicates patients without early HVD, and red indicates patients with early HVD. Curves were compared using the log-rank test. HF = heart failure.

patients with and those without early HVD is shown in Figure 3. Although the use of anticoagulation slightly and progressively increased during follow-up in patients without early HVD, the rate of anticoagulation therapy increased at 1 and 3 years in patients with early HVD. No effect of anticoagulation prescription at 1 year on durability outcomes (Supplemental Table 3), mean gradient and EOA was observed in patients with early HVD (Supplemental Figure 5).

TABLE 4 Clinical Outcomes According to Early HVD in the Propensity Score-Matched Population

	Early HVD (n = 68)	No Early HVD (n = 272)	sHR (95% CI)	*P* Value
Primary outcome				
Valve-related long-term clinical efficacy	121 (83-172)	56 (44-71)	0.46 (0.27-0.77)	0.003
Secondary outcomes				
Total death	99 (65-145)	107 (88-129)	0.85 (0.57-1.28)	0.436
Cardiovascular death	46 (26-74)	32 (24-43)	1.32 (0.64-2.73)	0.451
Reintervention	11 (3-30)	8 (3-14)	1.38 (0.27-7.13)	0.679
Stroke	42 (23-72)	12 (7-19)	3.71 (1.65-8.32)	0.002
Myocardial infarction	8 (1-25)	11 (6-18)	0.69 (0.15-3.12)	0.627
HF hospitalization	54 (31-87)	45 (34-58)	1.19 (0.62-2.26)	0.612
Type 2, 3, or 4 bleeding	16 (6-38)	27 (19-37)	0.60 (0.21-1.77)	0.364
Stage 2 or 3 BVD	126 (87-177)	24 (16-34)	6.34 (3.53-11.4)	<0.001
Stage 3 BVD	43 (23-72)	6 (3-12)	8.02 (2.91-22.1)	<0.001
Bioprosthetic valve failure	47 (27-78)	21 (14-30)	2.27 (1.07-4.85)	0.034

The incidence of each outcome is presented for each group as events per 1,000 patient-years (95% CI). Multivariable Cox analyses were used to assess the association between early HVD and total death and cardiovascular death. Fine and Gray's subdistribution hazard models with all-cause death as a competing risk were used to assess the associations between early HVD and reintervention, stroke, myocardial infarction, HF hospitalization, and major bleedings. Each model was adjusted for age, sex, BMI, chronic kidney disease, and valve-in-valve procedure.

Abbreviations as in Tables 1 and 3.

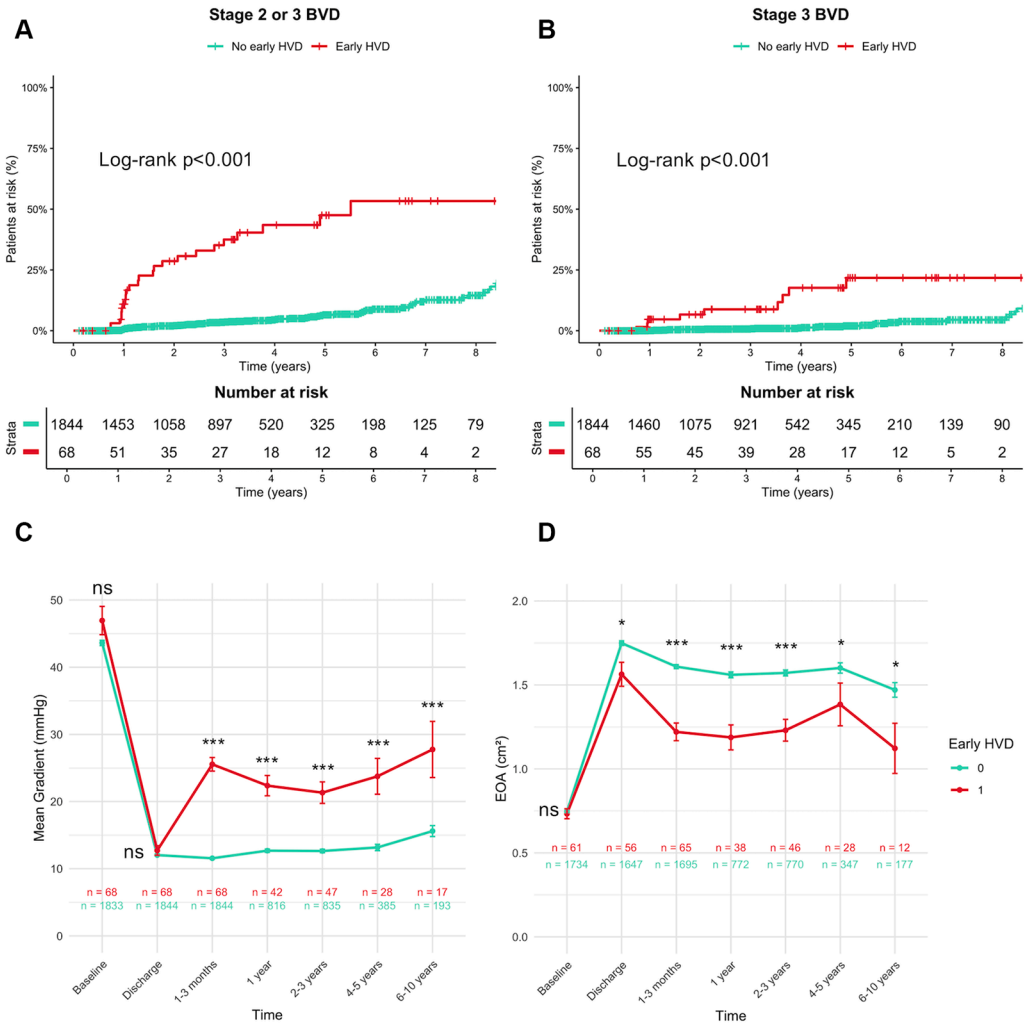
DISCUSSION

In this analysis of a large prospective registry cohort, we investigated the impact of early HVD on clinical and valve-related outcomes according to VARC-3 consensus and observed the following key findings: 1) early HVD occurred in 3.6% of the population; 2) the independent predictors of early HVD were a small annulus, valve-in-valve procedure, and the absence of anticoagulation at discharge; 3) early HVD was associated with impaired valve-related long-term clinical efficacy, a composite criterion associating BVF, stroke, and VARC-3 types 2 to 4 bleeding secondary to antithrombotic therapy used for valve-related concerns; 4) early HVD was linked to a higher incidence of moderate to severe BVD; and 5) long-term echocardiographic follow-up of patients with early HVD showed a persistent worsening of hemodynamic parameters over time.

SIGNIFICANCE OF EARLY HVD. In the present study, we defined early HVD as an increase of at least 10 mm Hg in the mean transaortic gradient between discharge echocardiography and follow-up echocardiography within 3 months after the procedure. Although this definition does not strictly align with the VARC-3 consensus on HVD,[10] it seems a reasonable approach to capture significant hemodynamic variations beyond intraindividual and interobserver variability of hemodynamic parameters. Data on BVD after TAVR according to VARC-3 definition remain relatively limited, with reports indicating a low short-term incidence of hemodynamically significant BVD.[12,13] Recently, Alaour et al[5] systematically assessed the incidence and timing of HVD after TAVR, reporting a cumulative incidence of stage 2 or 3 BVD of 2.2% at 1 year. Detecting early HVD within the first few weeks post-TAVR using the VARC-3 definition may lack sufficient sensitivity to identify clinically meaningful hemodynamic variations. In addition, these definitions primarily serve to stratify the severity of long-term structural valve deterioration. As our study focused on early hemodynamic changes, adopting a more sensitive definition may be clinically relevant. Notably, this definition has been previously used, identifying early HVD in 2.8% of patients within the first year after TAVR,[4] consistent with the 3.6% incidence observed in our study.

It is plausible that hemodynamic impairment within this early time frame after TAVR corresponds to leaflet thrombosis, as patient-prosthesis mismatch is associated with an elevated residual gradient immediately postprocedure,[14] whereas structural valve deterioration typically develops over a longer period.[15] Although only a subset of patients with early HVD underwent cardiac computed tomography, the majority had evidence of leaflet thrombosis, reinforcing the notion that leaflet thrombosis plays a central role in the pathophysiology of early HVD. Supporting this hypothesis, a small annulus, valve-in-valve procedure, and the absence of anticoagulation at discharge, 3 known risk factors of leaflet thrombosis,[8,16] were independently associated with the occurrence of early HVD in our study. Notably, bioprosthetic valve fracture was not routinely performed in valve-in-valve procedures during the study period, which may have contributed to suboptimal expansion of the transcatheter valve

FIGURE 2 Long-Term Bioprosthetic Valve Dysfunction and Evolution of Echocardiographic Parameters According to Early HVD Occurrence

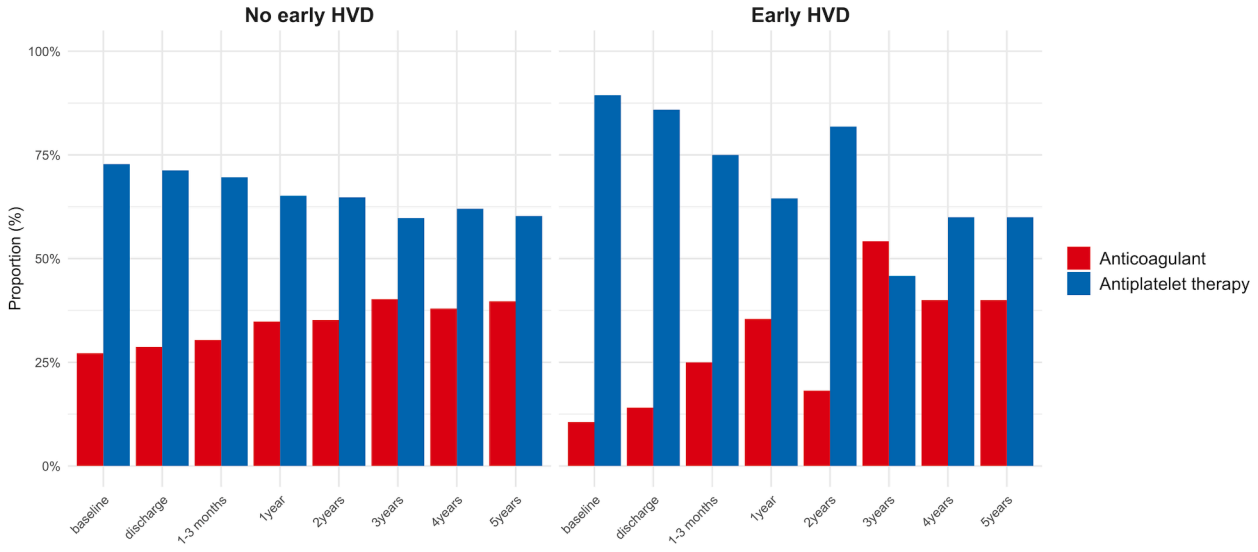


(A,B) Kaplan-Meier graphs for the incidence of stage 2 or 3 bioprosthetic valve dysfunction (BVD) (A) or stage 3 BVD (B) in the groups with and without early hemodynamic valve deterioration (HVD). Green indicates patients without early HVD, and red indicates patients with early HVD. Curves were compared using the log-rank test. (C,D) Evolution of mean gradient (C) and effective orifice area (EOA) (D) over time in the groups with and without early HVD. Values are presented as mean ± SD at each time point. Statistical comparisons of trajectories between groups were performed using a linear mixed-effects model with Satterthwaite's approximation. Reported *P* values correspond to time-by-group interaction terms. **P* < 0.05, ***P* < 0.01, and ****P* < 0.001.

and increased risk for early HVD in this subgroup. Other factors involved in the thrombotic process, such as inflammation, may contribute to the occurrence of early HVD and warrant further investigation.

Interestingly, the incidence of early HVD (3.6%) was slightly lower than the incidence of leaflet thrombosis, which ranges from 5% to 15% within the first months post-TAVR according to systematic computed tomographic analyses.[6,7,16] It is likely that early HVD captures only cases of leaflet thrombosis with the most significant hemodynamic impact. Whether all cases of leaflet thrombosis or only the most severe forms predispose patients to worse clinical and hemodynamic outcomes warrants further investigation, ideally incorporating systematical computed tomographic analysis.

FIGURE 3 Antithrombotic Therapy During Follow-Up According to Early HVD Occurrence



Evolution of antithrombotic therapy (anticoagulant and antiplatelet therapy) over time in the groups with and without early hemodynamic valve deterioration (HVD).

CLINICAL AND HEMODYNAMIC CONSEQUENCES OF EARLY HVD. Studies on the clinical impact of HVD remain relatively scarce and report conflicting findings. Consistent with previous data on long-term HVD,[5] early HVD in our study was not associated with an increased risk for all-cause or cardiovascular death. The VARC-3 consensus recommends using BVF to assess the clinical consequences of BVD. Although the cumulative incidence of BVD in patients without early HVD (4.2%) aligned with previously reported rates,[12,13,15] patients with early HVD demonstrated a significantly higher BVF incidence, reaching 16.2% during follow-up.

Lifetime management after TAVR has become a key focus in heart team discussion, particularly for younger patients.[17] Bioprosthetic valve durability is a major concern to prevent recurrent symptoms and the need for early valve reintervention. Several risk factors for impaired durability have been identified, including BMI, diabetes, smoking, renal insufficiency, baseline postoperative mean gradient ≥15 mm Hg, at least mild transprosthetic regurgitation, patient-prosthesis mismatch, lack of anticoagulation, and procedural factors such as valve-in-valve procedures and small valve sizes.[4,15,18] Early HVD may serve as a novel, easily measurable predictor strongly associated with the development of stage 2 or 3 and BVF. Importantly, all our analyses on bioprosthetic valve durability accounted for the substantial competing risk for death. Interestingly, echocardiographic follow-up of our cohort revealed that patients with early HVD exhibited persistent hemodynamic impairment over time, with a trend toward accelerated deterioration beyond 4 years.

Supporting the hypothesis that a rapid increase in transaortic gradient after TAVR serves as a surrogate marker of leaflet thrombosis, we observed a significant association between early HVD and an increased risk for stroke during follow-up, even after multivariable adjustment and competing risk analyses. Although early reports did not demonstrate an excess risk for cerebrovascular events in patients with leaflet thrombosis, a meta-analysis of 11,098 patients from 25 studies suggested a 2.6-fold increase of stroke or transient ischemic attack in those with leaflet thrombosis.[16] Early HVD, likely secondary to leaflet thrombosis, may be a factor explaining the gradual increase in stroke events over time after TAVR compared with surgical aortic valve replacement in some randomized clinical trials.[19,20] Similarly, the association between leaflet thrombosis and BVD has been documented,[21] further reinforced by the detrimental impact of the absence of anticoagulation on bioprosthetic valve durability.[22,23]

Emerging data support the pathophysiological continuum between leaflet thrombosis and structural valve deterioration.[8,15] Previous histologic analyses have shown that structural valve deterioration is a dynamic process driven by thrombosis, endothelialization, and inflammation, which collectively

contribute to valve remodeling, fibrosis, and calcification.[15] These findings suggest that thrombosis may serve as an active nidus for biological effectors, accelerating structural valve deterioration. Recently, Sato et al[24] conducted the largest systematic histopathologic assessment of transcatheter aortic valves explanted at different time points post-TAVR. They identified extrinsic calcification within leaflet thrombi, providing histologic evidence reinforcing the link between thrombosis and long-term structural valve deterioration.

In the modern era of expanding TAVR indications, composite endpoints are increasingly relevant to accurately characterize postprocedural outcomes. The VARC-3 consensus recommended valve-related long-term clinical efficacy to assess the long-term clinical consequences and failure modes of bioprosthetic valves.[10] This outcome is particularly relevant for evaluating the impact of early HVD, considering its potential role as a surrogate marker of leaflet thrombosis, which is linked to stroke and reduced durability. Additionally, it includes significant bleeding events related to antithrombotic therapies used specifically for suspected or confirmed leaflet thrombosis. The strong clinical relevance of this outcome justified its selection as the primary endpoint in our analysis.

Finally, the lack of statistical significance between early HVD and aortic valve reintervention should be interpreted with caution. The small number of reintervention events likely reflects the advanced age and high burden of comorbidities in the TAVR population, which may limit the feasibility of reintervention in cases of BVF. Additionally, early HVD patients more frequently had a history of prior aortic valve replacement and were treated with valve-in-valve procedures. This may introduce bias, as clinicians could be more prudent to consider reintervention in such cases. Given the significantly increased risk for stroke observed in patients with early HVD, the clinical impact of early HVD should not be underestimated, despite the nonsignificant reintervention data.

CLINICAL IMPLICATIONS. Our work may have important clinical implications. By demonstrating the association between early HVD and impaired valve-related long-term clinical efficacy, our findings reinforce the necessity of performing discharge echocardiography and hemodynamic assessment of bioprosthetic valves within the first 3 months after TAVR, in line with current guidelines.[2,3] Also, clinicians should recognize that patients with early HVD are at higher risk for adverse clinical and hemodynamic outcomes during follow-up.

Given the possible link between early HVD and leaflet thrombosis, this study paves the way for further research on tailored management strategies for these patients, including the role of transesophageal echocardiography and cardiac computed tomography in the diagnostic workflow. Additionally, antithrombotic strategies could be considered in this specific situation. Rapid changes in hemodynamic parameters on early post-TAVR echocardiography strongly suggest the possibility of leaflet thrombosis, which may warrant empirical oral anticoagulation, a strategy that has been shown to effectively reduce transprosthetic gradients.[9,25] The increased use of anticoagulation observed in patients with early HVD may reflect a therapeutic response to suspected leaflet thrombosis. In the absence of standardized recommendations, anticoagulation was likely initiated either following imaging confirmation of thrombosis or empirically in response to rising transprosthetic gradients. Overall, the specific operationalization and clinical validation of early HVD represent a novel and actionable concept for clinicians. Future studies using larger multicenter data sets with standardized and long-term echocardiographic follow-up are warranted to confirm and extend these findings.

STUDY LIMITATIONS. First, this study's observational design necessitates caution interpreting the associations observed, as causality cannot be established. This study was a retrospective analysis of prospectively collected data, which may introduce inherent biases.

Second, hemodynamic assessment was based on transthoracic echocardiographic findings, without adjudication by an independent echocardiographic core laboratory. Third, because of the definition of early HVD, which requires 2 echocardiographic assessments in the early period after TAVR, only patients with available hemodynamic data at discharge and within the first 3 months post-TAVR were included. As a result, 28% of the original cohort was excluded. This can partially be attributed to logistic reasons (our tertiary center covers a large geographic area, and many treated patients lived far away and refused to come back for follow-up echocardiographic examinations), as well as the impact of the COVID-19 pandemic, which significantly affected the feasibility of early echocardiographic follow-up.

Fourth, systematic transesophageal echocardiography or cardiac computed tomography was not

systematically performed in patients with early HVD to determine the underlying mechanism of rapid hemodynamic deterioration. Further studies incorporating systematic early hemodynamic assessment and computed tomography analysis are needed to confirm the thrombotic etiology of early HVD.

Fifth, the number of patients followed beyond 6 years, particularly in the early HVD group, was limited. Therefore, late estimates should be interpreted with caution, and confirmation in larger cohorts with extended follow-up is warranted.

Finally, data on key procedural parameters such as prosthesis oversizing, underexpansion, and implantation depth were not reported. As they may significantly influence valve hemodynamic status and durability, future studies incorporating these factors are needed.

CONCLUSIONS

In this study, early HVD occurred in 3.6% of patients after TAVR and was mainly related to small aortic annulus, valve-in-valve procedures, and a lack of anticoagulation. Early HVD was associated with worse outcomes during follow-up, including valve-related long-term clinical efficacy, stroke, stages 2 and 3 BVD, and BVF. Further studies are needed to confirm the thrombotic cause of early HVD, and to investigate the effect of anticoagulation in patients with early HVD.

ACKNOWLEDGMENTS Dr Trimaille personally acknowledges Fédération Française de Cardiologie, Groupe Insuffisance Cardiaque et Cardiomyopathies of the French Society of Cardiology, and Villa-M for their support during his year in Canada as a clinical research fellow.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Rodés-Cabau holds the Research Chair Fondation Famille Jacques Larivière for the Development of Structural Heart Interventions. Dr Trimaille has received a fellowship grant from Edwards Lifesciences. Dr Rodés-Cabau has received institutional research grants and consulting and speaking fees from Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Identifying new predictors of adverse outcomes is essential to optimize the lifetime management of patients undergoing TAVR.

WHAT IS NEW? Early HVD, defined as an increase of at least 10 mm Hg in mean transaortic gradient on echocardiography within the first 3 months after TAVR, was associated with reduced long-term valve-related clinical efficacy and increased risks for stroke, stage 2 or 3 BVD, and BVF.

WHAT IS NEXT? Further studies are needed to elucidate the underlying mechanisms of early HVD and to determine the most effective therapeutic strategies for affected patients.

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KEY WORDS **bioprosthetic valve failure, hemodynamic valve deterioration, leaflet thrombosis, transcatheter aortic valve replacement, stroke**

APPENDIX **For supplemental methods, tables, and figures, please see the online version of this paper.**

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Early Hemodynamic Valve Deterioration After TAVR

Don't Take It Lightly!

Ludwig T. Weckbach, MD,[a,b] Konstantin Stark, MD[a,b]

Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of patients with severe aortic stenosis. Although it was initially developed for patients with high surgical risk, the use of TAVR has been expanded to younger patients with low surgical risk and has proved to be safe and effective, with equivalent results compared with surgical aortic valve replacement.[1] Because of the treatment of patients with longer life expectancy, lifetime management and especially valve durability have become important issues to consider. In this regard, early structural valve deterioration, which has been assumed to be pathophysiologically linked to hypoattenuated leaflet thickening (HALT) or valve thrombosis, remains a major concern.[2] Although the incidence of HALT after TAVR of 10% to 30% across different studies is significant, its impact on structural valve deterioration and clinical events, particularly cerebral and systemic thromboembolism, remains controversial.[3,4] Most studies investigating HALT after TAVR used 4-dimensional computed tomography (CT), which provides solely morphologic data missing the hemodynamic impact of this finding. Early hemodynamic change, indicated by increased echocardiographic Doppler gradients over the aortic valve as a surrogate parameter for valve thrombosis, may be a simple approach to identifying particularly hemodynamically relevant cases of HALT.

In a study reported in this issue of *JACC: Cardiovascular Interventions*, Trimaille et al[5] evaluated the impact of early hemodynamic valve deterioration (HVD) on long-term clinical outcomes as well as bioprosthetic durability. HVD was defined by an increase of at least 10 mm Hg in the mean transaortic gradient on echocardiography conducted within the first 3 months after TAVR compared with discharge echocardiography. The hemodynamic change of Doppler gradients within this early time frame after TAVR is indicative of HALT or valve thrombosis, as patient-prosthesis mismatch would be evident immediately. In contrast, structural valve deterioration and sclerosis are unlikely to occur at this time point. The primary endpoint of this study was the valve-related long-term clinical efficacy according to the Valve Academic Research Consortium 3 consensus, which is defined as freedom from bioprosthetic valve failure (including valve-related mortality, aortic valve reintervention, and stage 3 HVD), freedom from valve-related stroke or peripheral embolism, and freedom from Valve Academic Research Consortium 3 types 2 to 4 bleeding secondary to or exacerbated by antiplatelet or anticoagulant agents.[6]

This large prospective registry cohort included 1,912 patients who underwent TAVR between 2007 and 2022. Within the predefined time period of 3 months in 68 patients (3.6%), early HVD was detected. Of note, 20 individuals (29%) with HVD underwent cardiac CT within the first year, with evidence of HALT in 15 patients (75%), highlighting a link between early HVD and thrombosis. However, CT was not systematically performed in this study, and therefore, HALT might explain HVD only partially. The incidence of early HVD is consistent with a previous study counting early HVD in 2.8% of patients within 1 year.[7] A small annulus, a valve-in-valve procedure,

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

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.09.011

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025
OCTOBER 27, 2025:2485-2487

and the absence of anticoagulation at discharge were independent predictors of early HVD in this study, which is in line with previous studies.[8,9] Valve-related clinical efficacy as defined earlier was significantly lower in patients with early HVD compared with patients without early HVD (adjusted HR: 0.43; 95% CI: 0.27-0.68; $P < 0.001$). This difference was driven by a higher incidence of bioprosthetic valve deterioration and failure as well as stroke, whereas bleeding was similar in both groups. A propensity score-matched analysis including 340 patients revealed very similar results for the primary endpoint (adjusted HR: 0.46; 95% CI: 0.27-0.77; $P = 0.003$) and its components. In the patient group with early HVD, increased transaortic gradients persisted, as opposed to the PARTNER 3 (Placement of Aortic Transcatheter Valve 3) CT substudy, in which spontaneous resolution of HALT was observed in more than 50% of affected patients.[10] In summary, this study suggests an association of early HVD with reduced bioprosthetic durability and an increased risk for stroke.

The investigators should be commended on this comprehensive large prospective study including patients over a period of 15 years with a median follow-up duration of 1,107 days. The propensity score-matched population demonstrated consistency with the overall population, reinforcing the main findings. This study adds to the existing evidence unraveling the impact of HALT, valve thrombosis, and early HVD on clinical outcomes. Although the investigators propose valve thrombosis as a possible underlying mechanism for early HVD, one needs to be cautious. Early HVD corresponded to HALT in the majority of individuals (75%) in whom CT was performed. The underlying cause for early HVD in the patients with no signs of HALT remains unclear. Moreover, the number of patients who actually underwent computed tomographic assessment (n = 20) is too small to draw a robust conclusion. Other mechanisms of elevated echocardiographic transaortic gradients should be taken into consideration. For instance, systemic blood pressure has been shown to affect echocardiographic transaortic gradients substantially and could have influenced different gradients between discharge and follow-up measurements.[11] Moreover, procedural factors such as valve underexpansion and changes in TAVR prosthesis geometry in valve-in-valve procedures might have an influence on HVD, but procedural factors were not assessed in this study.

The main finding of this study was the association of early HVD with bioprosthetic valve deterioration and stroke. Accordingly, a large meta-analysis including 20 studies comprising 12,128 patients also demonstrated a significantly increased risk for stroke in patients with clinical valve thrombosis.[12] In a prospective observational registry with post-TAVR computed tomographic angiography, HALT was associated with symptomatic HVD but did not affect mortality or cerebrovascular events. However, other TAVR trials could not link HALT or subclinical valve thrombosis to stroke or bioprosthetic valve deterioration.[3] Thus, the literature does not provide a clear picture on this topic.

Preventing these potential clinical events remains the most important issue in this context. Antiplatelet regimens were not differentiated in this study, but currently most patients after TAVR receive single antiplatelet therapy with aspirin in the absence of an indication for anticoagulation. Anticoagulation can effectively reduce HALT and valve thrombosis in TAVR patients, as shown in the GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) and ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) trials.[13,14] However, anticoagulation was not superior to antiplatelet therapy and even increased clinical events, including bleeding and mortality, in the GALILEO trial. Thus, standard administration of oral anticoagulation in patients without established indication may be harmful in this patient population. Determining "whom to treat" requires early identification of patients with affected leaflets. This is particularly relevant for patients with valve-in-valve procedures. Randomized studies are needed to decipher whether these patients may benefit from more intensive antithrombotic therapy. Future studies should address the pathophysiological mechanisms leading to HALT, valve thrombosis, and early HVD. Together with thorough echocardiographic follow-up of TAVR patients, this could help identify and treat patients at risk early. On the basis of the results of this study, standard echocardiographic follow-up should be performed in every patient within 3 months after TAVR, while HVD should trigger CT. In consideration of the results of both imaging modalities, intensification of anticoagulation should be proposed.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Prof Weckbach has received speaker honoraria from AstraZeneca, Bayer, and Philips Healthcare. Prof Stark has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS bioprosthetic valve failure, hemodynamic valve deterioration, leaflet thrombosis, stroke, transcatheter aortic valve replacement

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

ORIGINAL RESEARCH

STRUCTURAL

Clinical Outcomes of Redo Transcatheter Aortic Valve Replacement According to Computed Tomography Sizing

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ABSTRACT

BACKGROUND The optimal sizing strategy for redo transcatheter aortic valve replacement (TAVR) on the basis of computed tomographic (CT) planning is currently debated.

OBJECTIVES The aim of this study was to describe real-world practice for CT sizing and its impact on clinical outcomes of redo-TAVR, according to Valve Academic Research Consortium 3 definitions.

METHODS Consecutive patients undergoing redo-TAVR with preprocedural CT planning were retrospectively analyzed. Measurements of the landing zone (LZ) within the index transcatheter aortic valve (TAV-1) were obtained. The selected size of the second valve (TAV-2) was compared with that suggested by LZ measurements, categorizing patients as LZ concordant (matching size) or LZ discordant (deviating size).

RESULTS Among 150 patients, TAV-1 compression was observed in 97.3% of cases. Overall, 52% of patients received LZ-discordant TAV-2 sizes, mostly resulting in a larger than recommended TAV-2 with 21.2% (15.8%-24.8%) oversizing to the LZ and 7.1% (3.1%-10.9%) to the annulus. No annular rupture events occurred. Device success at 30 days was 73.3%. Median follow-up was 368 days (Q1-Q3: 96-611 days). The estimated rate of bioprosthetic valve failure at 1 year was 8.7% (95% CI: 3.1%-14.2%), without significant differences between the 2 groups. LZ perimeter $<$62 mm (HR: 4.19; 95% CI: 1.37-12.8; $P = 0.012$) and TAV-2 size smaller than the manufacturer sizing range for the aortic annulus (HR: 3.75; 95% CI: 1.25-11.2; $P = 0.018$) were independent predictors of bioprosthetic valve failure.

CONCLUSIONS In patients undergoing redo-TAVR with preprocedural CT planning, a sizing strategy enabling selective TAV-2 oversizing relative to the LZ was associated with favorable outcomes without increased procedural complications. Larger studies are needed to confirm these findings. (JACC Cardiovasc Interv. 2025;18:2488-2501)

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.034

Transcatheter aortic valve replacement (TAVR) for severe symptomatic aortic stenosis has expanded across the spectrum of surgical risk toward younger patients with longer life expectancy.[1,2] As a considerable proportion of these patients might exceed the lifespan of their first transcatheter aortic valve (TAV), reinterventions are likely to become increasingly common in the near future. Although considered a logical option to treat degenerated TAVs, redo-TAVR poses several technical challenges.[3-5] Among these, device sizing is particularly relevant to determine anatomical suitability for transcatheter reintervention and ensure optimal hemodynamic results.

Unlike surgical valves, TAVs have markedly different designs, and their expansion is directly affected by the interaction with the native aortic valve. In most cases, despite optimal technique, the index TAV (TAV-1) does not achieve its nominal shape and size after implantation.[6] This limits the translational outlook of in vitro bench studies for second TAV (TAV-2) sizing, as they recommend an excessive oversizing that might cause annular injury or significant TAV-2 underexpansion, potentially affecting valve function and durability. Current expert recommendations suggest a TAV-2 sizing strategy based on preprocedural computed tomographic (CT) measurements of the landing zone (LZ) within TAV-1 stent frame, which varies according to the specific TAV-in-TAV combination. The averaged area and perimeter derived from these measurements is used to select TAV-2 size on the basis of manufacturer instructions for use. In cases of borderline sizing, the assessment of patient's clinical characteristics and native aortic anatomy might further inform the decision.[7,8] Although this strategy seems attractive, enabling patient-specific and device-specific sizing, no data are available to support it.

The aim of this study was to describe real-world practice for CT sizing and its impact on clinical outcomes of redo-TAVR.

METHODS

STUDY DESIGN AND PATIENT POPULATION. This investigator-initiated multicenter registry retrospectively enrolled consecutive patients who underwent transcatheter implantation of a second TAV within a degenerated index TAV at 14 high-volume centers in Europe and North America between 2014 and 2024. Only patients with structural valve deterioration as the primary mechanism of index TAV failure were included. All redo-TAVR procedures were planned using CT imaging. The choice of TAV-2 design was left to the operator, according to local practice. Final decision on TAV-2 sizing was based on the comprehensive assessment of patient's clinical characteristics, native aortic anatomy, and preprocedural CT analysis of TAV-1 (Supplemental Table 1). Only patients with available preprocedural CT images before TAV-2 were considered eligible. Baseline CT images of the native aortic anatomy were also collected for analysis when available. To evaluate the association between LZ-based TAV-2 sizing and the outcomes of interest, the population was categorized into 2 groups: patients whose actual TAV-2 size matched manufacturer recommendations on the basis of LZ measurements (LZ concordant) and those whose actual TAV-2 size deviated from them (LZ discordant) (**Figure 1**). Subgroup analysis was conducted according to TAV frame height. The study protocol was approved at each center by the

ABBREVIATIONS AND ACRONYMS

BEV = balloon-expandable valve

BVF = bioprosthetic valve failure

CT = computed tomographic

LZ = landing zone

MEV = mechanically expandable valve

SEV = self-expanding valve

TAV = transcatheter aortic valve

TAVR = transcatheter aortic valve replacement

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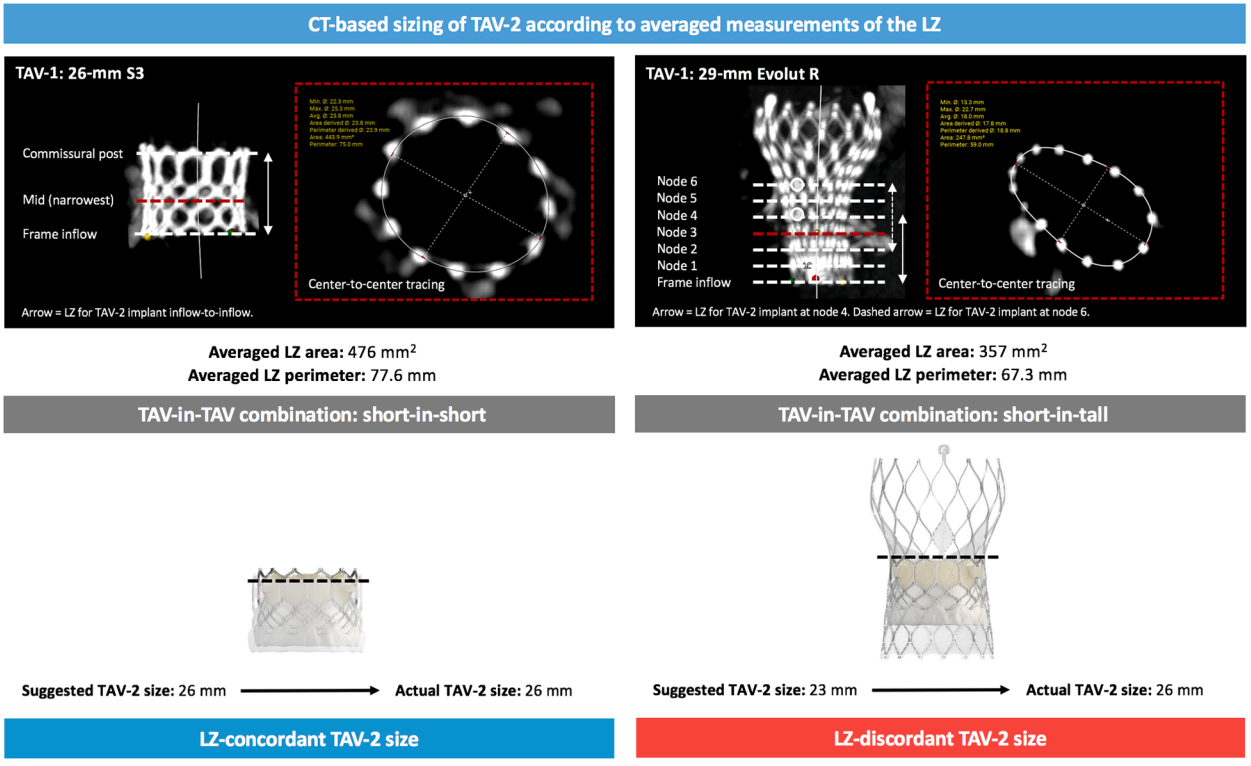
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 21, 2025; revised manuscript received August 18, 2025, accepted August 28, 2025.

FIGURE 1 **CT-Based Sizing**



Examples of computed tomography (CT)–based sizing of second transcatheter aortic valve (TAV-2) according to landing zone (LZ) analysis for short-in-short (left) and short-in-tall (right).

Institutional Review Board. All patients consented to the use of their medical records for research objectives.

TAV PLATFORMS. The TAV platforms were classified according to the expansion mechanism during the deployment as balloon-expandable valves (BEVs), mechanically expandable valves (MEVs), and self-expanding valves (SEVs). Degenerated TAV-1 included a range of BEVs, MEVs, and SEVs, while only BEVs and SEVs were used as TAV-2. According to the frame height, SEVs were considered tall-frame, while BEV and MEV are considered short-frame. The study population included all 4 different TAV-in-TAV combinations with reference to frame height: short-in-short, tall-in-short, tall-in-tall, and short-in-tall.

CT ANALYSIS. All the CT scans evaluated for this study were electrocardiographically gated and contrast enhanced and used a slice thickness of ≤1mm. The CT images were analyzed using 3Mensio imaging software (Pie Medical). Anonymized CT images were collected for core laboratory analysis at Clinique Pasteur, following a standardized protocol (Supplemental Figures 1 and 2).[8] When CT images transfer was restricted by local policies, the analysis was performed by local investigators at each site. To minimize interobserver variability, all participating centers underwent calibration training. In all cases, measurements were performed by expert investigators blinded to procedural outcomes to ensure objective assessment.

The area and perimeter of TAV-1 stent frame were measured at multiple planes, using the center-to-center tracing to minimize blooming artifacts, according to current recommendations.[8] The LZ position and the TAV-1 planes selected for TAV-2 sizing were determined by the specific TAV-in-TAV combination selected by the operator. The averaged area or perimeter of the LZ was used to select TAV-2 size on the basis of manufacturer instructions for use. The expansion of TAV-1 at the LZ was assessed by comparing CT measurements with the manufacturer or CT nominal dimensions of each platform.[9]

The degree of TAV-2 undersizing or oversizing relative to TAV-1 and the native aortic annulus was calculated by comparing the TAV-2 label size with the average LZ and annular measurements, respectively. Additionally, the actual TAV-2 size was evaluated to determine whether it fell within the valve-specific recommended sizing range for the patient's native aortic annulus. When baseline CT images were unavailable, the sizing range was inferred using TAV-1 label size, on the basis of manufacturer recommendations. The risk to the coronary arteries and the feasibility of coronary protection strategies on the basis of leaflet modification were assessed for future analyses, as previously described.

Information on the native aortic anatomy was derived from baseline CT images before index TAVR when available. Aortic valve morphology (tricuspid or bicuspid), the degree of annular or leaflet calcification, the annular area, perimeter and diameters, the sinotubular junction and sinus of Valsalva diameters, and the sinotubular junction and coronary height were obtained.

CLINICAL OUTCOMES. Baseline demographics, echocardiographic data, and procedural and follow-up clinical outcomes were collected by the local investigators at each institution using a dedicated case report form. Outcomes were defined according to the Valve Academic Research Consortium 3 definitions.[10] The primary outcome of interest was the rate of bioprosthetic valve failure (BVF) at follow-up adjudicated at each institution by local investigator. Other outcomes included technical success at the exit from procedure room, device success at 30 days, intended valve performance at 30 days, and mortality at follow-up. Inconsistencies were resolved by direct communication with the local investigators.

TABLE 1 Baseline Characteristics

	Overall (N = 150)	LZ Concordant (n = 72)	LZ Discordant (n = 78)	*P* Value
Clinical characteristics				
Age, y	82 ± 9	81 ± 7	80 ± 6	0.15
Female	73 (48.7)	37 (51.4)	36 (46.2)	0.52
BMI, kg/m^2	26.5 ± 5.3	25.8 ± 5.1	27.1 ± 5.6	0.16
BSA, m^2	1.7 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	0.16
Hypertension	134 (89.3)	63 (87.5)	71 (91)	0.48
Dyslipidemia	107 (71.3)	46 (63.9)	61 (78.2)	0.053
Diabetes	64 (42.7)	28 (38.9)	36 (46.2)	0.36
CKD	89 (59.3)	44 (61.1)	45 (57.7)	0.67
Dialysis	5 (3.3)	2 (2.8)	3 (3.8)	0.53
COPD	24 (16)	15 (20.8)	9 (11.5)	0.12
CAD	82 (54.7)	32 (44.4)	50 (64.1)	**0.016**
Prior PCI	52 (34.7)	23 (31.9)	29 (37.2)	0.50
Prior CABG	17 (11.3)	5 (6.9)	12 (15.4)	0.10
AF	54 (36)	24 (33.2)	30 (38.5)	0.51
Prior stroke	25 (16.7)	10 (13.9)	15 (19.2)	0.38
PAD	30 (20)	13 (18.1)	17 (21.8)	0.56
Permanent PM	35 (23.3)	13 (18.1)	22 (28.2)	0.14
NYHA functional class III or IV	107 (72.3)	55 (77.5)	52 (67.5)	0.17
STS score, %	5.8 (3.5-9.6)	6.3 (4.2-10.1)	5.4 (3.1-8.7)	0.10
Echocardiography				
LVEF, %	53 ± 12	54 ± 13	53 ± 11	0.60
LVEF ≤35%	17 (11.6)	11 (15.7)	6 (7.8)	0.13
MR moderate or greater	47 (31.3)	23 (31.9)	24 (30.8)	0.87
AR moderate or greater	91 (60.7)	42 (58.3)	49 (62.8)	0.57
EOA, cm^2	0.8 (0.6-1.2)	0.7 (0.6-1.1)	0.8 (0.6-1.4)	0.76
Mean gradient, mm Hg	32 ± 18	37 ± 17	34 ± 18	0.61
Index TAV failure mode				
Pure aortic stenosis	49 (32.7)	23 (31.9)	26 (33.3)	0.85
Pure aortic regurgitation	58 (38.7)	27 (37.5)	31 (39.7)	0.77
Mixed stenosis/regurgitation	43 (28.6)	22 (30.6)	21 (26.9)	0.62
Index TAV duration, y	5.8 (4.2-7.1)	5.8 (4.7-6.8)	5.7 (3.5-7.5)	0.92

Values are mean ± SD, n (%), or median (Q1-Q3). *P* values in boldface type denote statistical significance.

AF = atrial fibrillation; AR = aortic regurgitation; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; EOA = effective orifice area; LVEF = left ventricular ejection fraction; LZ = landing zone; MR = mitral regurgitation; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PM = pacemaker; STS = Society of Thoracic Surgeons; TAV = transcatheter aortic valve.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD or median (Q1-Q3) and were compared using Student's *t*-test or the Mann-Whitney *U* test, as appropriate. Categorical variables are presented as counts (percentage) and were compared using the chi-square test or the Fisher exact test. Binary logistic regression analysis was performed to identify predictors of computed tomography–discordant sizing. The cumulative incidence of clinical outcomes at 1 year was estimated using the Kaplan-Meier method, accounting for censoring in patients with follow-up shorter than 1 year. Group differences in time-to-event outcomes were assessed at 1 year using the log-rank test. Independent predictors of the primary outcome were identified using the Cox proportional hazards regression, following verification of the proportional hazards assumption. Univariable and multivariable analyses were adjusted for body surface area. Covariates for the multivariable model were selected on the basis of clinical relevance, eventually supported by statistical significance ($P < 0.10$) in univariable analysis (Supplemental Table 2). To account for potential between-center heterogeneity, a Cox mixed-effects model including a random intercept for study center was also fitted as a sensitivity analysis. Results are reported as HRs with 95% CIs. Optimal cutoff values for continuous predictors and their time-dependent performance were determined using the maximization of the log-rank statistic. All statistical tests were 2 tailed, with statistical significance defined as $P < 0.05$. Statistical analyses were performed using SPSS version 24.0 (SPSS). Survival curves were generated using Prism version 6 (GraphPad).

TABLE 2 CT Analysis of Native Anatomy, TAV-1, and Predicted TAV-2 Sizing

	Overall	*P* Value	LZ Concordant	LZ Discordant	*P* Value
Preindex TAV CT analysis	(N = 125)		(n = 62)	(n = 63)	
Tricuspid valve	108 (86.4)	–	54 (87.1)	54 (85.7)	0.82
Bicuspid valve	17 (13.6)	–	8 (12.9)	9 (14.3)	0.82
Annular or leaflet calcification	121 (98.4)	–	61 (98.4)	60 (95.3)	0.49
Calcium volume 800 HU, mm^3	570 (324-1,183)	–	502 (228-764)	611 (343-1,203)	0.24
Annular area, mm^2	433.9 ± 85.0	–	431.2 ± 95.6	436.5 ± 74.4	0.71
Annular perimeter, mm	75.1 ± 7.0	–	74.4 ± 7.8	75.6 ± 6.2	0.32
SOV diameter average, mm	31.2 ± 3.8	–	30.3 ± 3.7	31.8 ± 3.7	**0.043**
STJ height, mm	22.5 ± 3.7	–	21.5 ± 3.5	23.3 ± 3.7	**0.012**
STJ diameter, mm	27.9 ± 3.6	–	27.7 ± 3.5	28.1 ± 3.6	0.51
LCA height, mm	13.9 ± 3.5	–	13.5 ± 3.6	14.3 ± 3.4	0.26
RCA height, mm	16.1 ± 3.6	–	15.4 ± 3.7	16.7 ± 3.4	0.050
Pre-redo-TAVR CT analysis	(N = 150)	–	(n = 72)	(n = 78)	
TAV-1 design		–			0.50
Short-frame	73 (48.7)		33 (45.8)	40 (51.3)	
Tall-frame	77 (51.3)		39 (54.2)	38 (48.7)	
TAV-1 label size ≤23 mm	49 (32.7)	**<0.001**	24 (33.3)	25 (32.1)	0.86
Short-frame	41 (27.3)		18 (25)	23 (29.4)	0.80
Tall-frame	8 (5.3)		6 (8.3)	2 (2.5)	0.26
TAV-1 sizing to annular area, %	108.4 (104.1-114.1)	**<0.001**	107.9 (104.1-114.6)	108.5 (103.8-113)	0.83
Short-frame TAV-1	105.6 (102.3-110.2)		105.7 (102.1-109.5)	105.4 (101.9-110.9)	0.88
Tall-frame TAV-1	110.4 (106.5-117.4)		109.8 (105.9-120.3)	111.1 (106.9-115.8)	0.62
Average LZ area, mm^2	358.8 ± 65.6	**0.002**	367.2 ± 71.7	351.8 ± 59.6	0.15
Short-frame TAV-1	341.9 ± 68.9		347.2 ± 78.0	337.6 ± 61.1	0.55
Tall-frame TAV-1	374.8 ± 58.2		386.1 ± 60.3	365 ± 55.5	0.12
Average LZ perimeter, mm	67.4 ± 6.3	**0.001**	68.1 ± 6.4	66.8 ± 6.1	0.21
Short-frame TAV-1	65.7 ± 6.6		65.8 ± 7.1	65.6 ± 6.4	0.89
Tall-frame TAV-1	69.1 ± 5.4		70.3 ± 5.0	68.1 ± 5.7	0.12
LZ ellipticity index	1.14 ± 0.1	**<0.001**	1.12 ± 0.08	1.15 ± 0.13	0.23
Short-frame TAV-1	1.09 ± 0.06		1.08 ± 0.05	1.11 ± 0.06	**0.039**
Tall-frame TAV-1	1.18 ± 0.13		1.17 ± 0.10	1.20 ± 0.15	0.35
TAV-1 expansion to reference area, %	87.7 ± 6.2	**0.002**	88.7 ± 5.9	86.3 ± 6.1	**0.018**
Short-frame TAV-1	89.5 ± 6.5		89.7 ± 7.2	88.4 ± 6.0	0.43
Tall-frame TAV-1	85.9 ± 5.6		87.8 ± 4.4	84.3 ± 5.7	**0.004**
TAV-1 expansion to annular area, %	89.9 ± 6.3	**0.030**	91.5 ± 5.6	88.2 ± 6.1	**0.002**
Short-frame TAV-1	91.3 ± 6.2		91.5 ± 6.0	90.5 ± 6.2	0.54
Tall-frame TAV-1	88.7 ± 6.1		91.5 ± 5.2	86.4 ± 5.5	**<0.001**
Average TAV-1 implantation depth, mm	5.1 (3.4-7.4)	–	4.8 (3.1-7.2)	5.4 (3.6-7.8)	0.18
NSP above CRP LCA	104 (69.3)	–	50 (69.4)	54 (69.2)	0.97
NSP above CRP RCA	82 (54.7)	–	39 (54.2)	43 (55.1)	0.90
High risk for CO LCA	40 (26.7)	–	20 (27.8)	20 (25.6)	0.76
High risk for CO RCA	37 (24.7)	–	18 (25)	19 (24.4)	0.92
Center cusp to LCA angle, deg	27.6 ± 17.1	–	28.2 ± 16.8	27.2 ± 17.2	0.73
Center cusp to RCA angle, deg	30.5 ± 17.8	–	31.4 ± 17.9	28.9 ± 17.7	0.40

Continued on the next page

RESULTS

BASELINE CHARACTERISTICS. Among 38,665 patients who underwent TAVR at the participating centers between 2014 and 2024, 150 (0.4%) were eligible for inclusion in this study. Baseline clinical and echocardiographic characteristics at the time of redo-TAVR are displayed in Table 1. Overall, the mean age was 82 ± 9 years, and 73 of 150 patients (48.7%) were woman. The median time from index TAVR to reintervention was 5.8 years (Q1-Q3: 4.2-7.1 years), and the failure mode was pure aortic stenosis in 49 of 150 (32.7%), pure aortic regurgitation in 58 of 150 (38.7%), and mixed disease in 43 of 150 (28.6%).

NATIVE AORTIC ANATOMY. Overall, baseline CT imaging performed before TAV-1 implantation was available in 125 of 150 patients (84%) for centralized

TABLE 2 Continued

	Overall	*P* Value	LZ Concordant	LZ Discordant	*P* Value
CT TAV-2 sizing	(N = 150)	—	(n = 72)	(n = 78)	
TAV-in-TAV combination		—			
Short-in-short	39 (26)		9 (12.5)	30 (38.5)	**<0.001**
Tall-in-short	34 (23)		24 (33.4)	10 (12.8)	**0.003**
Tall-in-tall	12 (8)		7 (9.7)	5 (6.4)	0.45
Short-in-tall	65 (43)		32 (44.4)	33 (42.3)	0.79
TAV-2 design		—			**0.002**
Short-frame	104 (69.3)		41 (56.9)	63 (80.8)	
Tall-frame	46 (30.7)		31 (43.1)	15 (19.2)	
TAV-2 sizing to TAV-1, %	117.5 (111.3-112.9)	**<0.001**	111.5 (105.6-120.7)	121.2 (115.8-124.8)	**<0.001**
Short-frame TAV-2	122.7 (116.8-127.1)		107.1 (103.1-110.5)	121.2 (116.4-122.6)	**<0.001**
Tall-frame TAV-2	115.6 (108.9-121.2)		122.8 (116.9-126.3)	126.1 (111.1-132.4)	0.82
TAV-2 sizing to annulus, %	105.1 (100.6-110.6)	**<0.001**	103.6 (97.5-110.6)	107.1 (103.1-110.9)	**0.008**
Short-frame TAV2	110.2 (105.1-115.6)		99.3 (96.1-104.4)	105.3 (102.3-109.8)	**<0.001**
Tall-frame TAV-2	103.1 (98.9-108.7)		109.3 (104.4-113.2)	115.1 (107.8-119.3)	0.050

The degree of TAV expansion and sizing relative to reference structures was calculated as (actual measurement/reference measurement) × 100. Values <100 indicate underexpansion or undersizing, while values >100 indicate overexpansion or oversizing relative to the reference measurement. *P* values in **bold** denote statistical significance.

CO = coronary obstruction; CRP = coronary risk plane; CT = computed tomographic; LCA = right coronary artery; NSP = neoskirt plane; RCA = right coronary artery; SOV = sinus of Valsalva; STJ = sinotubular junction; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

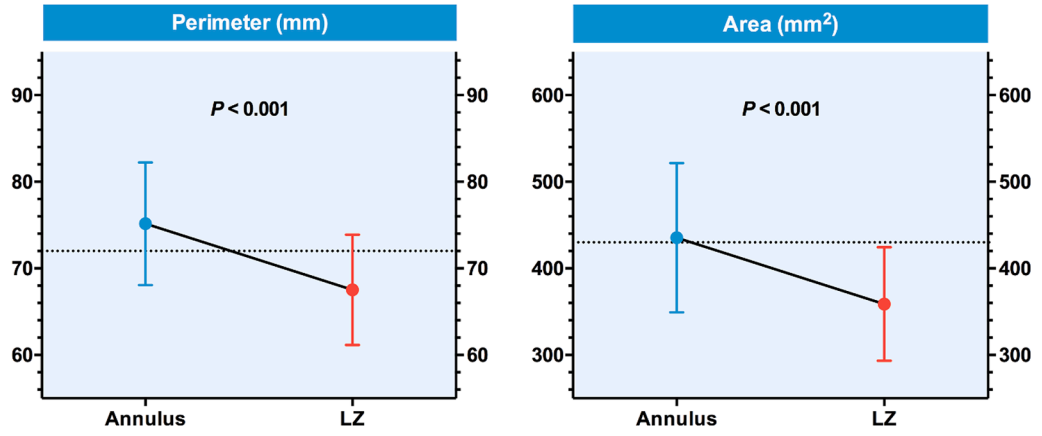
analysis. Baseline CT analysis is reported in Table 2. Tricuspid aortic valve morphology was observed in 108 of 125 cases (86.4%), with 121 of 125 (98.4%) presenting any degree of leaflet calcification and median calcium volume of 570 mm^3 (Q1-Q3: 324-1,183 mm^3). The average native aortic annular area and perimeter were 433.9 ± 85.0 mm^2 and 75.1 ± 7.0 mm, respectively.

CT ANALYSIS OF TAV-1. CT analysis of TAV-1 is reported in Table 2. Average TAV-1 expansion at the LZ was 87.7% ± 6.2% relative to the reference CT area and 89.9% ± 6.3% relative to the native aortic annular area, indicating extrinsic compression of TAV-1 by the surrounding anatomy. The average LZ area and perimeter were 358.8 ± 65.6 mm^2 and 67.4 ± 6.3 mm, corresponding to average reductions of 17.5% and 10.4% in the reference dimensions for TAV-2 sizing compared with the native annulus (Figure 2). Overall, 73 of 150 patients (48.7%) received a short-frame TAV-1 (85% BEVs and 15% MEVs) and 77 of 150 (51.3%) a tall-frame TAV-1 (100% SEVs). Compared with tall-frame TAV-1, short-frame TAV-1 were smaller (label size ≤23 mm) in a significant proportion of cases (56.2% vs 10.2%; $P < 0.001$) and showed lower predicted oversizing relative to the native aortic annulus (5.6% [2.3%-10.2%] vs 10.4% [6.5%-17.4%]; $P < 0.001$), resulting in significantly smaller area (341.9 ± 68.9 mm^2 vs 374.8 ± 58.2 mm^2; $P = 0.002$) and perimeter (65.7 ± 6.6 mm vs 69.1 ± 5.4 mm; $P = 0.001$) of the LZ. However, short-frame TAV-1 showed significantly greater expansion relative to the reference CT area (89.5% ± 6.5% vs 85.9% ± 5.6%; $P = 0.002$) and to the native aortic annulus area (91.3% ± 6.2% vs 88.7% ± 6.1%; $P = 0.030$), along with lower ellipticity (1.09 ± 0.06 vs 1.18 ± 0.13; $P < 0.001$) of the LZ.

COMPUTED TOMOGRAPHY–GUIDED TAV-2 SELECTION. Procedural details are reported in Table 2. Overall, 104 of 150 patients (69.3%) received a short-frame TAV-2 (100% BEVs) and 46 of 150 (30.7%) a tall-frame TAV-2 (100% SEVs). The resulting TAV-in-TAV combinations were short-in-short in 39 of 150 (26%), tall-in-short in 34 of 150 (23%), tall-in-tall in 12 of 150 (8%), and short-in-tall in 65 of 150 (43%). Short-frame TAV-2 presented significantly greater oversizing relative to TAV-1 LZ (22.7% [16.8%-27.1%] vs 15.6% [8.9%-21.2%]; $P < 0.001$) and to the native aortic annulus (10.2% [5.1%-15.6%] vs 3.1% [−1.1% to 8.7%]; $P < 0.001$) than tall-frame TAV-2. Predilatation was performed in 29 of 150 cases (19.3%): 8 of 39 (20.5%) for short-in-short, 8 of 34 (23.5%) for tall-in-short, 3 of 12 (25%) for tall-in-tall, and 10 of 65 (15.4%) for short-in-tall. Postdilatation was performed in 62 of 150 cases (41.3%): 16 of 39 (41%) for short-in-short, 22 of 34 (64.7%) for tall-in-short, 4 of 12 (33.3%) for tall-in-tall, and 20 of 65 (30.8%) for short-in-tall.

DISCORDANCE WITH LZ-BASED TAV-2 SIZING. TAV-2 sizing was discordant with LZ measurements in 78 of

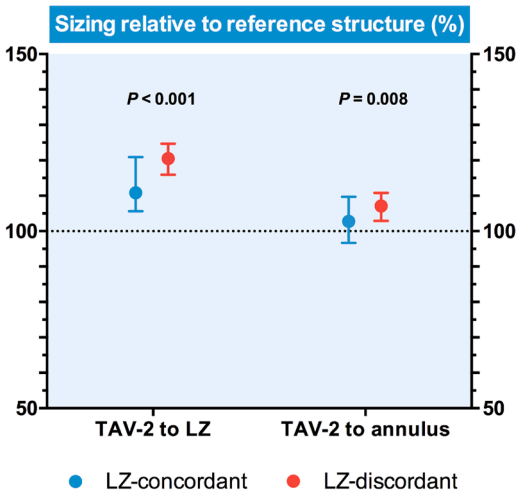
FIGURE 2 Reference Measurement Reduction



Variation in perimeter and area moving from the native aortic annulus to the landing zone (LZ) within the first transcatheter aortic valve stent frame. Values are presented as mean ± SD. Thresholds for small aortic annulus (perimeter <72 mm, area <430 mm^2) are highlighted (dashed lines).

150 patients (52%). Discordance resulted in larger TAV-2 in 92.3% (87.5% short-frame) and smaller TAV-2 in 7.7% (100% tall-frame). The proportion of short-frame and tall-frame TAV-1 was similar between the 2 groups. Conversely, the proportion of short-frame TAV-2 was significantly greater among patients with LZ-discordant sizing (80.8% vs 56.9%; $P = 0.002$), leading to more short-in-short (38.5%) and short-in-tall (42.3%) combinations in this group ($P < 0.001$). Similarly, the proportion of tall-frame TAV-2 was significantly greater in the LZ-concordant sizing (43.1% vs 19.2%; $P = 0.002$), leading to more tall-in-short (33.4%) and tall-in-tall (9.7%) combinations in this group ($P < 0.001$). Overall, patients receiving LZ-discordant TAV-2 sizing had significantly greater TAV-1 underexpansion because of external compression from the native anatomy. Accordingly, the average TAV-2 oversizing was 21.2% (15.8%-24.8%) relative to the LZ and 7.1% (3.1%-10.9%) relative to the native annulus (Figure 3). The degree of TAV-1 compression relative to the reference CT dimensions (OR: 1.06; 95% CI: 1.01-1.12; $P = 0.031$) and to the aortic annulus (OR: 1.09; 95% CI: 1.03-1.16; $P = 0.005$) were associated with an increased likelihood of LZ-discordant sizing. The sinotubular junction height was lower (21.5 ± 3.5 mm vs 23.3 ± 3.7 mm; $P = 0.012$) and the sinus diameter was smaller (30.3 ± 3.7 mm vs 31.8 ± 3.7 mm; $P = 0.043$) in LZ-concordant cases compared with LZ-discordant cases. The rates of predilatation (59.1% vs 72.7%; $P = 0.098$) and postdilatation (16.7% vs 34.8%; $P = 0.016$) during the index TAVR procedure were higher in LZ-discordant cases. Conversely, the rates of predilatation (20.8% vs 17.9%; $P = 0.655$) and postdilatation (41.7% vs 41.0%; $P = 0.937$) during the redo-TAVR procedure were similar between the 2 groups.

FIGURE 3 TAV-2 Sizing Relative to the Reference Structure



Values are presented as median (Q1-Q3). Values <100 indicate undersizing, while values >100 indicate oversizing. Abbreviations as in Figure 1.

TABLE 3 Procedural and 30-Day Outcomes

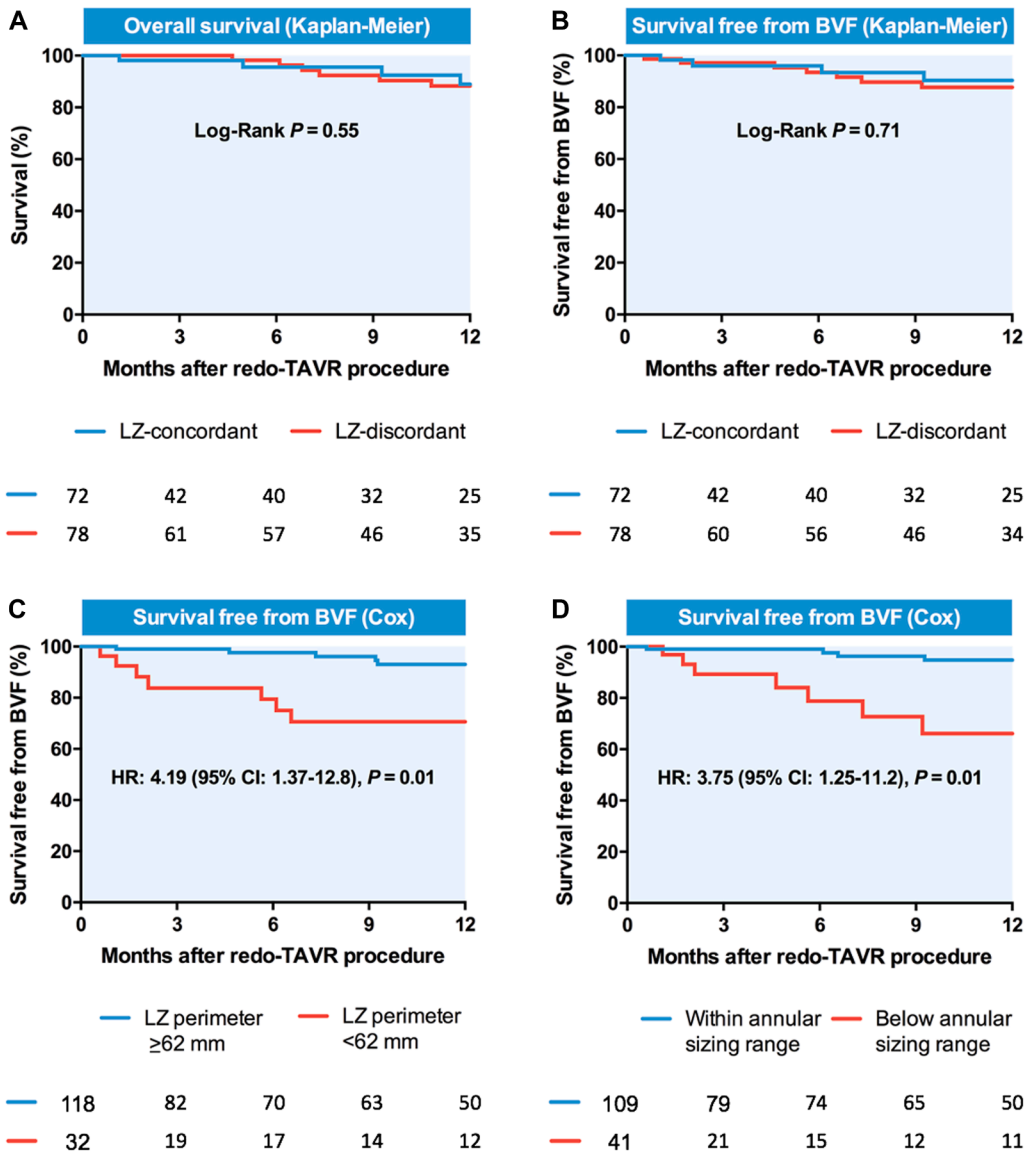
	Overall (N = 150)	LZ Concordant (n = 72)	LZ Discordant (n = 78)	*P* Value
Procedural outcomes				
Technical success	133 (88.7)	65 (90.3)	68 (87.2)	0.55
Procedural death	2 (1.3)	0	2 (2.6)	0.49
Device embolization	2 (1.3)	1 (1.4)	1 (1.3)	0.73
Annular rupture	0	0	0	–
Cardiac tamponade	0	0	0	–
Cardiac surgery	0	0	0	–
Coronary obstruction	7 (4.7)	3 (4.2)	4 (5.1)	0.78
Major vascular complication	8 (5.3)	3 (4.2)	5 (6.4)	0.72
Minor vascular complication	12 (8)	4 (5.6)	8 (10.3)	0.28
Major bleeding	6 (4)	2 (2.8)	4 (5.1)	0.68
Minor bleeding	12 (8)	6 (8.3)	6 (7.7)	0.88
Stroke	1 (0.7)	1 (1.4)	0	0.48
Acute kidney injury	2 (1.3)	2 (2.8)	0	0.23
New permanent pacemaker	11 (7.3)	4 (5.6)	7 (9.0)	0.42
Clinical outcomes at 30 d				
Device success	110 (73.3)	53 (73.6)	57 (73.1)	0.94
All-cause death	3 (2)	1 (1.4)	2 (2.6)	0.53
Valve-related death	2 (1.3)	0	2 (2.6)	0.49
Aortic reintervention	0	0	0	-
Intended valve performance	123 (82)	59 (81.9)	64 (82.1)	0.98
Mean gradient, mm Hg	13 ± 6	13 ± 6	14 ± 6	0.41
Mean gradient ≥20 mmHg	23 (15.6)	12 (16.9)	11 (14.5)	0.68
Aortic regurgitation moderate or greater	2 (1.4)	1 (1.4)	1 (1.3)	0.73
Paravalvular leak moderate or greater	2 (1.4)	1 (1.4)	1 (1.3)	0.73
EOA, cm^2	1.54 ± 0.36	1.60 ± 0.35	1.47 ± 0.36	0.10
iEOA, cm^2/m^2	0.86 ± 0.20	0.90 ± 0.19	0.82 ± 0.19	0.070
PPM	37 (42)	18 (38.3)	19 (46.3)	0.44
Severe PPM	7 (8)	2 (4.3)	5 (12.2)	0.24
NYHA functional class >II	10 (6.7)	6 (8.3)	4 (5.1)	0.43
Stroke	2 (1.3)	1 (1.4)	1 (1.3)	0.73
Acute kidney injury	2 (1.3)	2 (2.8)	0	0.23
New permanent pacemaker	12 (8)	4 (5.6)	8 (10.3)	0.28

Intended valve performance includes patients with vascular access, bleeding, coronary obstruction, stroke, or acute kidney injury not leading to death at 30 days. Thresholds for PPM definition vary with body mass index according to Valve Academic Research Consortium 3 definitions. EOA measurements were available for 88 of 150 patients (59%).

iEOA = indexed effective orifice area; PPM = patient-prosthesis mismatch; other abbreviations as in Table 1.

CLINICAL OUTCOMES. Procedural, 30-day, and 1-year outcomes were similar between the 2 groups, as shown in Table 3 and Figure 4. Overall, technical success was achieved in 133 of 150 cases (88.7%): 2 patients (1.3%) experienced procedural death (1 device embolization and 1 coronary obstruction), 2 (1.3%) device embolization, 7 (4.6%) coronary obstruction, and 8 (5.3%) major vascular complications. The 2 cases of device embolization occurred during low implant of a short-frame TAV-2 (LZ-concordant sizing in the first and LZ-discordant oversizing with predilatation in the second case) within a severely underexpanded tall-frame TAV-1 (LZ 65.1% and 69.5% of reference area), with the waist close to the upper part of the balloon. No annular rupture events were observed, despite the degree of oversizing in the LZ-discordant group. Device success at 30 days was achieved in 110 of 150 patients (73.3%). This result was driven mainly by high residual gradients in 23 of 150 cases (15.6%): 10 of 39 (25.6%) for short-in-short, 6 of 34 (17.6%) for tall-in-short, 0 of 12 (0%) for tall-in-tall, and 7 of 65 (10.7%) for short-in-tall. Severe patient-prosthesis mismatch occurred in 8% of cases. The median follow-up length was 368 days (Q1-Q3: 96-611 days). At 1 year, the estimated incidence of all-cause death

FIGURE 4 Clinical Outcomes at 1 Year



Kaplan-Meier analysis of overall survival and survival free from bioprosthetic valve failure (BVF) according to landing zone (LZ) concordance (A,B) and Cox analysis for survival free from BVF according to independent predictors from multivariable analysis (C,D).
TAVR = transcatheter aortic valve replacement.

was 12% (95% CI: 5.1%-18.8%), BVF 8.7% (95% CI: 3.1%-14.2%), and severe hemodynamic valve dysfunction 3.9% (95% CI: 0.2%-7.6%), on the basis of Kaplan-Meier analysis, without significant differences between LZ-concordant and LZ-discordant cases. Details on patients who experienced BVF at follow-up are reported in Supplemental Table 3. The maximization of the log-rank statistic identified LZ perimeter < 62 mm as the threshold providing the greatest separation between BVF-free survival curves ($P < 0.001$). The performance of this cutoff remained good over time (areas under the curve for BVF-free survival of 0.94, 0.74, and 0.75 at 96, 368, and 611 days). After adjusting for body surface area, the multivariable Cox proportional hazards regression analysis identified an LZ perimeter <62 mm (HR: 4.19; 95% CI: 1.37-12.8; $P = 0.012$) and a TAV-2 size smaller than the manufacturer sizing range for the

native aortic annulus (HR: 3.75; 95% CI: 1.25-11.2; $P = 0.018$) as independent predictors of BVF at 1 year (Supplemental Table 2). Long-term echocardiography data (beyond 1 year) were available for 45 of 150 patients (30%), including 19 of 72 in the LZ-concordant and 26 of 78 in the LZ-discordant group. Overall, at a median follow-up of 545 days (Q1-Q3: 373-1,097 days), effective orifice area was 1.60 cm^2 (Q1-Q3: 1.37-1.80 cm^2), mean gradient was 11 mm Hg (Q1-Q3: 9-16 mm Hg), and the rate of aortic regurgitation was 4.4%, without significant differences between the 2 groups.

DISCUSSION

This study is the first to evaluate the clinical outcomes of redo-TAVR according to CT sizing. The main findings are as follows: 1) in patients undergoing in vivo preprocedural CT planning for redo-TAVR, compression of TAV-1 by the native anatomy was frequently observed and was greater for tall-frame platforms; 2) this led to LZ-discordant sizing in 52% of cases, predominantly in patients with greater TAV-1 compression, resulting in a larger than recommended TAV-2 in most cases; 3) a CT TAV-2 sizing strategy integrating native annular dimensions and allowing selective oversizing relative to the LZ was associated with favorable outcomes without an increased risk for procedural complications; and 4) an LZ perimeter <62 mm and a TAV-2 size smaller than the recommended sizing range for the native aortic annulus were independent predictors of BVF at 1 year (**Central Illustration**).

Redo-TAVR is a valuable option to treat patients with degenerated TAVs. Previous registries have shown favorable procedural outcomes and lower mortality rates compared with surgical TAV explantation.[3-5] Nevertheless, redo-TAVR poses several technical challenges related to the complexity of TAV designs, and their interaction with the surrounding native aortic anatomy that might affect feasibility. Recent expert recommendations highlight the importance of preprocedural CT planning to evaluate the risk to the coronary arteries and select the optimal TAV-2 design and size. The redo TAV app has been recently released to facilitate procedural planning. In its workflow, TAV-2 sizing is based on the identification of a LZ within TAV-1 stent frame. Measurements of area and perimeter are performed at multiple levels across the LZ. Once these measurements are obtained, the averaged area or perimeter is used to select TAV-2 size on the basis of manufacturer instruction for use.[8] Although this strategy seems attractive, allowing patient-specific and device-specific sizing, its impact on hemodynamic performance and clinical outcomes remains to be assessed. Recent simulation studies suggested that TAV-1 underexpansion caused by external compression is common and that a TAV-2 sizing strategy on the basis of CT measurements of the LZ could significantly reduce the risk for excessive oversizing compared with in vitro recommendations.[11,12] However, this approach raises concerns about the consequences of potential TAV-2 undersizing on hemodynamic performance and long-term durability.

In the present study, underexpansion of TAV-1 relative to the reference CT dimensions was observed in 97.3% of cases. The average TAV-1 expansion at the LZ was 87.7% ± 6.2%, and it was significantly lower for tall-frame compared with short-frame TAVs ($P = 0.002$). Notably, the LZ fell below the commonly used threshold for the definition of small aortic annulus (area <430 mm^2 or perimeter <72 mm) in 86% of cases.[13] Therefore, a CT TAV-2 sizing strategy exclusively relying on LZ dimensions would lead to the selection of a TAV-2 that is inappropriate for the patient's aortic annulus in 62% of cases, potentially affecting valve hemodynamic status and durability (Supplemental Figure 3). Indeed, a very small LZ dimension (perimeter <62 mm) and the selection of a TAV-2 size too small for the patient's native aortic annulus were identified as independent predictors of BVF at 1 year. This sizing issue is particularly relevant for lifetime management, as it could preclude any possibility of transcatheter reintervention beyond the first TAVR procedure in a significant proportion of patients. Hence, in younger patients with long life expectancy and low surgical risk, these features may prompt consideration of surgical valve replacement with aortic root enlargement as a preferrable initial strategy.

In this study, operators selected a TAV-2 size discordant with the LZ measurements in 52% of cases overall, resulting in larger than recommended TAV-2 in 48%. In the LZ-discordant group, the average TAV-2 oversizing grade relative to the LZ was 21.2% (15.8%-24.8%), whereas oversizing relative to the native annulus was 7.1% (3.1%-10.9%). No annular rupture events occurred and, compared with previous data, this approach led to acceptable hemodynamic outcomes.[3] Although the decision to deviate from LZ-based sizing recommendations was not guided by a prespecified protocol, the degree of TAV-1 compression was associated with an increased likelihood of LZ-discordant sizing. In these cases, the operators opted for substantial TAV-2 oversizing

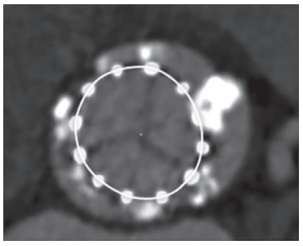
JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025
OCTOBER 27, 2025:2488-2501

CENTRAL ILLUSTRATION Study Overview and Main Findings

Clinical Outcomes of Redo-TAVR According to CT-Based Sizing

150 consecutive patients undergoing redo-TAVR with CT-based TAV-2 sizing at 14 centers

Landing Zone Concordant



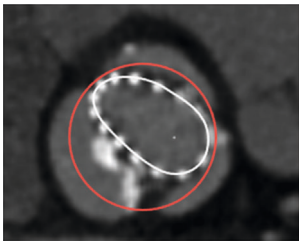
n = 72 (48%)

TAV-2 size matches LZ measurements

Averaged measurements at multiple levels according to TAV-in-TAV combination:
- Landing zone area
- Landing zone perimeter

Operator's choice based on:
- Clinical features
- Native aortic anatomy
- CT-based TAV-1 analysis

Landing Zone Discordant

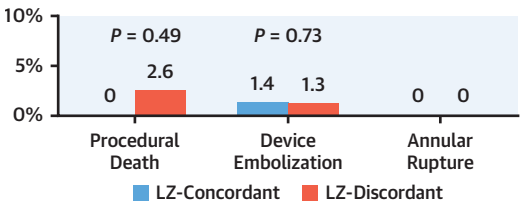


n = 78 (52%)

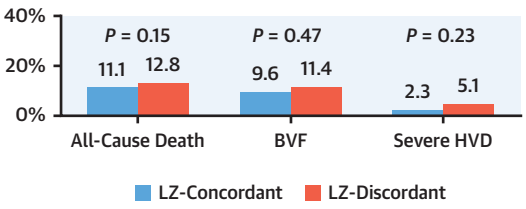
TAV-2 smaller: 7.7%

TAV-2 larger: 92.3%

Procedural Outcomes

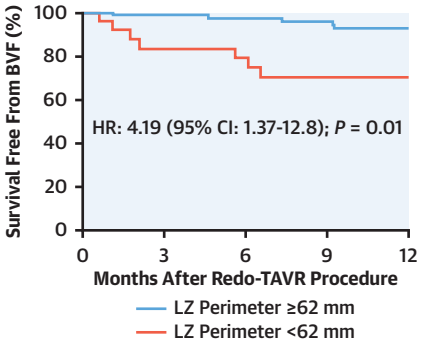


Clinical Outcomes at 1 Year

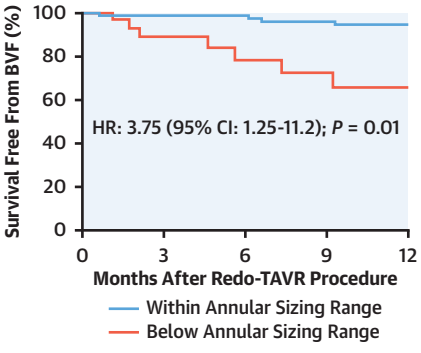


Survival Free From BVF

Patient Stratified by LZ Perimeter



Patients Stratified by TAV-2 Size



- In patients undergoing redo-TAVR with CT planning, in-vivo compression of TAV-1 was frequently observed.
- The selected TAV-2 size matched TAV-1 LZ measurements in 48% of cases.
- A comprehensive CT-based TAV-2 sizing enabling selective oversizing relative to the LZ was associated with favorable outcomes.
- LZ perimeter <62 mm and TAV-2 size smaller than the manufacturer sizing range for the native aortic annulus were independent predictors of BVF at 1 year.

Beneduce A, et al. JACC Cardiovasc Interv. 2025;18(20):2488-2501.

BVF = bioprosthetic valve failure; CT = computed tomography; LZ = landing zone; TAV = transcatheter aortic valve; TAVR = transcatheter aortic valve replacement.

relative to the constrained TAV-1 LZ, which nonetheless remained reasonable when referenced to the aortic annulus. The aortic root anatomy was smaller in LZ-concordant cases, suggesting that a smaller TAV-2 might have been selected to avoid coronary obstruction or annular injury. The distribution of TAV-2 designs between the 2 groups offers some additional insights. Short-frame BEVs were more prevalent in LZ-discordant cases, while tall-frame SEVs were more common in LZ-concordant cases, suggesting that the latter might have been favored in patients at risk for annular injury. However, no objective conclusions could be drawn from the data on this aspect. Uncertainty remains regarding the trade-off between the risk for native anatomy damage from oversizing and the risk for suboptimal hemodynamic performance from undersizing to fit the TAV-1 LZ.

The findings of this study should be considered hypothesis generating, suggesting that in selected cases, the expansion of TAV-1 may still be modifiable to some extent and that cautiously oversizing TAV-2 relative to the LZ to respect native annular dimensions could be a reasonable option. However, identifying cases in which this is feasible remains a challenge. In this study, no annular rupture events were observed, and TAV-2 oversizing did not predict adverse outcomes, underscoring the difficulty of defining an optimal sizing algorithm on the basis of these data. Additionally, the lack of postprocedural CT images did not allow us to define a threshold for excessive oversizing, which might result in TAV-2 underexpansion and leaflet pinwheeling, with potential risk for hypoattenuated leaflet thickening, impaired hemodynamic status, and early TAV-2 degeneration. A previous study focusing on short-in-short and short-in-tall combinations and including postprocedural CT analysis suggested that downsizing of TAV-2 compared with annular measurements could lead to underexpansion and suboptimal hemodynamic status, particularly in case of low implantation position of a short-frame TAV-2.[14] Finally, the role of procedural optimization remains to be explored. In a recent single-center pilot study of 30 patients undergoing redo-TAVR with 80% predilatation and 100% postdilatation, no high gradients or leaflet thrombosis were observed at 30 days, and expansion and circularity of TAV-1 improved compared with baseline, despite some residual underexpansion of both TAV-1 and TAV-2 on postprocedural CT analysis.[15] Future research should focus on developing computational models, on the basis of larger cohorts with postprocedural CT imaging, to predict the potential for further expansion of TAV-1 and balance the risk for native aortic injury against TAV-2 underexpansion. These tools could optimize patient-specific sizing and identify those in whom redo-TAVR is a realistic lifetime management strategy.

STUDY LIMITATIONS. First, the retrospective design inherently introduces selection bias, and the absence of a standardized decision-making algorithm meant that the choice to adhere to or deviate from CT LZ sizing was entirely operator driven. As such, it is difficult to control for confounding variables or infer causality between sizing strategy and outcomes.

Second, although CT analysis was performed following a standardized protocol, local constraints prevented central adjudication in all cases, introducing potential variability in key measurements, which could affect the reproducibility of these findings.

Third, the lack of postprocedural CT imaging prevented the assessment of actual frame expansion, deformation, leaflet function or thrombosis. This is particularly relevant in cases with substantial oversizing, in which assumptions regarding safety and efficacy cannot be fully validated. Additionally, the currently recommended center-to-center tracing method might overestimate the available space for TAV-2 expansion. Considering the potential impact of TAV-2 underexpansion on valve durability, the consequences of oversizing warrant further evaluation, and these patients should undergo regular annual surveillance.

Fourth, outcomes were site reported and not independently adjudicated by a clinical events committee, potentially resulting in underreporting or misclassification of relevant events such as BVF, paravalvular regurgitation, or prosthesis-patient mismatch.

Fifth, although relatively large for a niche patient population, the sample size remains limited. This, coupled with a low event rate, affected the power of multivariable analyses and the ability to detect differences in clinically meaningful outcomes across subgroups. Hence, the study lacked the power to fully address the impact of heterogeneity in TAV-in-TAV combinations, including the mechanical behavior of different frame types (short vs tall), radial force characteristics, and alignment strategies. These technical nuances likely influenced both sizing

decisions and outcomes but were not systematically analyzed.

Finally, the influence of TAV-1 commissural alignment and neoskirt height on TAV-2 selection, coronary obstruction risk, or future reaccess feasibility could represent important confounders that were not comprehensively explored in this analysis. Therefore, the results of this study should be considered hypothesis generating, and larger studies are required to further clarify the sizing issue for redo-TAVR.

CONCLUSIONS

In patients undergoing preprocedural CT planning for redo-TAVR, compression of TAV-1 was frequently observed. Relying exclusively on LZ dimensions would lead to the selection of a TAV-2 size inappropriate for the patient's aortic annulus in a relevant proportion of cases. A computed tomography-based TAV-2 sizing strategy integrating native annular dimensions and enabling oversizing relative to the LZ in selected cases was associated with favorable outcomes, without an increase in procedural complications. An LZ perimeter <62 mm and a TAV-2 size smaller than the recommended sizing range for the native aortic annulus were independent predictors of BVF at 1 year. The results of this study should be considered hypothesis generating, and larger studies are required to establish a patient-specific sizing strategy for redo-TAVR.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Beneduce has received speaker and/or consultant fees from Boston Scientific and Medtronic. Dr Abdel-Wahab's hospital has received speaker honoraria and/or consultant fees on his behalf from Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Khokhar has received speaker fees from Abbott, Boston Scientific and Medtronic. Dr De Backer has received institutional research grants and consulting fees from Boston Scientific. Dr Akodad has received consultancy fees from Abbott Laboratories, Edwards Lifesciences, and Medtronic. Dr Latib is a consultant or an advisory board member for Medtronic, Abbott Laboratories, Boston Scientific, Anteris Medical, Edwards Lifesciences, and Philips. Dr Buzzatti has received speaker honoraria and/or consultant fees from Biosensors and Meril. Prof Maisano has received grant and/or institutional research support from Abbott Laboratories, Medtronic, Edwards Lifesciences, Biotronik, and Boston Scientific; has received consulting fees, personal and institutional honoraria from Abbott Laboratories, Medtronic, and Edwards Lifesciences; and has received royalty income and intellectual property rights from Edwards Lifesciences. Dr Tchétché has received consultancy and proctoring fees from Abbott Laboratories, Edwards Lifesciences, Medtronic, and Boston Scientific. Dr Dumonteil has received consultancy and proctoring fees from Abbott Laboratories, Boston Scientific, Edwards Lifesciences, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Sizing is a relevant issue in patients undergoing CT planning for redo-TAVR. Current expert recommendations suggest sizing of TAV-2 on the basis of CT measurements of the LZ within TAV-1. However, the feasibility of this strategy and its impact on clinical outcomes remain to be assessed.

WHAT IS NEW? Compression of TAV-1 was common in patients undergoing CT planning for redo-TAVR. A CT TAV-2 sizing strategy allowing oversizing relative to the LZ in selected cases was associated with favorable outcomes without an increase of procedural complications. An LZ perimeter <62 mm and a TAV-2 size smaller than the manufacturer sizing range for the native aortic annulus were independent predictors of BVF at 1 year.

WHAT IS NEXT? Future research should focus on developing CT computational models to define patient-specific sizing strategies and identify those in whom redo-TAVR is a realistic lifetime management strategy.

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KEY WORDS balloon-expandable valve, redo-TAVR, self-expanding valve, TAVR, transcatheter aortic valve replacement, valve-in-valve

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

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Redo-TAVR Sizing in the Real World

Computed Tomography First, Judgment Always

Marco Barbanti, MD,[a,b] Giulia Laterra, MD[a,b]

Five years ago, the notion that we would be debating optimal sizing strategies for transcatheter valve-in-valve for failed transcatheter aortic valve replacement (TAVR) would have seemed premature. Yet as TAVR has expanded to younger, lower risk patients with longer horizons, the first waves of structural valve deterioration and valve failure are now arriving in routine practice.[1-4] Redo-TAVR is emerging as the preferred strategy for many of these patients.[5,6] However, redo-TAVR is not simply a repeat of the initial procedure or the treatment of a failed surgical aortic valve prosthesis. It poses unique anatomical and biomechanical challenges that necessitate careful and comprehensive assessment.[7]

Sizing is at the core of this challenge. In contrast to surgical bioprostheses, transcatheter valves rarely achieve nominal geometry. Frame underexpansion and ellipticity are common, driven by leaflet calcification, annular rigidity, and device-specific frame behavior.[8] As a result, the "landing zone" (LZ) for the second valve is typically the interior of the first stent frame, not the native annulus. This scenario limits the generalizability of bench data that assume perfect circular, nominal frames and often recommend aggressive oversizing that, in vivo, risks annular injury or imposes significant underexpansion of the second valve.[9]

The pragmatic response to this important issue has been to rely on computed tomography (CT) to characterize the actual in-frame LZ, derive area and perimeter at the expected inflow level, and map those measurements to manufacturer instructions for use (IFU), with clinical judgment for borderline cases and device- or anatomy-specific nuances. This approach appears functional but still lacks outcomes-based evidence validating how operators use CT to size the second valve and whether deviations from strict LZ-based sizing meaningfully affect safety or long-term performance.

In this issue of *JACC: Cardiovascular Interventions*, Beneduce et al[10] present an investigator-initiated, multicenter, retrospective registry across 14 high-volume centers in Europe and North America that included 150 consecutive redo-TAVR procedures performed for structural valve deterioration. Preprocedural CT was available in all cases. Operators selected the redo platform and size at their discretion, informed by clinical context and computed tomographic analysis. The investigators measured the LZ within the index transcatheter aortic valve (TAV-1) and compared the operator-selected second transcatheter aortic valve (TAV-2) to what would have been selected by strict LZ-to-IFU mapping. Patients were classified as LZ concordant or LZ discordant.[10]

The main findings of this study can be summarized as follows: 1) TAV-1 compression was observed in 97% of cases, confirming that non-nominal frames are common in cases of structural deterioration; 2) 52% of patients received LZ-discordant TAV-2 sizes, most often larger valves than what the strict LZ measurement would suggest; 3) in discordant cases, the median oversizing relative to the LZ was 21%, whereas annular-relative oversizing was more modest at 7%; 4) regarding safety and efficacy, notably, no cases of annular rupture were reported despite frequent oversizing relative to the LZ, and the Valve Academic Research Consortium 3 device success rate at 30 days was 73%; and 5) estimated bioprosthetic valve failure (BVF) at 1 year was 8.7%

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

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.09.012

(95% CI: 3.1%-14.2%), with no significant difference between the LZ-concordant and LZ-discordant groups. Independent predictors of recurrent BVF included an LZ perimeter <62 mm (HR: 4.19; 95% CI: 1.37-12.8) and selecting a TAV-2 smaller than the IFU annular sizing range (HR: 3.75; 95% CI: 1.25-11.2).

Three practice-level implications deserve emphasis. First, the in-frame anatomy (not the label size of the index device) is the relevant substrate for redo sizing. Computed tomographic interrogation of the true LZ is crucial. The near universal observation of TAV-1 compression among these cases validates this premise. Second, selective oversizing relative to the LZ appears safe in experienced hands. Operators frequently chose a larger TAV-2 than strict LZ-to-IFU mapping would suggest, achieving a median 20% LZ oversizing without annular rupture. Critically, annular-relative oversizing remained modest (7%), suggesting a balanced approach that secured anchoring and expansion while respecting annular constraints. Third, undersizing seems harmful: choosing a second valve below the IFU annular range increased the hazard of BVF. This likely reflects compromised expansion, suboptimal leaflet coaptation under higher gradient, and potential instability.

These data reinforce a simple rule: avoid major undersizing when the anatomy requires a definitive frame. The signal associated with small LZ perimeter (<62 mm) is clinically useful. It likely identifies valves implanted in constrained anatomy or small index frames where expansion is challenged. In such cases, one should anticipate higher gradients and prioritize strategies to optimize expansion (platform selection, predilatation when appropriate, cautious postdilation, and careful consideration of commissural alignment and future coronary access). Finally, the lack of early difference in BVF between LZ-concordant and LZ-discordant strategies should be interpreted with caution. The message is not that strict LZ-based IFU sizing is futile but that rigid adherence without clinical judgment is unnecessary and potentially counterproductive.

This study had several limitations. First, operators at times deviated from LZ guidance on the basis of clinical judgment, which is difficult to fully capture, and both index and redo devices varied across cases. This mirrors real-world practice but limits platform-specific inference. Second, the study was neither designed nor powered to adjudicate trade-offs among self-expanding, balloon-expandable, and mechanically expandable valves in specific pairings. Finally, the absence of an imaging and echocardiography core laboratory may have influenced sizing categorization and endpoint adjudication.

In conclusion, Beneduce et al[10] provide timely, practical evidence in the emerging field of redo-TAVR procedures. They show that the index TAV frame is rarely at nominal dimensions and that CT-based in-frame sizing is the appropriate starting point. Selective oversizing relative to the LZ, tempered by respect for the native annulus, appears both common and safe. Undersizing predisposes to early failure, and a small LZ perimeter identifies a higher risk substrate. These are pragmatic lessons we can apply now. As TAVR patients grow younger and live longer, redo procedures will move from the margins to the mainstream. Whether redo-TAVR fulfills its promise will hinge on precision computed tomographic planning, standardized yet flexible sizing, and device-specific strategies. This study does not settle the debate, but it raises its level, and in a rapidly evolving field, that is progress.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Barbanti is a consultant for Edwards Lifesciences, Boston Scientific, Abbott Vascular, and Medtronic. Dr Laterra has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS redo-TAVR, repeat TAVR, sizing, structural valve deterioration, transcatheter aortic valve replacement

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

ORIGINAL RESEARCH

STRUCTURAL

Long-Term Outcomes in Moderate and Severe Aortic Stenosis According to Extent of Cardiac Damage

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ABSTRACT

BACKGROUND Cardiac damage (CD) significantly affects the prognosis of patients with aortic stenosis (AS).

OBJECTIVES The aim of this study was to investigate the impact of CD on long-term survival in patients with moderate and severe AS.

METHODS In a pooled analysis of 2 single-center registries, patients with moderate or severe AS were included according to the presence of early (stages 0 and 1) or advanced (stages 2-4) CD.

RESULTS Among 1,096 patients with AS included between 2009 and 2023, 626 patients (mean age 78.9 ± 8.0 years, 33.1% women) had moderate (n = 343) or severe AS (n = 283). Advanced CD was present in 497 patients (79.4%), and the median follow-up duration was 7.4 years (Q1-Q3: 4.2-10.6 years). There was a gradual increase in the risk for 10-year mortality from moderate to severe AS and from early CD (moderate AS: reference; severe AS: adjusted HR [aHR]: 1.42; 95% CI: 0.75-2.72) to advanced CD (moderate AS: aHR: 1.91; 95% CI: 1.22-2.97; severe AS: aHR: 2.77; 95% CI: 1.73-4.45). At a median 347 days, 344 patients (54.9%) had undergone aortic valve replacement (AVR). In patients with advanced CD, AVR was associated with lower mortality compared with conservative management, irrespective of AS severity (moderate AS: aHR: 0.43; 95% CI: 0.28-0.66; severe AS: aHR: 0.27; 95% CI: 0.18-0.39). In patients with early CD, AVR was associated with lower mortality in patients with severe AS (aHR: 0.29; 95% CI: 0.10-0.86), but not in those with moderate AS (aHR: 0.61; 95% CI: 0.25-1.44).

CONCLUSIONS Ten-year mortality in patients with moderate and severe AS is importantly determined by CD extent. AVR was associated with lower mortality in patients with moderate AS and advanced CD. (JACC Cardiovasc Interv. 2025;18:2505-2516) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Manuscript received May 8, 2025; revised manuscript received August 15, 2025, accepted August 18, 2025.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2025.08.018

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025
OCTOBER 27, 2025:2505–2516

ABBREVIATIONS AND ACRONYMS

aHR = adjusted HR

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CD = cardiac damage

CT = computed tomography

CV = cardiovascular

LV = left ventricular

LVEF = left ventricular ejection fraction

RV = right ventricular

SVi = stroke volume index

Aortic stenosis (AS) affects 5.5% of individuals older than 75 years and is the leading cause of death of valvular heart disease in high-income countries.[1,2] Aortic valve replacement (AVR) remains the cornerstone of treatment but is reserved for patients with severe AS who are symptomatic or have additional risk factors.[3,4] European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American Heart Association/American College of Cardiology guidelines recommend no intervention for moderate AS, except when valve replacement is performed in conjunction with cardiac surgery for other reasons.[3,4]

However, patients with AS experience an increased mortality risk at all stages of disease.[5] Recent evidence challenges current recommendations for intervention, revealing a poorer prognosis in patients with moderate AS and prompting reconsideration of the optimal timing of AVR.[6,7] Several studies indicated that factors beyond the valve contribute to the adverse prognosis in patients with AS, shifting the focus from valvular hemodynamic status alone to include a more comprehensive assessment of cardiac function.[8-10] The cardiac damage (CD) classification proposed by Généreux et al[10] provides a framework for staging the severity of cardiac dysfunction on the basis of the extent of damage, ranging from no CD to left ventricular (LV) dysfunction, left atrial or mitral valve dysfunction, pulmonary vasculature or tricuspid valve damage, and ultimately right ventricular (RV) failure. The classification based on echocardiography effectively differentiates clinical outcomes in patients with severe AS undergoing AVR.[11-13]

Integration of the staging classification in the evaluation of AS graded according to hemodynamic severity may refine the optimal timing of intervention. To date, there is limited evidence on the importance of staging in addition to grading of AS on long-term clinical outcomes. Against this background, the aim of the present study was to explore the impact of CD on long-term clinical outcomes in patients with moderate and severe AS undergoing conservative management or AVR.

METHODS

POPULATION. The VARIATE registry is a prospective single-center registry including patients with valvular heart disease at Bern University Hospital in Switzerland. For the purpose of the present analysis, we considered patients with echocardiographic diagnoses of AS. In addition, we retrospectively identified patients with moderate or greater AS from the CARDIOBASE Bern PCI Registry, a prospective registry collecting data of consecutive patients undergoing percutaneous coronary intervention at Bern University Hospital (NCT02241291). Patients with AVR prior to inclusion into the registry and those with missing echocardiographic assessment were excluded from participation. Both registries were approved by the cantonal ethics committee, and all participants provided written informed consent for participation.

DATA COLLECTION. All baseline clinical and follow-up data were prospectively recorded in web-based databases maintained by the Clinical Trials Unit at the University of Bern. Baseline echocardiographic data were independently re-evaluated by specialized imaging experts. Aortic valve disease was assessed using transthoracic echocardiography conducted by experienced echocardiographers. The severity of AS was evaluated according to aortic valve area (AVA) and transvalvular mean gradient, following current guidelines.[3,4] Mean and peak transvalvular pressure gradients were calculated using the Bernoulli equation. AVA was calculated according to the continuity equation using velocity-time integrals of the LV outflow tract and aortic valve flow recordings. Mild AS was defined as AVA ≤2.0 cm^2 or mean transvalvular gradient >10 mm Hg. Moderate AS was defined as AVA ≤1.5 cm^2 or mean gradient ≥20 mm Hg. High-gradient severe AS was characterized by AVA ≤1.0 cm^2 or mean gradient ≥40 mm Hg. Classical low-flow, low-gradient AS was defined as AVA ≤1.0 cm^2, mean gradient <40 mmHg, stroke volume index (SVi) ≤35 mL/m^2, and LVEF <50%. Paradoxical low-flow, low-gradient AS was defined as AVA ≤1.0 cm^2, mean gradient <40 mm Hg, SVi <35 mL/m^2, and LVEF >50%. Normal-flow, low-gradient AS was defined as AVA ≤1.0 cm^2, mean gradient <40 mm Hg, SVi >35 mL/m^2, and LVEF >50%. Contrast-enhanced computed tomography (CT) was used to support the diagnosis of severe AS in case of transvalvular mean gradient <40 mm Hg, on the basis of clinical judgment. Extra-aortic valve CD was assessed on echocardiography according to the proposed classification.[10] Patients were classified into the following 5 stages: stage 0, no extra-aortic valve CD; stage 1, LV damage (systolic LV dysfunction, LV hypertrophy, LV diastolic dysfunction grade >II); stage 2, left atrial or mitral valve damage (left atrial dilatation, moderate or severe mitral regurgitation, or

presence of atrial fibrillation); stage 3, pulmonary vasculature or tricuspid valve damage (pulmonary hypertension, moderate or severe tricuspid regurgitation); and stage 4, RV damage (systolic RV dysfunction). RV dysfunction was assessed on the basis of quantitative criteria, following the guideline recommendations.[14] Categorical variables were created for each of the aforementioned criteria (Supplemental Table S1). Patients were hierarchically classified into the most advanced CD stage if at least 1 of the criteria was met within that stage and were then categorized according to extent of CD: those with CD stages 0 and 1 were classified as early CD, while those with CD stages 2 to 4 constituted the advanced CD group. Patients who could not be classified in any of the stages were excluded from the present analysis. Follow-up was performed at 1, 3, 5 and 10 years. Clinical data were collected through standardized interviews, documentation from referring physicians, and hospital discharge summaries. Transthoracic echocardiography or transesophageal echocardiography was performed as clinically indicated. Follow-up evaluation took place at every echocardiographic examination performed at the University Hospital of Bern but was not prescheduled for certain time intervals.

STATISTICAL ANALYSIS. Normality was assessed using the Shapiro-Wilk test, skewness, and kurtosis indexes. Categorical variables are reported as counts and percentages and were compared using the chi-square test for independent variables. In the case of normal distribution, continuous variables are expressed as mean ± SD and were compared using Student's *t*-test; non-normally distributed data are presented as median (Q1-Q3) and were compared using the Mann-Whitney *U* test, the Wilcoxon signed rank test, or the Kruskal-Wallis test, as appropriate. All-cause and cardiovascular (CV) mortality are expressed as counts and incidence rates and were computed using the Kaplan-Meier method with group comparisons conducted using the log-rank test. Cox proportional hazards regression analysis was performed to evaluate the associations of AS severity, CD extent, and AVR with survival outcomes, and results are reported as HRs with 95% CIs, adjusted for age, sex, transvalvular mean gradient, and SVi. To account for baseline differences between the 2 registries, we also included the registry of origin as a fixed effect in the Cox regression models. In addition, a 2 × 2 × 2 factorial model was constructed to assess the individual effects of the aforementioned 3 main factors and their interactions. HRs were estimated for each main effect and interaction term. A 1:1 propensity score–matched analysis was performed using the nearest neighbor method to account for the probability of undergoing AVR. The propensity score was estimated using age, sex, diabetes, prior myocardial infarction, advanced CD, and transvalvular mean gradient. *P* values <0.05 were considered to indicate statistical significance. Analyses were performed using RStudio version 4.1.2 (R Foundation for Statistical Computing).

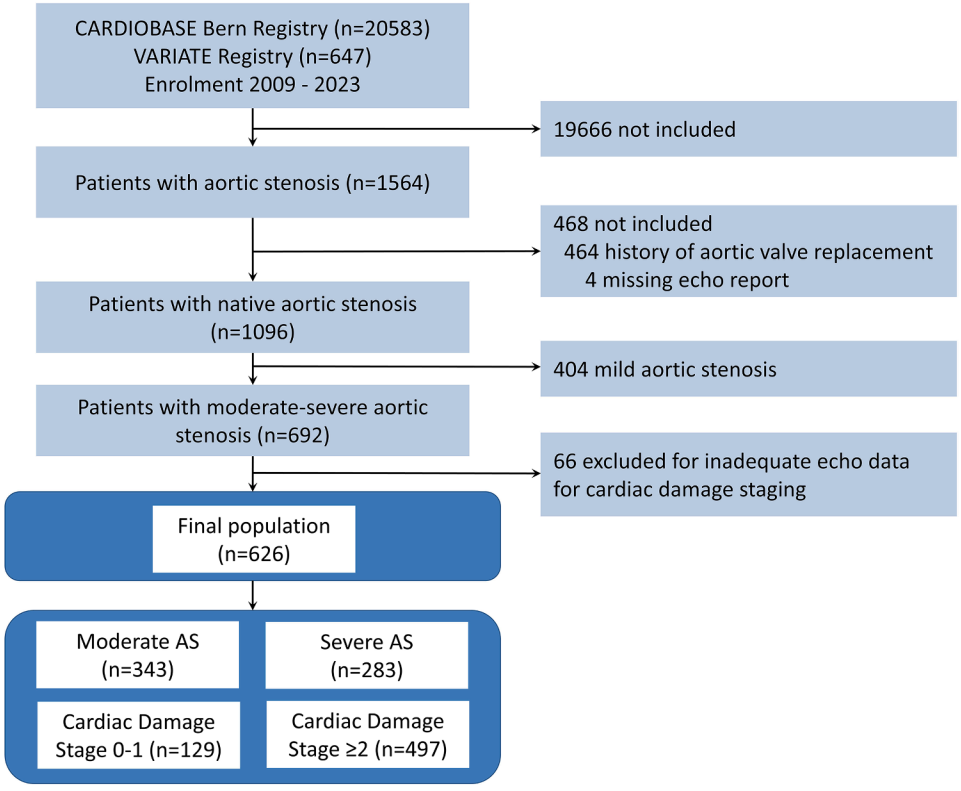
RESULTS

Among 21,230 patients enrolled in the 2 registries between February 2009 and February 2023, 1,096 patients with AS were identified (947 from the CARDIOBASE Bern PCI Registry and 149 from the VARIATE registry), of whom 404 had mild AS. After the exclusion of 66 patients with inadequate echocardiographic detail for CD staging, 343 of 626 (54.8%) with moderate and 283 of 626 (46.2%) with severe AS remained for the purpose of the present analysis. Among patients with more than mild AS, advanced CD was present in 497 of 626 patients (79.4%), including 267 of 343 (77.8%) of those with moderate AS and 230 of 283 (81.2%) of those with severe AS (**Figure 1**).

CLINICAL CHARACTERISTICS. The clinical characteristics of the study participants are summarized in **Table 1**. The median age of the population was 78.9 ± 8.0 years, and 207 of 626 of the patients (33.1%) were women. Patients with moderate AS were younger than those with severe AS (77.4 ± 8.3 years vs 80.7 ± 7.2 years; $P < 0.001$), and patients with early CD were younger than those with advanced CD (76.2 ± 8.9 years vs 79.6 ± 7.6 years; $P < 0.001$). Otherwise, baseline characteristics were comparable between patients with moderate vs severe AS and those with early vs advanced CD, respectively (**Table 1**, Supplemental Table S2).

IMAGING CHARACTERISTICS. In the overall population, the transvalvular mean gradient and AVA were 24.9 ± 13.4 mm Hg and 0.99 ± 0.29 cm^2, respectively. Among patients with severe AS, 83 of 283 (29.3%) had high-gradient AS; 117 of 283 (41.3%) had classical low-flow, low-gradient AS; 77 of 283 (27.2%) had paradoxical low-flow, low-gradient AS; and 6 of 283 (2.1%) had normal-flow, low-gradient AS. Patients with severe AS (mean gradient 31.7 ± 14.5 mm Hg, AVA 0.77 ± 0.20 cm^2) had a higher prevalence of LV hypertrophy (202 of 274 [73.7%] vs 222 of 339 [65.5%]; $P = 0.035$), LV diastolic dysfunction grade > 2 (61 of 151 [40.4%] vs 52 of 186 [30.0%]; $P = 0.020$) and pulmonary hypertension (44 of 277 [15.9%] vs 23 of

FIGURE 1 Study Flow Chart



AS = aortic stenosis.

TABLE 1 Clinical Characteristics

	Overall (N = 626)	Moderate AS (n = 343)	Severe AS (n = 283)	*P* Value, AS Grade	Early CD (n = 129)	Advanced CD (n = 497)	*P* Value, CD Extent
Age, y	78.9 ± 8.0	77.4 ± 8.3	80.7 ± 7.2	<0.001	76.2 ± 8.9	79.6 ± 7.6	<0.001
Female	207 (33.1)	102 (29.7)	105 (37.1)	0.085	35 (27.1)	172 (34.6)	0.085
Smoking	71 (11.3)	44 (12.8)	27 (9.5)	0.69	12 (9.3)	59 (11.9)	0.69
Atrial fibrillation	140 (22.4)	70 (20.4)	70 (24.7)	0.056	17 (13.2)	123 (24.7)	0.005
eGFR, mL/min/1.73 m^2	58.9 ± 27.8	64.1 ± 29.2	52.7 ± 24.8	<0.001	67.3 ± 29.9	56.8 ± 26.9	<0.001
eGFR < 60 mL/min/1.73 m^2	318 (50.8)	149 (43.4)	169 (59.7)	<0.001	53 (41.1)	265 (53.3)	0.014
Family history of CAD	107 (17.1)	64 (18.7)	43 (15.2)	0.84	22 (17.1)	85 (17.1)	0.84
Hypertension	451 (72.0)	253 (73.8)	198 (70.0)	0.748	93 (72.1)	358 (72.0)	0.75
Diabetes	178 (28.4)	98 (28.6)	80 (28.3)	0.42	32 (24.8)	146 (29.4)	0.42
Dyslipidemia	368 (58.8)	212 (61.8)	156 (55.1)	0.26	84 (65.1)	284 (57.1)	0.26
Previous MI	81 (12.9)	54 (15.7)	27 (9.5)	0.80	18 (14.0)	63 (12.7)	0.80
Previous CVE	89 (14.2)	50 (14.6)	39 (13.8)	0.141	12 (9.3)	77 (15.5)	0.14
PAD	88 (14.1)	47 (13.7)	41 (14.5)	0.77	17 (13.2)	71 (14.3)	0.78
COPD	54 (8.6)	31 (9.0)	23 (8.1)	0.56	6 (4.7)	48 (9.7)	0.018
Previous CABG	85 (13.6)	50 (14.6)	35 (12.4)	0.20	12 (9.3)	73 (14.7)	0.18

Values are mean ± SD or n (%).

AS = aortic stenosis; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CD = cardiac damage; COPD = chronic obstructive pulmonary disease; CVE = cerebrovascular event; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PAD = peripheral atherosclerotic disease.

TABLE 2 Echocardiographic Characteristics

	Overall (N = 626)	Moderate AS (n = 343)	Severe AS (n = 283)	*P* Value
Mean aortic gradient, mm Hg	24.9 ± 13.4	19.2 ± 8.4	31.4 ± 15.0	<0.001
Aortic valve area, cm^2	0.99 ± 0.29	1.18 ± 0.21	0.76 ± 0.20	<0.001
Stages of cardiac damage				0.36
Stage 0 (no cardiac damage)	45 (7.2)	27 (7.9)	18 (6.4)	
Stage 1 (LV damage)	84 (13.5)	49 (14.3)	35 (12.4)	
Stage 2 (LA/mitral valve damage)	315 (50.2)	177 (51.6)	138 (48.8)	
Stage 3 (pulmonary vasculature/tricuspid valve damage)	82 (13.1)	37 (10.8)	45 (15.9)	
Stage 4 (RV damage)	100 (16.0)	53 (15.5)	47 (16.6)	
Individual components of cardiac damage				
LV hypertrophy	424/613 (69.2)	222/339 (65.5)	202/274 (73.7)	0.035
LV diastolic dysfunction grade ≥2	113/337 (33.5)	52/186 (30.0)	61/151 (40.4)	0.020
LV systolic dysfunction	248/626 (39.6)	130/343 (37.9)	118/283 (41.7)	0.37
LA dilatation	461/624 (73.9)	251/341 (73.6)	210/283 (74.2)	0.93
Moderate/severe mitral regurgitation	111/624 (17.8)	55/341 (16.1)	56/283 (19.8)	0.25
Pulmonary hypertension	67/612 (10.9)	23/335 (6.9)	44/277 (15.9)	<0.001
Moderate/severe tricuspid regurgitation	77/623 (12.4)	39/340 (11.5)	38/283 (13.4)	0.46
RV systolic dysfunction	100/626 (16.0)	53/343 (15.4)	47/283 (16.6)	0.74
Moderate/severe aortic regurgitation	36 (6.0)	23 (6.9)	13 (4.7)	0.16

Values are mean ± SD, n (%), or n/N (%).
AS = aortic stenosis; LA = left atrial; LV = left ventricular; RV = right ventricular.

335 [6.9%]; $P < 0.001$), compared with those with moderate AS (mean gradient 19.2 ± 8.4 mm Hg, AVA 1.19 ± 0.21 cm^2). CT was performed in 246 of 626 patients (39.3%) overall, with a significantly lower median calcium volume ($P < 0.001$) in those with moderate AS (95 mm^3; Q1-Q3: 60-130 mm^3) compared with those with severe AS (378 mm^3; Q1-Q3: 202-504 mm^3). Detailed echocardiographic assessment is presented in Table 2.

LONG-TERM OUTCOMES. During a median follow-up time of 7.4 years (Q1-Q3: 4.2-10.6 years), 343 of 626 patients died (10-year cumulative incidence 77.7%; 95% CI: 72.7%-83.3%). At 10 years, all-cause mortality was higher in patients with severe AS compared with those with moderate AS (adjusted HR [aHR]: 1.65; 95% CI: 1.34-2.29), and in patients with advanced CD compared with those with early CD (aHR: 1.88; 95% CI: 1.35-2.62) (Figure 2). Of the patients who died during follow-up, 156 of 343 (45.5%) experienced CV death. At 10-year follow-up, patients with severe AS had a higher incidence of CV death compared with those with moderate AS (aHR: 1.46; 95% CI: 1.03-2.07). Additionally, the presence of advanced CD vs early CD was a significant predictor of CV mortality (aHR: 2.05; 95% CI: 1.26-3.33). The 10-year risk for death and CV mortality gradually increased according to the severity of AS and the extent of CD (Table 3). Severe AS with early CD was associated with a similar but numerically higher risk for death compared with moderate AS with early CD (aHR: 1.42; 95% CI: 0.75-2.72). Conversely, patients with moderate AS and advanced CD (aHR: 1.91; 95% CI: 1.22-2.97) and those with severe AS and advanced CD (aHR: 2.77; 95% CI: 1.73-4.45) experienced a significantly increased risk for mortality compared with patients with moderate AS and early CD (Figure 3).

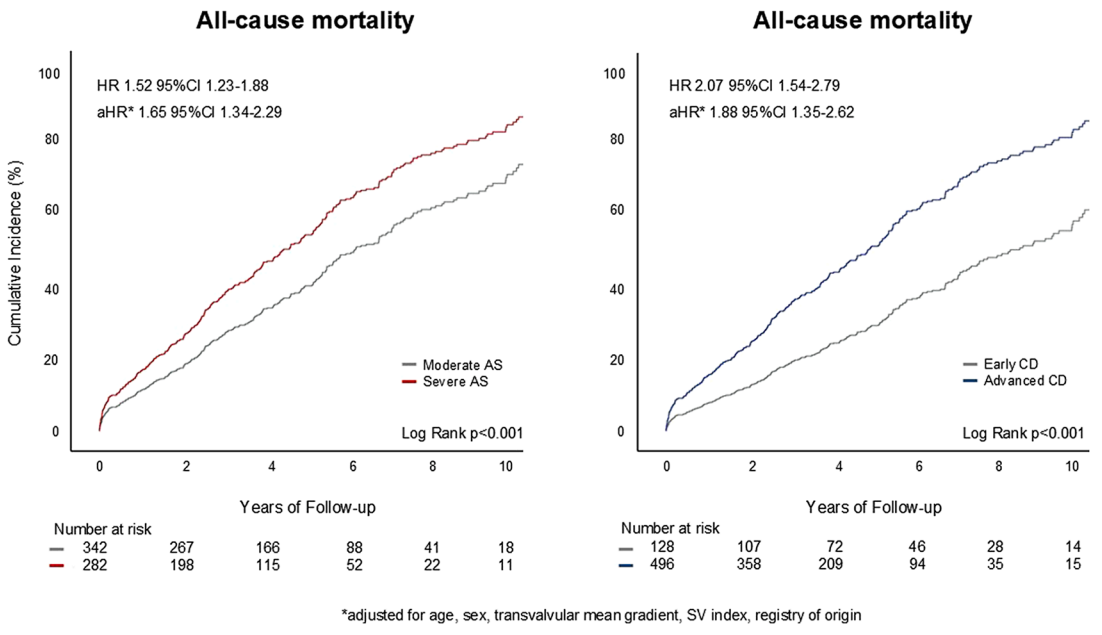
In a Cox regression model including main effects and interactions, advanced CD was the only factor significantly associated with increased 10-year mortality (HR: 2.10; 95% CI: 1.17-3.75). No significant interactions were found between the grade of AS severity, advanced CD, and AVR (Supplemental Table S3).

The findings were consistent across both registries, showing that the presence of advanced vs early CD was a stronger predictor of long-term mortality (aHR: 1.92 [95% CI: 1.43-2.59] for the CARDIOBASE Bern PCI Registry; aHR: 39.4 [95% CI: 1.29-1,375.20] for VARIATE) than severe vs moderate AS (aHR: 1.56 [95% CI: 1.26-1.95] for the CARDIOBASE Bern PCI Registry; aHR: 1.27 [95% CI: 0.55-2.93] for VARIATE).

A sensitivity analysis was conducted to assess the impact of advanced CD, defined as stages 3 and 4, compared with early CD (stages 0-2), and the results remained consistent (Supplemental Figure S1).

Clinical and echocardiographic characteristics as well as outcomes of patients with mild AS compared with moderate and severe AS are shown in

FIGURE 2 10-Year All-Cause Death According to AS Severity and CD Extent



aHR = adjusted HR; AS = aortic stenosis; CD = cardiac damage; SV = stroke volume.

Supplemental Table S4, Supplemental Table S5, and Supplemental Figure S2, respectively.

AVR. A total of 344 of 626 patients (54.9%) underwent AVR at a median time of 347 days; 246 of 344 patients (71.5%) underwent transcatheter AVR and 98 of 344 (28.5%) underwent surgical AVR.

Baseline and echocardiographic characteristics of patients treated conservatively compared with those undergoing AVR are shown in **Table 4**. The rate of AVR was 35.6% (122 of 343) among patients with moderate AS (36 of 76 [47.4%] in those with early CD and 86 of 267 [32.2%] in those with advanced CD) and 78.4% (222 of 283) among patients with severe AS (44 of 53 [83.0%] in those with early CD and 178 of 230 [77.4%] in those with advanced CD).

Patients with moderate AS underwent AVR after a median of 749 days. At baseline, patients with moderate AS undergoing AVR had a higher mean transvalvular gradient (23.7 ± 8.4 mm Hg vs 16.9 ± 7.5 mm Hg; $P = 0.001$) and a lower AVA (1.15 ± 0.22 cm^2 vs 1.20 ± 0.20 cm^2; $P = 0.043$) compared with those with moderate AS treated conservatively. Preoperative echocardiographic data were available for 116 of 122 patients (95.1%). Only a minority (22 of 116 [18.9%]) progressed from moderate to severe AS prior to AVR. The mean preoperative transvalvular gradient was 29.4 ± 10.8 mm Hg, and the median AVA was 1.03 cm^2 (Q1-Q3: 0.83-1.23 cm^2). Compared with baseline, this represented a mean increase in gradient of +5.9 mm Hg (95% CI: +4.2 to +7.6 mm Hg; $P < 0.001$) and a decrease in AVA of −0.21 cm^2 (95% CI: −0.13 to −0.27 cm^2; $P = 0.044$). Among patients with moderate AS undergoing AVR, 37 of 122 (30.3%) underwent surgical AVR, including 10 of

TABLE 3 Cumulative Incidence of 10-Year Mortality According to AS Severity and Extent of Cardiac Damage

	Moderate AS (n = 343)		Severe AS (n = 283)	
	All-Cause Death	CV Death	All-Cause Death	CV Death
Early cardiac damage (n = 129)	24 (54.7%) (38-72%)	12 (31.8%) (15-48%)	23 (69.7%) (51-88%)	10 (30.3%) (13-47%)
Advanced cardiac damage (n = 497)	138 (80.2%) (71-89%)	60 (40.9%) (27-54%)	150 (85.2%) (78-92%)	72 (51.5%) (36-63%)

Event rates were estimated using Kaplan-Meier analysis and are reported as count (cumulative incidence) (95% CI).

AS = aortic stenosis; CV = cardiovascular.

37 (27.0%) who underwent concomitant coronary artery bypass graft surgery and 2 of 37 (5.4%) who underwent combined 2-valve surgery.

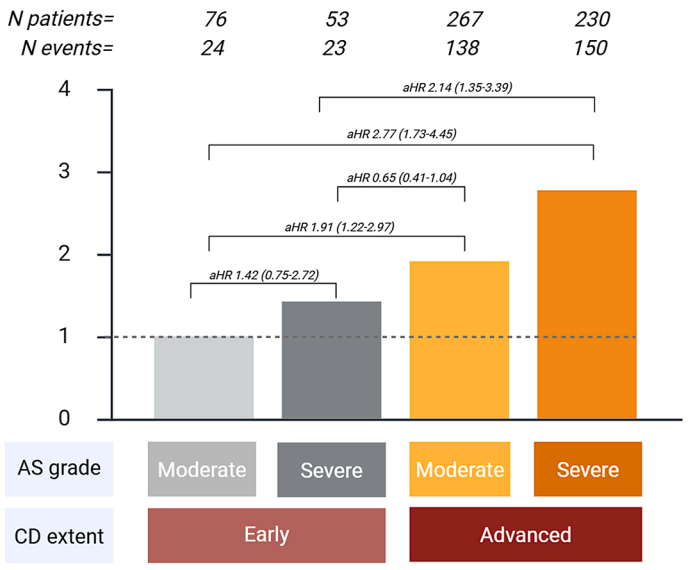
Overall, patients undergoing AVR exhibited lower mortality rates at follow-up compared with those managed conservatively (aHR: 0.47; 95% CI: 0.36-0.63). In patients with early CD, AVR was associated with a significantly lower incidence of death in patients with severe AS (aHR: 0.29; 95% CI: 0.10-0.86), but not in patients with moderate AS (aHR: 0.61; 95% CI: 0.25-1.44). In patients with advanced CD, AVR was associated with a significantly lower rate of mortality compared with conservative management irrespective of AS grade (moderate AS: aHR: 0.43; 95% CI: 0.28-0.66; severe AS: aHR: 0.27; 95% CI: 0.18-0.39) (**Figure 4**). In a matched cohort of 112 pairs, AVR remained significantly associated with reduced mortality (HR: 0.52; 95% CI: 0.35-0.76) (Supplemental Table S6).

DISCUSSION

This registry-based analysis of patients with AS, incorporating detailed echocardiographic data and long-term follow-up, reveals the following key findings: 1) advanced CD is common in patients with moderate and severe AS; 2) the presence of advanced CD significantly influences the long-term prognosis of patients with moderate and severe AS, reinforcing the concept that staging of AS is as critical as grading of its severity; and 3) AVR is associated with lower mortality in patients with moderate AS with advanced CD and in patients with severe AS irrespective of CD (**Central Illustration**).

Current guidelines define 3 grades of AS severity, each categorized by specific echocardiographic thresholds.[3,4] However, it has become evident that the pathologic consequences of AS are not limited to progressive narrowing of the aortic valve orifice but extend to LV remodeling and upstream sequelae, including left atrial and right heart dysfunction, initiating a deleterious cascade that contributes to impaired prognosis.[15] In this context, the CD staging system has proved effective in providing prognostic insights for patients with severe AS, as well as those with moderate and even mild AS.[10,16] In the present study, advanced CD was frequently observed not only in patients with severe AS, but also in those with moderate AS. Several reasons may account for this observation. In some individuals, CD appears to be part of the pathologic cascade triggered by AS,

FIGURE 3 10-Year Mortality Risk Using Moderate AS and Early CD Patients as Reference



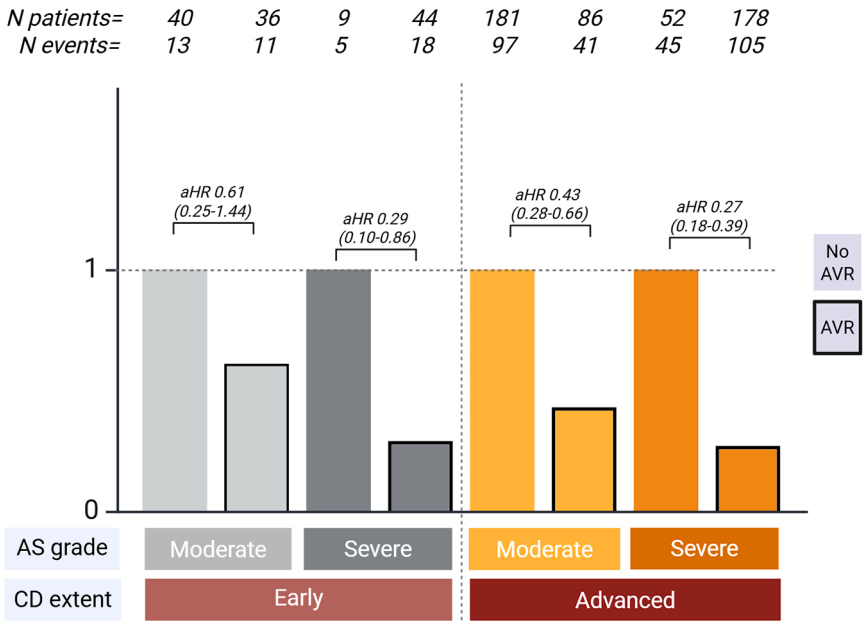
Abbreviations as in **Figure 2**.

TABLE 4 Clinical and Echocardiographic Characteristics of Patients Treated Conservatively Compared With Those Undergoing AVR

	Conservative (n = 282)	AVR (n = 344)	*P* Value
Age	78.9 ± 7.9	78.9 ± 8.2	0.90
Female	86 (34.4)	121 (39.2)	0.25
Smoking	31 (11.0)	30 (11.6)	0.91
Hypertension	202 (71.6)	249 (72.4)	0.94
Diabetes	93 (33.0)	85 (24.7)	0.045
Dyslipidemia	164 (58.2)	204 (59.3)	0.92
Previous MI	44 (15.6)	37 (10.8)	0.15
Previous CVE	42 (14.9)	47 (13.7)	0.78
Previous CABG	42 (14.9)	43 (12.5)	0.57
Mean aortic gradient, mm Hg	18.5 ± 9.5	30.2 ± 13.9	<0.001
Aortic valve area, cm^2	1.10 ± 0.26	0.89 ± 0.28	0.059
Early CD	49 (17.4)	80 (23.3)	0.074
Advanced CD	233 (82.6)	264 (76.7)	0.074
Stages of cardiac damage			0.004
Stage 0	20 (7.1)	25 (7.3)	
Stage 1	29 (10.3)	55 (16.0)	
Stage 2	140 (49.6)	175 (50.9)	
Stage 3	32 (11.3)	50 (14.5)	
Stage 4	61 (21.6)	39 (11.3)	

Values are mean ± SD or n (%).
AVR = aortic valve replacement; other abbreviations as in **Table 1**.

FIGURE 4 Impact of AVR Compared With Conservative Management at Follow-Up



AVR = aortic valve replacement; other abbreviations as in Figure 2.

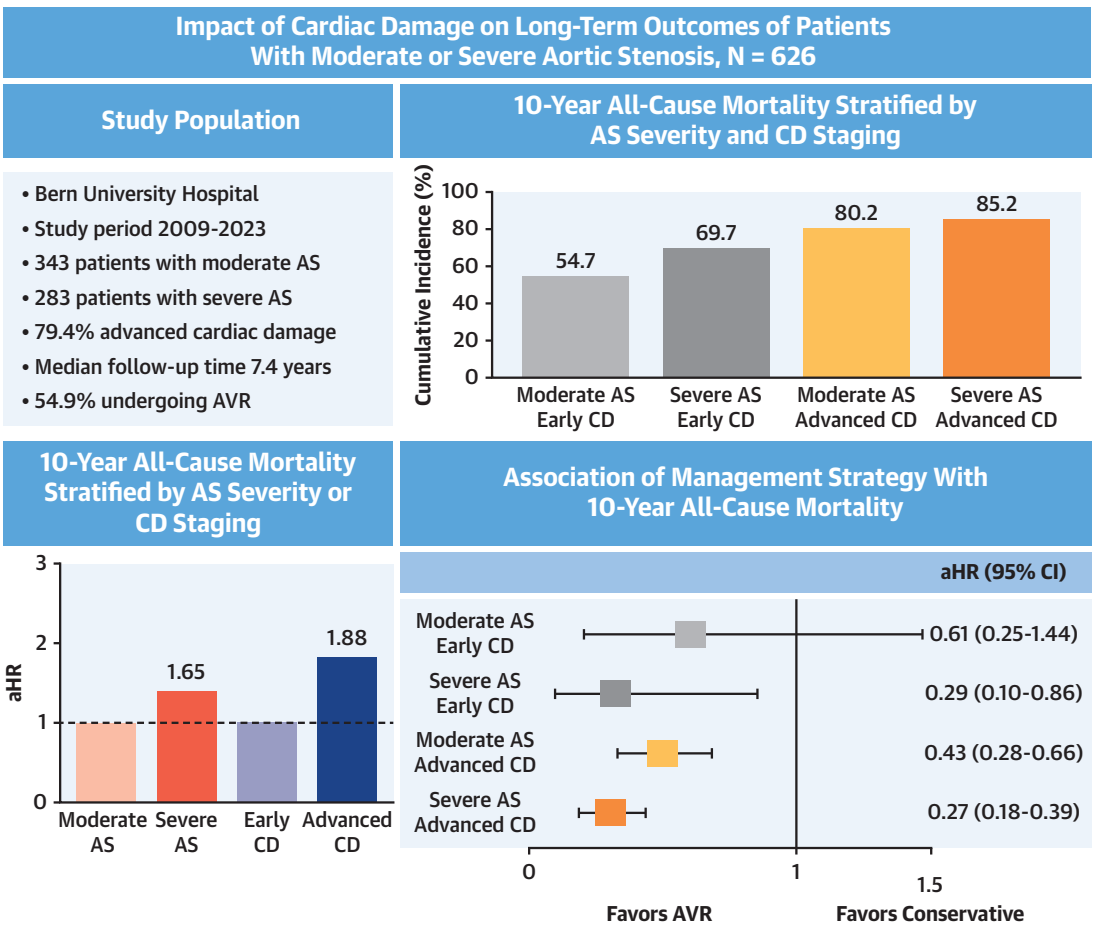
representing a consequence of the disease process. In elderly patients, exercise intolerance may be concealed by a predominantly sedentary lifestyle or misattributed to aging, potentially contributing to delayed clinical presentation. In others, however, CD is unrelated to AS and is a comorbidity rather than a complication. CD has even been found in patients with mild AS, supporting the role of coexisting conditions in its development. Irrespective of the etiology, patients with CD may be more vulnerable to the excessive LV afterload caused by AS, putting them at an increased risk for CV events across the spectrum of AS grades.

At 10-year follow-up, advanced CD was strongly associated with mortality in both moderate and severe AS, conferring a nearly 2-fold increased risk for death. Indeed, CD damage staging may be a more powerful prognostic discriminator than AS grading in patients with relevant AS. This notion is supported by the observation that patients with moderate or severe AS had comparable 10-year survival if they had early CD. Conversely, the combination of advanced CD and moderate AS carried a higher mortality risk, potentially representing an advanced stage of disease progression. This finding has significant implications. AS should be viewed as a continuous process, in which prognosis is determined by the interplay between valve disease and secondary cardiac injury rather than valve hemodynamic status in isolation. Moreover, our observation raises the question of whether the traditional grading system of AS could be improved by the integration of CD staging.

The gradual increase in mortality risk as a function of grading and staging of AS also calls into question the optimal timing of intervention.[17-19] Our findings showed a benefit of AVR not only in patients with severe AS irrespective of CD but also in those with moderate AS and advanced CD. Findings from the TAVR-UNLAOD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure) trial suggest that early intervention may not beneficial for all patients with moderate AS and that LVEF may not be a reliable discriminator for prognosis in those undergoing transcatheter AVR.[20]

Previous retrospective studies have investigated the potential benefits of AVR in patients with moderate AS. In a study by Jean et al,[17] 262 patients with moderate AS were matched with patients with no AS. Over a median follow-up period of 2.9 years, AVR was associated with improved survival in patients with moderate AS. Another study evaluated 508 patients with moderate AS and preserved LVEF. Each patient's survival was compared with age- and sex-matched population-based expectations. During the 4-year follow-up period, 22.2% of patients underwent AVR for progression to severe AS, with AVR being

CENTRAL ILLUSTRATION **Pooled Analysis of Patients With Moderate or Severe AS in the VARIATE and CARDIOBASE Bern PCI Registries**



AS = aortic stenosis; AVR = aortic valve replacement; CD = cardiac damage.

independently associated with improved 6-year survival.[6] Our study is in line with these findings: approximately 1 in 5 moderate AS patients progressed to severe AS prior to AVR at a median time of 2 years.

The definition of advanced CD applied in our study may help better define the optimal timing of AVR in moderate AS by focusing on the severity of the mechanical repercussion of AS rather than relying solely on LV function (stage 1). In our exploratory analysis, patients with moderate AS and advanced CD undergoing AVR exhibited lower mortality rates compared with those with conservative management. Patients with moderate AS and early CD showed a numerically lower risk for death with AVR compared with conservative management, though this finding was not statistically significant.

Accordingly, in our study, LV systolic dysfunction alone was not a reliable predictor of mortality in patients with moderate AS. Previous observational data found that the risk for short-term death was increased only when moderate AS was associated with CD stage >2.[11] Our findings corroborate this observation in a population with a substantially longer follow-up period, nurturing the hypothesis

that the development of advanced CD may define the optimal timing of AVR in patients with moderate AS. Early AVR might reverse diffuse interstitial fibrosis associated with CD, thereby resulting in improved long-term outcomes.[21] In previous analyses, 15% to 30% of patients showed improvements in CD stage after AVR.[13,22] The potential impact of early intervention in patients with moderate AS and high-risk features requires, however, further investigation. The decision to undertake AVR should be carefully considered, and the early procedural risks must be weighted against the long-term mortality risk related to CD with conservative management. Two ongoing clinical trials (PROGRESS [Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR; NCT04889872] and EXPAND TAVR II [NCT05149755]) will yield further insights into the clinical benefit of early intervention in patients with moderate AS and delineate the importance of CD in this patient population.

Finally, in our study, approximately 1 in 5 patients with severe AS did not undergo AVR. This finding aligns with prior data from the EURObservational Research Programme Valvular Heart Disease II survey, in which the rate of treatment remained relatively low, with 79.4% of patients with severe AS undergoing AVR.[23] Although our data set does not include detailed information on the specific reasons why AVR was not performed in individual cases, it is likely that certain patients may have presented with severe frailty or advanced comorbid conditions (eg, terminal malignancy, severe dementia), in which case AVR might have been deemed disproportionate to the risks involved. Others may have declined intervention because of personal concerns or fear of surgery or transcatheter AVR. The issue of undertreatment in severe AS has been previously documented and our findings confirm this trend, highlighting the need for continued efforts to optimize referral pathways in this high-risk population.

STUDY LIMITATIONS. First, even if most clinical data were collected prospectively, the present analysis is retrospective and is subject to inherent limitations. Although comorbidities were comparable between groups, selection bias (ie, preferential adoption of AVR in patients with fewer comorbidities and willing to undergo intervention) cannot be ruled out. In addition, the CARDIOBASE Bern PCI Registry includes patients undergoing percutaneous coronary intervention, which has an impact on CD and clinical outcomes. However, this effect persists uniformly across groups of grades and stages of AS.

Second, the present study did not consider symptom status, which is likely just as important in risk stratification for patients with moderate AS as it is for those with severe AS. However, a recent trial involving patients with asymptomatic severe AS found that AVR was associated with a lower incidence of the composite primary endpoint of death of any cause, stroke, or unplanned CV hospitalization, suggesting that delaying intervention until symptom onset may not be advisable.[24] Moreover, in moderate AS, symptoms may be driven by concomitant non-AS CD, which could bias the indication for AVR and contribute to poorer outcomes.

Third, aortic valve calcification was assessed using contrast-enhanced CT. Although this approach was applied consistently to all patients in our study, it is not the standard method for aortic calcium quantification, which is typically performed using noncontrast CT.

Fourth, a significant proportion of patients with severe AS had low-flow, low-gradient AS (41.3% classical, 27.2% paradoxical). In accordance with current guidelines, additional diagnostic measures, such as dobutamine stress echocardiography or noncontrast CT, are required to accurately classify these patients. In our study, contrast-enhanced CT was used in such cases, while data on stress echocardiography were not available. Consequently, some patients with moderate or pseudosevere AS may have been misclassified as having severe AS.

Finally, although stratifying patients into small subgroups may heighten the risk for overstratification and type I error, the absence of significant interactions among AS grade, CD, and AVR is reassuring.

CONCLUSIONS

In our analysis, 10-year mortality of patients with moderate and severe AS was importantly determined by the extent of CD. In addition, AVR was associated with lower rates of mortality compared with conservative management in patients with moderate AS with advanced CD and patients with severe AS irrespective of CD. Our findings support the notion that the integration of CD staging in addition to AS grading refines the prognostic assessment of AS and call for further research on the optimal timing of intervention in patients with moderate AS.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Angellotti is supported by a research grant provided by the CardioPath PhD program. Dr Heg is employed by the Department of

Clinical Research, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, the Department of Clinical Research is involved in the design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. Dr Lanz has received speaker fees to the institution from Edwards Lifesciences and Abbott Laboratories. Dr Samim has received funding for an online course from Edwards Lifesciences. Dr Praz has received travel expenses from Edwards Lifesciences, Abbott Vascular, Medira, Siemens Healthineers, and InQB8 Medical Technologies; and has received a research grant to the institution from Abbott Vascular. Dr Windecker has received research, travel, and/or educational grants to the institution from Abbott Laboratories, Abiomed, Alnylam, Amicus Therapeutics, Amgen, AstraZeneca, Bayer, B. Braun, Bioanalytica, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cordis Medical, CorFlow Therapeutics, CSL Behring, Daiichi-Sankyo, Edwards Lifesciences, Fumedica, GE Healthcare, Guerbet, IACULIS, Inari Medical, Janssen AI, Johnson & Johnson, Medalliance, Medtronic, Merck Sharp & Dohme, Neovii Pharmaceutica, Neutromedics, Novartis, Novo Nordisk, OM Pharma, Optimapharm, Orchestra BioMed, Pfizer, Philips, Sanofi, Servier, Shockwave Medical, Siemens Healthineers, Sinomed, Sahajanand Medical Technologies, Vascular Medical, and V-Wave. Dr Windecker serves as an advisory board member and/or a member of the steering or executive groups of trials funded by Abbott Laboratories, Amgen, Abiomed, Edwards Lifesciences, EnCarda, Medtronic, Novartis, and Sinomed, with payments to the institution but no personal payments; is a member of the steering or executive committee groups of several investigator-initiated trials that receive funding from industry without impact on his personal remuneration. Dr Pilgrim has received research, travel, and educational grants to the institution without personal remuneration from Biotronik, Boston Scientific, Edwards Lifesciences, and ATSens; and has received speaker fees and consultancy fees to the institution from Biotronik, Boston Scientific, Edwards Lifesciences, Abbott Laboratories, Medtronic, Biosensors, and Highlife. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Patients with AS experience an increased mortality risk at all stages of disease. CD is a key factor in determining the prognosis of patients with AS.

WHAT IS NEW? The extent of CD significantly affects the 10-year survival of patients with moderate and severe AS. CD staging might be as important as AS grading in defining the prognosis of patients with AS.

WHAT IS NEXT? Our findings suggest that future research should focus on the benefit and timing of AVR in patients with moderate AS.

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KEY WORDS aortic stenosis, aortic valve replacement, cardiac damage

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

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

ORIGINAL RESEARCH

STRUCTURAL

30-Day and 1-Year Outcomes of Navitor Transcatheter Aortic Valve in Low- or Intermediate-Risk Patients

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ABSTRACT

BACKGROUND The Navitor transcatheter aortic valve is a self-expanding, intra-annular valve indicated for patients with severe aortic stenosis (AS) at high or extreme surgical risk.

OBJECTIVES The aim of this study was to assess the safety and effectiveness of the Navitor valve in severe AS patients at low or intermediate surgical risk.

METHODS VANTAGE (Evaluation of TAVR Using the Navitor Valve in a Global Investigation) is a prospective, single-arm, multicenter study. The primary effectiveness endpoint was moderate or greater paravalvular leak (PVL) at 30 days; the primary safety endpoint was all-cause mortality or fatal stroke or stroke with disability at 12 months. Both endpoints were assessed against a performance goal (PG) when the sample size requirements were met. Clinical events and imaging assessments were evaluated by an independent committee and a core laboratory, respectively.

RESULTS A total of 434 patients (203 at low risk, 231 at intermediate risk) underwent Navitor implantation between July 2021 and November 2024 across 36 sites in Europe, Australia, and Israel. The mean Society of Thoracic Surgeons Predicted Risk of Mortality scores were 1.5% and 2.6% for the low- and intermediate-risk groups. Technical success was 97.0%, with no procedural mortality. At 30 days, no patients had moderate or greater PVL (0%), which was significantly lower than the PG of 6.6% ($P < 0.0001$). In the first 262 patients with 12-month follow-up completed, the rate for all-cause mortality or fatal stroke or stroke with disability was 2.3%, also significantly lower than the PG of 11.3% ($P < 0.0001$). Sustained hemodynamic performance (mean gradient 8.0 mm Hg, effective orifice area 1.8 cm^2) was seen through 12 months.

CONCLUSIONS The Navitor valve demonstrated favorable safety and performance outcomes at 12 months, supporting its expansion to low- and intermediate-risk populations. (JACC Cardiovasc Interv. 2025;18:2517–2527)

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ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2025.08.021

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

EOA = effective orifice area

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire overall summary score

KM = Kaplan-Meier

PG = performance goal

POD = postoperative day

PPI = permanent pacemaker implantation

PROM = Predicted Risk of Mortality

PVL = paravalvular leak

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAV = transcatheter aortic valve

TAVR = transcatheter aortic valve replacement

UCB = upper confidence bound

Transcatheter aortic valve replacement (TAVR) has evolved from a treatment reserved for patients with severe aortic stenosis (AS) who are at high or extreme surgical risk to a standard therapy across all risk categories.[1-6] The latest guidelines from the American Heart Association/American College of Cardiology and the European Society of Cardiology no longer prioritize only surgical risk as the main criterion for recommending TAVR. Instead, patient age, life expectancy, and anatomical conditions are additional factors for considerations when choosing between TAVR and surgical aortic valve replacement (SAVR).[7,8] This shift reflects accumulating evidence supporting the safety and effectiveness of TAVR in lower risk populations.

The Navitor valve (Abbott Structural Heart) is an intra-annular, self-expanding transcatheter aortic valve (TAV) evolved from the Portico platform, with design enhancements aimed at minimizing paravalvular leak (PVL) and improving hemodynamic performance. The Navitor valve has been approved for patients with symptomatic, severe AS who are at high or extreme surgical risk on the basis of evidence from the Portico Next Generation Approval study (NCT04011722, Navitor investigational device exemption), which demonstrated promising clinical and hemodynamic results in this population.[9,10]

The VANTAGE (Evaluation of TAVR Using the NAVITOR Valve in a Global Investigation; NCT04788888) study was designed to assess the safety and performance of the Navitor valve in patients with symptomatic, severe AS who are considered at low or intermediate surgical risk, thereby extending the indication for this valve to meet the continually evolving TAVR therapeutic space. This report presents the 30-day and 12-month clinical outcomes from the VANTAGE study.

METHODS

STUDY DESIGN AND POPULATION. The VANTAGE study is a prospective, single-arm, multicenter, international clinical investigation designed to evaluate the safety and performance of the Navitor valve system in patients with severe AS at low or intermediate surgical risk. Eligible patients had symptomatic, severe native AS and were classified as low or intermediate surgical risk by the multidisciplinary heart team, which includes cardiothoracic surgeons and interventional cardiologists. Surgical risk was assessed using the Society of Thoracic Surgeons (STS) adult cardiac surgery risk calculator along with clinical judgement based on frailty indexes and comorbidities not captured by risk calculators, in accordance with current TAVR guidelines.[7,8,11] Risk classification was determined by the local heart team and confirmed by a central screening committee (Supplemental Files 1 to 3). Multislice computed tomography was required for all candidates during the screening process to assess aortic anatomy suitability. In general, patients were excluded if they had congenital unicuspid or bicuspid valve morphology, annular eccentricity ratio <0.73, annular dimensions outside the treatment range, or severe calcification of the left ventricular outflow tract. Full inclusion and exclusion criteria are detailed in Supplemental File 4. All participants provided written informed consent prior to enrollment and were scheduled for follow-up at 30 days, 12 months, and annually thereafter up to 10 years. Disposition of consented patients is detailed in Supplemental File 5. The study was conducted in accordance with the Declaration of Helsinki and received appropriate ethical oversight at each participating site and country.

STUDY DEVICE AND PROCEDURE. The Navitor valve is a self-expanding, repositionable valve featuring a nontapered stent design, large stent cells, and 3 intra-annular bovine pericardial leaflets. The valve is available in 5 sizes (23, 25, 27, 29, and 35 mm), accommodating aortic annular diameters between 19 and 30 mm. Major enhancements of the Navitor valve include the active NaviSeal cuff to mitigate PVL and a more uniform chronic outward radial force across all sizes. The Navitor valve is delivered via the FlexNav Delivery System, engineered for enhanced flexibility and stable positioning. The 23- and 25-mm valves are compatible with the 14-F equivalent FlexNav Delivery System for vessels ≥5.0 mm in diameter, while the 27-, 29-, and 35-mm valves require the 15-F

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

Manuscript received July 31, 2025; revised manuscript received August 19, 2025, accepted August 20, 2025.

equivalent system for vessels ≥5.5 mm. Multislice computed tomography was used to ensure accurate device sizing and procedural planning. The procedure was conducted under general or local anesthesia per site protocols, with the TAV delivered via transfemoral or alternative access routes. If implantation depth or positioning was suboptimal, the protocol allowed the valve to be resheathed and repositioned prior to full release.

STUDY ENDPOINTS AND DEFINITIONS. The primary safety endpoint was a composite of all-cause mortality or fatal stroke or stroke with disability at 12 months, assessed in the attempted population, defined as all subjects in whom the FlexNav Delivery System was inserted into the vasculature. The primary effectiveness endpoint was moderate or greater PVL at 30 days, on the basis of echocardiographic assessment at 30 days by the core laboratory. This endpoint was assessed in the implanted population in whom functional Navitor valves remained implanted at 30 days. The implanted population was defined as patients successfully implanted with Navitor valves at the end of the index procedure. Secondary endpoints included: 1) mean change in mean transvalvular gradient from baseline to 12 months (implanted population); 2) mean change in effective orifice area (EOA) from baseline to 12 months (implanted population); and 3) mean change in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS) from baseline to 12 months (attempted population). Functional status was evaluated using the 6-minute walk test and NYHA functional class. All clinical endpoints were adjudicated using Valve Academic Research Consortium 3 definitions[12] and evaluated by an independent core laboratory and clinical event committee.

STATISTICAL ANALYSIS. Baseline and procedural characteristics were summarized using descriptive statistics. A sample size of 262 patients was required for the hypothesis test of the primary safety endpoint of all-cause mortality or fatal stroke or stroke with disability at 12 months against the mixed-risk performance goal (PG) of 11.3%. A sample size of 434 was required for the hypothesis test of the primary effectiveness endpoint of moderate or greater PVL at 30 days against a PG of 6.6%. PG and sample size derivation are detailed in Supplemental File 6.

All 30-day outcomes were reported as proportional rates in the full study cohort of 434 patients (total cohort), while 12-month outcomes were presented as Kaplan-Meier (KM) estimates in the first 262 consecutively registered patients with 12-month follow-up completed (first 262 cohort). Cohort breakdown is detailed in Supplemental File 7. Statistical significance was defined as a P value <0.05. No imputation was performed for missing data. All analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

POPULATION AND BASELINE CHARACTERISTICS. Between July 2021 and November 2024, 434 patients underwent Navitor implantation at 36 sites across 9 countries in Europe (Austria, Denmark, France, Germany, Italy, the Netherlands, Spain, Switzerland, and the United Kingdom), Australia, and Israel. Of these, 46.8% (n = 203) were classified as low risk and 53.2% (n = 231) as intermediate risk. The mean STS Predicted Risk of Mortality (PROM) scores were 1.5% and 2.6% in the low- and intermediate-risk groups, with mean frailty scores of 0.4 and 0.9, respectively. The mean ages were 75.1 years (low risk) and 79.1 years (intermediate risk); 46.8% and 52.8% were women, respectively. Patients in the intermediate-risk group had a higher prevalence of comorbidities (**Table 1**).

PROCEDURAL CHARACTERISTICS AND OUTCOMES. Procedural characteristics for all and stratified by risk group are presented in **Table 2**. Conscious sedation was used in 59.2% of patients. Transfemoral access was used in all but 1 patient (99.8%), with axillary access used in 1 patient. Preimplantation balloon valvuloplasty was performed in 90.8% of patients and postimplantation balloon valvuloplasty in 32.8%. In 45.1% of cases, no resheathing was required.

Technical success was achieved in 97.0% overall, with success rates of 97.5% in the low-risk group and 96.5% in the intermediate-risk group. There were no procedural mortalities. In 2 cases, the Navitor valve was not implanted: 1 patient received an alternative TAV because of incompatible aortic valve anatomy for Navitor, and the other was converted to SAVR because of valve embolization. In another 3 cases, a second Navitor valve was required because of valve embolization (Supplemental Table 1).

PRIMARY AND SECONDARY ENDPOINTS. Primary and secondary endpoints are summarized in **Table 3** and Supplemental Table 2. Both primary endpoints were met. At 30-day echocardiographic follow-up, there were no instances of moderate or greater PVL (0%; 97.5% upper confidence bound [UCB]: 0.9%), significantly lower than the prespecified PG of 6.6% ($P < 0.0001$). One patient, who had mild PVL noted on postimplantation echocardiography but did not undergo postdeployment valvuloplasty during the index procedure, was found to have moderate PVL on postoperative day (POD) 1. Balloon valvuloplasty was

TABLE 1 Baseline Characteristics

	Low Risk (n = 203)	Intermediate Risk (n = 231)	Total (N = 434)
Age, y	75.1 ± 3.2	79.1 ± 3.7	77.2 ± 4.0
Female	46.8 (95/203)	52.8 (122/231)	50.0 (217/434)
NYHA functional class			
II	79.8 (162/203)	72.3 (167/231)	75.8 (329/434)
III	20.2 (41/203)	27.7 (64/231)	24.2 (105/434)
IV	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
STS PROM score, %	1.5 ± 0.5	2.6 ± 1.2	2.1 ± 1.1
STS PROM score [0%, 3%]	100.0 (203/203)	69.7 (161/231)	83.9 (364/434)
STS PROM score [3%, 7%]	0.0 (0/203)	30.3 (70/231)	16.1 (70/434)
STS PROM score [7%, 100%]	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
EuroSCORE II, %	1.4 ± 0.6	2.1 ± 1.2	1.8 ± 1.0
Total frailty score (out of 4)[a]	0.4 ± 0.5	0.9 ± 0.8	0.6 ± 0.7
0	65.0 (132/203)	34.2 (79/231)	48.6 (211/434)
1	32.5 (66/203)	45.0 (104/231)	39.2 (170/434)
2	2.5 (5/203)	19.5 (45/231)	11.5 (50/434)
3	0.0 (0/203)	1.3 (3/231)	0.7 (3/434)
4	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
Diabetes	31.0 (63/203)	30.3 (70/231)	30.6 (133/434)
Chronic lung disease	6.4 (13/203)	10.8 (25/231)	8.8 (38/434)
Kidney disease	2.5 (5/203)	10.4 (24/231)	6.7 (29/434)
Hypertension	76.8 (156/203)	80.1 (185/231)	78.6 (341/434)
Hyperlipidemia	68.5 (139/203)	61.9 (143/231)	65.0 (282/434)
Coronary artery disease	21.7 (44/203)	28.1 (65/231)	25.1 (109/434)
Myocardial infarction	4.4 (9/203)	4.8 (11/231)	4.6 (20/434)
Coronary artery bypass graft	1.0 (2/203)	5.2 (12/231)	3.2 (14/434)
Percutaneous transluminal coronary angioplasty with stent	17.7 (36/203)	19.9 (46/231)	18.9 (82/434)
Cerebrovascular accident	3.0 (6/203)	5.2 (12/231)	4.1 (18/434)
Peripheral vascular disease	2.0 (4/203)	4.8 (11/231)	3.5 (15/434)
Pulmonary hypertension	3.9 (8/203)	9.5 (22/231)	6.9 (30/434)
Cancer	13.3 (27/203)	20.3 (47/231)	17.1 (74/434)
Permanent pacemaker	3.9 (8/203)	6.5 (15/231)	5.3 (23/434)
Atrial fibrillation	14.3 (29/203)	23.4 (54/231)	19.1 (83/434)
First-degree atrioventricular block	3.4 (7/203)	7.8 (18/231)	5.8 (25/434)
Left bundle branch block	2.5 (5/203)	6.1 (14/231)	4.4 (19/434)
Right bundle branch block	5.4 (11/203)	8.7 (20/231)	7.1 (31/434)
Mean annular diameter, mm	24.0 ± 2.0	23.9 ± 2.1	23.9 ± 2.1
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Mean aortic gradient, mm Hg	48.8 ± 9.9	47.7 ± 11.2	48.2 ± 10.6
Ejection fraction, %	59.9 ± 6.7	60.9 ± 7.6	60.4 ± 7.2
Aortic regurgitation moderate or greater[b]	15.8 (32/203)	10.0 (23/231)	12.7 (55/434)
Mitral regurgitation moderate or greater[b]	8.9 (18/203)	6.9 (16/231)	7.8 (34/434)
Tricuspid regurgitation moderate or greater[b]	9.9 (20/203)	5.2 (12/231)	7.4 (32/434)

Values are mean ± SD or % (n/N). [a]The frailty assessment includes 5 evaluations: 1) Katz Index of Independence in Activities of Daily Living, scored from 0 to 6, with higher scores indicating greater independence in daily living activities (1 frailty point is assigned if the value is at or below 4); 2) grip strength (kilograms), with 1 frailty point assigned if the value is at or below the sex- and body mass index-based threshold; 3) time to walk 5 meters (seconds), with 1 point assigned if the time is at or above the sex- and height-based threshold; 4) Albumin level, with one point assigned if <3.5 g/dl; and 5) albumin level, with 1 point assigned if <3.5 g/dL. [b]Per eligibility criteria, no patients had severe aortic, mitral, or tricuspid regurgitation at baseline.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; PROM = Predicted Risk of Mortality; STS = Society of Thoracic Surgeons.

performed on POD 7, which successfully resolved the PVL, with no PVL seen on 30-day echocardiography. A sensitivity analysis treating this case as a failure yielded an event rate of 0.2% (97.5% UCB: 1.3%), still well below the PG (Supplemental Table 3). In the first 262 cohort, the KM estimate of all-cause mortality or fatal stroke or stroke with disability at 12 months was 2.3% (97.5% UCB: 5.0%), also significantly lower than the PG of 11.3% ($P < 0.0001$). The primary safety endpoint events included 2 deaths (both in the intermediate-risk group; 1 patient with baseline left ventricular hypertrophy experienced left ventricular outflow tract obstruction on day 6 and died on day 10, and the other patient died on day 338 of unknown causes) and 4 strokes with disability (3 in the intermediate-risk group). The primary safety endpoint was also evaluated in the total cohort incorporating all available follow-up data, yielding a KM rate of 1.7% (97.5% UCB: 3.4%), which was lower than the PG ($P < 0.0001$) (Supplemental Table 4).

The 3 secondary endpoints were evaluated in the first 262 cohort. From baseline to 12 months, the mean transvalvular gradient decreased from 42.8 to 8.0 mm Hg, yielding an average reduction of 34.8 mm Hg (97.5% UCB: −33.3 mm Hg; PG: −10 mm Hg; $P < 0.0001$); the EOA increased from 0.8 to 1.9 cm^2, yielding an average increase of 1.1 cm^2 (97.5% lower confidence bound: 1.0 cm^2; PG: 0.4 cm^2; $P < 0.0001$); and the KCCQ-OS improved from 70.6 to 86.1 points, yielding an average increase of 15.5 points (97.5% lower confidence bound: 12.7 points; PG: 5 points; $P < 0.0001$). All secondary endpoints were met (Supplemental Table 2).

30-DAY OUTCOMES FOR THE TOTAL COHORT. Thirty-day outcomes for the total cohort are presented in **Table 4**. The intermediate-risk group experienced a higher overall rate of adverse events compared with the low-risk group. Two cardiovascular deaths occurred within 30 days (0.5%), both in the intermediate-risk group. One patient with a history of permanent atrial fibrillation experienced a sudden stroke following the procedure and died of multiorgan failure on POD 4. The other patient, who had baseline left ventricular hypertrophy, developed left ventricular outflow tract obstruction on POD 6 and died on POD 10. The overall stroke rate at 30 days was 1.6%, with rates of 1.0% in the low-risk group and 2.2% in the intermediate-risk group. Type 3 or 4 bleeding occurred in 2.5% of the low-risk patients and 4.8% of the intermediate-risk patients; all episodes were type 3 bleedings. Major vascular complications were reported in 3.0% of low-risk patients and 5.6% of intermediate-risk patients. There were no coronary obstruction events. Aortic reintervention was

required in 2 patients (0.5%). One underwent SAVR on POD 26 because of type A aortic dissection. The other, as previously described, received balloon valvuloplasty on POD 7 to treat moderate PVL. The 30-day rate of valve- or procedure-related or other cardiovascular rehospitalization was 7.1% (6.4% in low-risk patients and 7.8% in intermediate-risk patients), with the majority (6.2%) being valve or procedure related, mostly because of conduction disturbances (n = 8) or arrhythmias (n = 5). The new permanent pacemaker implantation (PPI) rate among patients without pacemakers at baseline was 18.7% overall, with rates of 15.9% in the low-risk group and 21.3% in the intermediate-risk group.

12-MONTH OUTCOMES IN THE FIRST 262 COHORT. Twelve-month outcomes for the first 262 cohort are presented in **Table 5**, with rates stratified by STS-PROM score shown in Supplemental Table 5. The cumulative KM rate of all-cause mortality was 0.0% in the low-risk group and 1.4% in the intermediate-risk group. The corresponding estimates for all strokes were 1.6% and 3.6%, respectively. Two patients required coronary access during follow-up because of progression of pre-existing coronary artery disease, both of which were successfully performed. The overall rate for valve- or procedure-related or other cardiovascular rehospitalization was 16.0% at 12 months, with 6.5% attributed to valve- or procedure-related causes. Prosthetic valve endocarditis was reported in 1 patient (0.4%). Clinically significant valve thrombosis occurred in 5 patients (1.9%), with 2 cases in the intermediate-risk group and 3 in the low-risk group.

HEMODYNAMIC AND FUNCTIONAL PERFORMANCE. The mean transvalvular gradient decreased from 42.8 ± 11.1 mm Hg at baseline to 8.4 ± 4.0 mm Hg at discharge and remained at 8.0 ± 4.5 mm Hg at 12 months. The mean EOA increased from 0.7 ± 0.2 cm^2 at baseline to 1.9 ± 0.5 cm^2 at discharge and was maintained at 1.8 ± 0.5 cm^2 at 12 months (**Figure 1A**). Hemodynamic outcomes were consistent across risk groups (Supplemental Figures 1 and 2) and in paired analysis (Supplemental Figure 3 and Supplemental Table 6). Paired analyses confirmed significant improvements across all follow-up time points (Supplemental Table 6). At 30 days, 86.4% of patients had none or trace PVL, which sustained at 84.0% at 12 months, with no moderate or severe PVL observed at 30-day and 12-month follow-up (**Figure 1B**).

NYHA functional class improved significantly by 30 days and remained stable at 12 months. Most patients (80.6%) improved by at least 1 class. Consistent results were observed across both low- and

TABLE 2 Procedural Outcomes and Characteristics

	Low Risk (n = 203)	Intermediate Risk (n = 231)	Total (N = 434)
Technical success[a]	97.5 (198/203)	96.5 (223/231)	97.0 (421/434)
Technical failure mode			
Procedural mortality	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
Unsuccessful access, delivery of the device, or retrieval of the delivery system	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
Failure of correct positioning of a single Navitor valve into the proper anatomical location	1.5 (3/203)	0.9 (2/231)	1.2 (5/434)
Surgery or intervention related to the device[b] or to a major vascular or access-related, or cardiac structural complication	2.0 (4/203)	3.0 (7/231)	2.5 (11/434)
Conscious sedation	58.1 (118/203)	60.2 (139/231)	59.2 (257/434)
Transfemoral access	99.5 (202/203)	100.0 (231/231)	99.8 (433/434)
Axillary access	0.5 (1/203)	0.0 (0/231)	0.2 (1/434)
Preimplantation balloon valvuloplasty	88.7 (180/203)	92.6 (214/231)	90.8 (394/434)
Postimplantation balloon valvuloplasty	33.7 (68/202)	32.0 (74/231)	32.8 (142/433)
Number of resheathing			
0	48.3 (97/201)	42.4 (98/231)	45.1 (195/432)
1	30.3 (61/201)	32.0 (74/231)	31.3 (135/432)
2	17.9 (36/201)	16.9 (39/231)	17.4 (75/432)
3	3.0 (6/201)	7.4 (17/231)	5.3 (23/432)
4	0.5 (1/201)	1.3 (3/231)	0.9 (4/432)
Implanted valve size			
23 mm	5.0 (10/201)	8.7 (20/231)	6.9 (30/432)
25 mm	29.4 (59/201)	28.1 (65/231)	28.7 (124/432)
27 mm	29.9 (60/201)	31.2 (72/231)	30.6 (132/432)
29 mm	31.3 (63/201)	26.8 (62/231)	28.9 (125/432)
35 mm	4.5 (9/201)	5.2 (12/231)	4.9 (21/432)
TAVR implantation time, min	9.2 ± 5.7	8.9 ± 5.9	9.0 ± 5.8
Procedure time, min	57.7 ± 26.4	58.6 ± 22.9	58.2 ± 24.6
Length of hospital stay, d	3.6 ± 1.9	3.7 ± 2.9	3.6 ± 2.5

Values are % (n/N) or mean ± SD. [a]Per Valve Academic Research Consortium 3 definition, technical success includes freedom from procedural mortality, successful vascular access, delivery and deployment of a single prosthetic valve in the correct anatomical position, retrieval of the delivery system, and absence of surgery or intervention related to the device (excluding permanent pacemaker) or major vascular, access-related, or cardiac structural complications upon exit from the procedure room. [b]Excluding permanent pacemaker.

TAVR = transcatheter aortic valve replacement.

TABLE 3 Primary Safety and Effectiveness Endpoints

	Low Risk	Intermediate Risk	Total
Primary effectiveness endpoint: moderate or greater PVL at 30 d (n = 434)[a,b]	0.0 (0/196)	0.0 (0/222)	0.0 (0/418)
Primary safety endpoint: all-cause mortality or fatal stroke/stroke with disability at 12 mo (n = 262)[c,d]	0.8 (1)	3.6 (5)	2.3 (6)
All-cause mortality	0.0 (0)	1.4 (2)	0.8 (2)
Fatal stroke/stroke with disability	0.8 (1)	2.2 (3)	1.5 (4)
Fatal stroke	0.0 (0)	0.0 (0)	0.0 (0)
Stroke with disability	0.8 (1)	2.2 (3)	1.5 (4)

Values are % (n/N) or % (n). [a]Proportional rate. [b]Sixteen patients did not have 30-day echocardiographic data available or evaluable by the core laboratory and were therefore excluded from the analysis. [c]Kaplan-Meier rate. [d]Risk group distribution in the first 262 cohort: 139 intermediate-risk patients and 123 low-risk patients.

PVL = paravalvular leak.

TABLE 4 30-Day Outcomes in the Total Cohort

	Low Risk (n = 203)	Intermediate Risk (n = 231)	Total (N = 434)
All-cause mortality	0.0 (0/203)	0.9 (2/231)	0.5 (2/434)
Cardiovascular mortality	0.0 (0/203)	0.9 (2/231)	0.5 (2/434)
Valve-related mortality	0.0 (0/203)	0.4 (1/231)	0.2 (1/434)
All stroke	1.0 (2/203)	2.2 (5/231)	1.6 (7/434)
Fatal stroke/stroke with disability	0.5 (1/203)	1.3 (3/231)	0.9 (4/434)
Transient ischemic attack	0.0 (0/203)	1.7 (4/231)	0.9 (4/434)
Stage 3/4 acute kidney injury	0.0 (0/203)	0.9 (2/231)	0.5 (2/434)
Type 3/4 bleeding	2.5 (5/203)	4.8 (11/231)	3.7 (16/434)
Major vascular complication	3.0 (6/203)	5.6 (13/231)	4.4 (19/434)
Major access-related nonvascular complications	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
Major cardiac structural complications	0.5 (1/203)	0.9 (2/231)	0.7 (3/434)
Myocardial infarction	0.0 (0/203)	2.6 (6/231)	1.4 (6/434)
Coronary obstruction requiring intervention	0.0 (0/203)	0.0 (0/231)	0.0 (0/434)
Valve embolization	1.0 (2/203)	0.9 (2/231)	0.9 (4/434)
Aortic valve reintervention	0.5 (1/203)	0.4 (1/231)	0.5 (2/434)
Rehospitalization[a]	6.4 (13/203)	7.8 (18/231)	7.1 (31/434)
Valve and procedure related	4.9 (10/203)	7.4 (17/231)	6.2 (27/434)
New permanent pacemaker implantation[b]	15.9 (31/195)	21.3 (46/216)	18.7 (77/411)

Values are proportional rate. Clinical definitions per Valve Academic Research Consortium-3. [a]Valve-related or procedure-related hospitalization or other cardiovascular hospitalization. [b]Site-reported rate in patients without pacemakers at baseline.

intermediate-risk groups (**Figure 2A**, Supplemental Table 7). Similarly, substantial gains were seen in 6-minute walk distance and KCCQ-OS, with improvements maintained through 12 months, irrespective of risk group (**Figures 2B and 2C**).

TABLE 5 12-Month Outcomes in the First 262 Cohort

	Low Risk (n = 123)	Intermediate Risk (n = 139)	Total (n = 262)
All-cause mortality or all stroke	1.6 (2)	5.0 (7)	3.4 (9)
All-cause mortality	0.0 (0)	1.4 (2)	0.8 (2)
Cardiovascular mortality	0.0 (0)	1.4 (2)	0.8 (2)
Valve-related mortality	0.0 (0)	0.7 (1)	0.4 (1)
All stroke	1.6 (2)	3.6 (5)	2.7 (7)
Fatal stroke/stroke with disability	0.8 (1)	2.2 (3)	1.5 (4)
Transient ischemic attack	1.6 (2)	2.9 (4)	2.3 (6)
Myocardial infarction	0.8 (1)	1.4 (2)	1.1 (3)
Coronary obstruction requiring intervention	0.0 (0)	0.0 (0)	0.0 (0)
Successful coronary access when needed	100.0 (2)	NA	100.0 (2)
Aortic valve reintervention	0.0 (0)	0.0 (0)	0.0 (0)
Rehospitalization[a]	13.0 (16)	18.7 (26)	16.0 (42)
Valve and procedure related	5.7 (7)	7.2 (10)	6.5 (17)
New permanent pacemaker implantation[b]	15.1 (18)	27.8 (36)	21.7 (54)
Prosthesis valve endocarditis	0.0 (0)	0.7 (1)	0.4 (1)
Clinically significant valve thrombosis	2.4 (3)	1.5 (2)	1.9 (5)

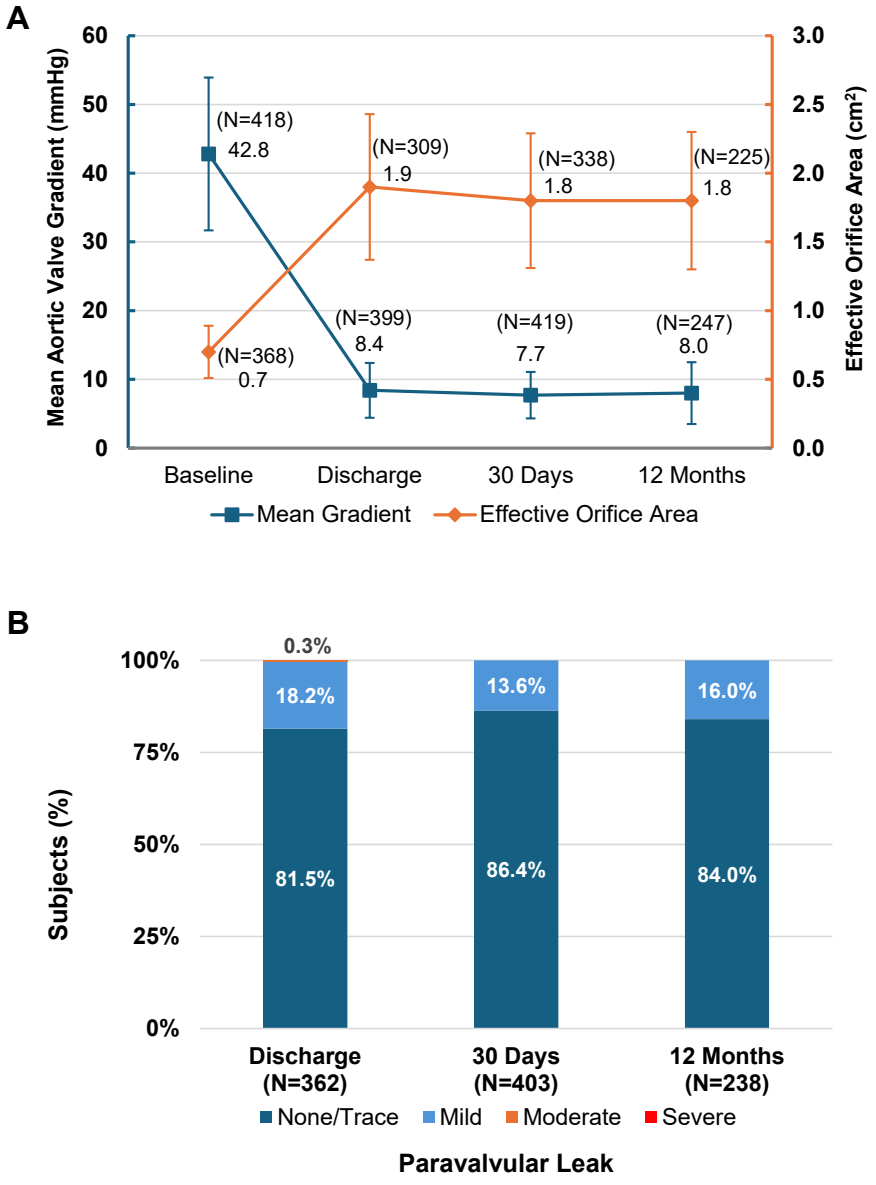
Values are Kaplan-Meier estimate event rate (number of subjects with event). [a]Valve-related or procedure-related hospitalization or other cardiovascular hospitalization. [b]Site-reported rate in patients without a pacemaker at baseline.

DISCUSSION

VANTAGE is the first clinical trial to report outcomes of the Navitor valve in patients at low or intermediate surgical risk. The present findings demonstrate a high technical success rate and favorable 30-day and 12-month outcomes with the valve. The trial met its primary effectiveness endpoint, primary safety endpoint, and all 3 secondary endpoints (**Central Illustration**).

Patients enrolled in VANTAGE were categorized as intermediate or low surgical risk by an independent subject screening committee. Patients in the low-risk group were younger, had lower STS PROM scores, and exhibited fewer frailties and comorbidities. They experienced generally better clinical outcomes and fewer adverse events at both 30 days and 12 months compared with those in the intermediate-risk group. Low-risk patients in VANTAGE were similar in age (75.1 years vs 74.1 and 73.3 years, respectively) and STS PROM scores (1.5% vs 1.9% and 1.9%, respectively) to those in the Evolut Low Risk and PARTNER (Placement of Aortic Transcatheter Valve) 3 low-risk trials.[13,14] Intermediate-risk patients in VANTAGE were similar in age to those in SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) and PARTNER 2-S3i (79.1 years vs 79.9 and 81.9 years, respectively) intermediate-risk trials; however, the mean STS PROM score in VANTAGE intermediate-risk patients (2.6%) was lower than in SURTAVI (4.4%) and PARTNER 2-S3i (5.2%). This is not unexpected, as the STS risk calculator has been updated since the approval of intermediate-risk indication for other TAVR devices. Notably, the updated calculator has been shown to yield lower scores for the same patient profiles.[15,16] This recalibration has directly affected the STS PROM scores in contemporary trials such as ACURATE IDE (Safety and Effectiveness Study of ACURATE Valve for Transcatheter Aortic Valve Replacement).[17] ACURATE IDE enrolled 28.6% high- or extreme-risk, 36.9% intermediate-risk, and 34.5% low-risk patients from 2019 to 2023, with an overall STS PROM score of just 2.3%. In comparison, VANTAGE enrolled 53.2% intermediate-risk and 46.8% low-risk patients, with an overall STS PROM score of 2.1%, which was nearly the same as in ACURATE IDE. This demonstrates a consistent downward trend in calculated STS PROM scores over time. The screening committee of VANTAGE used a combination of STS PROM score, frailty, age, and other clinical factors to risk-stratify eligible patients, which explains why patients with STS PROM scores <3% were deemed at intermediate operative risk. Moreover, the analysis

FIGURE 1 Echocardiographic Performance Through 12 Months

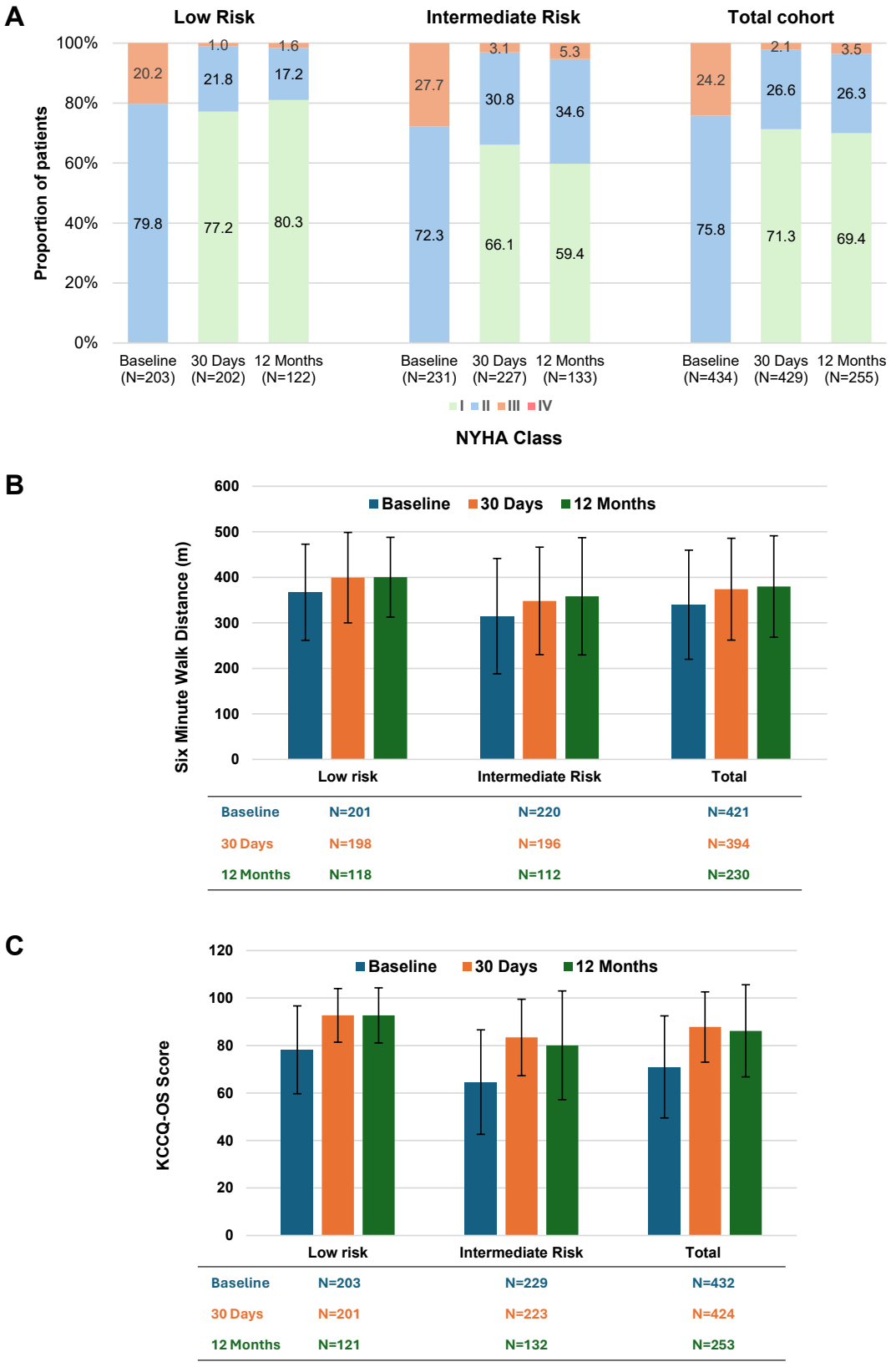


Hemodynamic performance is shown from baseline through 12 months. Data from baseline to 30 days reflect the total cohort, while 12-month data are based on the first 262 cohort. (A) Mean aortic valve gradient and effective orifice area. (B) Paravalvular leak.

of 12-month outcomes revealed that intermediate-risk patients with STS PROM scores <3% had an average rate of all-cause mortality or fatal stroke or stroke with disability (3.8%) comparable with that of intermediate-risk patients with STS PROM scores ≥3% (3.0%), yet notably higher than that observed in low-risk patients (0.8%) (Supplemental Table 5), validating the assignment of these patients with STS PROM scores <3% to intermediate risk.

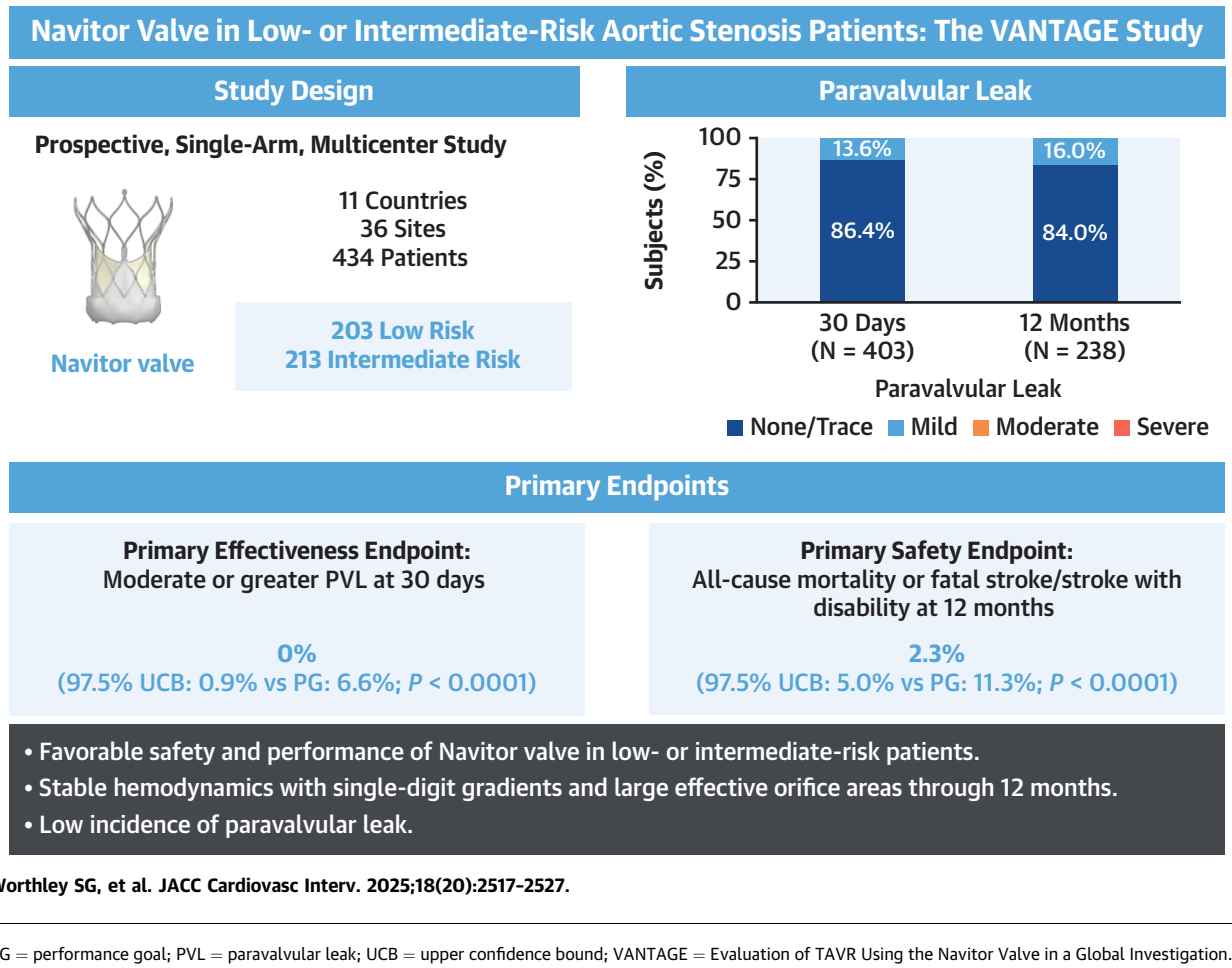
The primary safety endpoint of all-cause mortality or fatal stroke or stroke with disability at 12 months was met by a wide margin (2.3%; 97.5% UCB: 5.0%), significantly lower than the PG of 11.3% ($P < 0.0001$). The specific KM rate for the intermediate-risk group was 3.6%, which was lower than the rates reported in SURTAVI (8.1%) and PARTNER 2-S3i (8.4%).[18,19] This difference was driven primarily by a lower 12-month all-cause mortality rate in the VANTAGE

FIGURE 2 NYHA Functional Class, 6-Minute Walk Distance, and KCCQ-OS Score Through 12 Months



Functional status is shown from baseline through 12 months. Data from baseline to 30 days reflect the total cohort, while 12-month data are based on the first 262 cohort. (A) NYHA functional class. (B) Six-minute walk distance (mean ± SD). (C) Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS) (mean ± SD).

CENTRAL ILLUSTRATION **VANTAGE Study Overview and Findings**



PG = performance goal; PVL = paravalvular leak; UCB = upper confidence bound; VANTAGE = Evaluation of TAVR Using the Navitor Valve in a Global Investigation.

intermediate-risk group (1.4%) compared with SURTAVI (6.7%) and PARTNER 2-S3i (7.4%). In the VANTAGE low-risk group, the KM rate for all-cause mortality or fatal stroke or stroke with disability at 12 months was 0.8%, which was lower than in Evolut Low Risk (2.9%) and comparable with PARTNER 3 (1.0%).[13,14] The technical success rate (97.0%) of the Navitor valve was high in this trial, with no procedural mortality. There were no cases of coronary obstruction requiring intervention, and the aortic reintervention rate was low. These favorable outcomes support the safety of the Navitor valve in a contemporary TAVR practice.

The need for new PPI at 30 days in the low-risk and intermediate-risk groups was 15.9% and 21.3%, respectively, which is comparable with rates reported in pivotal trials of other self-expanding valves (25.9% with CoreValve [Medtronic] or Evolut R [Medtronic] in SURTAVI and 17.4% with CoreValve, Evolut R, or Evolut PRO in Evolut Low Risk).[14,18] A previous subanalysis of the Portico Next Generation Approval study (Navitor investigational device exemption) identified implantation depth as a modifiable risk factor that significantly influences the incidence of new PPI, independent of baseline conduction abormalities.[20] The latest generation of the Navitor valve family, Navitor Vision (which was not used in VANTAGE), features a design improvement with the addition of 3 radiopaque markers positioned approximately 3 mm from the inflow edge of the valve, which improve valve visibility during deployment and serve as visual landmarks to guide optimal

implantation depth. Training programs that emphasize procedural best practices, focusing on optimal implantation depth and strict adherence to the cusp overlap technique during valve deployment, may help mitigate PPI rates with the Navitor valve, similar to the outcomes observed with Evolut in the Optimize PRO study.[21]

The primary effectiveness endpoint was met in the full study cohort, with no cases of moderate or greater PVL at 30 days, which compares favorably with other TAVs in the pivotal trials.[13,14,17,19] At 30 days, 13.6% mild PVL was observed, which was relatively low compared with PARTNER 2-S3i with the SAPIEN 3 (Edwards Lifesciences) (45%), Evolut Low Risk with the CoreValve, Evolut R, or Evolut PRO (36.0%), and PARTNER 3 with the SAPIEN 3 (28.7%); this rate with the Navitor valve is also lower than that with the Evolut group (38.1%) and comparable with that with the SAPIEN 3 group (15.7%) in the contemporary ACURATE IDE trial. These findings underscore the value of the active outer sealing cuff made of ultrahigh-molecular weight polyethylene that accommodates diverse aortic anatomies and synchronizes with the cardiac cycle to reduce PVL.

The study demonstrated excellent hemodynamic performance at 12 months, with single-digit gradients (8.0 ± 4.5 mm Hg) and large EOAs (1.8 ± 0.5 cm^2), consistent across both risk groups. Notably, these outcomes were achieved in a cohort with a high proportion of women, who generally present with smaller aortic annuli. Similarly good hemodynamic results have been reported in real-world observational studies.[22-24] These findings challenge the assumption that superior hemodynamic status is exclusive to supra-annular valve design. The favorable hemodynamic outcomes may be explained by the cylindrical inflow design of the Navitor stent, which allows full leaflet opening and a large EOA. These hemodynamic benefits were observed alongside with meaningful functional improvements, including substantial gains in NYHA functional class, KCCQ-OS, and 6-minute walk test distance over the 12-month follow-up period.

STUDY LIMITATIONS. First, VANTAGE is a single-arm trial without a contemporary control group, limiting direct comparisons with other TAVs. Although outcomes were benchmarked against PGs derived from prior TAVR pivotal trials, differences in patient selection and procedural techniques may affect comparability.

Second, an independent screening committee evaluated patient eligibility. The screen failure rate was 33.2%. This process may have introduced inherent selection bias. Third, with follow-up still ongoing, 12-month outcomes were available only for the first 262 patients. Complete 12-month data will be reported in due course.

CONCLUSIONS

The Navitor valve demonstrated favorable safety and performance at 30 days and 12 months in treating patients with symptomatic, severe AS who are at low or intermediate surgical risk, supporting its expanded use in low- and intermediate-risk patients.

ACKNOWLEDGMENTS The authors thank all the investigators, institutions, and patients participating in the VANTAGE study; Kai Koo, PhD, Feiyi Jia, PhD, and Cathy Mei, PhD (Abbott), for their contributions to data analysis; and Yuheng Jia, MD, PhD (Abbott), for her assistance with manuscript preparation and editing, including the development of tables and figures.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The study was sponsored by Abbott. Dr Worthley has served as a proctor and consultant for Edwards Lifesciences and Abbott; and is a shareholder of Tree Peaks Medical. Dr Giordano has received proctorship fees from Abbott, Meril, and MicroPort. Dr Corcione has received proctorship fees from MicroPort. Dr Nombela-Franco has served as a proctor and consultant for Abbott, Edwards Lifesciences, and Boston Scientific. Dr De Marco is a consultant and has provided paid expert testimony for Abbott and Boston Scientific. Dr Walton has served as a proctor for Medtronic, Edwards Lifesciences, and Abbott; has served on medical advisory boards for Medtronic, Abbott, and Edwards Lifesciences; and has received grant support from Medtronic, Abbott, and Edwards Lifesciences. Dr Bedogni has served as a proctor and consultant for Abbott, Medtronic, Meril, and Boston Scientific. Dr Möllmann has received honoraria from Abbott, Boston Scientific, Edwards Lifesciences, Meril, and SMT. Dr De Backer has received institutional research grants and consulting fees from Abbott. Dr Leroux has served as a proctor for Medtronic. Dr Manoharan has served as a proctor for Abbott and Medtronic. Dr Tchétché has served as a consultant for Abbott Vascular. Dr Taramasso has received consultancy fees from Abbott, Edwards Lifesciences, Medtronic, Boston Scientific, Biosensor, Shenqi Medical, CardioValve, CoreMedic, StarTric, Simulands, HiD Imaging, and OneCrea Medical. Dr Li is an employee of Abbott. Dr Kuo is an employee of Abbott. Dr Van Mieghem has received research grant support from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Meril, Pie Medical, PulseCath, and Teleflex; and has received consultancy fees from Abbott, Abiomed, Adjust Medical, Alleviant Medical, AnchorValve, Anteris, Approxima, Boston Scientific, Daiichi-Sankyo, Haemonetics, LUMA Vision, Materialise, Medtronic, Percassist, Pie Medical, Polares, PulseCath, Secure Closure, Supira Medical, Siemens, and Vivasure.

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PERSPECTIVES

WHAT IS KNOWN? The Navitor TAV is a self-expanding, intra-annular valve approved for treating patients with severe AS at high or extreme surgical risk.

WHAT IS NEW? The VANTAGE study demonstrated excellent safety and performance of the Navitor valve in low- and intermediate-risk patients at 30 days and at 12 months.

WHAT IS NEXT? These results support the indication expansion of Navitor to low- and intermediate-risk populations.

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KEY WORDS aortic valve stenosis, Navitor, TAVI, TAVR, transcatheter aortic valve implantation, transcatheter aortic valve replacement

APPENDIX For supplemental methods, tables, and figures as well as the clinical investigation plan and the statistical analysis plan, please see the online version of this paper.

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EDITORIAL COMMENT

A New VANTAGE Point in TAVR

Bridging Procedural Outcomes and Future Therapeutic Options

Amit N. Vora, MD, MPH,[a] Grant W. Reed, MD, MSc[b]

As transcatheter aortic valve replacement (TAVR) has become the dominant treatment strategy for severe symptomatic aortic stenosis, valve selection has become more nuanced than ever before. In an older, higher risk population, the focus was predominantly on excellent technical outcomes and shorter term results. However, with the increasing popularity of TAVR in a younger, lower risk population, the focus has shifted toward valve durability and lifetime management, including coronary reintervention and suitability of subsequent valve-in-valve procedures. Nevertheless, excellent early outcomes remain the sine qua non of successful treatment, as long-term results are immaterial if the immediate outcomes are unfavorable.[1]

Fortunately, the 2 most widely used platforms in current practice, the Edwards Lifesciences SAPIEN S3 and Medtronic Evolut transcatheter heart valves, have each reported excellent short- and long-term outcomes (to 5 years) to date.[2-5] Both low-risk trials have mandated follow-up to 10 years, and thus there will be more granular durability data to help guide decision making in the coming years. However, each platform has unique nuances with respect to lifetime management, because of the inherent differences in their unique frame and leaflet heights, cell size and structure, skirt designs, and leaflet material. Accordingly, there has been extensive work on planning subsequent procedures depending on the initial valve choice.[6,7]

More recently, the Abbott Navitor platform was approved for severe aortic stenosis in high- and extreme-risk patients. The current Navitor design platform has several design elements that may facilitate subsequent procedures. The intra-annular leaflet position with shorter leaflet height and large cell design affects the coronary risk plane and may simplify coronary reaccess as well as a subsequent TAV-in-TAV procedure. A major limitation of the first-generation Portico valve, was the high rate of paravalvular leak (PVL), noted to be 6.3% at 30 days in the PORTICO IDE (Portico Re-Sheathable Transcatheter Aortic Valve System US IDE Trial) study.[8] Subsequent device and delivery system iterations of the Navitor system led to a reduction of moderate or greater PVL to 1.8% in the CONFIDENCE (Controlled Delivery for Improved Outcomes With Clinical Evidence) registry.[9] The current Navitor platform has an outer and inner sealing skirt designed to further reduce the risk for PVL. However, there have been only limited studies demonstrating the safety and efficacy of the platform in contemporary use among lower risk patients.

In this issue of *JACC: Cardiovascular Interventions*, Worthley et al[10] describe 30-day and 1-year outcomes with the Navitor platform in 434 patients at low or intermediate surgical risk in the VANTAGE (Evaluation of TAVR Using the Navitor Valve in a Global Investigation) trial. The study, which enrolled patients at 36 centers across 3 continents, demonstrated excellent in-hospital results, with Valve Academic Research Consortium 3-defined technical success at 97.0%, no procedural mortality, and no moderate or greater PVL by 30 days. Additionally, all-cause mortality was 0.5% and all-cause stroke was 1.6% at 30 days. Hemodynamic performance of the valve was excellent, with single-digit mean gradients sustained to 1 year.

The investigators deserve congratulations for performing a well-done study that highlights the excellent procedural and short-term results that are

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

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.09.007

possible with this platform. These results demonstrate the importance of appropriate patient selection and operator skill. All patients were screened by a central committee, and 33.2% of patients were deemed to be ineligible. To put this in perspective, the screen failure rates in PARTNER 3 (Placement of Aortic Transcatheter Valve 3) and Evolut Low Risk trial were 34.2% and 14.8%, respectively. Further clarity on anatomical and clinical exclusions may facilitate replication of these results in contemporary practice. Patients at low and intermediate risk were eligible for the study, and this risk determination was multifactorial. Nevertheless, the study population likely veered toward a lower risk population, as 83.9% of patients had Society of Thoracic Surgeons Predicted Risk of Mortality scores <3%, with a mean score of 2.1 ± 1.1; this compares with 1.9% ± 0.7% in the TAVR arms of both PARTNER 3 and Evolut Low Risk (the investigators do note modifications in the Society of Thoracic Surgeons Predicted Risk of Mortality calculator over time). Additionally, the low rate of all-cause mortality at 12 months (0.8%) among the 262-patient subcohort is a combination both of the excellent procedural results but also reflects the lower risk nature of the population (by comparison, 1.0% in PARTNER 3 and 2.4% in Evolut Low Risk).[3,5]

Although the study met the prespecified primary safety and efficacy endpoints, there are some important points to consider. Given the rapid pace of innovation in the structural heart space, it is difficult to compare these results with those from intermediate-risk trials that commenced approximately a decade prior and from which these performance goals were derived. As such, a performance goal of 6.6% for moderate or greater PVL may not be acceptable in contemporary practice, especially compared with commercially available platforms. Patients in the study were treated according to best practices to ensure appropriate frame expansion and mitigation of PVL, with >90% of patients undergoing balloon aortic valvuloplasty prior to valve implantation, and approximately one-third underwent postdilation of the valve frame. In this study, 1 patient had moderate PVL that required valve reintervention and postdilation within 30 days of the index procedure. Additionally, 1 patient did not have the Navitor valve implanted, because of unfavorable anatomy, and 4 patients had valve embolization (1 converted to surgery, 3 with a second valve implanted). Although the rates of PVL are reassuring, a broader effectiveness endpoint may have captured these important outcomes as well.

One potential area for improvement in short-term outcomes may be lowering the rate of permanent pacemaker implantation (PPI), which was 18.7% at 30 days. As prior studies have noted an association between PPI and adverse outcomes, such a high rate, particularly in a younger population, may yield downstream consequences in the ensuing decades. Although the rate of PPI was 17.4% in the Evolut Low Risk trial, more recent studies such as Optimize PRO FX Addendum have demonstrated single-digit rates of PPI with the cusp overlap technique by allowing a more precise, shallower deployment.[11] Nevertheless, the consequences associated with shallower implantation may include greater risk for valve embolization (already ~1% in this study) along with additional challenges with coronary reintervention and subsequent valve interventions due to a more compromising coronary risk plane. Like the Evolut FX+ transcatheter aortic valve, the current Navitor Vision platform has radiopaque markers at the inflow; this platform was not used in this study and may allow more precise depth assessment prior to release. Continued refinement of best practice implantation technique ensuring adequate predilation, systematic assessment for valve underexpansion, and a slow, steady release technique may allow consistent deployment at the desired depth and balancing immediate risk for conduction system abnormality with facility of future reinterventions.

The promising results of the VANTAGE trial set the stage for the ongoing ENVISION IDE (Safety and Effectiveness of Navitor in Transcatheter Aortic Valve Implantation; NCT05932615) study, which currently is randomizing low- and intermediate-risk patients to the Navitor platform vs currently available commercial platforms. The study seeks to randomize up to 1,500 patients across >100 sites worldwide, with a primary composite endpoint of all-cause mortality or all stroke at 12 months post-procedure. Patients in this study, as in the other low-risk studies, will be followed for 10 years, which will shed light on the long-term durability and hemodynamic performance of the platform. Given the excellent procedural and 1-year outcomes seen in VANTAGE, the expectation will be for similar results in the larger, randomized population.

As the field of TAVR matures, additional valve platforms will be needed to address the limitations inherent to the current device technology. The

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OCTOBER 27, 2025:2528–2530

Navitor valve is a step in the right direction and provides desirable design elements with respect to future reintervention. The excellent results of the VANTAGE study are an important landmark toward indication expansion of the Navitor valve in low- and intermediate-risk patients. As lifetime management considerations will remain the focus as TAVR expands into a younger patient population, thoughtful device choice and implant techniques may prove critical in our patients' ability to tolerate future reintervention safely and optimize lifelong management of their aortic valve disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Vora is a consultant for Medtronic and Edwards Lifesciences. Dr Reed is a consultant for Abbott Laboratories, Boston Scientific, and Edwards Lifesciences.

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KEY WORDS Navitor, pacemaker, self-expanding valve, TAVR

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

VIEWPOINT

Attempting to Define the Boundaries of Medical Futility in Contemporary Interventional Cardiology

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The field of interventional cardiology is propelled by ongoing advances in percutaneous and surgical therapies. The emphasis on technological innovation may at times conflict with the foundational medical ethic of "do no harm." This tension is particularly pronounced in a substantial subset of patients undergoing transcatheter interventions who are elderly, frail, and burdened with comorbidities that may significantly limit the potential benefit of such procedures.

Although newer devices and techniques offer expanded therapeutic possibilities, a difficult but essential question persists: when should advanced cardiac interventions be withheld in critically ill patients whose chances of meaningful clinical improvement are marginal? This dilemma is particularly relevant in cases of postprocedural complications, when the operator may experience a strong emotional desire to continue salvage efforts. Despite the frequency of such scenarios, there is limited structured education on this topic during general or interventional cardiology fellowship training. Furthermore, research on optimal strategies for navigating these complex decisions remains sparse.

DEFINING CATEGORIES OF FUTILITY SITUATIONS THAT MAY INFLUENCE APPROPRIATENESS DECISIONS

Medical futility refers to the clinical judgment that a medical intervention is unlikely to produce meaningful benefit for the patient. Historically rooted in the inability to achieve a specific physiological outcome such as restoring spontaneous circulation after cardiac arrest, this concept has evolved to include broader considerations such as patient-centered goals, quality of life, and ethical responsibility. It is critical to acknowledge that medical futility is inherently subjective. Judgments often vary according to clinical experience, patient values, and cultural perspectives.

Two primary forms of futility are recognized: quantitative and qualitative. *Quantitative futility* refers to situations in which the probability of achieving a desired physiological effect, such as survival beyond 30 days or recovery of consciousness, is exceedingly low, often cited as <1% to 5% or, in some contexts, <50% when combined with high morbidity or poor quality of life. *Qualitative futility* applies when an intervention may achieve a biological effect, such as maintaining circulation or respiration, but the anticipated outcome is one the patient would find unacceptable, such as a permanent vegetative state, chronic ventilator dependence, or survival with profound cognitive or functional impairment.

In practice, the determination of futility is not purely statistical or technical but must integrate clinical evidence, prognostic tools (eg, Society of Thoracic Surgeons risk score, European System for Cardiac Operative Risk Evaluation II score), and, most important, the patient's own values and

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

Manuscript received July 7, 2025; revised manuscript received September 8, 2025, accepted September 17, 2025.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.09.016

definitions of acceptable outcomes. Formalizing this concept through structured decision making, multidisciplinary dialogue, and ethics support may help ensure that care remains goal concordant and ethically grounded, even when high-risk interventions are being considered.

Although widely used in clinical discourse, the term *medical futility* lacks a universally accepted definition, especially in interventional cardiology. In an international study on decision making for older adults, Kalra et al[1] identified substantial variation in perceptions of futility, particularly between the United States and countries with different health care frameworks.

In current cardiovascular intervention literature, 30-day mortality and health-related quality of life are recognized as coequal and complementary metrics for evaluating procedural success, patient selection, and the true value of care.[2] Thirty-day mortality offers an objective, time-bound measure of short-term safety, while health-related quality of life reflects the broader and longer term patient-centered outcomes, including functional independence, recovery trajectory, and quality of daily living. Both are essential for determining whether an intervention provides meaningful benefit, particularly in elderly, frail, and highly comorbid individuals.

SHORT-TERM MORTALITY

Despite rapid technological progress, short-term mortality remains a concern, particularly among elderly, frail, and highly comorbid patients. A 2023 study published in the *Journal of the Society for Cardiovascular Angiography & Interventions* reported that among 137,164 patients undergoing percutaneous coronary intervention (PCI), 2,121 (1.55%) died within 30 days postdischarge.[3] Notably, more than one-half (55.6%) of these deaths occurred within the first 10 days. Independent predictors of early mortality included advanced age, cardiogenic shock, and chronic kidney disease.[3]

Furthermore, in a large nationwide cohort study, Cordova Sanchez et al[4] examined >139,000 cancer patients who underwent PCI and reported a 30-day mortality rate of 20.1%, driven largely by comorbid conditions such as malignancy and bleeding risk. Although approximately 80% of patients survived beyond the first month, the study highlighted the persistent clinical challenge in identifying in advance which patients are at highest risk for early mortality despite technically successful interventions.[4]

QUALITATIVE FUTILITY

There are multiple decision points at which qualitative futility judgments regarding clinical decision must be made, including but not limited to the initiation of mechanical circulatory support (MCS), which requires clearly defined endgame criteria and may or may not allow shared decision making; the decision to undertake a complex, high-risk interventional procedure, for which balanced shared decision making is a priority; intraprocedural decisions regarding the extent of the procedure, which are ideally anticipated and addressed at the time the initial procedural decision is made; and intraprocedural decisions about how to respond to complications, which often must be made "on the fly" without the benefit of shared decision making.

However, survival alone does not capture the broader burden of recovery or the value of intervention. Numerous studies have shown that elderly patients who survive intensive care unit (ICU) stays or advanced cardiac interventions often experience persistent functional decline, new dependencies in daily living, and eventual institutionalization.[5] Health-related quality-of-life tools such as the EQ-5D and activities of daily living assessments have been used to quantify the risk for adverse outcomes, particularly following ICU stays or hospitalizations for heart failure. These studies suggest that escalation of care may not always align with patient-centered goals, particularly when meaningful recovery or independent living is unlikely, even in the context of procedural survival.[5]

ETHICAL CONSIDERATIONS GUIDING APPROPRIATENESS DETERMINATION

From an ethical standpoint, continuing aggressive treatment in medically futile scenarios may violate the 4 foundational principles of biomedical ethics: beneficence, nonmaleficence, autonomy, and distributive justice. Thus, the ethical imperative is to minimize harm, respect informed preferences, and steward health care resources responsibly. Overtreatment in the setting of medical futility is not only clinically ineffective but also ethically indefensible.

BENEFICENCE. Beneficence is undermined when interventions no longer provide therapeutic benefit and merely prolong suffering.

NONMALEFICENCE. The edict to "do no harm" is breached when patients undergo arduous burdensome treatments, such as painful invasive procedures

or prolonged ICU stays, without realistic hope of recovery.

AUTONOMY. Autonomy must be upheld by honoring informed decisions made by patients or their surrogates. It is meaningful only when choices are based on accurate and realistic information. Offering futile care may create false hope and compromise informed consent.

DISTRIBUTIVE JUSTICE. Distributive justice is challenged when scarce health care resources are diverted to nonbeneficial interventions in futile circumstances, potentially limiting access to those more likely to benefit.

APPROPRIATENESS DETERMINATIONS IN EMERGENT VS ELECTIVE CIRCUMSTANCES

With increasing use of extracorporeal membrane oxygenation and MCS devices, such as microaxial flow pumps, critically ill patients, particularly older adults, are often maintained in a state of "metastability" while awaiting recovery or further intervention. This approach has at times blurred the boundary between lifesaving therapy and medical futility. In patients with poor baseline function or progressive decline, such technologies can unintentionally prolong suffering. In 2024, Blumer et al[6] reported a concomitant rise in temporary MCS use among patients older than 75 years with cardiogenic shock and issued a scientific statement recommending age-adjusted risk stratification prior to device escalation. Their recommendation emphasized balancing potential benefit against the risks of aggressive intervention and advocated for shared decision making and early palliative care involvement. Klein et al[7] reported that although microaxial flow pumps and other MCS devices are increasingly used in older patients with cardiogenic shock, their benefit/risk profile remains uncertain in this cohort. These trends raise concern that device proliferation may paradoxically worsen outcomes when not aligned with patient-centered goals.

Despite initiatives by organizations such as the American Medical Association to define ethical frameworks for medical futility beyond palliative care, consensus remains elusive because of the inherently subjective and value-laden nature of the term. Cardiovascular guidelines, including those for procedures such as PCI and transcatheter aortic valve replacement, acknowledge the concept of medical futility, especially when treating high-risk populations. These guidelines emphasize shared decision making, in which clinicians and patients assess not only technical feasibility of a procedure but also the likelihood of meaningful survival or quality-of-life improvement. Recognizing futility supports ethical medical care and underscores the importance of multidisciplinary discussions, early palliative care involvement, and individualized care planning in interventional cardiology.

In high-acuity settings such as the ICU or catheterization laboratory, decisions regarding the initiation of MCS or the withdrawal of life-sustaining therapies are often made under intense time pressure, sometimes within minutes. These compressed time frames may preclude comprehensive shared decision making, especially when patient preferences are undocumented or surrogate decision makers are unavailable. Such urgency can lead to reflexive escalation rather than thoughtful, patient-centered care, increasing the risk for invasive interventions with questionable benefit. To mitigate this, some institutions have developed structured protocols such as "code comfort." These are designed to provide a rapid, standardized response when aggressive interventions are no longer appropriate. Under code comfort, a team often including palliative care, nursing, and physicians is activated to shift care from life prolonging to comfort focused. This model ensures that dignity, symptom relief, and quality of life are prioritized, especially in situations in which escalation would likely cause more harm than benefit.

Advance care planning also plays a pivotal role. When patients' values, goals, and preferences are proactively documented, clinicians are better equipped to make aligned decisions during high-stakes emergencies. Embedding advance care planning into routine clinical workflows promotes ethically sound, goal-concordant care, even under acute time constraints.

DECISION-MAKING PROCESSES AND ALGORITHMS

To address the current variability and subjectivity in decision making for critically ill cardiac patients, a structured, goal-directed framework is needed in a stepwise, multidisciplinary model that guides clinicians through key inflection points in the care trajectory of patients undergoing interventional or surgical cardiac procedures. Although tools such as early palliative care integration, improved risk stratification, and preference documentation continue to evolve, this framework provides a practical, interim solution. It promotes timely, patient-centered transitions between escalation and de-escalation when appropriate.

HEART TEAM REVIEW

In today's fragmented, subspecialty-focused, and less primary physician-centric approach, a critical but often overlooked issue arises. In the past, a single physician often guided a patient's full clinical course, including procedural decisions grounded in long-term familiarity with the patient's values. Today, these decisions may fall to the interventional cardiologist, who may lack comprehensive understanding of the patient's goal or longitudinal history. This fragmentation introduces ethical tension, especially in patients with complex comorbidities and uncertain outcomes.

We advocate a "heart team" approach, similar to that used for revascularization decision making, in which informed consent becomes a structured, collaborative dialogue among the primary ream, interventionalists, palliative care, and surrogate decision makers. In addition, informed consent, rather than serving as a last-minute legal formality, in complex, high-risk cases should be a deliberative, multidisciplinary conversation. Although more time consuming, this approach fosters shared understanding and ensures that decisions align with patient values and goals of care.

SHARED-DECISION MAKING

In situations in which expected benefits are uncertain or patients lack full decision-making capacity, a distinction should be made between informed consent, in which the patient or surrogate fully understands and agrees to the intervention, and informed assent, in which the team seeks the patient's or surrogate's willingness to proceed, even if understanding or authority is limited. Assent acknowledges medical uncertainty while preserving the ethical integrity of patient-centered care. Embedding ethics consultations or structured shared decision-making tools into this process may bridge communication gaps and ensure that care remains anchored in patients' definitions of dignity, hope, and acceptable outcomes. This team can incorporate specialties including but not limited to interventional cardiology, intensivist, cardiothoracic, heart failure, palliative care, and ethics.

GOALS FOR EDUCATION AND TRAINING PRACTICES

General and interventional cardiology fellows are typically well trained in procedural techniques and hemodynamic assessment but often receive limited education on navigating end-of-life conversations. Integrating structured ethical and clinical decision-making frameworks may be useful taught in internal medicine programs and augmented in fellowships. Case-based learning involving palliative care principles can prepare trainees for difficult, value-based discussions. Within the discipline of cardiology, advanced heart failure teams provide a useful model, having evolved into multidisciplinary units skilled in balancing advanced therapies with realistic outcomes and patient preferences. Interventional cardiology teams could benefit from a similar collaborative training with ethics, palliative care, and critical care specialists.

Beyond didactics, incorporating real-world case simulations and interdisciplinary team-based discussions is a valuable educational strategy. These experiences promote systematic, patient-centered approaches that weigh technological possibilities alongside compassion and ethical principles. Furthermore, research is needed to develop evidence-based guidelines for deescalating or discontinuing interventions. Currently, decisions to initiate or withdrawal advanced therapies often hinge on physician discretion and family input, rather than standardized, objective protocols.

Such data could include validated risk scores such as the Society of Thoracic Surgeons risk score and the European System for Cardiac Operative Risk Evaluation II score, hemodynamic parameters (such as cardiac output, lactate levels, and mixed venous oxygen saturation), biomarkers (eg, troponin, brain natriuretic peptide), and frailty indexes. These tools may help quantify physiological reserve, procedural risk, and the likelihood of meaningful recovery, thereby facilitating more transparent, evidence-informed decision making.

PROPOSED SOLUTIONS

We propose 4 primary strategies to address these issues.

First, develop guidelines. Professional societies including the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions should consider developing consensus guidelines for end-of-life decision making in interventional cardiology.

Second, integrate palliative care education and instruction into general and interventional cardiology fellowships. This includes formal didactics, case-based learning, interdisciplinary simulations, and measurable competencies aligned with Accreditation

Council for Graduate Medical Education milestones. Key skills should include leading goals-of-care meetings, applying validated prognostic tools, and initiating comfort-focused care. Although formal palliative cardiology tracks are not yet established, pilot curricula do exist. For example, Kavalieratos et al[8] advocated integrating palliative care into heart failure training, offering a potential model for interventional programs.

Third, expand research and CME, promoting research into ethical decision making. Future studies should evaluate current practices among interventionalists and test frameworks that enhance clarity and consistency. CME on palliative approaches, shared decision making, and medical futility should be offered to practicing clinicians to ensure alignment with evolving best practices.

Last, the interventional cardiology program should create a formal program that conducts mid- to late-term follow-up evaluations of the outcomes of their patients at high futility risk. Frequently, the interventional program's last contact with the patient is 1 to several days following the procedure or the decision not to perform the procedure. This will foster the educational goal advocated in this paper. The interventional team can acquire a great deal of informative clinical perspective from late-term follow-ups.

CONCLUSIONS

Interventional cardiology needs structured frameworks to guide decisions for critically ill patients and those with complications, including integrating palliative care, advancing research, and creating guidelines for comfort-focused care when futility is reached. These steps, relevant across procedural specialties, promote ethically grounded, goal-concordant care that prioritizes patient values and dignity.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Al'Aref is supported by NIH 2R01 HL12766105 & 1R21 EB030654, receives royalty fees from Elsevier and consultancy fees from Shockwave Medical. The other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS advanced mechanical support, comfort care, interventional cardiology, medical futility

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

IMAGES IN INTERVENTION

Evaluation of Transcatheter Aortic Valve Stent Frame Expansion Using Intravascular Ultrasound

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Transcatheter aortic valve (TAV) underexpansion can affect valve performance, durability, and risk for leaflet thrombosis and is associated with adverse clinical outcomes (**Figure 1**).[1-3] Intraprocedural evaluation of TAV stent frame expansion is currently limited to fluoroscopy, which may be unreliable despite multiple projections or transesophageal echocardiography, which is more invasive. We demonstrate the potential utility of intravascular ultrasound (IVUS) to assess and treat TAV underexpansion (**Figure 2**).

Following TAV deployment, a 10-Hz IVUS catheter (Philips Healthcare) is advanced along a 0.035-inch stiff left ventricular guidewire, distal to the inflow of the valve. A manual pull back at 1 to 5 mm/s is performed, and TAV geometry can be assessed at multiple stent frame levels. IVUS can objectify TAV frame underexpansion and, after postdilatation, demonstrate a significant increase in TAV area, which is not appreciable on fluoroscopy (**Figures 3 and 4**, Video 1).

This ability to perform a rapid and noninvasive assessment of TAV frame expansion and geometry may be useful in challenging scenarios such as heavily calcified bicuspid AS or valve-in-valve procedures, in which TAV underexpansion may be anticipated.[3,4] Furthermore, with TAVR expanding to younger populations, the longer term impact of achieving a uniform and well-expanded TAV may become increasingly relevant. However, although underexpansion is increasingly linked to adverse clinical outcomes, there are comparatively few data demonstrating that postdilatation to correct underexpansion is associated with improved longer term clinical outcomes.[5] Additionally, postdilatation can be associated with an increased risk for periprocedural complications or damage to TAV leaflets.

Therefore, further studies are warranted to evaluate the effectiveness of different intraprocedural imaging techniques, such as IVUS, to identify TAV underexpansion and to determine the acute procedural and longer term risks and benefits associated with corrective postdilatation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Khokhar has received speaker fees from Abbott and Boston Scientific. Dr De Backer has received institutional research grants and consulting fees from Abbott, Boston Scientific, and Medtronic. Dr Kobari has received speaker fees from Abbott and Boston Scientific. Dr Bieliauskas has received institutional research grants and consulting fees from Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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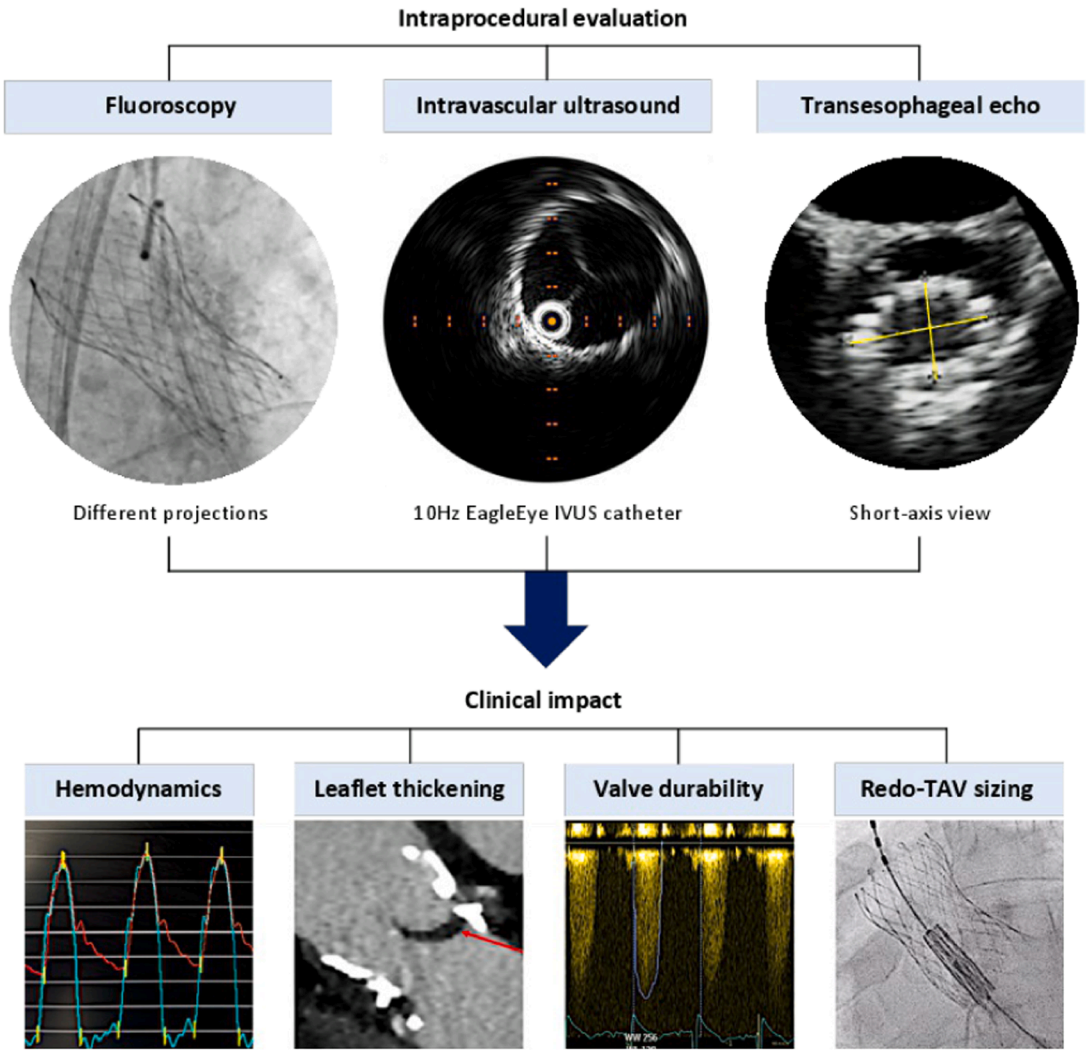
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 6, 2025; revised manuscript received June 22, 2025, accepted July 2, 2025.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2025.07.002

FIGURE 1 Evaluation and Clinical Impact of TAV Stent Frame Expansion



IVUS = intravascular ultrasound; TAV = transcatheter aortic valve.

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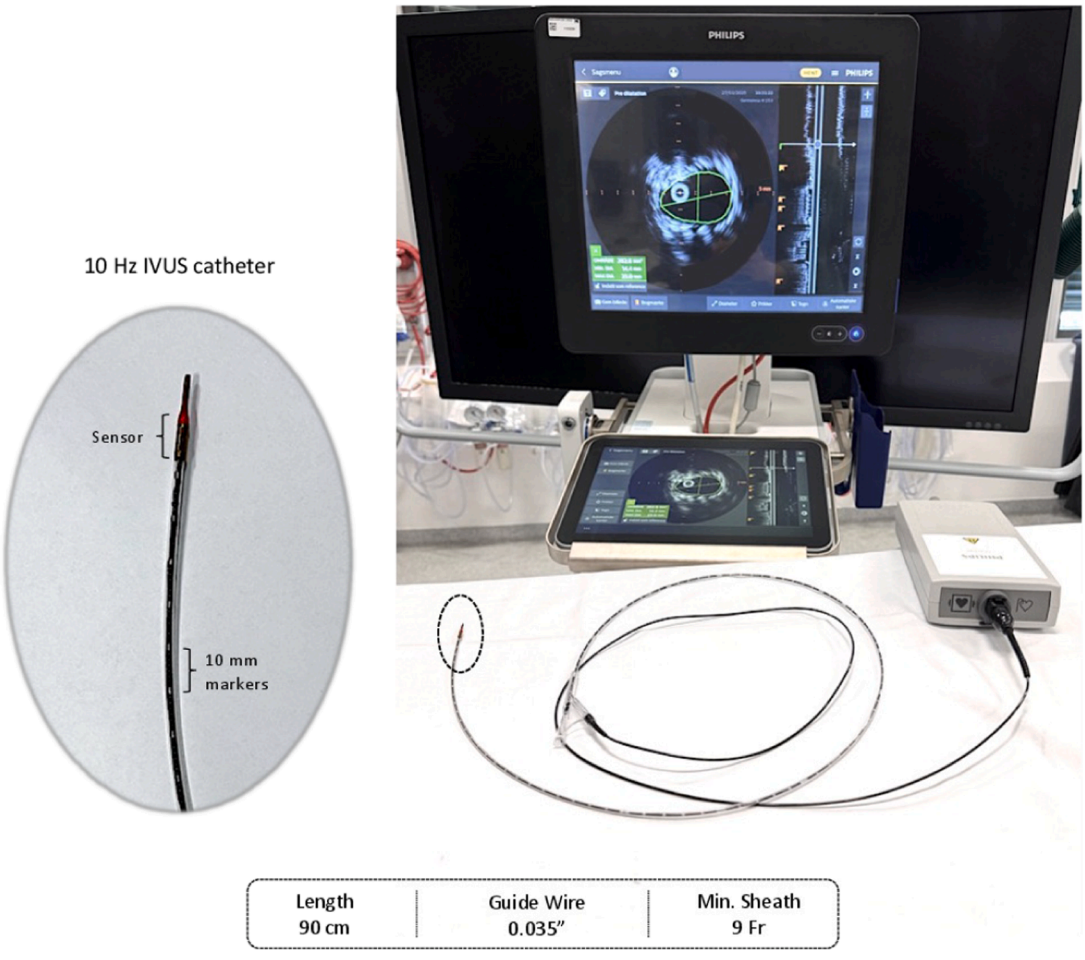
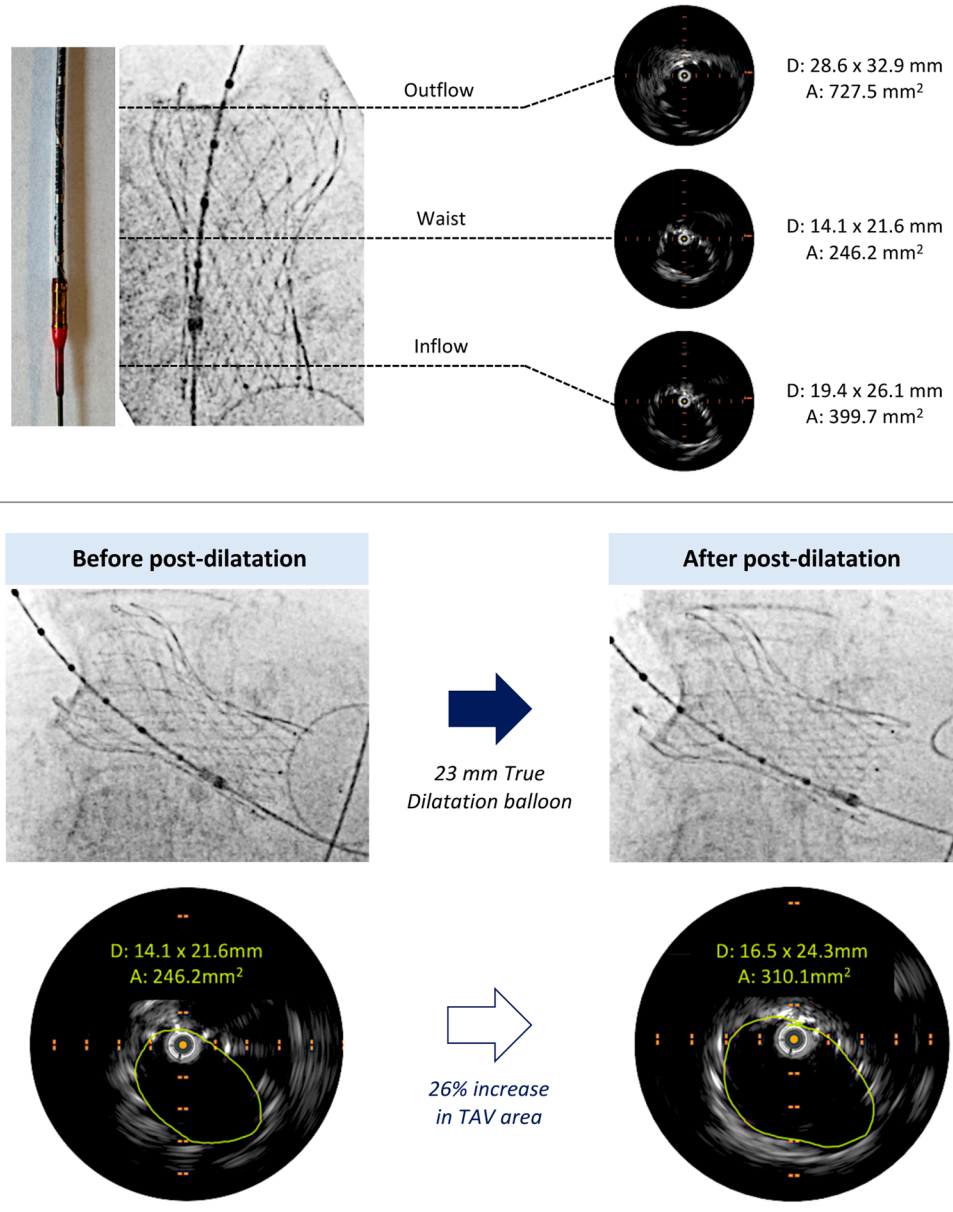
FIGURE 2 **Setup for IVUS Imaging During Transcatheter Aortic Valve Replacement**



The Volcano intravascular ultrasound (IVUS) catheter (Philips Healthcare) is 0.035-inch guidewire compatible, with a distally located sensor and 10-mm calibration markers. Min. = minimum.

FIGURE 3 **IVUS Evaluation of Evolut FX+ Expansion and Geometry in Bicuspid Aortic Stenosis**



Despite effective predilatation, intravascular ultrasound (IVUS) evaluation confirmed an underexpanded and eccentric Evolut FX+ (Medtronic). After postdilatation, IVUS confirmed increased circularity and a 26% increase in transcatheter aortic valve (TAV) area. A = area; D = diameter.

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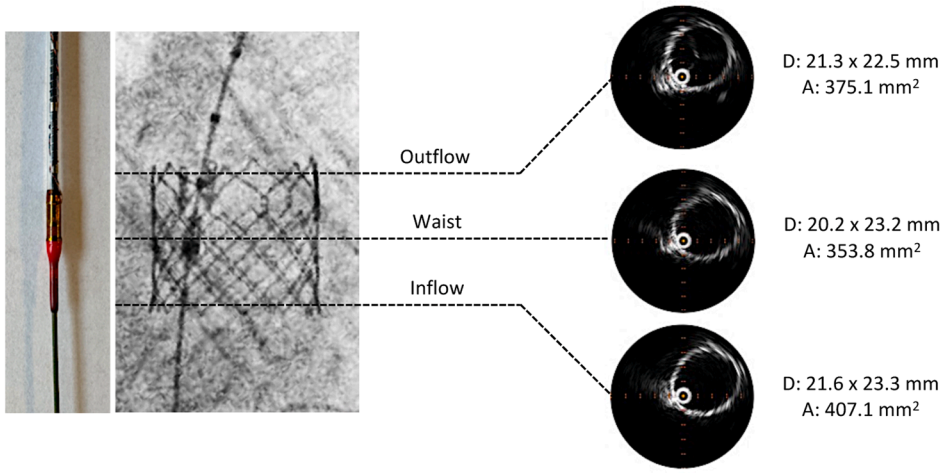
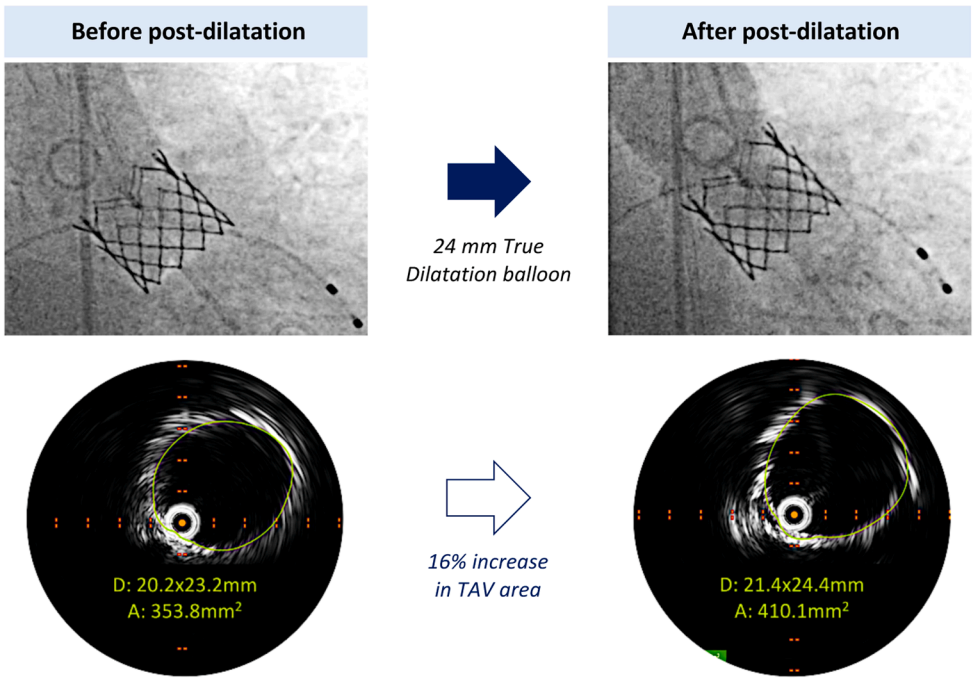
FIGURE 4 **Intravascular Ultrasound Evaluation of DurAVR Expansion and Geometry in Severely Calcific Aortic Stenosis**





Intravascular ultrasound evaluation confirmed an underexpanded DurAVR (Anteris Technologies), which improved after postdilatation, resulting in a 16% increase in tricuspid aortic valve (TAV) area. A = area; D =diameter.

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KEY WORDS intraprocedural optimization, stent frame expansion, transcatheter aortic valve replacement, vascular ultrasound

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

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

IMAGES IN INTERVENTION

Transatrial Stent Bridging for Malignant Cavoatrial Junction Obstruction

Salvage Therapy in Metastatic Thyroid Cancer

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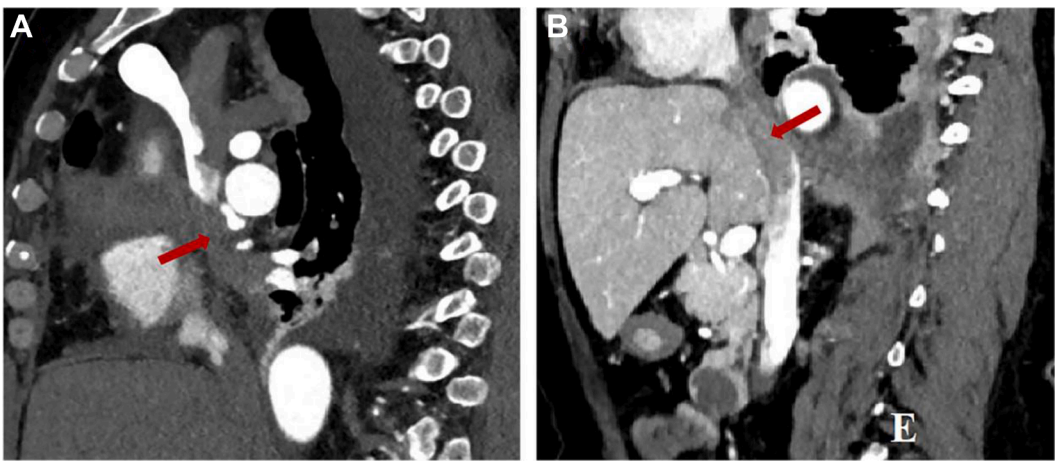
A 73-year-old woman with hypertension presented with progressive dyspnea and hemoptysis. She underwent thyroidectomy for refractory differentiated thyroid cancer 3 years before. One month before admission, imaging revealed progression with pulmonary and pleural metastases, complicated by pulmonary embolism and right atrial thrombus.

Computed tomographic angiography demonstrated extensive filling defects within the superior vena cava (SVC) and inferior vena cava (IVC) (Figure 1). Venography confirmed critical SVC stenosis with

FIGURE 1 Computed Tomographic Angiography



(A) Superior vena cava stenosis (red arrow). (B) Inferior vena cava stenosis (red arrow).

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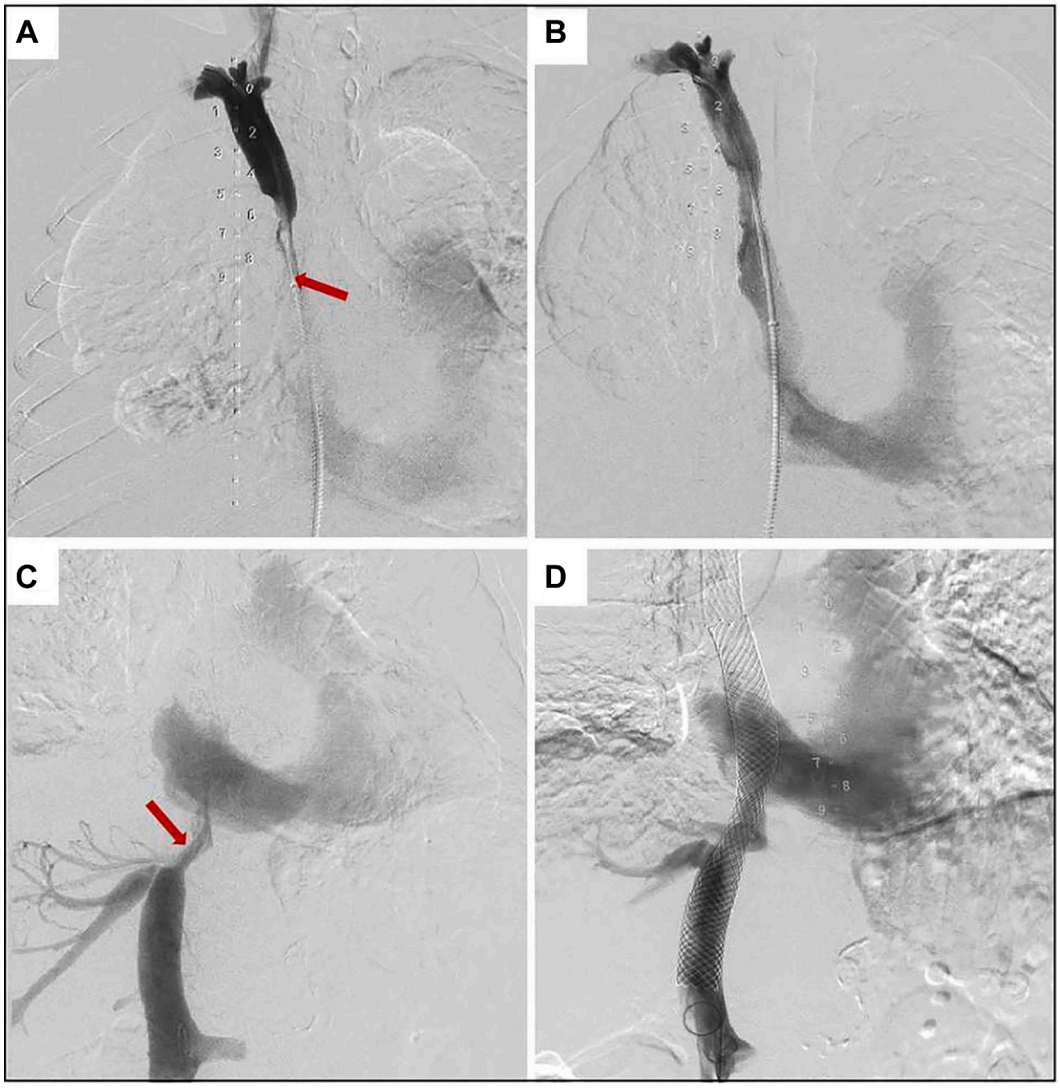
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 23, 2025; accepted July 11, 2025.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.07.018

FIGURE 2 **Vena Angiography**

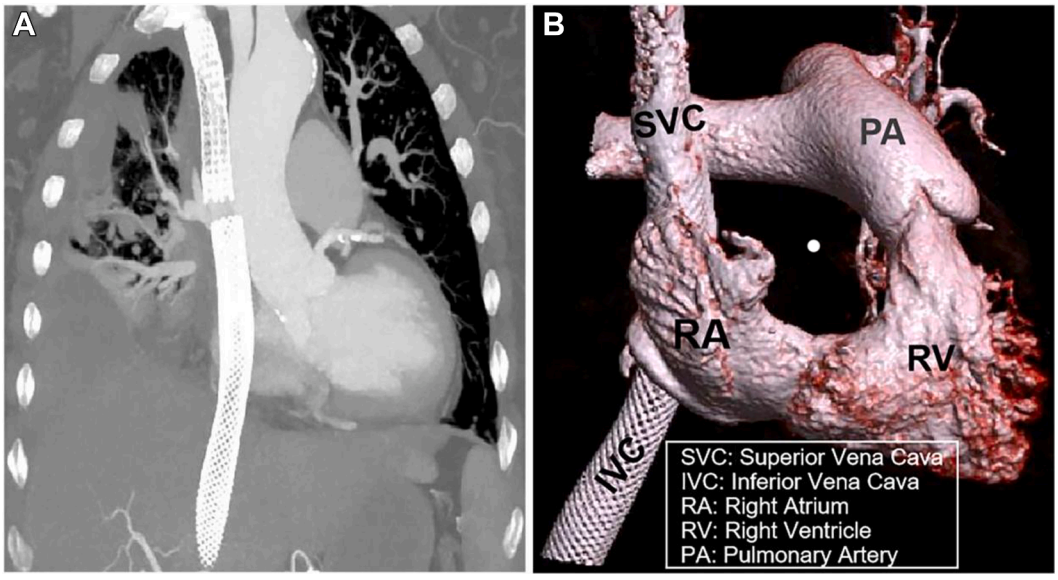


(A,B) Superior vena cava angiography before and after stent placement. (C,D) Inferior vena cavography before and after transatrial stent placement. Red arrows indicate the sites of stenoses.

minimal antegrade flow (Figure 2A). Intravascular biopsy revealed metastatic epithelial-derived thyroid carcinoma. A 14 × 60 mm self-expanding bare-metal stent (Boston Scientific) was deployed across the SVC obstruction. Postprocedural venography documented restored SVC patency with resolution of collateral circulation. Subsequent IVC venography revealed an obstructing tumor thrombus extending from the hepatic segment to the right atrium, causing >90% stenosis with retrograde hepatic vein filling. After balloon angioplasty was performed, transient luminal improvement was achieved.

The patient exhibited a recurrence of exertional dyspnea, abdominal distension, and lower extremity edema within 2 weeks. Venography confirmed in-stent restenosis (Figure 2B). Following multidisciplinary consensus, a novel transatrial approach was undertaken. A 16 × 120 mm self-expanding stent (Boston Scientific) was deployed from the SVC to the IVC hepatic segment, traversing the right atrium

FIGURE 3 Follow-Up Computed Tomographic Angiography



(A) Sagittal oblique maximum-intensity projection computed tomographic angiography. (B) Three-dimensional multiplanar reconstruction.

(**Figure 2C**, Video 1). Immediate IVC patency was achieved without procedural complications (**Figure 2D**). The patient reported significant symptom resolution and was discharged on rivaroxaban (20 mg/d). Follow-up at 3 months showed preserved stent integrity without fracture or deformation, though slight migration was observed (**Figure 3A and 3B**). The patient died of tumor progression at 5 months without malignant arrhythmia occurrence.

Endovascular intervention with stenting has become the first-line treatment of care for SVC obstruction.[1] This case suggests that in patients with refractory stenosis at the cavoatrial junction, a traversing atrial stent may provide a viable salvage option to decrease risk for arrhythmia and stent migration associated with conventional approaches.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the National Natural Science Foundation of China (grant 82400072). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS caval vein stenosis, metastatic thyroid cancer, transatrial stent

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

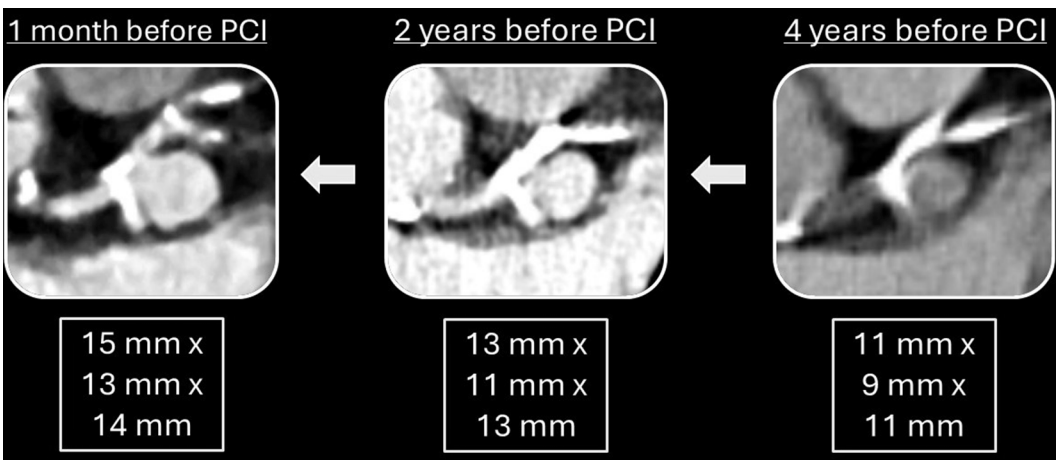
IMAGES IN INTERVENTION

Novel Treatment of Left Main Bifurcation Aneurysm With Intrasaccular Flow Disruptor

Conor M. Lane, MB BCh,[a] Waleed Brinjikji, MD,[b] Jason H. Anderson, MD,[a,c] Rajiv Gulati, MD, PhD[a]

A 74-year-old man was noted to have a large saccular coronary artery aneurysm (CAA) arising from the distal left main bifurcation during preoperative coronary angiography prior to aortic valve replacement and coronary artery bypass grafting (CABG). Serial imaging showed progressive coronary aneurysm enlargement (**Figure 1**) and percutaneous intervention was pursued following CABG. Anatomy was felt to be suboptimal for stent-assisted coiling, and after multidisciplinary discussion, implantation of an intrasaccular flow disruptor was planned. Dual antiplatelet therapy with was

FIGURE 1 **Preprocedural Imaging**



PCI = percutaneous coronary intervention.

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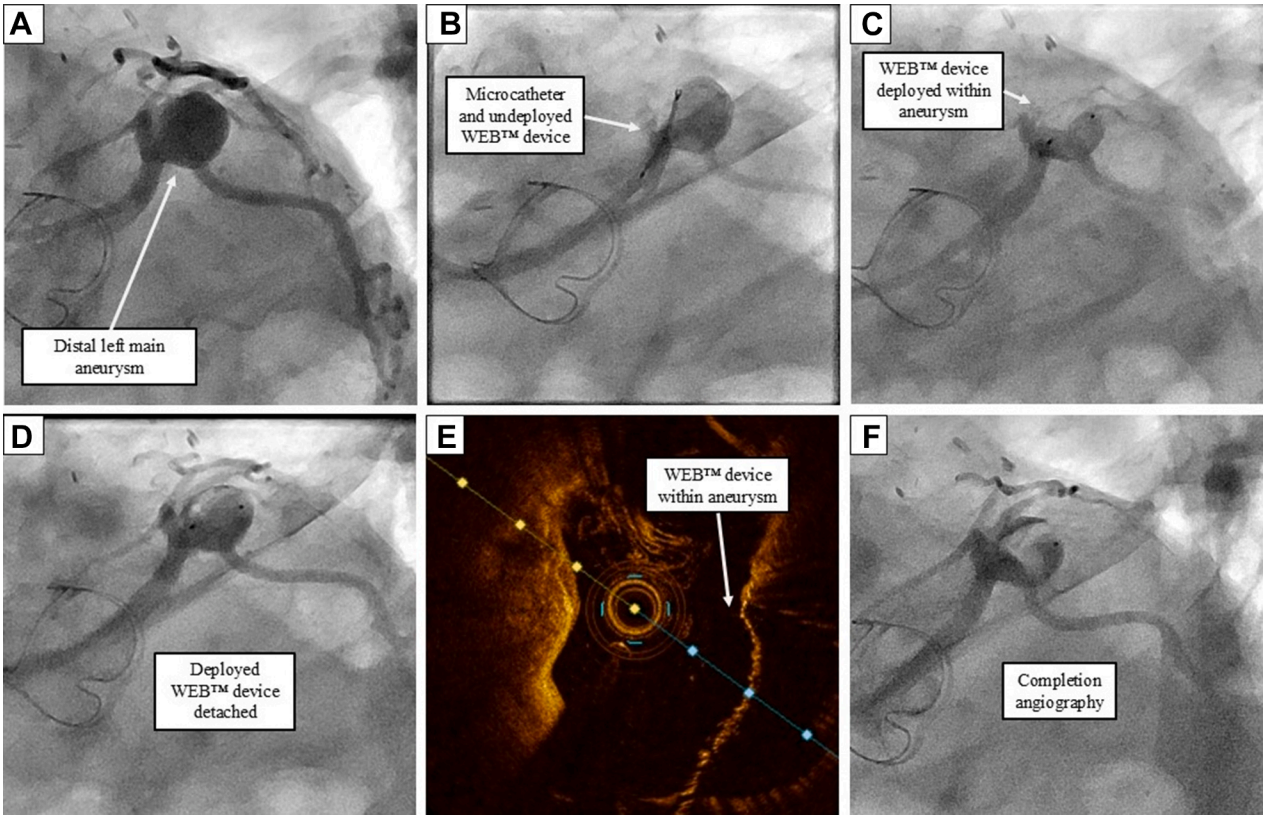
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 7, 2025; accepted May 29, 2025.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.05.040

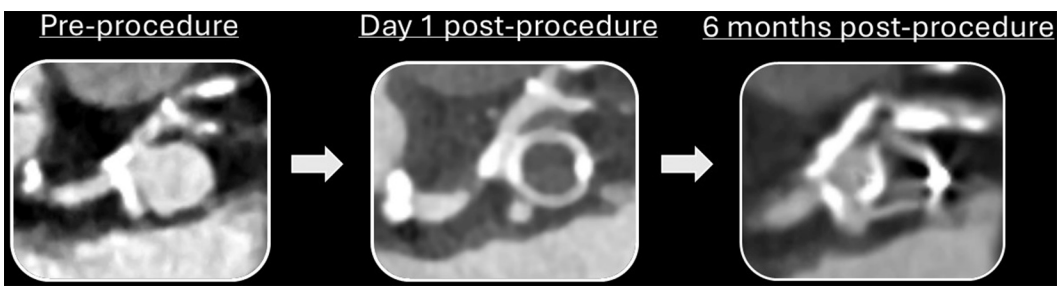
FIGURE 2 Case Images



(A) Distal left main aneurysm; (B) microcatheter and undeployed WEB device; (C) WEB device deployed within aneurysm; (D) deployed WEB device attached; (E) WEB device within aneurysm; and (F) completion angiography.

administered periprocedurally. The right radial artery was accessed with a 7-F sheath, and a 7-F XB 3.5 guide catheter was used to engage the left main coronary ostium. Angiography was performed in multiple projections to delineate the aneurysm, neck, and bifurcation (Figure 2A). The aneurysm was then wired with a 0.024-inch soft guidewire and the delivery catheter was positioned in the aneurysm, with position confirmed in multiple views (Figure 2B). A WEB SLS 11 Device (Terumo) was delivered easily and the position was modified to optimize space occupation without protrusion into the native

FIGURE 3 Postprocedural Imaging



coronary system (Figure 2C). Once an ideal position was achieved, the device was released in a standard manner (Figure 2D). Completion optical coherence tomography was performed from the left anterior descending coronary artery that confirmed excellent positioning at the aneurysm neck without protrusion (Figure 2E). Completion angiography confirmed excellent positioning and indicated evolving stasis as expected (Figure 2F). No coronary compromise was observed. The procedure was tolerated well, and no acute complications were observed. Follow-up computed tomography angiography confirmed correct device placement and absent residual flow to the coronary aneurysm at day 1 and 6 months post-procedure (Figure 3). The patient was discharged on low-dose aspirin for 6 weeks.

Left main bifurcation CAAs are a challenging clinical entity. Surgical resection is complex due to the location of the left main behind the pulmonary artery. Intrasaccular flow disruptors have demonstrated efficacy and safety in treating intracranial bifurcation aneurysms.[1] In this case, we report the novel use of an intrasaccular flow disruptor to successfully treat a large CAA of the left main artery.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS coronary aneurysm, intrasaccular flow disruptor, percutaneous coronary intervention

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

IMAGES IN INTERVENTION

A Modified POT-Side-POT Technique for Distal Stent Expansion in Bifurcation PCI

The OTUS Strategy

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Provisional stenting remains the standard approach for coronary bifurcation lesions, as supported by the European Bifurcation Club (EBC) consensus.[1] The re-proximal optimization technique (rePOT) is widely used for its procedural simplicity.[2] However, the CRABBIS (Comparison of Results Achieved by Different Ballooning Techniques in Bifurcation Stenting) study highlighted its limitations, especially in achieving optimal distal stent expansion compared with the POT-kissing-POT (PKP) technique.[3]

To address this issue, we propose OTUS (Optimization Technique Using a Single balloon), a simplified rePOT variant using 1 compliant balloon (CB) for both proximal and distal optimization, with pressure guided by Finet's law to ensure uniform stent apposition and procedural efficiency.

The OTUS sequence includes the following steps:

1. Initial POT is performed after stent deployment using a CB inflated at high pressure, sized according to the proximal main vessel diameter using the manufacturer's balloon compliance chart (procedural sequence shown in **Figures 1 and 2**).
2. Rewiring through the distal stent struts is followed by side branch dilation with a specific non-CB (**Figures 3 and 4**).
3. The same CB is reintroduced and inflated at low pressure across the carina to perform the distal optimization technique (DOT), targeting the distal main vessel diameter according to the compliance chart (**Figure 5**).
4. The same CB is then reinflated proximally at a pressure selected from the compliance chart, to match the proximal main vessel diameter, completing the final POT (rePOT) (**Figures 6 to 8**).

For example, if the proximal main vessel (D1) is 4.0 mm, the side branch (D3) is 2.5 mm, and the distal main vessel (D2) is 3.39 mm (per Finet's law: $D1 = 0.678 \times [D2 + D3]$), a Sapphire 3.5-mm CB (OrbusNeich) reaches 3.39 mm at 4 atm and 4.03 mm at 16 atm.

OTUS maintains the simplicity of the rePOT strategy while addressing its main limitation, distal underexpansion, through the use of a single CB and tailored pressure modulation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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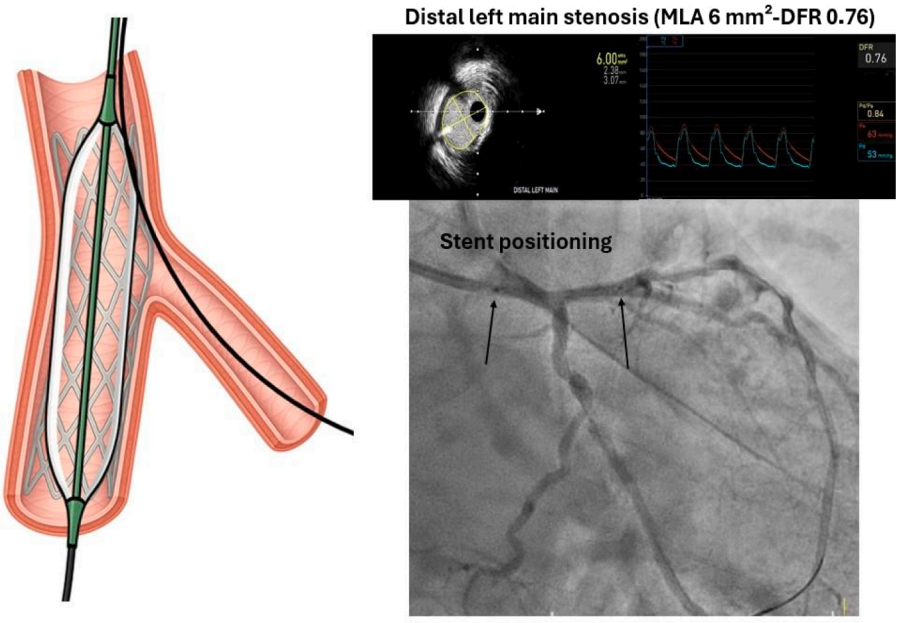
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 26, 2025; accepted July 23, 2025.

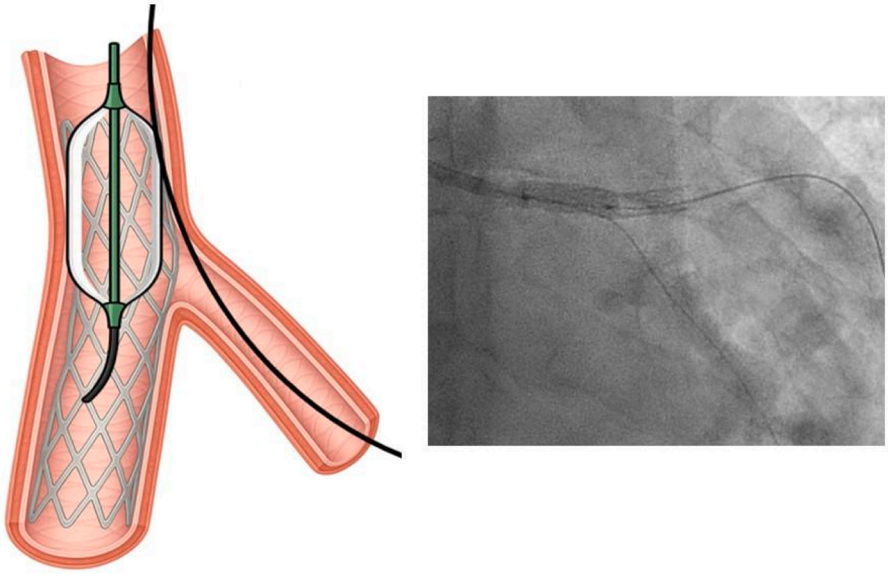
ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2025.07.026

FIGURE 1 **Stent Deployment**



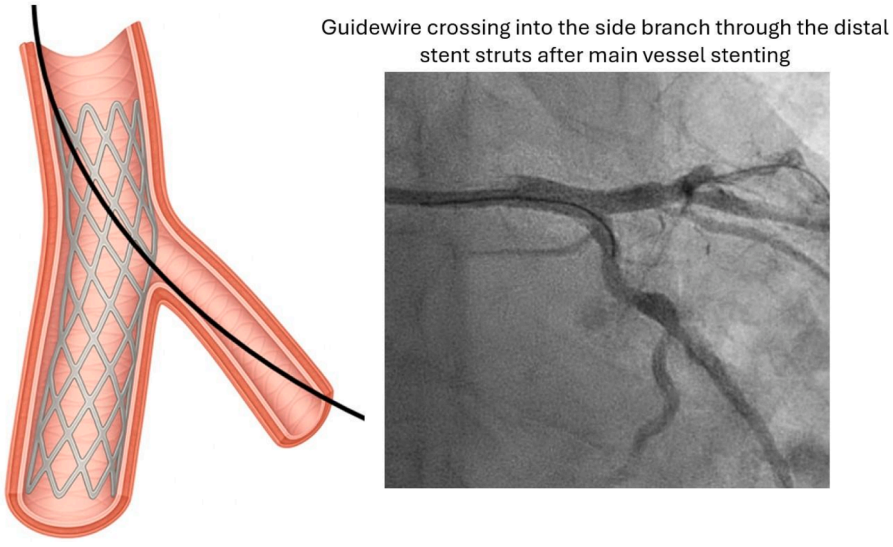
(Left) schematic representation of stent deployment in the left main bifurcation. (Top right) intravascular ultrasound (IVUS) image of distal left main stenosis with MLA 6 mm^2 and DFR 0.76. (Bottom right) angiographic view showing stent positioning (arrows). DFR = diastolic hyperemia-free ratio; MLA = minimal lumen area.

FIGURE 2 **Initial Proximal Optimization Technique**



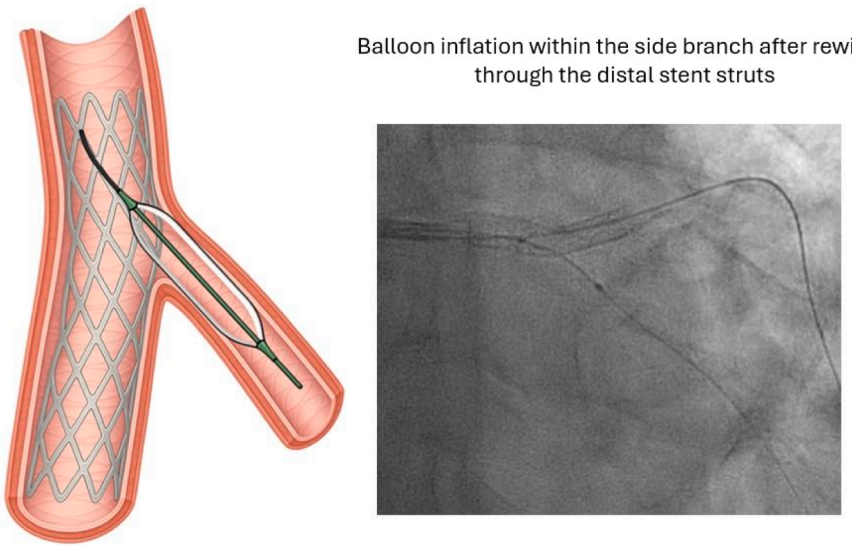
(Left) schematic illustration of proximal optimization technique (POT) with compliant balloon sizing to the proximal main vessel. (Right) angiographic image of POT balloon inflation.

FIGURE 3 Rewiring Through the Distal Stent Struts



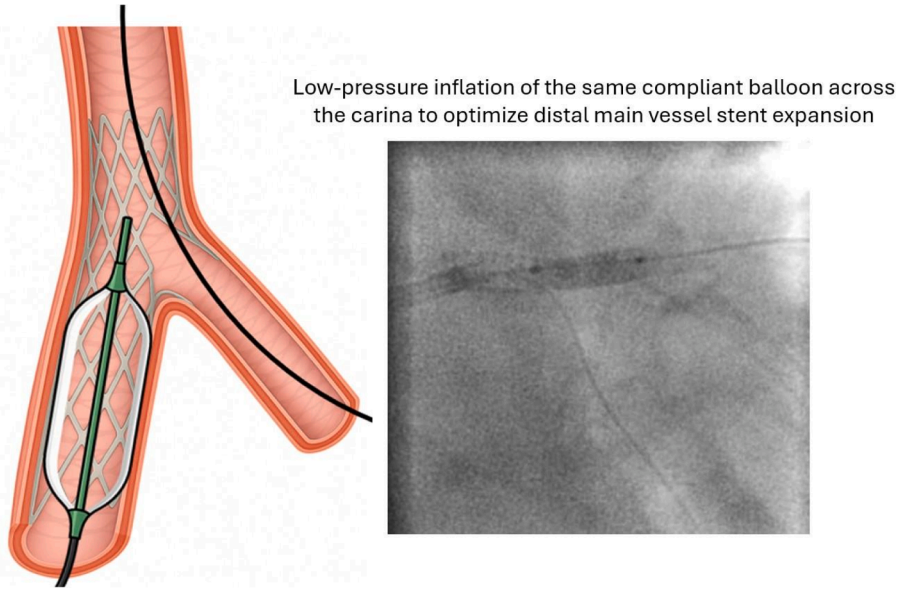
(Left) schematic showing guidewire passage into the side branch through distal stent struts. (Right) angiographic view of guidewire crossing into the side branch.

FIGURE 4 Side Branch Dilation



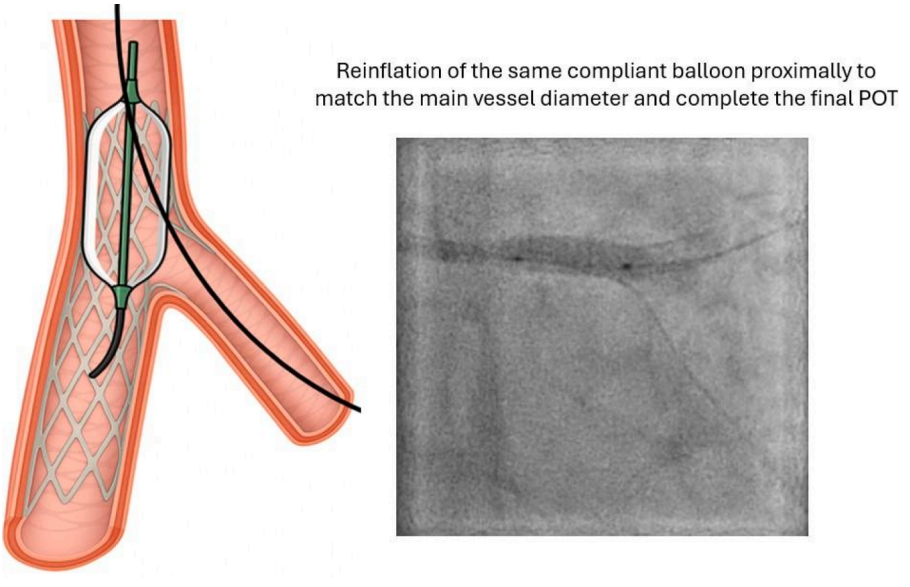
(Left) schematic representation of non compliant balloon dilation in the side branch after rewiring. (Right) angiographic image showing non compliant balloon inflation in the side branch.

FIGURE 5 **Distal Optimization Technique**



(Left) schematic illustrating low-pressure inflation of the same compliant balloon across the carina. (Right) angiographic image showing compliant balloon inflation for distal stent optimization.

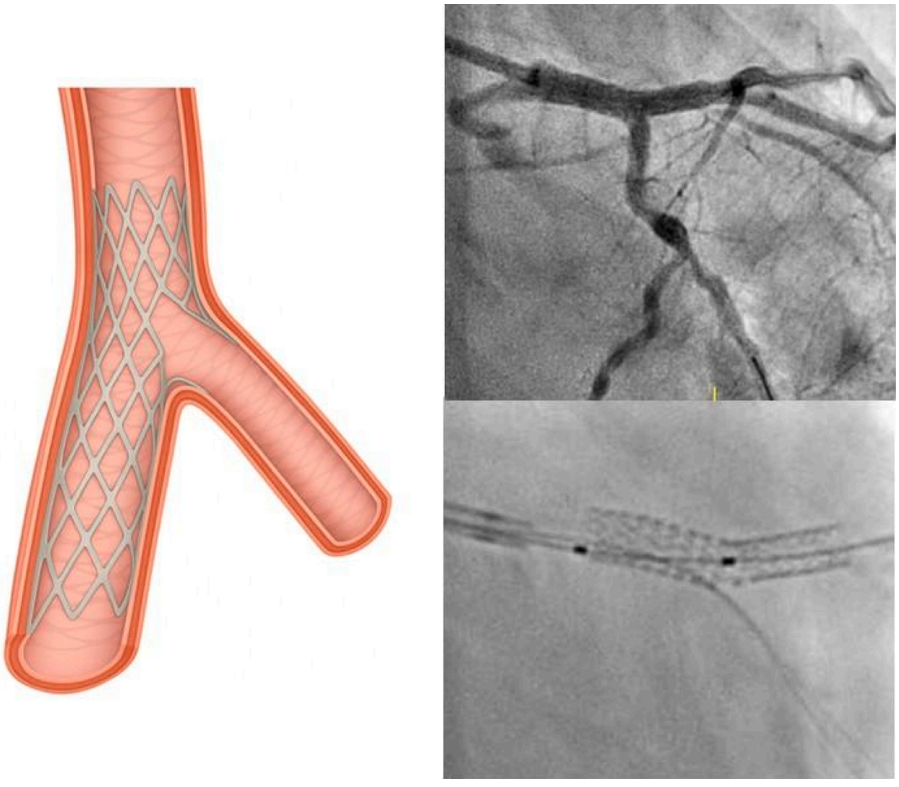
FIGURE 6 **Final POT (re-POT)**



(Left) schematic showing proximal compliant balloon re-inflation to match proximal main vessel diameter. (Right) angiographic image of rePOT inflation. POT = proximal optimization technique.

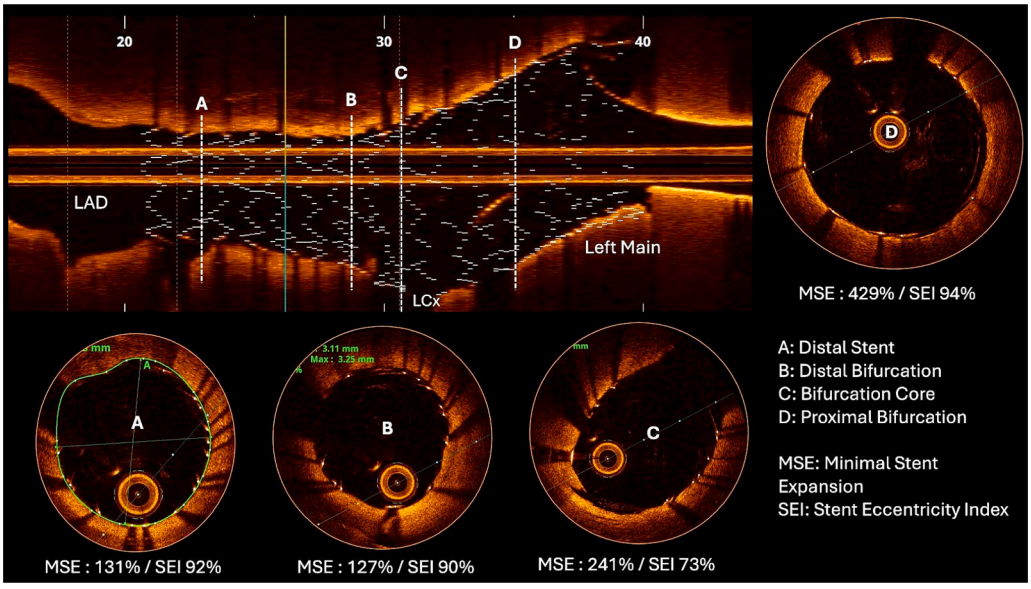
JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025
OCTOBER 27, 2025:2548-2553

FIGURE 7 Final Result



(Left) schematic illustration of the final stent configuration. (Right) angiographic views, including StentBoost, demonstrating the optimized final result after OTUS sequence.

FIGURE 8 **OCT Pullback**



Cross-sectional and longitudinal views of the left main bifurcation after stenting using the OTUS strategy. Four regions of interest are analyzed: minimal stent expansion (MSE) and stent eccentricity index (SEI) are quantified for each segment, demonstrating optimal expansion and symmetry across the bifurcation. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; OCT = optical coherence tomography.

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KEY WORDS coronary bifurcation, optimization technique, percutaneous coronary intervention, provisional stenting, rePOT

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025

IMAGES IN INTERVENTION

Novel Hydraulic-Assisted Unkinking of a Guide Catheter During PCI

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A 56-year-old man presented with inferior ST-segment elevation on electrocardiography. He underwent primary percutaneous coronary intervention (PCI) via 6-F right radial access. Diagnostic angiography revealed a codominant coronary system, with a nonculprit left coronary system (**Figure 1**). A nonselective right coronary acquisition showed a high-anterior takeoff from the right coronary sinus with severe proximal stenosis (Video 1).

Difficulty engaging a guide catheter was anticipated. During manipulation, a Judkins right 4 guide catheter kinked (**Figure 2**). Conventional maneuvers, including counter-rotational untwisting and attempts to cross the kink with a 0.035-inch exchange-length guidewire and a 0.014-inch angioplasty guidewire, failed to restore patency.

Time was of the essence. Complex unkinking techniques[1,2] would be time-consuming and require femoral access. Completing PCI via alternative access before addressing the kinked catheter would also delay reperfusion. A novel technique, a hydraulic-assisted technique, was therefore used. A 0.014-inch guidewire was advanced to the kink (**Figure 3**), and hydraulic pressure was delivered through a syringe connected to the Y-connector side port along with subtle catheter withdrawal (**Figure 4**). Hydraulic expansion of the lumen created sufficient gapping to permit guidewire passage and, if necessary, ballooning of the kink. In this case, hydraulic pressure alone resolved the kink, enabling safe catheter exchange (Video 2).

The procedure resumed with a three-dimensional right coronary catheter. Lesion predilatation was performed, followed by deployment of a drug-eluting stent (Video 3) and successful revascularization (Video 4).

Key insights are as follows. 1) Hydraulic-assisted guidewire advancement offers a rapid means of unkinking and, if successful, eliminates the need for more complex techniques such as femoral conversion or snare retrieval. 2) This technique requires clear radiological evidence of a kink and rapid implementation. 3) The technique is more readily applied for right-sided guide catheter kinking, as the system is already closed with a Y-connector in place, ensuring an air-free system.

Although promising, this method requires cautious use because of risks such as catheter rupture and embolism. Bench testing should determine safe indeflator pressures and assess how fluid viscosity affects lubrication and wire passage, key factors in hydrodynamic contrast recanalization during chronic total occlusion PCI.

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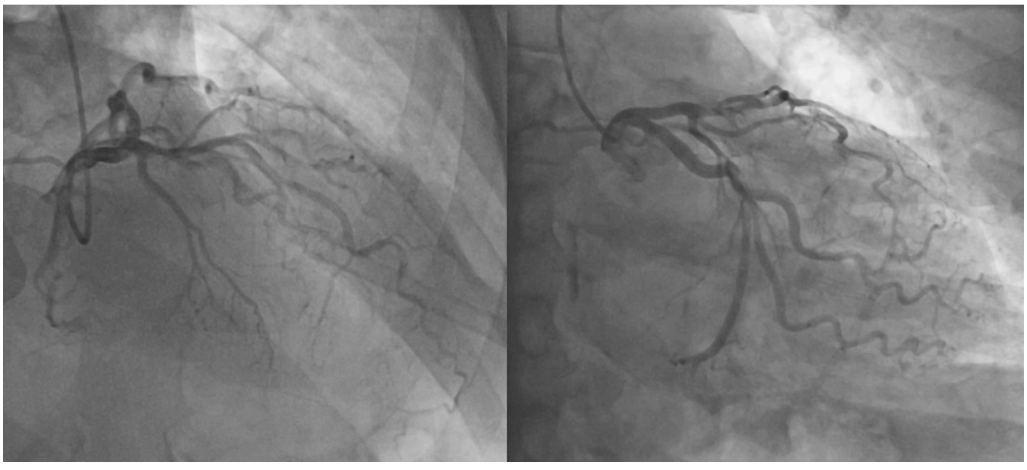
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 9, 2025; revised manuscript received July 29, 2025, accepted August 8, 2025.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2025.08.007

FIGURE 1 Left Coronary Angiography



Demonstrates the nonculprit left coronary system.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Ruzsa has received personal fees from Abbott Laboratories and Cordis, outside the present work. Dr Toth has received personal fees from Abbott Laboratories, Medtronic, Biotronik, and Boston Scientific, outside the present work. Dr Harb has received consulting fees from Medtronic and Shockwave Medical, outside the present work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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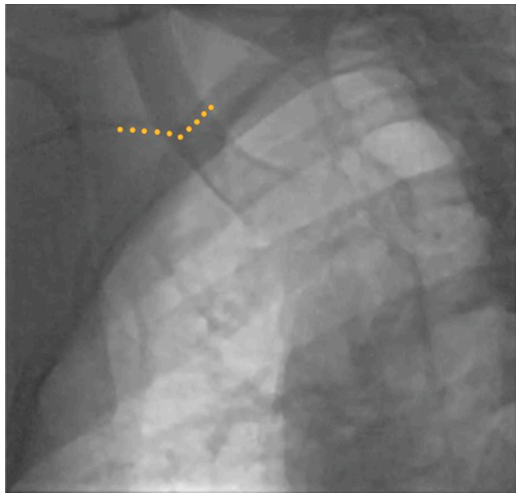
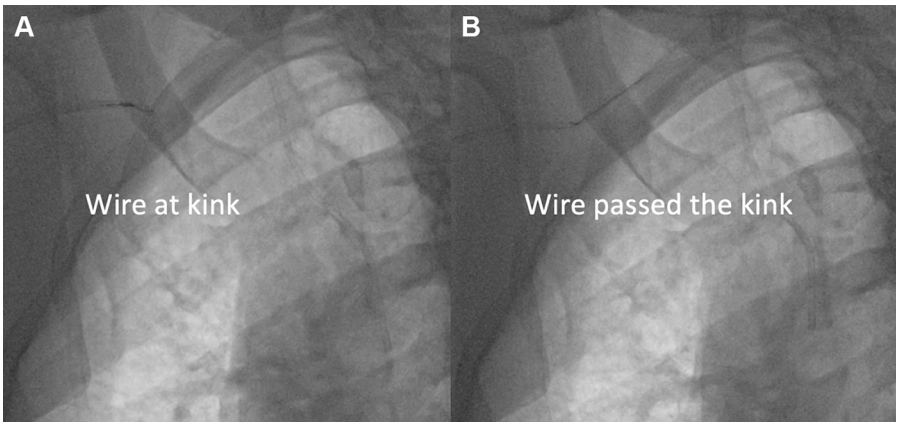
FIGURE 2 Kinked Judkins Right 4 Guide Catheter



Fluoroscopic frame showing the acute kink in the Judkins right 4 guide catheter (amber dots).

FIGURE 3 Guidewire Negotiation of Kinked Catheter



(A) Fluoroscopic frame showing the 0.014-inch guidewire tip halted at the acute bend of the kinked Judkins right 4 catheter. (B) Subsequent frame demonstrating successful passage of the guidewire beyond the kink.

FIGURE 4 Schematic Illustration of Hydraulic-Assisted Catheter Unkinking

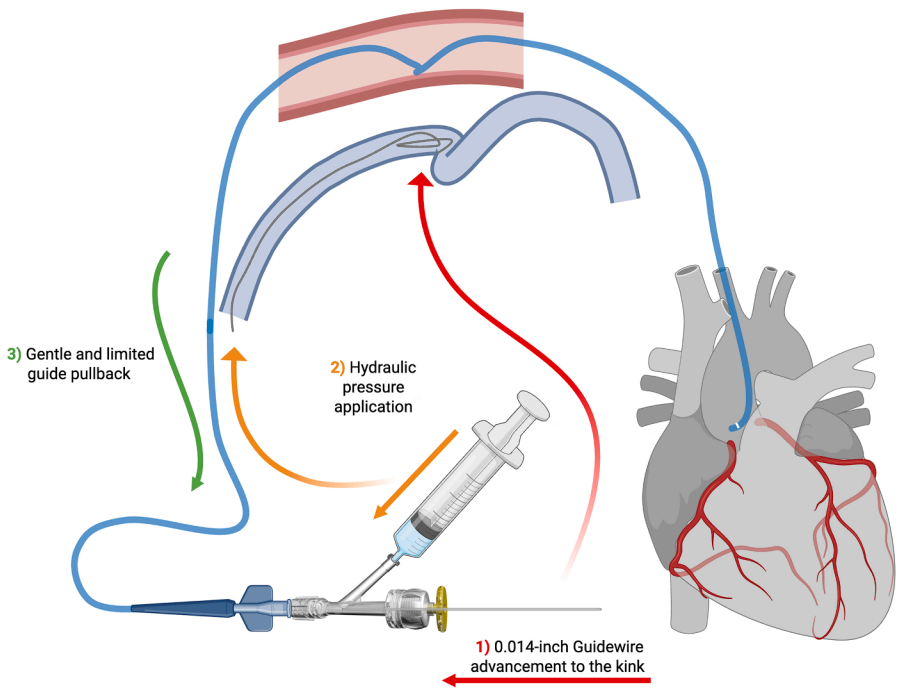


Diagram showing 3 key steps: 1) Advancement of a 0.014-inch guidewire to the kink (red arrow); 2) application of hydraulic pressure via syringe at the Y-connector (amber arrow); 3) gentle, limited pull back of the guide catheter to restore lumen patency (green arrow). Created using BioRender (https://BioRender.com/52dhvzu).

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KEY WORDS catheter complications, hydraulic-assisted unkinking, kinked catheter, percutaneous coronary intervention

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

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

Letters

RESEARCH LETTER

Leaflet Thrombosis After Transcatheter Tricuspid Valve Replacement

Transcatheter tricuspid valve replacement (TTVR) patients are prone to bleeding events, but less is known about their thrombotic risk.[1] We aim to report characteristics of patients with computed tomography (CT)-diagnosed hypoattenuated leaflet thickening (HALT) with reduced leaflet motion (RLM) after TTVR.

This was a retrospective, single-site analysis of patients undergoing postprocedural CT. The computed tomographic protocol consisted of quantifying HALT and RLM according to current criteria.[2] Institutional Review Board approval was obtained prior to conducting this retrospective analysis.

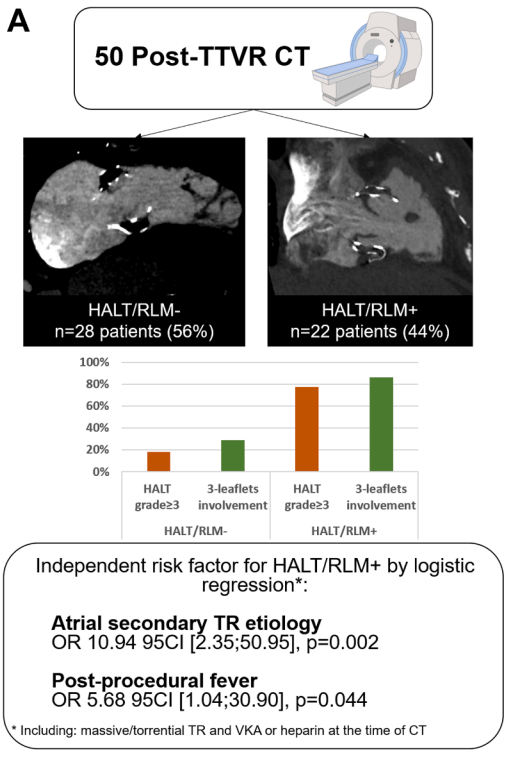
Between 2017 and 2024, 50 of 80 patients who underwent TTVR (62.5%) underwent post-implantation CT (median 39 days after TTVR; Q1-Q3: 29-94 days): 16 studies (32%) were performed because of the presence of thickened and/or restricted leaflet motion on transthoracic echocardiography (TTE), with 34 (68%) performed routinely. CT-diagnosed HALT was present in 39 patients, 22 had associated RLM (HALT/RLM+; 44.0%). The septal leaflet was most frequently affected (16 of 39 leaflets). HALT/RLM+ incidence was 62.5% (10 of 16) in patients undergoing CT for abnormalities on TTE. In the routine group, leaflets could not be visualized in 8 patients, of whom 2 (25%) had HALT/RLM+. Compared with 28 patients without RLM (HALT/RLM−), HALT/RLM+ patients were older, had lower body mass index, and had higher N-terminal pro-brain natriuretic peptide (Figure 1B). Anticoagulation (AC) regimen differences at the time of CT did not reach statistical significance between subgroups (3.6% vs 22.7% were off AC, 35.7% vs 22.7% were on vitamin K antagonist [VKA] or heparin, and 60.7% vs 54.5% were on direct oral AC; $P = 0.103$). On baseline CT, patients with HALT/RLM+ had higher right ventricular (RV) ejection fractions and higher end-systolic right atrial (RA)/RV volume ratios (3.1 [Q1-Q3: 2.7-3.9] vs 2.5 [Q1-Q3: 1.9-3.3]; $P = 0.008$). On baseline TTE, patients with HALT/RLM+ had significantly less massive or torrential tricuspid regurgitation (TR) and a higher prevalence of atrial secondary TR (aSTR) (n = 15 [68.2%] vs n = 4 [14.3%]; $P < 0.001$). In patients with massive or torrential TR (n = 44), baseline invasive right atrial V wave was markedly lower in the HALT/RLM+ population (5.5 mm Hg [Q1-Q3: 2.8-9.3 mm Hg] vs 11 mm Hg [Q1-Q3: 8.6-14.8 mm Hg]; $P = 0.037$). In line with the higher prevalence of aSTR, end-systolic septolateral oversizing 5 mm below the annulus was numerically larger in the HALT/RLM+ subgroup (29.5% ± 18.8% vs 19.8% ± 14.3%; $P = 0.078$), without any significant difference in implanted TTVR valve sizes ($P = 0.15$).

Ten patients with HALT/RLM+ (45.5%) had post-TTVR fever, compared with 5 (17.9%) in the HALT/RLM− group ($P = 0.035$), with no evidence for infection. Four patients were diagnosed with HALT/RLM+ within the first 24h postprocedurally (period off AC). HALT/RLM+ was associated with a higher grade 3 or 4 HALT ($P < 0.001$) and involvement of all 3 leaflets ($P < 0.001$) (Figure 1A). At the time of CT, TTE showed no significant difference in tricuspid valve mean gradient (MG) (3.4 mm Hg [Q1-Q3: 2.7-3.9 mm Hg] in the HALT/RLM− group vs 3.2 mm Hg [Q1-Q3: 2.2-4.3 mm Hg] in the HALT/RLM+ group; $P = 0.923$).

By logistic regression, aSTR and fever were statistically associated with the presence of HALT/RLM+ (Figure 1A). Among the HALT/RLM+ patients, 9 (40.9%) had AC intensification (switch to heparin [n = 1] or a VKA [n = 7] or higher target international normalized ratio [n = 1]) after post-TTVR CT. Repeat CT in 6 patients showed resolution of HALT in 5 (83.3%), resulting in a median MG decrease from 4.1 to 1.6 mm Hg ($P = 0.043$). The only case that did not resolve was in a patient transitioned to a VKA with poor medication compliance. Similarly, the unique patient who underwent AC de-escalation for infra-therapeutic international normalized ratio (switched from a VKA to direct oral AC) showed HALT worsening on repeat CT. On last follow-up TTE (629 ± 451 days), and after HALT management, MG was lower in the HALT/RLM+ group (n = 18) compared

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.07.022

FIGURE 1 Leaflet Thrombosis After TTVR



B

	HALT/RLM - (n=28)	HALT/RLM + (n=22)	P value
Baseline clinical characteristics			
Age	80 [70;84]	83 [81;85]	0.036
Female	17 (60.7)	18 (81.8)	0.106
BMI (kg/m²)	25.1 [23.5;29.6]	20.8 [19.1;25.3]	0.004
Prior sternotomy	18 (64.3)	7 (31.8)	0.023
Prior neoplasia	7 (25)	11 (50)	0.068
Prior gastrointestinal bleeding	6 (21.4)	0 (0)	0.021
NT-proBNP (pg/mL)	976 [721;1923]	1648 [1257;3487]	0.018
Baseline computed tomography			
RV ejection fraction (%)	54.3 [48.9;58.5]	58.4 [54.1;64.4]	0.017
End-systolic RA/RV volume ratio	2.5 [1.9;3.3]	3.1 [2.7;3.9]	0.008
Baseline echocardiography			
Absolute RV free-wall longitudinal strain (%)	26.1±6.0	27.8±5.8	0.316
Massive/torrential TR	27 (96.4)	17 (77.3)	0.039
Atrial secondary TR	4 (14.3)	15 (68.2)	<0.001
RA strain reservoir (%)	10.9 [8.3;14.4]	12.2 [9.3;14.7]	0.325
Anticoagulant regimen at the time of diagnosis			0.103
None	1 (3.6)	5 (22.7)	
Vitamin K antagonist or heparin	10 (35.7)	5 (22.7)	
Direct oral anticoagulant	17 (60.7)	12 (54.5)	

(A) Main study results showing a 44% incidence of hypoattenuated leaflet thickening (HALT) with reduced leaflet motion (RLM). (B) Differences in major characteristics between patients with and those without HALT-related RLM, showing a higher prevalence of atrial secondary tricuspid regurgitation (TR). BMI = body mass index; CT = computed tomography; NT-proBNP = N-terminal pro-brain natriuretic peptide; RA = right atrial; RV = right ventricular; TTVR = transcatheter tricuspid valve replacement.

with the HALT/RLM− group (n = 24) (2.4 mm Hg [Q1-Q3: 1.6-3.3 mm Hg] vs 3.4 mm Hg [Q1-Q3: 2.7-4.3 mm Hg]; $P = 0.013$).

Thrombosis on the venous side relies on 2 main triggers: low-flow status and altered blood composition (ie, inflammatory cells and hypoxemia).[3] The presence of aSTR is a significant predictor of HALT/RLM+, likely serving as a marker for a number of factors contributing to lower RA contractile function with lower flow rates: greater RA/RV volume ratio, lower invasive V wave, lower RA strain, and lower diastolic gradients at follow-up. The presence of fever is also a significant predictor of HALT/RLM+, likely serving as a marker for factors contributing to local and/or systemic inflammation: greater oversizing (particularly 5 mm below the annulus) and possible baseline hematologic predisposition (both inflammation and thrombogenicity) associated with heart failure with preserved ejection fraction, a common etiology of aSTR.[4] Together, the low flow and inflammatory response create a milieu for thrombus formation. Finally, transtricuspid diastolic flow is not uniform across the annulus, with lower velocity flows near the restricted septal side, which may explain the greater septal leaflet HALT/RLM positivity.

Limitations of this study are its small sample size and the possible selection bias in patients undergoing post-TTVR CT, introducing the risk for incidence overestimation.

HALT/RLM+ was reported in 44% of highly selected patients undergoing post-TTVR CT. aSTR etiology and postprocedural fever independently predicted its occurrence. At mid-term follow-up, TTVR MG improved in patients with HALT/RLM+ who underwent AC intensification. TTE has shown limitations to detect HALT/RLM+ cases. When feasible, post-TTVR CT should be performed in routine practice to define the true incidence of HALT/RLM and assess its role in antithrombotic treatment adaptation and outcomes.

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The authors are grateful to Laralab for their exceptional expertise that greatly contributed to the feasibility of this work. Dr Le Ruz's research fellowship was funded by Fédération Française de Cardiologie, Groupement Interrégional de la Recherche Clinique et de l'Innovation Grand Ouest, the Franco-American Fulbright program, the Monahan Foundation, the Interventional Cardiology Department at Columbia University Irving Medical Center, and Centre Hospitalier Universitaire de Nantes. Dr Nazif has received consulting fees or honoraria from Medtronic, Boston Scientific, Teleflex, Encompass Technologies, and Opsens Medical; and has received institutional research grants from Edwards Lifesciences, Boston Scientific, Medtronic, and Abbott Laboratories. Dr George has received consulting fees from Boston Scientific, Edwards Lifesciences, Cardiomech, Mitre Medical, AtriCure, VDyne, Valcare Medical, DurVena, MITRx, and Johnson & Johnson. Dr Vahl has received institutional funding to Columbia University Irving Medical Center from Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic, and Siemens Healthineers; and has received consulting fees from Abbott Vascular, Boston Scientific, and Siemens Healthineers. Dr Leon has reported institutional clinical research grants from Abbott Laboratories, Boston Scientific, Edwards Lifesciences, Medtronic, and JenaValve. Dr Kodali has received grant support, paid to his institution, from Medtronic, Boston Scientific, and Abbott Vascular; has received consulting fees from Abbott Vascular, Claret Medical, Admedus, and Meril Life Sciences; and holds equity options in BioTrace Medical, Dura Biotech, and Thubrikar Aortic Valve. Dr Hahn has received speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences, Medtronic, Philips Healthcare, and Siemens Healthineers; has held institutional consulting contracts for which she receives no direct compensation with Abbott Structural, Edwards Lifesciences, Medtronic, and Novartis; and is chief scientific officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored tricuspid valve trials, for which she receives no direct industry compensation. Dr Lebehn has received consulting fees from Sutra Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

Letters

RESEARCH LETTER

Anatomical Suitability for Heterotopic CAVI in Patients With Severe Tricuspid Regurgitation Rejected for Orthotopic Intervention

Heterotopic caval valve implantation (CAVI) may represent the only viable therapeutic option for patients with severe tricuspid regurgitation (TR) who are not suitable candidates for transcatheter orthotopic interventions.[1] The TricValve system (Products + Features) is a CAVI device that demonstrated high procedural success rates and sustained functional improvement at 1-year follow-up in the TRICUS EURO (Safety and Efficacy of the TricValve® Transcatheter Bicaval Valves System in the Superior and Inferior Vena Cava in Patients With Severe Tricuspid Regurgitation) study.[1-3] However, evidence remains limited regarding the proportion of patients with suitable caval anatomy, in terms of both size and morphology, for successful CAVI implantation.

We analyzed anonymized data from 644 European patients (April 2023 to December 2024) who underwent chest computed tomography (CT) using the company's platform to evaluate anatomical suitability for heterotopic CAVI using the TricValve system after being deemed unsuitable for an orthotopic procedure. We then identified those who ultimately underwent the intervention following anatomical acceptance.

We obtained superior vena cava (SVC) and inferior vena cava (IVC) measurements to determine suitability for 25-, 29-, and 31-mm devices and for 31-, 35-, and 41-mm devices, respectively. SVC acceptance criteria included confluence of the SVC-right atrium (RA) >14 mm, SVC-top of the pulmonary artery (PA) diameter 19 to 34 mm, SVC-middle of the PA diameter 22 to 31 mm, and length of the SVC-RA confluence to the middle of the PA of >35 mm and to the PA-RA junction of >50 mm. IVC measurement criteria included IVC-RA junction diameter 24 to 41 mm, IVC-top of the hepatic veins (HVs) diameter 24 to 35 mm, IVC-below the HVs diameter 21 to 43 mm, and length of the IVC-RA junction to the top of the HVs of >6 mm and below the HVs length of <38 mm. We reported the percentage for categorical variables and the mean and SD for continuous variables. This study received the proper ethical oversight.

Of 644 patients, 3% lacked computed tomographic data. Among 626 with computed tomographic scans, 87% (n = 544) were eligible and 13% (n = 82) were rejected for CAVI, due mainly to extreme IVC dilation (61%), enlarged HV ostium (16%), high HV occlusion risk (10%), small SVC or IVC anatomical size (10%), and other causes (3%). The mean measurements of the SVC were SVC-RA confluence diameter of 21.7 ± 3.1 mm, SVC-top PA diameter of 24.2 ± 3.5 mm, SVC-middle PA diameter of 26.1 ± 4.3 mm, and length of the SVC-RA confluence to the middle PA of 46.5 ± 8.1 mm and to the PA-RA junction of 76.7 ± 12 mm. The mean measurements of the IVC were IVC-RA junction diameter of 32.4 ± 4.7 mm, IVC-top of the HVs diameter of 31.3 ± 4.4 mm, IVC-below of the HVs of 32. 5 ± 6.7 mm, and length from the IVC-RA junction to the top of the HV of 9 ± 5.2 mm and below the HV of 34 ± 5.2 mm.

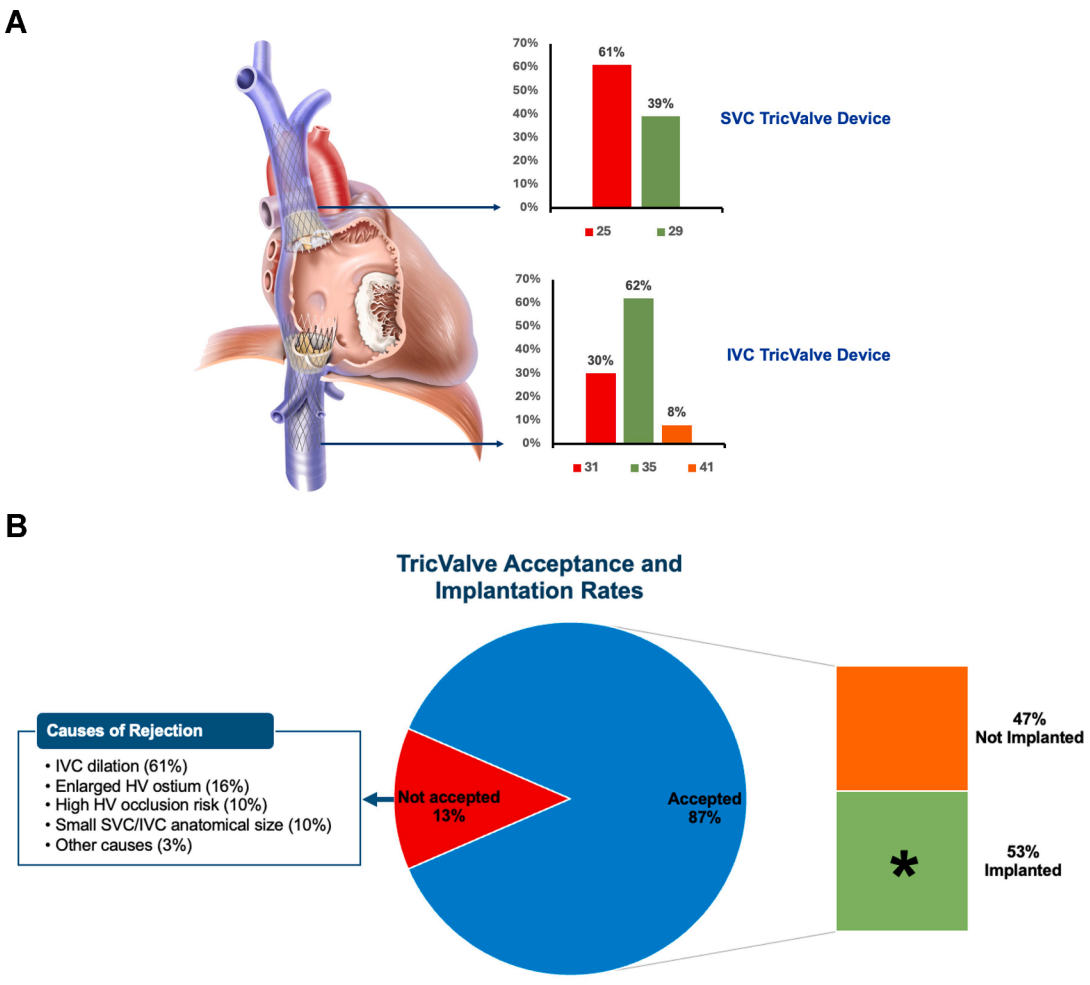
In the SVC, the most assessed devices for deployment were the 25-mm (61%) and 29-mm (39%) devices. In the IVC, the 35-mm device was the most evaluated for implantation (62%), followed by the 31-mm device (30%) and finally the 41-mm device (8%). The procedure was successfully done in 45% of all patients and in 53% of those suitable for the procedure. Reasons for nonimplantation were unclear and appeared related to physician judgment, patient clinical condition, or operational restraints; these patients may have received an alternative procedure or medical therapy (**Figure 1**). CAVI rates were similar across years: 54% in 2023 and 53% in 2024.

To our knowledge, this is the first study to report acceptance rates for CAVI in patients with severe TR while also providing detailed anatomical measurements relevant to this population. Interestingly, approximately 90% of high-risk patients previously rejected for orthotopic procedures were deemed anatomically suitable for CAVI; however, the reasons why only about 50% of these patients ultimately underwent implantation remain unclear.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.003

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 20, 2025
OCTOBER 27, 2025:2561-2563

FIGURE 1 Assessed Bicaval TricValve Devices With Procedural Acceptance and Implantation Rates



(A) Distribution of the different types of devices implanted in the superior vena cava and inferior vena cava. (B) Heterotopic cava valve procedure acceptance rates, causes of rejection, and corresponding implantation rates in eligible patients. *All devices were successfully implanted. HV = hepatic veins; IVC = inferior vena cava; SVC = superior vena cava.

Notably, CAVI represents a promising therapeutic alternative for patients with severe TR who are not candidates for orthotopic procedures because of advanced disease or unfavorable anatomy.

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

Letters

RESEARCH LETTER

Lack of Calibration Degrades the Performance of Clinical Prediction Models

A Case of CTO Scores

In prediction modeling, the discriminative ability of a model is often held as the singular indication of its performance. The most common discrimination metric is the C-statistic (equivalent to the area under the receiver-operating characteristic curve [AUROC] for binary outcomes). Although good discrimination is necessary, it is not sufficient for accurate model performance.

An equally important yet rarely assessed measure of model performance is calibration. Model calibration indicates whether the risk estimates are consistent with the observed outcomes. The discordance of the observed and predicted risks are signs of under- or overfitting in the developed model.[1] This association is visualized by a calibration curve estimated either from a logistic regression of the outcomes on the predicted risks or by a nonparametric smoother (locally weighted scatterplot smoothing, splines). For a well-calibrated model, the curve is close to the main diagonal of the unit square. Deviations from the diagonal can span the entire unit range or be localized and suggest model miscalibration.

The calibration can be quantified by the mean calibration (MC), or the average difference between predicted and observed risks, and the calibration slope (ie, the slope of the logistic regression model used to estimate the calibration curve). For a perfectly calibrated model, the slope is 1; slope <1 indicates model overfit and slope >1 model underfit. In turn, MC quantifies the overall bias and represents the difference (logit scale) between the observed and predicted risks. For a perfectly calibrated model, MC $= 0$, whereas MC <0 indicates that the risks are overestimated and MC >0 that they are underestimated, on average. Importantly, calibration, just like discrimination, must be assessed on the testing set, external to the development data. If the same data are used for model development and validation, the model performance is overestimated, and the model needs to be adjusted for optimism.

Here, we evaluated the calibration of the 4 risk models used for predicting technical success in percutaneous coronary intervention for chronic total occlusion (CTO): the J-CTO (Multicenter CTO Registry in Japan) score, clinical and lesion-related (CL) score, PROGRESS-CTO (Prospective Global Registry for the Study of CTO Intervention) score, and EuroCTO (CASTLE) score.[2] The original derivations heavily emphasized AUROC, briefly mentioning the Hosmer-Lemeshow test as evidence of calibration. That test, however, is underpowered in detecting and reductive in characterizing poor calibration.

We follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines[3] to evaluate the 4 scores using an external validation set from the PROGRESS-CTO registry. We include 42 centers with at least 40 cases from 2015 to 2022 (to exclude data used in the original PROGRESS-CTO score). Only records with complete data across all scores' components were used (n = 7,872).

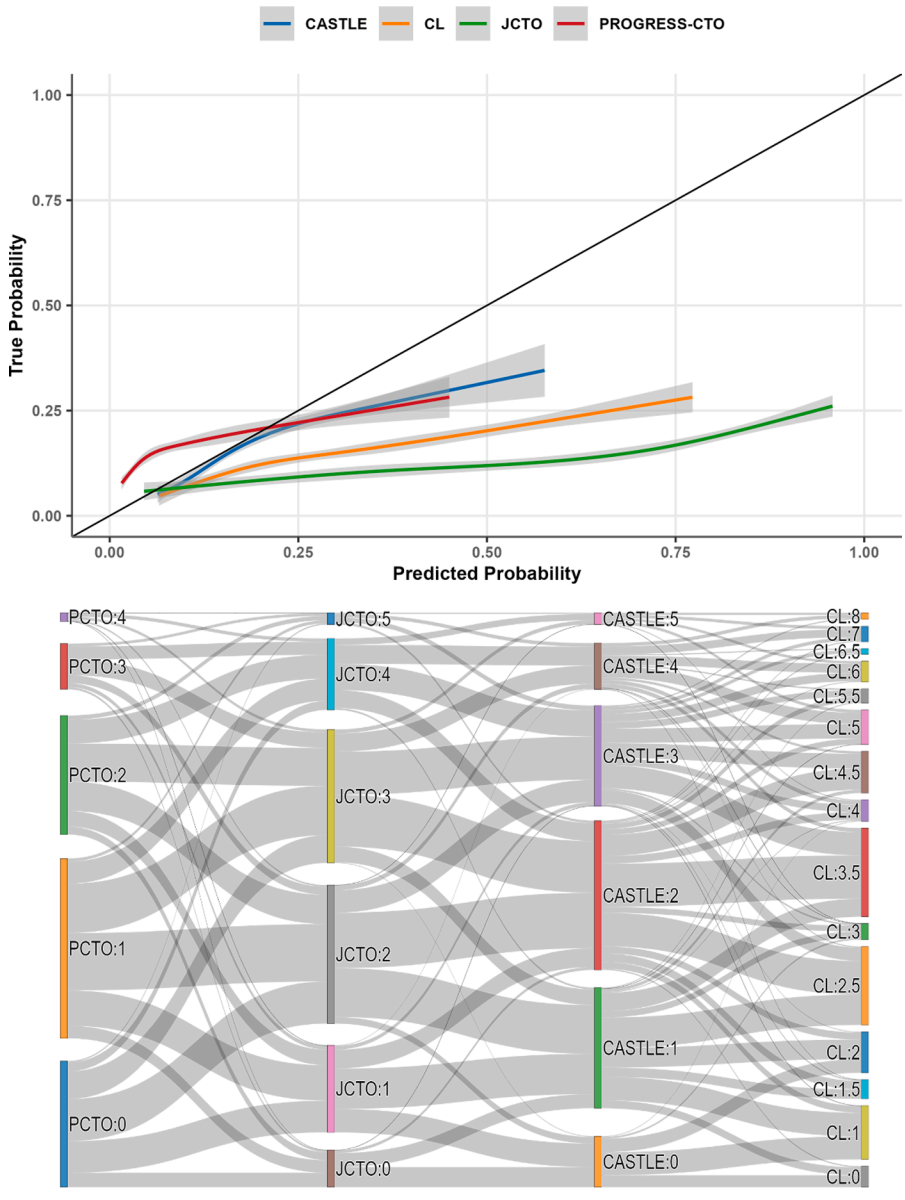
For each score, the calibration curves were estimated using restricted cubic splines from the observed outcomes on the predicted probabilities. The MCs and calibration slopes were estimated as described earlier; the corresponding SEs were used to test MC $= 0$ and slope $= 1$, respectively. The permutation F-test was used to assess the difference in risk scores across the models; the sampling distribution of the F-statistic was estimated via bootstrap ($B = 2{,}000$) by permuting the score labels within each subject.

The study cohort had a median age of 65 years (Q1-Q3: 57-71 years); 81% were men, 42% had diabetes, 89% had hypertension, and 84% had dyslipidemia. The technical failure rate was 13.6%. Discrimination by AUROC varied between 0.61 and 0.67.

The estimated MCs were as follows: for the J-CTO score, 0.377 (95% CI: 0.369-0.386); for the CL score, 0.140 (95% CI: 0.132-0.148); for the PROGRESS-CTO

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.08.001

FIGURE 1 **Estimated Calibration Curves and Derived Risk Classifications for the 4 Prediction Models**



(Top) The calibration curves deviate from the ideal (diagonal line), suggesting that the 4 models tend to underestimate the risks. The curves were estimated using restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles. (Bottom) Lack of calibration leads to inconsistencies in risk estimations, as seen by haphazard changes in risk designations among scores (columns). If the classifications were aligned, one would see parallel connections among risk categories. Here, colored blocks represent low to high (top to bottom) risk classes per respective definitions. CASTLE = EuroCTO; CL = clinical and lesion-related; J-CTO = Multicenter CTO Registry in Japan; PCTO = Prospective Global Registry for the Study of CTO Intervention; PROGRESS-CTO = Prospective Global Registry for the Study of CTO Intervention.

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score, −0.061 (95% CI: −0.069 to −0.054); and for the CASTLE score, 0.022 (95% CI: 0.015-0.029), indicating that on average, the risk is underestimated by all scores but PROGRESS-CTO, which slightly overestimates the risk. The corresponding calibration slopes were 0.31 (95% CI: 0.27-0.36), 0.49 (95% CI: 0.42-0.56), 0.39 (95% CI: 0.33-0.45), and 0.89 (95% CI: 0.78-0.99) (**Figure 1A**). All MCs and slopes differed ($P < 0.001$) from the corresponding ideal calibration values (MC = 0, slope = 1). Furthermore, the risk classifications varied considerably between the 4 models (bootstrap $P < 0.001$) (**Figure 1B**).

This study demonstrates that lack of calibration degrades model performance, leading to inaccurate and inconsistent risk estimates. This problem is not confined to the 4 models presented here but is widespread. For reliable performance, prediction studies should follow rigorous design standards as outlined in the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines.[3] Rigor should apply not only to model evaluation but to all aspects of its development, including sample size estimation, handling of missing data, and development and validation framework.[4,5]

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

Letters

TO THE EDITOR

A Protective Effect of Smoking on Repeat Revascularization

Another Example of Collider Stratification Bias

Smoking is a well-established risk factor for endothelial damage and increased thrombogenesis, yet Presch et al[1] report, paradoxically, that smoking is associated with a lower risk for repeat revascularization. It is hard to conceive why the endothelium would react differently if it had experienced a previous revascularization procedure. More likely, the observed protective role is due to collider risk stratification bias, which has successfully explained the obesity, aspirin, and previous smoking paradoxes, among many others.[2-4] This bias arises when study selection (in this case patients undergoing revascularization) is a collider, affected by both smoking and other (unmeasured) risk factors, creating a spurious association through an induced backdoor pathway. Study selection here was determined by the performance of revascularization, which is not randomly assigned. Smokers are more likely to undergo initial revascularization, and therefore, nonsmokers who undergo revascularization tend to have substantially higher levels of other (unmeasured) risk factors, strong predictors for future revascularization. In a simulation study (see https://github.com/brophyj/collider-bias.git), an assigned smoking HR of 1.36 is reduced to 0.87 (95% CI: 0.82 to 0.92) when the general population is conditioned on the performance of an initial revascularization (the collider). This reversal is a classic example of collider bias, in which conditioning on a collider variable, influenced by both the exposure and an unmeasured confounder, distorts the true effect.

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ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2025.04.053

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 18, NO. 20, 2025

PUBLISHED BY ELSEVIER

Letters

TO THE EDITOR

When Pressures Disagree

Is PPGi the Missing Link in Coronary Physiology?

The recent paper by Revaiah et al[1] provides timely insights into the mechanistic underpinnings of discordance between fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) by analyzing disease pattern using the pull back pressure gradient index (PPGi). The finding that discordant FFR−/iFR+ lesions are primarily diffuse, whereas FFR+/iFR− lesions are typically focal, reinforces the view that physiological indexes reflect not only lesion severity but the nature of disease distribution.

This pattern-based interpretation opens several avenues for further exploration. One important question is whether discordant lesions should be managed differently depending on the underlying physiological phenotype. For example, given the reduced efficacy of percutaneous coronary intervention in diffuse disease, should FFR−/iFR+ lesions with low PPGi be more often deferred, even in the presence of ischemic thresholds?

The study also underscores the limited agreement between visual and physiological disease classification. This discrepancy raises the possibility that physiology-derived metrics such as PPGi could enhance lesion assessment when angiographic ambiguity or borderline indexes are present.[2] Could routine integration of PPGi into decision making help standardize care, particularly in vessels with intermediate stenosis or discordant physiology?

Revaiah et al[1] have added meaningful evidence to the ongoing dialogue around physiology-guided care. Their findings support further investigation into whether understanding the nature, not just the severity, of coronary artery disease physiology can refine patient selection and enhance the impact of revascularization.

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Dr Skalidis is supported by grant from the Gottfried and Julia Bangerter-Rhyner Foundation and from the Professor Dr Max Cloëtta Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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ISSN 1936-8798/$36.00
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