



Engineering perspective on transcatheter aortic valve implantation

Transcatheter aortic valve (TAV) implantation has emerged as a revolutionary, minimally invasive treatment for inoperable or high-risk surgical patients with severe symptomatic aortic stenosis. Since the first-in-man procedure in 2002, over 50,000 TAVs have been implanted worldwide. Fundamental differences in application and design exist between TAV implantation and surgical aortic valve replacement. Computational and experimental fluid dynamics are powerful techniques used in engineering to fully understand the implications of this new intervention. The computational and experimental TAV literature to elucidate TAV hemodynamics in comparison with stented bioprotheses is reviewed in this article. The authors then identify key areas where further work is needed to expand this technology to younger and healthier patients.

KEYWORDS: circulation = computational and experimental techniques = heart valve = hemodynamics = transcatheter aortic valve

Transcatheter aortic valve (TAV) implantation (TAVI) has emerged as a ground-breaking treatment for inoperable or high-risk surgical patients with severe symptomatic aortic stenosis (AS) [1-4]. Since the first-in-man procedure in 2002 [5], TAVI has rapidly been adopted, with over 50,000 procedures performed in 40 countries [6]. Early- and mid-term results of TAVI have steadily improved with reduction in morbidity and mortality with greater operator experience [6-8]. TAVI procedural mortality ranges from 3–11% overall [6,9–14]. Transfemoral (TF) TAVI 30-day mortality has declined to <10% in the most recent series and was 3.4% in the randomized PARTNER 1A trial [2,6,9]. In a significant percentage of AS patients, mainly the very elderly and those with severe comorbidities, the risk of surgical aortic valve replacement (AVR) has been considered prohibitive, and these patients have not been offered surgery [15]. TAVI has reduced the proportion of unoperated severe AS patients [16] and has become the standard-ofcare for these inoperable patients [1,6]. On the other hand, for the vast majority of acceptablerisk patients, surgical AVR currently remains the gold standard treatment for severe symptomatic AS. Operative mortality has also decreased over time in a population of surgical patients with greater mortality risk due to increasing comorbidities [17]. AVR mortality was <1.3% in patients <70 years old, <3.5% in patients <80 years old and <5% in patients <85 years old, based on the Society of Thoracic Surgeons' database in 2006 [17]. Given the excellent surgical outcomes

in carefully selected elderly patients [18,19], use of the interdisciplinary heart valve team of cardiologists and cardiac surgeons that understand predictors of surgical AVR and TAVI mortality [20,21] is critical for appropriate procedure selection for a given patient [10,22,23]. As such, consensus guidelines for TAVI and institutional and operator experience have been developed [24,25]. In order to expand TAVI to lower-risk patients, currently well served by surgical AVR, understanding the fundamental differences between these two procedures and between valve designs of TAVs and surgical bioprostheses is necessary.

In TAVI, TAVs are crimped, inserted through a catheter and implanted by expanding TAVs within diseased valves via percutaneous or minimally invasive approaches. Unlike surgical AVR, native stenosed aortic valves are not excised. TAVs are not sutured into the annulus like surgical valves; however, they rely upon diseased valves for fixation. TAVs, as such, are subjected to a risk of migration, which does not apply to surgical valves. TAV design fundamentally differs from surgical valves in that TAVs consist of stents that must be expanded with the valve leaflet framework within the stent, whereas surgical mechanical and stented bioprostheses have a rigid framework, which houses the valve leaflets. Since diseased aortic valves have variable shapes and sizes, TAVs are expanded to a variable degree, unlike surgical valves, which are not expanded, but are inserted with consistent dimensions based on their rigid sewing rings. In addition, leakage around TAVs

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or paravalvular leakage is a greater issue than for surgical valves, where suturing of the valves to the annulus prevents such leakage, unless technical problems occur.

Given the fundamental differences between surgical AVR and TAVI, computational and experimental assessment of TAVs from an engineering perspective is essential to evaluate the efficacy and pitfalls of this new intervention. In this review, computational and experimental TAV studies to present an overview of TAV hemodynamics in comparison with surgical stented bioprostheses are summarized. Furthermore, the authors identify and discuss key areas where further work is needed to expand this technology to younger and healthier patients.

Transcatheter valves

Two TAVs are currently in clinical use in the USA: balloon-expandable Edwards TAV (Edwards SAPIEN, and SAPIEN XT; Edwards Lifesciences, CA, USA) and self-expanding Medtronic CoreValve® ReValving System (CoreValve ReValving Technology; Medtronic Inc., MN, USA). Edwards SAPIEN is commercially available and US FDA-approved for use in inoperable patients. The SAPIEN TAV was investigated in the PARTNER trial [1-4], which demonstrated a clear survival advantage of TAVI over medical therapy in inoperable patients and noninferiority of TAVI with respect to surgical AVR in high-risk surgical patients. Medtronic CoreValve is in the midst of a multicenter randomized controlled clinical trial in the USA. In addition to these two valves, to our knowledge, 18 TAVs are in active development, eight of which now have first-in-man implantation results [9,26-34], while two are CE mark approved in Europe: Symetis ACURATE TATM (Symetis SA, Lausanne, Switzerland) and JenaValveTM (JenaValve, Munich, Germany)[10].

Edwards SAPIEN valve

The Cribier-Edwards TAV was the firstgeneration, balloon-expandable TAV constructed from a stainless steel tubular frame with three equine pericardial leaflets and a fabric sealing cuff at the bottom third of the stent to reduce paravalvular leak. In second-generation SAPIEN TAVs, valve leaflets were changed to bovine pericardium, treated with a ThermaFix anticalcification process, and the sealing cuff was extended to the bottom two-thirds of the stent. The SAPIEN TAV is currently available in two sizes, 23-mm diameter × 14-mm height, designed to fit annulus sizes ranging from

18-22-mm and 26-mm diameter × 16-mm height, for annulus sizes of 21–25 mm [35,36]. SAPIEN TAVs can be deployed either through TF or transapical (TA) approach. The thirdgeneration SAPIEN XT is CE Mark approved and has an advantageous low-profile stent design (FIGURE 1). Modification to a cobalt-chromium stent from stainless steel allowed thinner struts while improving radial strength and circularity. Valve leaflets of this TAV are modeled based on the design of surgical Carpentier-Edwards pericardial bioprostheses. Recently, 20-mm and 29-mm SAPIEN XT have become commercially available in Europe for smaller and larger aortic annulus sizes. The lower-profile design permits reduction in arterial sheath size to 16-20 Fr [9] compared with 22 and 24 Fr delivery systems for the SAPIEN TF approach.

Medtronic CoreValve

Medtronic CoreValve is constructed from three pericardial leaflets mounted in a self-expandable Nitinol stent (FIGURE 2). Bovine leaflets in firstgeneration devices were changed to porcine pericardium in second-generation devices. The stent frame is considerably longer than the SAPIEN, with 50-mm length and consists of three different sections with unique material properties. The lower section sits within the annulus and protrudes into the left ventricular outflow tract (LVOT); it has high radial force for device expansion and anchoring within calcified valves. The middle stent segment containing TAV leaflets is constrained in diameter to avoid obstruction of coronary artery flow. The upper stent section is designed to be wider in diameter, to function as a landing zone in the ascending aorta, allowing stent fixation and preventing distal migration. CoreValve is available in three sizes, 26-mm diameter designed for 20-23 mm annulus sizes, 29-mm diameter for 23-27 mm annulus sizes, and 31-mm diameter for 26-29 mm annulus size [9,10,37]. Fixation to the ascending aorta requires ≤45-mm diameter at the sinotubular junction. CoreValve, with its 18 Fr delivery system, can be deployed through percutaneous TF or, in severe peripheral vascular disease, through subclavian/transaxillary or transaortic approaches [38].

TAV hemodynamics

In vitro TAV hemodynamics

TAV hemodynamics are complex in nature, and a better understanding of how flow around and near TAV may affect the aortic root is required. 2D particle image velocimetry (PIV) is an established method to visualize flow vectors in a system. 2D PIV captures the instantaneous velocity distribution of particle-seeded flow on a selected plane, illuminated by a pulsed laser sheet. The light scattered by the particles on the plane is recorded by a camera and the tracer particles are tracked frame by frame. Displacement of the particles is then converted to velocity using the small time frame between the illuminating laser pulses. 2D PIV can provide detailed quantitative data on TAV fluid dynamics, and is valuable for investigating how various TAV designs alter hemodynamics. Only one published study, to date, has evaluated the in vitro hemodynamics of actual 23-mm SAPIEN using 2D PIV. While pulse duplicator studies have been performed by industries to obtain FDA approval, published in vitro data regarding SAPIEN XT and CoreValve are lacking. Using 2D PIV and an in vitro pulse duplicator, which simulated the left heart with blood pressure of 112/74 mmHg, Stuhle et al. investigated flow dynamics downstream of the 23-mm SAPIEN in a transparent silicone ascending aorta without sinuses, combined with a flexible aortic arch subjected to pulsatile flow [39]. Aortic flow was characterized by acceleration, peak flow, and deceleration phases. During acceleration, velocities were 0.2-0.3 m/s and the velocity vector field was parallel to the aortic wall. During peak flow, SAPIEN demonstrated a central orifice jet flow profile with 0.87 m/s peak velocity and 10-12-mm width during maximum flow. Peak velocity was slightly higher than that of native aortic valves. Ambilateral vortices, forming a vortex ring parallel to the stream, surrounded the central orifice jet with greater counterclockwise than clockwise vorticity. Ambilateral vortices with 0.4-0.5 m/s peak velocities turned clockwise in the upper part of the aorta with an angular velocity of 277°/s, and turned counterclockwise in the lower part with an angular velocity of 335°/s. Maximum shear strength was 26,284/s². Shear strength and strain rate were high during peak flow, but otherwise low at other phases. Calculated wall shear stress at the aortic wall was 1-1.2 Pa. Precise characterization of TAV hemodynamics offers insight into how flow through TAV may affect the ascending aorta.

In vivo TAV fluid dynamics

Just as 2D PIV can illustrate flow patterns *in vitro*, an *in vivo* method to provide quantitative and qualitative data on blood velocity and flow patterns with extraordinary detail is 4D flow



Figure 1. Edwards SAPIEN XT. Courtesy of Edwards Lifesciences (CA, USA).

MRI. Clinically, Markl et al. [40] reported detailed 3D representation of blood flow around a 26-mm SAPIEN using 4D flow MRI of a 79-year-old patient 6 months after TAVI. Timeresolved 3D contour lines depicted the direction of blood flow as traces measured the velocity. This 3D streamline visualization revealed abnormal blood flow patterns, not present in normal aortic flow, including a marked helical flow fully developed during mid-systole and extending towards the arch during early and middiastole (FIGURE 3). This strongly asymmetrical outflow jet forming along the right anterior outer curvature of the ascending aorta differed from normal flow patterns, characterized by a mild-to-moderate right-handed helix in systole, with mild retrograde flow in the ascending aorta and arch during early diastole [40]. Peak systolic flow was 2.1 m/s, which was higher than 2D PIV measurements (0.87 m/s) [39]. The difference in peak systolic velocity may be due to patient-specific anatomy/cardiac output, valve size and the degree of TAV expansion within the annulus. A dual retrograde jet pattern indicative of paravalvular leak was detected during diastole with 19 ml calculated retrograde flow and moderate 20% regurgitant fraction. 4D flow MRI may play an important role in assessing post-TAVI aortic regurgitation (AR), complementing traditional echocardiography, while also elucidating complex flow patterns around the TAV.

Computational TAV studies ■ Migration forces applied on TAVs

Unlike surgical valves, TAVs are not secured within the annulus by sutures and are subject to antegrade and retrograde forces. Antegrade forces are applied on TAVs mainly due to



Figure 2. Medtronic CoreValve® System. Reprinted with permission from Medtronic, Inc. (MN, USA).

blood ejection and its magnitude may increase over time due to TAV degeneration. On the other hand, retrograde forces are exerted on TAVs during diastole due to the high pressure gradient across the closed valve. Quantifying these forces that could potentially dislodge TAVs has been essential. Dwyer et al. characterized flow through TAVs and used computational fluid dynamics (CFD) simulations to quantify forces that could potentially dislodge the prosthesis [41]. A 3D geometric model and mesh of the ascending aorta were generated based on anatomic measurements from the literature, while a second mesh, generated to model an implanted TAV, was merged with an aortic mesh at the annulus. A detailed description of flow through the model in a time-dependent mannor was simulated using Navier-Stokes equations and blood flowing in the aorta was modeled as a Newtonian fluid. The peak central jet velocity was 1.47 m/s which was in agreement with PIV measurements considering that the CFD study used a 24-mm TAV within the aortic sinus at 120/80 mm [39]. Total force on the TAV was obtained by performing an unsteady control volume analysis to determine the force necessary to hold the TAV in the root. The control volume was defined by the mesh which surrounds the TAV and the inlet and exit areas of the TAV. There were four contributions to the force: first, fluid momentum flux at the inlet and exit of the TAV; second, unsteady change of momentum in the valve control volume; third, dynamic pressure force on the TAV; and fourth, viscous shear stresses on the TAV outer wall. Total antegrade force exerted on the TAV during systole was 0.60 N at peak flow, 99% of which

was in the direction of axial flow. The largest contributor to force was the dynamic pressure gradient through the TAV. In addition, total retrograde force on the TAV was estimated based on the net pressure force applied on the closed valve during diastole. Antegrade force was approximately ten-times smaller than retrograde force (6.01 N) on TAV during diastole. The simulation demonstrated that TAV migration into the left ventricle was of greater concern than antegrade ejection, assuming frictional forces were not present.

In a subsequent study to determine how antegrade migration forces increase with TAV stenosis over time, Dwyer et al. evaluated hemodynamic changes within the TAV created by calcification and degeneration of TAV leaflets [42]. The TAV orifice area was reduced by 35 and 78% to replicate TAV sclerosis and stenosis, respectively. Based upon computational simulations, sclerosis increased the total force on the TAV by 63% (0.60-0.98 N), and advancement of degeneration from sclerosis to stenosis was accompanied by an 86% increase in total force (1.82 N). As a result, TAV stenosis led to a significant increase in the forces applied to TAVs during systole. However, migration forces on TAVs were still greater into the left ventricle than distally, even with significant TAV stenosis.

To counteract these antegrade and retrograde migration forces, TAVs are implanted with a radial force exerted on the aortic annulus. Tzamtzis et al. conducted numerical analyses of the radial force exerted by 26-mm CoreValve and SAPIEN [43]. Understanding of the TAV radial force exerted on the aortic wall and annulus has been crucial in TAV migration and reducing complications of atrioventricular block. Excessive TAV radial force is believed to damage the conduction system and can result in atrio-ventricular block. Selfexpanding CoreValve TAVs exerted radial or hoop forces that were dependent upon LVOT diameter, with forces in the 2-7 N range in the recommended 20-23-mm implantation range during expansion, but quickly dropping to zero as LVOT increased to 26 mm. The flared distal portion of CoreValve (25 mm in diameter) exerted a constant hoop force of 3 N on the ascending aorta. By contrast, SAPIEN radial force was not only dependent on LVOT diameter, where hoop force again decreased with increasing LVOT diameter, but also was dependent upon LVOT stiffness. However, for LVOT stiffness of <600 kPa/%, SAPIEN hoop force was nearly constant at 12-14 N for LVOT

diameters of 22 mm, but rapidly fell to zero with increasing LVOT size or stiffness. Despite differences in valve design and implantation, CoreValve and SAPIEN exerted similar magnitude forces, but varied significantly within the recommended implantation range. As such, radial force differences between CoreValve and SAPIEN could not explain the higher incidences of atrio-ventricular block observed after CoreValve implantation, which may relate more to depth of TAV positioning. The sudden drop in both CoreValve and SAPIEN radial force at the upper end of the recommended implantation ranges suggested that valve dislodgement remains a potential risk for patients with large LVOT.

Clinically, TAVs have migrated, but rarely, and have done so not only into the left ventricle, but also distally into the aorta during deployment [44-49]. Calcified leaflets and annulus of AS valves are also believed to provide frictional forces on TAVs to prevent migration, which were not part of the above simulations. As such, migration into the left ventricle has occurred when TAVs were deployed too far below the annulus, where TAVs did not have sufficient contact with calcified annulus and leaflets and were subjected to large retrograde migration forces [46,50,51]. On the other hand, TAVs have migrated distally during valve deployment, particularly if incorrect rapid pacing did not allow cardiac standstill and cardiac ejection of TAVs occurred when they were implanted too high above the annulus [44,47,52,53]. When TAVs were not anchored within the annulus and were deployed above the valve, they would lodge distally based upon the size of the aorta in relation to TAV size. When the aortic diameter became smaller than that of TAVs, TAVs implanted in that region, anywhere from the arch to the descending thoracic aorta [44,47]. TAVs in that location would still be subjected to large retrograde forces, but they were oversized in that location relative to aortic diameter, preventing further proximal or distal migration. Thus, in order to counter both antegrade and retrograde migration forces clinically, TAVs have been oversized by 2-3 mm in relation to aortic annulus diameter to achieve appropriate valve anchoring and decrease the degree of paravalvular regurgitation. Frictional force provided by oversizing aids in preventing TAV migration after deployment. Since TAV anchoring with the calcified AS leaflets is believed to provide an additional frictional



Figure 3. 3D streamlines in the left ventricle and aorta during different time frames in the cardiac cycle. Color coding denotes local absolute blood flow velocity. Marked helical flow denoted by yellow arrows. Helix flow from right to anterior along outer curvature of the ascending aorta denoted by white open arrows.

AAo: Ascending aorta; DAo: Descending aorta; LV: Left ventricle; t: Time. Reproduced with permission from [40].

force, TAVs have not been implanted in patients with primarily AR and a lack of calcium clinically.

■ Contact forces on TAVs & stresses on the aortic root & AS valve

Finite element (FE) analyses (FEA) of TAVI yield valuable data on the biomechanics of TAV-aortic root interactions. FEA is a numerical technique that is used to analyze stress and strain distribution in materials. FEA have provided supporting data that calcified leaflets and oversizing help to prevent migration. Wang et al. [54] and Capelli et al. [55] performed TAVI FEA using patientspecific aortic root geometry recreated from computed tomography (CT) images. In a 77-yearold patient with tricuspid AS and 21-mm annulus, Wang investigated contact forces (normal and shear) between a SAPIEN XT cobalt-chromium stent and the aortic root with a deployed TAV diameter of 23.1 × 24.6 mm. FEA excluded TAV leaflets, but included diseased AS valves, with calcifications with material properties of hydroxyapatite crystal. Contact normal force on the TAV stent was 149.02 N, while contact shear force was 12.58 N. A cross-sectional view of the deformed aortic root at maximum TAV expansion revealed that calcification of AS leaflets deformed the aortic annulus in a noncircular fashion leaving gaps between the TAV stent frame and annulus,

identifying potential sites of paravalvular leakage. Average and peak maximum principal stress (MPS) on aortic sinus tissue and diseased AS leaflets, at and near the calcium deposits, were also determined. The greatest peak MPS was noted at AS leaflet calcifications (641.2 MPa) and the transition zone between calcification and native tissue (44.41 MPa). In comparison, the average MPS in noncalcified leaflet tissue was 2.91 MPa and, in aortic sinus tissue, 0.87 MPa. Such high stress at the calcified leaflets suggested that AS leaflets carried substantial loads and helped secure the TAV in position [54]. High-stress concentration was also observed at the leaflet-root attachment lines and at the aortic wall between leaflets where the aortic root contacted TAV stent struts, supporting the need for oversizing to increase TAV contact with the root. On the other hand, such high stresses in the calcified regions can be a double-edged sword, with the potential for tissue tearing and breakdown of calcium deposits, which may increase risk of stroke [41].

FEA of TAV leaflet stresses

While the above FEA excluded TAV leaflets, stresses exerted on TAV leaflets are important to understand with respect to TAV durability. For surgical bioprostheses, leaflet design including attachment to the supporting stent, as well as leaflet stresses have widely been considered to be critical for bioprosthetic durability [56]. These principles similarly apply to TAV durability. Li et al. performed FEA of three scallop-shaped leaflets similar in design to surgical Carpentier-Edwards PERIMOUNT bioprosthesis and SAPIEN XT TAV, but without a stent, using bovine and porcine pericardium of variable thickness 0.2, 0.25, 0.3, and 0.35 mm [57]. Peak MPS/maximum principal strain occurred near leaflet commissures, with the lowest stress/strain near leaflet-free edges. In the fully loaded (closed leaflet) configuration, peak MPS of TAV with bovine pericardium (915.52 kPa) was lower than that with porcine pericardium (1565.80 kPa); however, both were greater than that in surgical bovine pericardial bioprostheses (663.2 kPa). Bovine pericardium had lower stresses than porcine pericardium for matched leaflet thickness, suggesting inherent material property differences. For both bovine and porcine pericardial leaflets, the thinner the pericardium utilized for leaflets, the greater the peak MPS. Based on engineering calculations of the available cross-sectional area for leaflets within a 22 Fr delivery catheter, leaflets <0.35 mm were required. Newer

16–18 Fr delivery systems would require much thinner leaflets (~0.2 mm). Given that surgical bioprosthetic leaflets are typically ≥0.35 mm thickness, both inherent differences in material properties and thinner TAV leaflets are expected to result in higher TAV leaflet stresses, as seen here. Such high TAV leaflet stresses, compared with surgical bioprostheses, may impact on, and shorten, TAV durability in comparison with surgical bioprostheses.

In general, computational studies may be used to optimize the location of TAVs within the aortic root and predict coronary ostia obstruction and paravalvular leakage. Creating patient-specific computational models may, in the future, provide clinical advantages by predicting how various TAVs interact within a patient's given anatomy to optimize the choice of TAV as the number of approved devices increases. As patient-specific LVOT stiffness, diseased valve calcification and LVOT size impact the radial force for TAV deployment, more accurate models to aid clinical TAVI planning will need to be developed to account for in vivo patient aortic root material properties. Currently, in vivo determination of aortic root material properties is a topic of ongoing research.

Considerations of endovascular approach

Impact of TAV

crimping/balloon-expansion on calcification and structural integrity While leaflet stress based on leaflet thickr

While leaflet stress based on leaflet thickness, material properties, and deployed leaflet geometry may be critical factors in determining TAV durability, another difference in TAV and surgical bioprosthesis is that TAVs are crimped to fit into delivery catheters and then expanded, unlike surgical valves that are stored at nominal dimensions and implanted. Kiefer et al. investigated the impact of TAV leaflet crimping then uncrimping on calcification and structural morphology compared with surgical bioprosthetic leaflets [58]. SAPIEN 26-mm TAVs were crimped into a 24 Fr delivery system for 1 h, 1 day and 1 month, and leaflets were implanted in a subcutaneous rat model to investigate calcification and histopathology. No differences in calcification levels were seen among TAV leaflets crimped for various intervals, or between crimped and uncrimped TAV leaflets. Furthermore, no difference in calcification was seen among all TAV leaflets and surgical bioprostheses. However, increasing time in the crimped state led to marked

structural changes in collagen, which showed fragmentation. Crimping for less than a day had relatively fewer changes in ultrastructural morphology. This study suggested that crimping did not necessarily impact degeneration by calcification; however, the duration of crimping should be kept to a minimum to preserve leaflet structural integrity.

In another study, de Buhr et al. studied impairment of pericardial leaflet structure from balloon expansion [59]. Custom-made stents with two different closed-cell designs were laser cut from a 22-mm diameter stainless steel tube. Treated calf pericardial strips were mounted in the stents and crimped onto a standard balloon catheter. The stents were expanded to a maximum pressure of 2 bar within 1 s and the pressure was held for 3 s. Immediately after the expansion procedure, the pericardium was uncoiled from the stent and the histology of the pericardial tissue was analyzed. Histologic analysis revealed strut imprints on the valve tissue, disruption to the surface of the tissue and disrupted collagen fibers. The study suggested that disruption of pericardial tissue structures due to balloon expansion may result in early functional valve failure; however, further investigation regarding the clinical relevance of the observed tissue injury is essential.

In vitro study of deployment force & aortic intimal damage

Although interaction between TAV and the aortic wall is important for TAVI and biomechanics studies, the endovascular aspect of this procedure is also of interest. Catheter insertion through the femoral or subclavian artery is routine in cardiac catheterization, but TAVI utilizes much larger delivery device profiles. Furthermore, patients with calcifications in the aorta (porcelain aorta) could have devastating neurovascular complications if plaques were disrupted. An in vitro study of a TF approach to the ascending aorta measured the deployment force required to advance two commercially available delivery systems, 22 and 18 Fr, in 15 fixed cadaveric human aortas, which were not pressurized or fluid-filled [60]. Greater deployment force was required the further the delivery system was advanced and the 22 Fr system failed to cross the iliac arteries in eight cases, of which three also could not pass the abdominal and thoracic aorta. The 18 Fr system was successfully deployed in all cases. Median deployment forces for 18 and 22 Fr systems were 3.0 and 3.6 N, respectively

for the iliac artery, 5.6 and 4.9 N, respectively for the abdominal and thoracic aorta, and 11.5 and 12.1 N, respectively for the aortic arch. In comparison, the deployment force for a 30 Fr TA approach was 8.4 N. After the 22 Fr TF approach, all specimens had undergone major intimal abrasions in the descending aorta and aortic arches upon endoscopic examination of the intima. Limitations of this study include tissue fixation, which significantly reduces vessel wall compliance, and lack of a pressurized pulsatile deployment system. Nonetheless, attention to the TAVI approach should not be underestimated given that aortic damage from delivery systems can result in significant complications.

Impact of TAV oversizing on valvular hemodynamics

TAV oversizing has been the clinical paradigm to overcome dislodgment forces and achieve appropriate valve anchoring. However, oversizing leads to TAV stent underexpansion from its nominal dimensions which could adversely impact on valvular hemodynamics [61]. Unlike surgical stented bioprosthetic valves, where leaflets are mounted within a rigid framework and valve kinematics are highly consistent, optimal TAV function requires valve expansion to nominal dimensions. Underexpanded TAVs are expected to function suboptimally with increased transvalvular pressure gradient (TVG) and impaired leaflet coaptation. Since individual patients have patient-specific AS geometry and dimensions, TAV underexpansion is variable, as demonstrated by CTs of pre- and post-TAVI diameters [62]. To investigate the hemodynamic impact of TAV underexpansion, it is useful to constrain TAV expansion in a systematic fashion, such as within rigid bioprosthetic sewing rings. This valve-in-valve implantation has had clinical application in patients with degenerated stented bioprostheses.

Azadani *et al.* investigated the impact of transcatheter valve-bioprosthesis size mismatch on valve-in-valve implantation [63]. TAVs were created based on the 23-mm SAPIEN TAV design. TAVs were implanted within normal 19, 21 and 23-mm Carpentier–Edwards PERIMOUNT bioprostheses with internal diameters of 18, 20 and 22 mm, respectively. Valves were tested in a custom-built pulse duplicator system based on International Organization of Standardization (ISO) 5840 and FDA standards. Acceptable valve-in-valve hemodynamics were achieved only in 23-mm

bioprostheses with no significant change in mean TVG in comparison with normal 23-mm bioprostheses $(5.93 \pm 0.87 \text{ to } 8.27 \pm 1.19 \text{ mmHg};$ p = 0.052). However, excess pericardial leaflet tissue relative to stent orifice area resulted in severe and moderate stenosis in 19 and 21-mm bioprostheses, respectively. Mean TVG increased from 16.18 ± 2.20 to 45.53 ± 12.54 mmHg (p = 0.004) in 19-mm bioprostheses, and from 11.84 ± 1.88 to 28.18 ± 9.03 mmHg (p = 0.004) in 21-mm bioprostheses. In all three cases, valve-in-valve implantation was associated with mild valvular regurgitation. There was no evidence of migration. They concluded that the rigid bioprosthetic annulus and stent posts offered a suitable TAV landing zone; however, implantation of an oversized TAV, if not fully expanded to nominal dimensions, could adversely impact on valvular hemodynamics.

Impact of deployed geometry & asymmetry of TAV stent

Deformation of TAV in aortic root

SAPIEN and CoreValve TAVs are designed with circular cross-sectional stent geometry, though SAPIEN is cylindrical and CoreValve is hourglass in shape. Studies have demonstrated that the native aortic annulus is elliptical in shape [62,64–66], and aberrations from a perfectly circular aortic annulus can be expected with severe calcifications. Noncircular annulus geometry after TAVI, whether from native anatomy or calcification, may result in paravalvular leakage.

Sirois et al. performed a computational analysis of TAV hemodynamics before and after TAV implantation [67]. The aortic root geometry was acquired from CT images of a patient with no known valve disease. The healthy valve geometry was numerically deformed into a shape that mimics that of a stenotic valve through a FE simulation. This deformed valve geometry was subsequently used as the baseline for a TAV implantation simulation. A combination of FEA and CFD were used to assess TAV hemodynamics before and after TAV implantation. First, FE simulations were performed to obtain the leaflet geometry of the stenotic valve and the leaflet geometry of TAV after implantation. Valve leaflet geometry was extracted from FE simulation and used to create a CFD model. Two scenarios were explored in this study. First, a TAV was expanded into an open native valve, whereby the top of the leaflets were above the top of the TAV stent. In this scenario, the TAV stent was deployed and expanded to an outer diameter of 23 mm within the native valve geometry. In the second scenario,

the TAV was expanded into a partially closed native valve whereby the top of the leaflets were below the top of the TAV stent. In this scenario, native valve leaflets were removed and 0.5-mm thickness was added to the TAV stent to represent the effect of calcified leaflets. A velocity profile was obtained before and after TAV intervention. Prior to TAV intervention, a narrow orifice was observed by the stenotic valve resulting in a high-velocity central jet extending well into the ascending aorta. A peak velocity of 4.25 m/s was observed at 1 ms following peak systole. After TAVI, peak velocities of 2.56 and 2.65 m/s were observed 7 ms after peak systole for scenarios one and two, respectively. In contrast with native calcified valves, the peak velocity occurred in a very small region along a fold at the base of the TAV leaflets in both postdeployment scenarios. Qualitative validation of the computational model was made using select data obtained from TAV clinical trials.

■ TAV leaflet stresses with asymmetric TAV stent configuration

Given the naturally elliptical shape and significant stiffness of aortic annulus, some degree of asymmetry in deployed TAV configuration is to be expected, as demonstrated in clinical imaging studies of post-TAVI geometry [62,68]. Furthermore, differences in AS geometry in bicuspid and tricuspid AS also impact upon TAV stent geometry [61,69]. Circularity has been defined as eccentricity <10%. Eccentricity was calculated as 1-minimum external stent diameter/maximum external stent diameter. In general, balloon-expandable TAVs quite often maintained circularity (FIGURE 4), where within four levels of TAV stent, circularity ranged from 74-90% [70], but as high as 96% in another study [71]. However, when studied for the ability to maintain cylindrical shape fluoroscopically from bottom to top of the SAPIEN TAV (FIGURE 5), the deployed SAPIEN did not achieve cylindrical deployment after expansion in all cases [72,73]. Such differences along the TAV stent resulted in leaflet-to-stent mismatch in 12-33% of patients. TF SAPIEN deployment resulted in greater longitudinal TAV deformation than the TA approach, though leaflet-stent mismatch was less, 12 versus 33%, respectively. On the other hand, Schultz et al. studied self-expanding CoreValve TAVs and demonstrated incomplete and nonuniform expansion of Nitinol stents, with only 17% circularity and then only at levels of central coaptation and commissures (FIGURE 6) [68]. Asymmetry at the ventricular

end corresponded to the conformation of the CoreValve stent to elliptical LVOT geometry, facilitating TAV anchoring and apposition to reduce paravalvular leakage. The middle section of CoreValve, housing TAV leaflets, was overall better expanded and more symmetrical than the other sections.

Sun *et al.* investigated the effects of implanted TAV elliptical geometry on TAV leaflet stress and strain using FEA wand CFD [74]. Degree of TAV elliptical shape was determined by eccentricity of an ellipse e:

$$e = \sqrt{1 - \left(\frac{b}{a}\right)^2}$$

where a and b were length of the major and minor axes of ellipse, respectively. Modeled eccentricities were based on elliptical TAVs in Schultz et al. [68]. Modeled TAV eccentricities of 0.3, 0.5 and 0.68 were studied in two-valve orientation scenarios, one having the ellipse major axis aligned with one of the leaflet coaptation lines (S1), while the other had the ellipse axis perpendicular to one of the leaflet coaptation lines (S2). Peak stress increased with increase of eccentricity. Peak MPS' of elliptical TAV leaflets ranged from 1220.99 to 1451.76 kPa for S1, and from 1055.79 to 2227.35 kPa for S2. Compared with circular TAV expanded to nominal dimensions, peak stresses increased by 59% for S1 and by 143% for S2. While circular nominal TAV had nearly identical peak stresses among the three leaflets (1% difference), elliptical TAVs had unequal stress distribution among the three leaflets with a maximum difference of approximately 50%. These elevated, asymmetric stresses are concerning for potentially accelerating device fatigue and TAV degeneration. For eccentricity >0.5, central regurgitation occurred, which was greater in S1 than S2 and corresponded to 1-2 plus AR. S1 resulted in larger central regurgitation area while S2 had the greatest peak leaflet stresses. Valve deployment orientation with respect to calcification was also important to consider since a large calcification perpendicular to the TAV leaflet coaptation line was predicted to result in greater regurgitation. Both paravalvular regurgitation and increased central regurgitation from eccentricity are primarily concerns for TAVs, not surgical bioprostheses where sutures prevent paravalvular leakage and eccentricity is not an issue (within nominally implanted bioprostheses).

Experimentally, Young *et al.* studied the impact of noncircular TAV stent geometry



Figure 4. Transcatheter aortic valve circularity on computed tomography. (A–D) Computed tomography of aortic root with left ventricular outflow tract and four planes of evaluation of deployed SAPIEN Transcatheter aortic valve. (E–H) Circularity of transcatheter aortic valve from ventricular side up to aortic side. Reproduced with permission from [70].

on TAV hemodynamics, using cylindrical 26-mm TAV with a Nitinol stent within a pulse duplicator [75]. Configurations studied included: nominal (26.5-mm diameter), triangular (with commissures at corners vs commissures rotated to align midway between corners), elliptical and severely undersized (20.5-mm diameter circular), with two variations: 'half' conformation, where only TAV inflow portion was constrained to the geometry and 'full' conformation, where the entire TAV length was constrained to the geometry. Hemodynamics were assessed, including TVG, effective orifice area (EOA), and regurgitant fraction due to intravalvular leakage. Nominal shape had statistically higher TVG (6.2 mmHg) than the other configurations, except for the severely undersized valve (16.0 mmHg) and full triangle with commissures in the corner. Nominal shape had a smaller EOA (1.6 cm²) than triangular and elliptical shapes, and also had a smaller regurgitant fraction (6.7%) except for half- and full-undersized configuration (4.0 and 6.8%, respectively). Elliptical and triangle shapes had significantly higher regurgitant fraction, ranging from 10-12.7%. This study confirms the results from the CFD elliptical studies, which demonstrate that non-nominal stent geometry increased intravalvular leakage, particularly with triangular and elliptical configurations. Alterations in leaflet coaptation were visualized for triangular and elliptical TAV geometries to account for the increased regurgitant fraction. Increased TAV leaflet stresses may impact TAV durability, while increased paravalvular leakage and central



Figure 5. Deployed SAPIEN on fluoroscopy. (A) Biconical shape of SAPIEN stent frame was seen most commonly. **(B)** Conical shape. *Waist zone and shortest diameter. Reproduced with permission from [72].

regurgitation adversely impacts upon valve performance.

Transvalvular energy loss measurement

Another significant difference between surgical valves and TAVs is that paravalvular leakage is a nearly unavoidable phenomenon after TAVI, but is infrequent after surgical AVR, where suturing of the valve into the annulus prevents leakage around the valve unless technical complications present. TAVI within a calcified valve results in paravalvular leakage, despite TAV oversizing and use of a fabric cuff at the TAV base along the annulus [76]. Paravalvular leaks occur up to 70% of the time, mostly mild, but occasionally moderate in severity [71]. Recently, TAVI registry data from Germany demonstrated poorer shortterm outcomes, with increased in-hospital mortality, in patients with at least moderate paravalvular leak following TAVI [77]. Clinically, TAVs match and may even exceed hemodynamic performance of surgically implanted bioprostheses based on clinical hemodynamic criteria routinely used in practice: TVG, EOA and blood flow velocity [78,79]. However, none of these standard criteria take into account regurgitation in diastole.

Energy loss, a well-known engineering concept, allows the assessment of TAV hemodynamics, not only during systole, but also during diastole where regurgitation occurs. By using transvalvular energy loss, the focus can be shifted from TAV systolic function to the effect of TAV performance on the ventricle during the entire cardiac cycle [80]. Azadani *et al.* evaluated TAV hemodynamic performance using transvalvular energy loss based upon principles of conservation of energy in an *in vitro* pulse duplicator [81]. Energy loss was assessed by the difference in energy flux entering and leaving the control volume, which spanned LVOT through the aortic root during one cardiac cycle. A detailed description of the energy loss calculation was described by Heinrich *et al.* [82]. Changes in gravitational and kinetic energy were negligible with respect to changes in pressure energy. Energy loss (Φ) during forward flow, closing flow and leakage flow was calculated separately by integrating instantaneous flow (Q_{valve}) through the valve and instantaneous pressure gradient (ΔP) during each time period:

$$\begin{split} \phi_{\text{Forward flow}} &= \int_{t0}^{t1} Q_{\text{valve}} \times \Delta P \times dt \\ \phi_{\text{Closing flow}} &= \int_{t1}^{t2} Q_{\text{valve}} \times \Delta P \times dt \\ \phi_{\text{Leakage flow}} &= \int_{t2}^{t3} Q_{\text{valve}} \times \Delta P \times dt \end{split}$$

Where $t_0 =$ beginning of forward flow through the valve, $t_1 = end$ of forward flow, $t_2 = time$ of valve closure, $t_3 =$ end of one cardiac cycle. Total energy loss was the sum of energy loss during forward, closing, and leakage flow periods. Azadani et al. [81] demonstrated that substantial energy loss occurred during diastole in the presence of paravalvular leakage. For surgical bioprostheses that did not have paravalvular leakage, total energy loss decreased with increasing valve size. Overall, 23-mm Carpentier-Edwards PERIMOUNT bioprostheses demonstrated less total energy loss (213.25 ± 31.35 mJ) when compared with 21-mm PERIMOUNT bioprostheses $(298.00 \pm 37.25 \text{ mJ}; \text{ p} = 0.008)$ and 19-mm PERIMOUNT bioprostheses $(330.00 \pm 36.97 \text{ mJ}; p = 0.003)$. The 23-mm TAV, at nominal dimension in a rubber silicone ring that prevented paravalvular leakage, had similar energy loss to the 23-mm PERIMOUNT TAV. Energy loss was 182.67 ± 13.05 mJ (p = 0.062) during forward flow, $5.00 \pm 1.00 \text{ mJ}$ (p < 0.001) during closing flow, and $53.33 \pm 16.50 \text{ mJ} (p = 0.695)$ during leakage flow. However, in the presence of mild paravalvular leakage, such as valve-in-valve within 23-mm bioprosthesis, TAVI imposed a significantly higher workload on the left ventricle $(365.33 \pm 8.02 \text{ mJ}; p < 0.001)$ than an equivalently sized surgically implanted bioprosthesis.

Transvalvular energy loss is a more appropriate criterion to assess TAV performance, by determining valvular hemodynamics during the entire cardiac cycle. Transvalvular energy loss may become the new benchmark for comparing the hemodynamic performance of TAVs with surgical valves clinically. Given the *in vitro* nature of determining energy loss, determination of *in vivo*

D2–D1 median (IQR)				
n = 30 patients	Ventricular end	Nadir of leaflets	Central coaptation	Commissures
Circular	2.2 (2.0–2.3)	1.8 (1.5–2.2)	1.2 (0.7–1.8)	1.1 (0.5–1.7)
Noncircular	4.4 (3.8–6.7)	4.5 (3.3–5.6)	3.3 (2.8–4.0)	-
Circular			$\langle \rangle$	
Noncircular		A A	\bigcirc	

Figure 6. Deployed CoreValve on computed tomography in patients with circular versus noncircular deployment. Difference between largest and smallest diameter, D2–D1. D1: Smallest diameter; D2: Largest diameter; IQR: Interquartile range. Reproduced with permission from [68].

energy loss calculations by echocardiography will be required. However, energy loss has not been routinely used clinically because direct calculation of energy loss requires complex and invasive measurements of simultaneous temporal pressures and velocities. As yet, no echocardiography measurements have been developed to estimate energy loss, and further developments in this area would be invaluable. While mild-to-moderate AR following TAVI may not have significant clinical impact in high-surgical risk patients, this degree of paravalvular leakage may have considerable consequences long-term if TAVs are expanded to younger and healthier patients.

TAVI within degenerated bioprosthetic valves

Computational and experimental studies not only identify new concepts for valve assessment such as the energy loss above, but are also useful in expanding technology to other indications. Capelli *et al.* performed patient-specific FEA of 26-mm SAPIEN TAVI without TAV leaflets in various morphologies to computationally demonstrate the feasibility of TAVI for degenerated bioprostheses (valve-in-valve implantation) [55]. Four patients had degenerated bioprostheses: 23-mm Carpentier–Edwards PERIMOUNT Magna, 23-mm SopranoTM, 25-mm Carpentier–Edwards PERIMOUNT, and 25-mm St Jude Epic, while one patient had severe AR years after valvuloplasty for congenital tricuspid stenosis. The highest von Mises stresses occurred at strut junctions for all models ranging from 414 to 477 MPa, while stress values were <250 MPa for the length of the stent zigzags and vertical bars. Based on these stresses, final open stent configuration was guaranteed, but was noted to have geometrical asymmetries, which led to nonuniform stress distribution on the stent struts. Since maximum von Mises stress did not exceed that of stainless steel American Iron and Steel Institute (AISI) 316L (515 MPa), no stent fractures were anticipated immediately after SAPIEN TAVI, though TAV stent failure might still occur over the long term due to asymmetric stress distribution on TAV stents subjected to the pulsatile loading conditions of the cardiac cycle. For valve-in-valve, MPS in the aortic root was 0.1 MPa, while that in the native root was ten-times higher, demonstrating that the bioprosthesis acted as a landing zone for TAVs, while TAV interaction with the native root was necessary for fixation. The FEA demonstrated the feasibility of TAVI under different conditions and assessed the risk of coronary ostia obstruction.

TAVI offers an attractive option for patients with degenerated bioprostheses (valve-in-valve concept). Experimentally, Azadani *et al.* investigated the feasibility and hemodynamics of valve-in-valve implantation [83]. TAVs created based on the 23-mm SAPIEN valve design were implanted within degenerated 19, 21, and 23-mm Carpentier--Edwards PERIMOUNT bioprostheses (n = 6



Figure 7. In vitro TAVI within degenerated bioprostheses. (A) 23-mm TAVI within 21-mm degenerated PERIMOUNT bioprosthesis. (B) 23-mm TAVI within 19-mm degenerated PERIMOUNT bioprosthesis. Reproduced with permission from [83].

each). Bioprosthetic degeneration was simulated using BioGlue® to achieve a mean TVG of 50 mmHg. Valves were tested in a custom-built pulse duplicator system based on ISO 5840 and FDA standards. TAVs demonstrated excellent hemodynamics after implantation within 23-mm degenerated bioprostheses with significant reduction in TVG (50.9 ± 4.7–9.1 ± 4.1 mmHg; p < 0.001). Furthermore, TAVI within a 21-mm degenerated bioprosthesis significantly reduced TVG (52.3 ± 7.0-19.5 ± 5.0 mmHg; p < 0.001). However, the obtained TVG was significantly higher than that with surgical valve re-replacement using 21-mm PERIMOUNT bioprosthesis, 12.4 ± 2.0 mmHg; p < 0.02. In 19-mm PERIMOUNT bioprosthesis, TAVI did not improve TVG $(57.1 \pm 4.3 - 46.5 \pm 9.3 \text{ mmHg})$; p = 0.09). Incomplete stent expansion resulted in excess pericardial tissue relative to stent orifice area and led to severe stenosis (FIGURE 7). These in vitro results demonstrated that the rigid annulus and

stent posts of bioprostheses constrained oversized TAVs and prevented full stent expansion. These results correspond well with case series of valve-invalve implantation clinically [84], and demonstrate how in vitro experimentation could provide a useful guide for clinical feasibility. Valve-in-valve implantation within 23 mm or larger bioprostheses yielded good hemodynamic results, while TAVI in 21-mm bioprostheses had variable hemodynamics that were usually acceptable, although mean TVG was often elevated, suggesting incomplete relief of obstruction [85]. The 23-mm TAVI in a 19-mm bioprosthesis was too much of a size mismatch, so, to date, no 19-mm degenerated bioprostheses have been treated by 23-mm TAVI. With the anticipation of 20-mm TAV sizes, Azadani et al. investigated the feasibility of treating 19 and 21-mm degenerated bioprostheses with 20-mm TAVI [86]. While 20-mm TAVs retrogradely migrated in the left ventricle with 21-mm PERIMOUNT bioprostheses, 20-mm TAVI relieved bioprosthetic stenosis in 19-mm PERIMOUNT bioprostheses (54.9 ± 5.4 to 23.5 ± 3.9 mmHg; p = 0.006), and 21-mm porcine bioprostheses (35.2 ± 8.9 to 16.8 ± 4.1 mmHg; p = 0.03), but were ineffective for 19-mm porcine bioprostheses. They also demonstrated that TAVI orientation in degenerated bioprostheses had no impact on hemodynamics or coronary flow. These experimental studies paved the way for the first-inman valve-in-valve implantation of a 20-mm TAV within a 19-mm degenerated bioprosthesis [87].

While TAV oversizing is necessary to achieve appropriate valve anchoring and decrease paravalvular regurgitation, oversizing may lead to TAV stent underexpansion, which could adversely impact upon valvular hemodynamics and long-term durability. Another possible solution to achieve acceptable hemodynamics is a supravalvular TAV where the valve within the TAV stent is situated above the bioprosthesis. As a result, TAV leaflets can be fully expanded to nominal size, while the lower portion of the stent provides appropriate valve anchoring. Azadani et al. demonstrated that the 23-mm supravalvular TAV successfully relieved bioprosthetic stenosis in a wide range of bioprosthetic sizes (19-, 21and 23-mm PERIMOUNT bioprostheses) [88]. Obtained TVGs were comparable to standard surgical valve replacement of equivalent size.

New imaging techniques & methods for TAVI

Due to the minimally invasive nature of TAVI, medical imaging modalities play a crucially important role for ensuring a successful procedure. However, challenges remain in interpreting the complex aortic root anatomy and patient variability to ensure successful and ideal device placement. While TAVI started with 2D fluoroscopy and TEE, incorporation of specially designed engineering software with modern imaging technologies has improved, and will continue to vastly improve, the TAVI procedure. Dynamic image overlay is being routinely incorporated for accurate TAV placement. Other possibilities include rapid prototyping to assist in TAVI simulation and optimization prior to the procedure and TAVI performed entirely under real-time MRI (rtMRI) guidance. Image processing techniques have been developed to guide TAV placement, given the patients' particular anatomical features [89,90]. Karar et al. developed a method to assist TAV placement during live 2D fluoroscopy by automatically displaying the target area for TAV deployment [90]. A 3D mesh of aortic root geometry was developed from intra-operative C-arm CT images and the estimated target area for TAV was defined based on eight anatomical landmarks: two coronary ostia, three commissure points, and the nadir of three leaflet cusps. The 3D root and target area were then automatically overlaid on live fluoroscopic images for deployment. Grbic et al. developed a novel method to fuse data from pre- and intra-operative imaging from multiple modalities by aligning the images based on anatomical landmarks to generate an accurate 3D aortic root for TAV deployment intra-operatively [89]. Clinical application of these computational algorithms in imaging significantly improves the accuracy of TAV deployment. In the future, the ability to predict the deployed TAV configuration within a specific patients' anatomy, if added to such algorithms, may be used to optimize choice of TAV for that patient, in reducing paravalvular leak, and minimizing TAV leaflet stress to increase durability.

One method to simulate TAV deployment was performed by Schmauss *et al.*, where CT scan data was used to create a rapid 3D prototype model of a patient's aorta with extensive calcifications [91]. In this case, creating a physical model of patient anatomy allowed them to simulate TAVI experimentally and anticipate difficulties with implantation within a porcelain aorta with small noncompliant sinuses. They devised a strategy for implantation that was successful in this case.

The notion of CoreValve TAVI being performed under rtMRI guidance has been explored and provides attractive benefits over traditional fluoroscopy [92-94]. rtMRI offers an unrestricted scan plane orientation and unsurpassed soft tissue contrast with simultaneous device visualization, allowing for potentially enhanced accuracy with regards to proper TAV placement. Furthermore, rtMRI does not expose the patient and physicians to ionizing radiation, or require nephrotoxic contrast media. Kahlert et al. demonstrated the feasibility of CoreValve TAVI using rtMRI in swine [93,94]. Procedural success was achieved in five out of six cases with one procedural complication with inadvertent operator error resulting in ventricular perforation from the delivery catheter. This complication was noted immediately with rtMRI. Overall, the authors reported that TAVI with rtMRI allowed for better procedural navigation and device placement. Postinterventional success was confirmed with ECG-triggered time-resolved cine true fast imaging with steady-state precession and flow-sensitive phase contrast sequences. Intended valve position was confirmed by autopsy of swine.

Future perspective

TAVI has revolutionized the treatment of inoperable and high-risk patients with severe AS and, inevitably, will be offered to patients of lesser surgical risk. What cutoff should trigger choosing TAVI over surgical AVR, based on predicted mortality risk from the Society of Thoracic Surgeons, will depend on some of the fundamental differences in TAV and surgical bioprosthesis design and implantation. The primary concerns regarding TAV versus surgical bioprostheses in younger healthier patients will be durability, paravalvular leakage, hemodynamics based on energy loss and stroke. Surgical bioprostheses have good and predictable long-term durability based on decades of clinical experience and continued refinement in leaflet technology with anticalcification strategies. On the other hand, TAVs have unknown longterm durability. TAV leaflets are thinner than surgical bioprostheses and are expected to have higher leaflet stress based on thickness and asymmetric deployed geometry. Bovine and porcine pericardium have different mechanical properties. How significant the expected higher TAV versus bioprosthesis leaflet stresses will be in impacting on durability is unknown. Better in vitro and in vivo methods for determining durability are required since standard testing by ISO and FDA standards does not account for deployed TAV configurations clinically, which can be undersized, noncircular/elliptical, or circular but not cylindrical. While accelerated wear testing may be performed in such configurations, the impact on the calcification

Executive summary

Transcatheter aortic valve & surgical bioprosthesis differences

- Critical design differences in surgical stented bioprostheses and transcatheter aortic valves (TAVs) include:
- Surgical valve leaflets are housed within a rigid stented framework, whereas TAV leaflets are mounted within an expandable stent framework, which is crimped for vascular access and then expanded during deployment.
- Surgical stented bioprostheses have consistent and reproducible leaflet kinematics due to the rigid framework in which the leaflets are housed that maintains constant dimensions, while TAV leaflets are expanded to a variable degree based upon the geometry of the calcified annulus and degree of TAV stent expansion, which affects not only the diameter of expansion, but also the symmetry and circularity of expansion.
- TAV leaflets have different mechanical properties to surgical bioprosthetic leaflets since CoreValve[®] (Medtronic Inc., MN, USA) uses
 porcine not bovine pericardium, and although SAPIEN (Edwards Lifesciences, CA, USA) uses the same bovine pericardium as their
 surgical valves, the leaflet thickness of SAPIEN XT is less than PERIMOUNT in order to fit into the smaller 18 Fr delivery catheters.
- Surgical bioprostheses are stored at nominal dimensions and implanted. Crimping and expansion of TAV leaflets may have an unknown impact on long-term durability.

TAV hemodynamics

In vitro TAV fluid dynamics demonstrated a central orifice jet flow surrounded by ambilateral vortices that turned clockwise in the upper portion of the aorta and counter clockwise in the lower portion of the aorta. In vivo TAV 3D streamline visualization revealed marked helical flow, a strongly asymmetrical outflow jet forming along the right anterior outer curvature of the ascending aorta during mid-systole and extending towards the arch during early and mid-diastole.

TAV computational studies on antegrade & retrograde migration forces, radial contact forces & TAV leaflet stresses

- TAV retrograde migration into the left ventricle was of greater concern than antegrade ejection during TAV implantation (TAVI), since retrograde forces were a magnitude greater during diastole than antegrade systolic forces when frictional forces and oversizing were ignored. Implant location within the annulus is of paramount importance to prevent both retrograde and antegrade migration.
- Despite the differences in valve design and implantation, CoreValve and SAPIEN exerted radial contact forces of similar magnitude but these forces greatly varied within the recommended range of implantation sizes. Both valves had sudden drops in radial force at the upper end of the recommended ranges with remaining concern for valve dislodgement in the large left ventricular outflow tract.
- On the other hand, finite element analyses (FEA) of TAV oversizing relative to annulus size in calcified valves suggested the contact normal forces are vastly greater than migration forces, as were contact shear forces, supporting TAV oversizing to prevent migration.
- FEA suggested that TAV leaflet stresses were significantly higher than surgical bioprostheses and that pericardial leaflets made from porcine rather than bovine material had much greater leaflet stress.

Considerations of the endovascular approach with respect to the impact of TAV crimping on calcification, structural morphology & deployment force to deliver transfemoral versus transapical TAVI

- TAV crimping did not impact on calcific degeneration in a rat subcutaneous calcification model, but led to ultrastructural changes with collagen fragmentation based on duration of crimping. The duration of crimping should be kept to a minimum to avoid structural damage to TAV leaflets.
- In vitro investigation of TAV deployment (transfemoral vs transapical) demonstrated that deployment force was greater with the transfemoral than transapical approach.

The impact of TAV oversizing on valvular hemodynamics

The degree of TAV oversizing with respect to annulus impacts on valvular hemodynamics, such that minimal oversizing results in acceptable TAV hemodynamics, but significant oversizing, as demonstrated with small bioprostheses for valve-in-valve implantation, can result in moderate-to-severe stenosis.

The impact of deployed geometry & asymmetry of the TAV stent

- Due to the elliptical nature and inherent stiffness of the aortic annulus, deployed TAV geometry can demonstrate asymmetry of the TAV stent. Balloon-expandable TAVs, in other words SAPIEN and SAPIEN XT, demonstrated a much higher degree of circularity than self-expanding TAVs. That is, CoreValve, where CoreValve conformed to the elliptical geometry at the annulus. However, even SAPIEN valves did not have uniform deployment when studied for cylindrical deployment from the top to the bottom of the TAV, such that some degree of leaflet-to-stent mismatch occurred.
- TAV ellipticity affected leaflet coaptation; FEA and computational fluid dynamics demonstrated greater TAV leaflet stresses with increased ellipticity, which may reduce long-term durability. Thinner leaflets, required for smaller delivery systems, would also increase stresses exerted on TAV leaflets to potentially additionally reduce long-term durability. Biological interaction of the diseased aortic valve left behind with the TAV stent and leaflets over time is unknown. Determination of TAV durability based on these issues requires modification of standardized valve durability testing to examine the impact of leaflet asymmetry, changes in leaflet coaptation, lack of TAV nominal dimensions, and leaflet thickness on results of accelerated wear testing. Standardized accelerated wear testers should include components of *in vitro* calcification to mimic the *in vivo* degeneration process.
- Increasing TAV ellipticity also increased paravalvular and central aortic regurgitation. In vitro studies of deformed TAVs showed that, while nominal shape had the largest transvalvular gradient, elliptical and triangular-shaped TAVs had a significantly higher regurgitation fraction.

Executive summary (cont.)

Transvalvular energy loss measurement

Paravalvular leak and central regurgitation associated with TAVI increases energy loss during diastole. As such, total energy loss is an essential new benchmark by which to compare valve prostheses, since traditional evaluation of valve hemodynamics only accounts for systolic energy loss using transvalvular pressure gradient, effective orifice area, and peak transvalvular velocity, but does not account for diastolic energy loss with paravalvular leakage. Noninvasive measurements of energy loss will be crucial for comparison of TAVs with surgical valves.

TAVI within degenerated bioprosthetic valves

Computational and *in vitro* hemodynamic studies have demonstrated the feasibility of valve-in-valve implantation of TAVs for degenerated bioprostheses. Using *in vitro* studies helps to predict optimal TAV sizing and hemodynamics. Based on experimental hemodynamic results, TAVI within degenerated bioprosthetic valves is a promising option for elderly and high surgical risk patients. The rigid bioprosthetic annulus and stent posts offered a suitable landing zone for TAVs. However, the rigidity of the bioprostheses can constrain an oversized TAV and prevent full stent expansion. Valve-in-valve hemodynamics in small degenerated bioprostheses may be improved by using supravalvular TAV design where the valve leaflets sit above the bioprosthesis or smaller TAV devices.

New imaging techniques & methods for TAVI

Computational algorithms have and are being developed to optimize TAV deployment in the correct anatomic location by combining pre- and intra-operative computed tomography coregistration with fluoroscopic anatomic landmarks. Such improvements will facilitate the success of the technique and reduce complications of migration, and paravalvular leakage. Patient-specific TAVI simulations may be useful in the future to optimize which TAV designs are the most beneficial for a given patient as well as to predict final TAV configurations. Such future work will lay the groundwork for the application of TAVI in healthier and younger patients, where long-term durability and good hemodynamic performance will be necessary.

process in vivo is unknown. While paravalvular leakage is rare after surgical AVR, such leakage is common after TAVI. Moderate/severe paravalvular leakage or AR post-TAVI has been associated with increased in-hospital [77] and longterm mortality [95]. Since TAVI patients with negligible-to-mild AR have done well so far in the short-term, it is important to reduce the incidence of this complication. As well as developing new TAV designs, continued improvements in imaging software to more accurately deploy the TAV in the proper position will help to avoid this complication. However, further work to develop better TAVI simulations in patient-specific AS may lead to appropriately sized TAVs, prediction of AR, and should optimize which TAV may minimize AR postprocedure is needed. While TAVs demonstrate better relief of transvalvular gradients than surgical bioprostheses [78], these hemodynamic measures during systole do not reflect total energy loss during the entire cardiac cycle which would include diastolic AR. Development of in vivo measurements of total energy loss will be important for accurate comparison of TAVs and surgical bioprostheses

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with respect to hemodynamic performance. Finally, in lower risk patients, risk of stroke after AVR is minimal, while it is unknown with TAVI. TAV expansion within the calcified aortic valve would still be expected to carry risks of embolization and stroke, though younger patients would not be expected to carry a significant atheroma burden in the aortic arch. Stroke risk of TAVI versus surgical AVR in lowerrisk patients would be a crucial evaluation, given the devastating consequences of stroke.

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