 doi:10.20944/preprints202204.0304.v1

Biomechanics of Transcatheter Aortic Valve Implant

*Francesco Nappi[1]; Sanjeet Singh Avtaar Singh MD[2]; Pierluigi Nappi[3]; Antonio Fiore[4,5]

Institutional affiliations

[1] Department of Cardiac Surgery, Centre Cardiologique du Nord. 93200, Saint-Denis, France

[2] Department of Cardiothoracic Surgery, Aberdeen Royal Infirmary, Aberdeen, AB25 2ZN, United Kingdom

[3] Department of Clinical and Experimental Medicine; University of Messina. 98122 Messina, Italy

[4] Department of Cardiac Surgery, Hôpitaux Universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris, 94000 Creteil, France

[5] Advanced Surgical Technologies Sapienza University of Rome. 00185 Rome RM, Italy

***Corresponding author**

Francesco Nappi, MD

Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis (CCN)

36 Rue des Moulins Gémeaux,93200 Saint-Denis, France

Tel: +33149334104

Fax: +33149334119

Email: francesconappi2@gmail.com

 doi:10.20944/preprints202204.0304.v1

Abstract

Transcatheter aortic valve implantation (TAVI) has grown exponentially within the cardiology and cardiac surgical spheres. It has now become a routine approach for treating aortic stenosis. Several uncertainties have been raised about TAVI in comparison to conventional surgical aortic valve replacement (SAVR). The primary concerns are with regards to the longevity of the valves. Several factors have been identified that may predict poor outcomes following TAVI. These include the lesser-used finite element analysis (FEA) to quantify the properties of calcifications that affect TAVI valves. This can also be used in conjunction with other integrated software to ascertain the functionality of these valves. Other imaging modalities are now widely available such as Multi-detector Row Computed Tomography(MDCT) which can accurately size the aortic valve annulus.. This may help reduce the incidence of paravalvular leaks and regurgitation which may necessitate further intervention. Structural valve degeneration (SVD) remains a key factor with varying results from current studies. The true incidence of SVD in TAVI compared to SAVR remains unclear with the lack of long term data. It is now widely accepted that both are part of the armamentarium and are not mutually exclusive. Decision-making for the appropriate intervention should be made via shared decision-making involving the heart team.

Keywords; Transcatheter aortic valve implantation; Surgical aortic valve replacement**;** Structural valve degeneration; Transcatheter heart valves

 doi:10.20944/preprints202204.0304.v1

1. Introduction

The transcatheter aortic valve implantation (TAVI) was first implanted by Cribier et al 20 years ago [1]. Over the years evidence has grown on the efficacy and safety of this novel modality that is now a major cornerstone in the treatment of structural heart disease. These minimally invasive procedures restore valve functionality in patients with calcific aortic valve stenosis (AVS) and have become a routine approach. [2-18]. In symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindications to the use of transcatheter aortic valve implantation by transfemoral access, TAVI is recommended. TAVI is considered an adequate treatment option as an alternative to standard surgical aortic valve replacement (SAVR) after shared decision-making, weighing the balance between expected patient longevity and valve durability [19-25]. Evidence suggested that TAVI (compared to standard medical and surgical options) had lower rates of death from any cause. Mid and long-term follow-up proved no evidence of restenosis or prosthesis dysfunction. [6,9-11,18,26-30] Moreover, recent randomized clinical trials (RCT), meta-analysis, and propensity score analysis, confirming registry reports, revealed satisfactory outcomes of TAVI in terms of feasibility, long-term hemodynamics, and functional improvement. [12,14,27,31-34] However, the first and second generations of implanted transcatheter heart valves (THV) disclosed a high percentage of moderate to severe perivalvular aortic regurgitation [35], offering evidence to highlight the causes that determine one of the most frequent complications associated with TAVI, which was correlated with an increased rate of mortality [36]. During repeated follow-ups, the emerging data raised concerns about incomplete apposition of the prosthesis related to calcification or annular eccentricity [37], undersizing of the device, and incorrect positioning of the valve thus identifying the most common determinants of paravalvular aortic regurgitation [38].

Based on these observations, the criteria of utmost importance to avoid complications are the appropriate determination of the size of the annulus, correct evaluation of the calcifications, and adequate sizing of the prosthetic valve. Preoperative planning with biomechanical assessments in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

patients for whom TAVI is recommended as suggested by international guidelines and by standardized endpoint definitions for transcatheter aortic valve implantation dictated in the Valve Academic Research Consortium-2 (VARC-2) consensus document. [19,20,38]

Here we address an overview of the use of computational biomodelling that can improve understanding of the complex mechanical processes regulating the working of these new devices for aortic root implantation. Using advanced computational tools that integrate patient-specific information, it is thereby possible to obtain accurate modeling of the self and balloon-expandable devices used to treat severe aortic valve stenosis [19-52] **Figure 1**

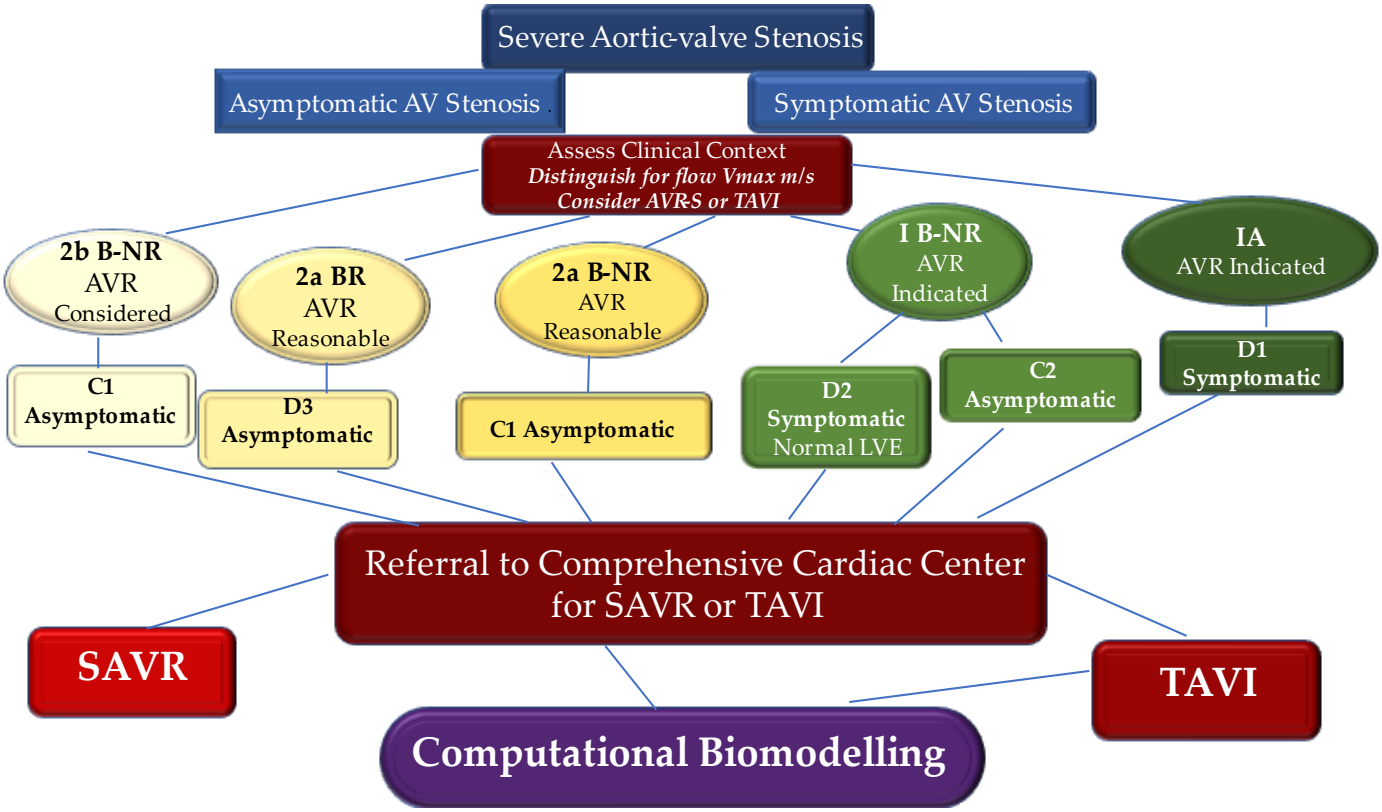


Figure 1. Decision Tree for treatment of severe AVS based on international guidelines and the VARC-2 consensus document. Recommendations from the 2020 international guidelines (ACC/AHA/ESC) for the treatment of patients with valvular heart disease. Clinical factors and imaging findings are shown in green and yellow boxes as well as AVR recommendations according to Class (Strength) of Recommendation and Level (Quality) of Evidence. Treatment recommendations are shown in Red boxes. 1A, 1B-NR, 2aB-NR, 2a B-R, and 2b NR are the COR indicates the strength of recommendation, including the estimated magnitude and assurance of

 doi:10.20944/preprints202204.0304.v1

advantage in relation to risk. The LOE rates the quality of scientific evidence supporting the intervention based on the type, quantity, and consistency of data from clinical trials and other sources. Computational biomodeling is a suitable method for a predictive evaluation of TAVI performance. Abbreviations : AVS, aortic valve stenosis ; COR, class of recommandation ; LOE, level of evidence ; SAVR, standard aortic valve replacement ; HF, heart failure ; LVF, left ventricular function ; TAVI, transcatheter aortic valve implant, VARC, Valve Academic Research Consortium

2. Engineering to Study the Features of Implanted Transcatheter Heart Valve

Transcatheter aortic valve implantation is becoming the prime destination on the road map for translational research since its first ideation and use in paediatric cardiac surgery to circumvent the complication of reopening the sternum and reoperation. [53] Using the Finite Element Analysis (FEA) methodology, we marked the crucial differences between the biomechanics of the aorta and pulmonary artery. [54,55]. We performed a tensile test in the native pulmonary artery and native aorta. Evidence suggested that tissue response to stressors of the pulmonary valve leaflets disclosed a stiffer behavior than the aortic valve and a decreased deformation for applied loads as high as 80kPa (600 mmHg) was recorded. Importantly, the biomechanics of the valve annulus displayed less deformable structures of the root suggesting that the weaker points of the PA were depicted in the free walls of the pulmonary artery (PA) distal to the valve. The aortic root suitably accommodated increasing hemodynamic loads without meaningful deformation. Again, the differential analysis performed on samples cut longitudinally and circumferentially revealed a different behavior for both aorta and pulmonary artery. The circumferential strength of the PA was greater than the aortic one, while the similar properties for the longitudinal direction were comparable. Our results suggested that the PA may exhibit a consensual increase in stress and strain in both directions while the aorta revealed better adaptability in the longitudinal direction and a steeper curve in the circumferential response, potentially suggesting the non-aneurysmatic tendency of pulmonary artery root compared to the aorta. [54]

The innovative use of FEA for research in cardiovascular science related to the mitral valve, pulmonary artery, and aorta[41-43,50-52,56-68] can provide an understanding of structural changes in biological systems such as degenerative processes of leaflet and vessel wall stresses thereby aimed to prevent the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

procedural failures. The distinct measurement of biomechanical stress results in different applicability from studies such as leaflet stresses related to the geometry of stented porcine and bovine pericardium xenograft [57] or examining stresses in the aortic root and calcified aortic valve aimed to prevent the risk of rupture [41,44,59-61,69]. Recently, the benefits associated with the use of FEA applied to TAVI were established in a landmark paper from Xuan et al. The investigators thoroughly evaluated TAVI with leaflets, stent, polyethylene terephthalate, and sutures to predict the mechanism leading to structural valve degeneration of THV devices. [56]

2.1 Confluence of engineering and medical sciences

Finite element analysis is the discipline that rests about the geometric algorithmic prediction of stress and the evaluation of deformation coefficients in complex structures, through a complex system of predictable mathematical calculation applied to well-divided small geometric areas.). [69] We have learned that from its first applications in the field of cardiac surgery, which date back to about twenty years, the use of FEA has development slowly despite the possible achievement of its substantial progress. Since its introductory applications, the FEA methodology has been noted for a very limited applicability in clinical practice. This 'distrust' is pertinent in the surgical disciplines, which are based on clinical evidence, to offer their own field of research to speculative data without correlated clinical evidence. [40-43,54,55,59-62,68]

Before the paradigm shift that radically changed the treatment of symptomatic calcific aortic stenosis, clinical and experimental studies produced scientific evidence without the use of FEA. Easier, more understandable methodologies and probably more reliable ones have been used to test hypotheses and prove theses. The revolutionary technology of the novel method that makes up the most advanced platforms for the treatment of structural heart diseases meant SAVR had given way to the advent of TAVI. The rapid technological advancement has made it possible to obtain 3 generations of balloon-expandable devices in a span of 6 years and has given new impetus to the FEA. [2-18]

 doi:10.20944/preprints202204.0304.v1

In this context, the findings of Smuts et al developed new concepts for different percutaneous aortic leaflet geometries. [70] Instead, Wang et al. [60] and Sun et al [71] studied the post-operative behavior of TAVI from a mechanical and hemodynamic point of view. A crucial advancement in the application of FEAs was offered by Capelli et al. [45] who effectively analyzed the feasibility of TAVI in morphological conditions considered borderline cases for the percutaneous approach, paving the way for the treatment of failed bioprosthetic aortic valves with the use of TAVI.

A patient-specific simulation based on FEA that takes into account all procedures and with the potential to produce the post-operative prosthesis simulations, by means of inclusion in the analysis of the biological valve needlework into the metal structure, was reported by our group in a landmark paper almost 10 years ago. [72] We subsequently reported evidence by comparing the postoperative medical data with the biomechanical investigation method. Recently we developed a systematic TAVI simulation approach, tailored for clinical practice, on patients receiving both a self-expandable Medtronic Corevalve (Medtronic, Minneapolis, Minnesota,USA) and a balloon-expandable SAPIEN (Edwards Lifesciences, Irvine, Calif). The studies based on the analysis of preoperative medical imagining of patients who have undergone TAVI are of particular interest. [39-41,50-52] The final goal-driven from these studies is to predict the post-operative performance of the prosthesis with respect to the specific anatomical characteristics and potential complications such as structural/non-structural valve degeneration and thrombosis. [56]

Likewise, the new evidence emerging from these studies strengthened previous ones on the potential high levels of stress to which devices for THV implantation are subjected. Previous studies have revealed, both in a static or boundary condition as well as during a fatigue stress simulation, that in individuals who are managed with THV procedure, the predictable duration of TAV1 may be shorter than those who received a surgically implanted aortic bioprostheses. This evidence confirms that leaflet deformation and stresses are significantly higher in the TAVI, especially near commissures and along the stent attachments. [57,73]

 doi:10.20944/preprints202204.0304.v1

2.2 Medical image processing

Biomechanical simulations using FEA analysis, starting from preclinical evaluations, have offered an original contribution as an advanced tool for clinical support for the following reasons. First, the aortic valve model is complete including both the aortic sinuses and the native valve leaflet as well as the material model considered is calibrated on human data. Second, the calcified plaque is included in the model and it is based on the image recording. Finally, the geometry of the prosthetic stent is very precise, obtained from micro-tomography (micro-CT) reconstruction. [39-41,50-52]

Another substantial advantage that makes this analysis reliable is represented by the possibility of obtaining post-operative data collected by physicians for the follow-up of individuals. These data are used for comparison with the numerical results obtained by the FEAs, with the ultimate goal of evaluating the capabilities of the proposed simulations to predict procedural outcomes. [40,50]

Concerns related to validating the TAVI simulation are crucial as it can be usually difficult to obtain good quality postoperative data and images from standard post-operative procedures. Another point of divergence concerns postoperative CT control which is sometimes excluded from routine protocols for TAVI because these patients are often frail, it is not recommended to overload the kidneys with additional doses of contrast and to avoid high doses of radiation for the patient who is often in critical condition. Instead, the evaluations on the outcome of the procedure are offered by intraoperative CT scan as well as by follow-up echotomography. [74-76]

The computational framework adopted to simulate the implantation of TAVI includes four main phases which are: processing of the medical images, creation of models suitable for analysis, the performance of the required analysis permits integrating the clinical procedure, and finally the post-processing of the simulation results and subsequent comparison with the follow-up data. [39-41,44,50-52] Figure 2

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

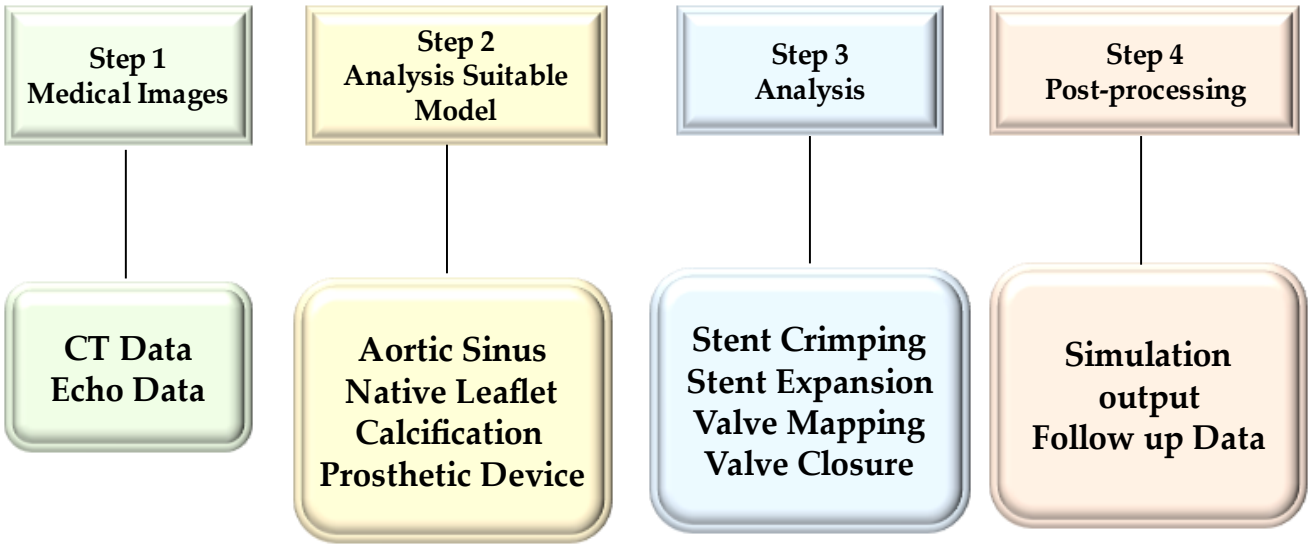


Figure 2. Depicts the computational framework aimed to simulate the implantation of TAVI. Four sections from Step 1 to 4 of the worked-out modeling strategy are identified. The extrapolated images (ECHO, CT) allow establishing a biomodeling on which to perform the simulations. The data obtained from the simulations are compared to the data that emerged in the follow-up. Abbreviations; CT; computed tomography

Morganti et al worked on a biomechanical simulation model for TAVI starting from a standardized approach to scan the main parameters with cardiac CT. Preoperative examinations were obtained using a dual-source computed tomography scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany). Investigators achieved contrast-enhanced images using iodinated contrast medium that was injected as follows: scan direction, cranio-caudal ; slice thickness, 0.6mm ; spiral pitch factor, 0.2 ; tube voltage, 120kV. [40,41] Our group has developed a reliable protocol for the quality of the CT images which must subsequently be processed using FEA analysis. [39,50-52] **(Figure 3).**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

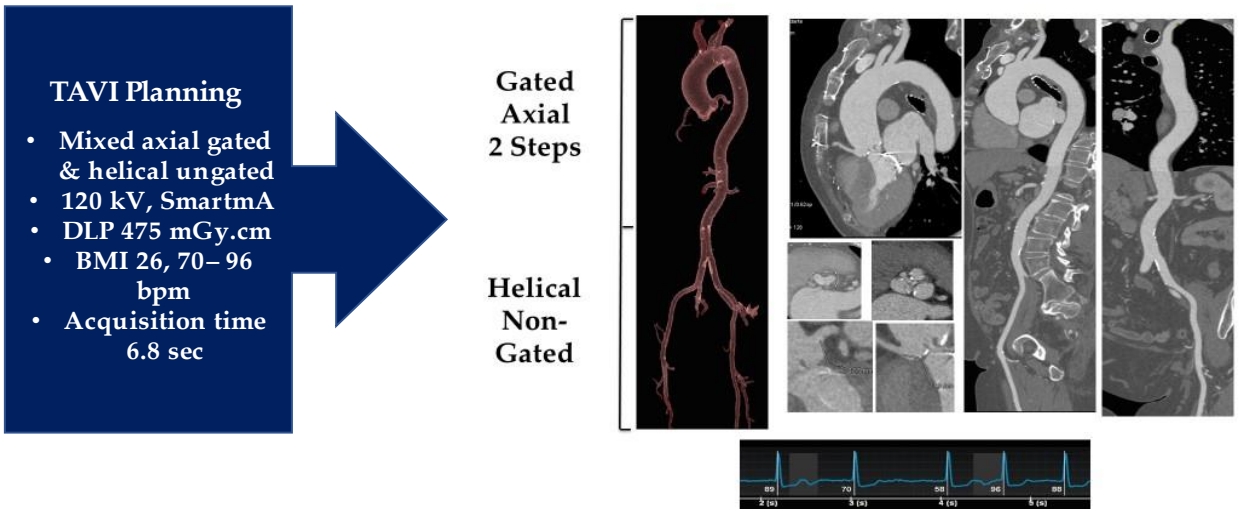


Figure 3. Depict the 3D CT Scan protocol for patients receiving TAVI. It is designed to ensure all steps of the transcatheter procedure. The figure report an example in which the exam was done in 6.8 sec with only 640 mGy.cm. A precise planning to support the intervention was conferred. Abbreviations; DLP, Dose Length Product; mGy, microgray

With a complete cardiac cycle at one beat (0-100%) and with an acquisition Dose Length Product (DLP) equal to 459 microgray (mGy) / cm we offered an optimal image quality to be processed for biomechanics. They allowed the functional evaluation of the aortic valve, the morphological study of the aortic valve and the anatomical determination of the AVS. [39] **(Figure 4).**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

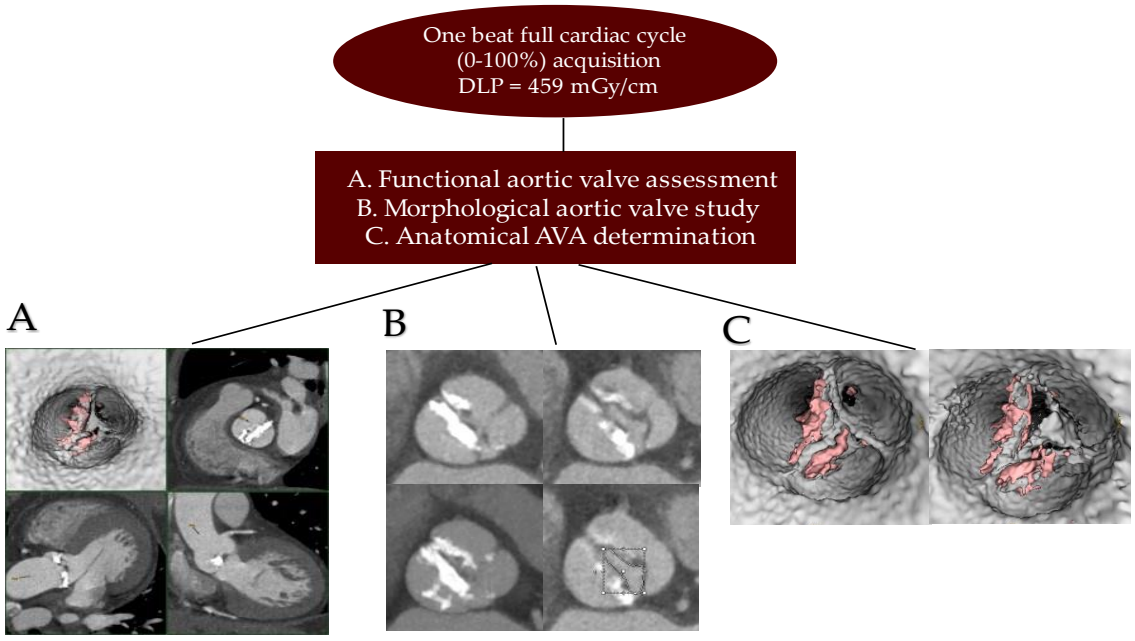


Figure 4 DICOM from 3D CT Scan serves to extract the RAW data that allow definition of functional aortic valve assessment (A), morphological aortic valve features (B) and anatomical aortic valve characteristics (C); Abbraviations in other figures.

Scientific reports that describe image analysis using established theoretical approaches have provided solid answers on the active contour segmentation process which has experienced robust implementation. Despite the existence of powerful segmentation methods, the needs of clinical research have continued to be met, to a large extent, using manual slice-by-slice tracking. The landmark study of Yushkevich et al., performed in the context of a neuroimaging study of childhood autism, bridged the gap between methodological advances and routine clinical practice. The investigators have developed a revolutionary open source application called ITK-SNAP. This application aims to make the segmentation of level sets easily accessible to a wide range of users, including those with little or no mathemathical skills. SNAP proved to be a reliable and efficient application compared to manual tracking. [77]

Therefore, the most common method of obtaining a reliable model from the CT data set is their processing using ITK-Snapv2.4 as described by Yushkevich et al. [77]. Specifically, a confined region of interest as that represented by the aortic root, that is comprised from the left ventricular outflow at the sinotubular junction, is extracted from the entire reconstructed body by exploiting the contrast

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

enhancement, nibbling and segmentation capabilities of the software. Again, the effectiveness of the TK-Snapv2.4 is highlighted using different Hounsfield unit thresholds, through which it is possible to distinguish the calcium agglomerates of the surrounding healthy tissue and evaluate it at intervals of both position and size. Once the segmented regions have been extracted, it is possible to export the aortic lumen morphology, as well as the calcium deposits like stereolitographic (STL) files. [39-41,50-52]

(Figure 5)

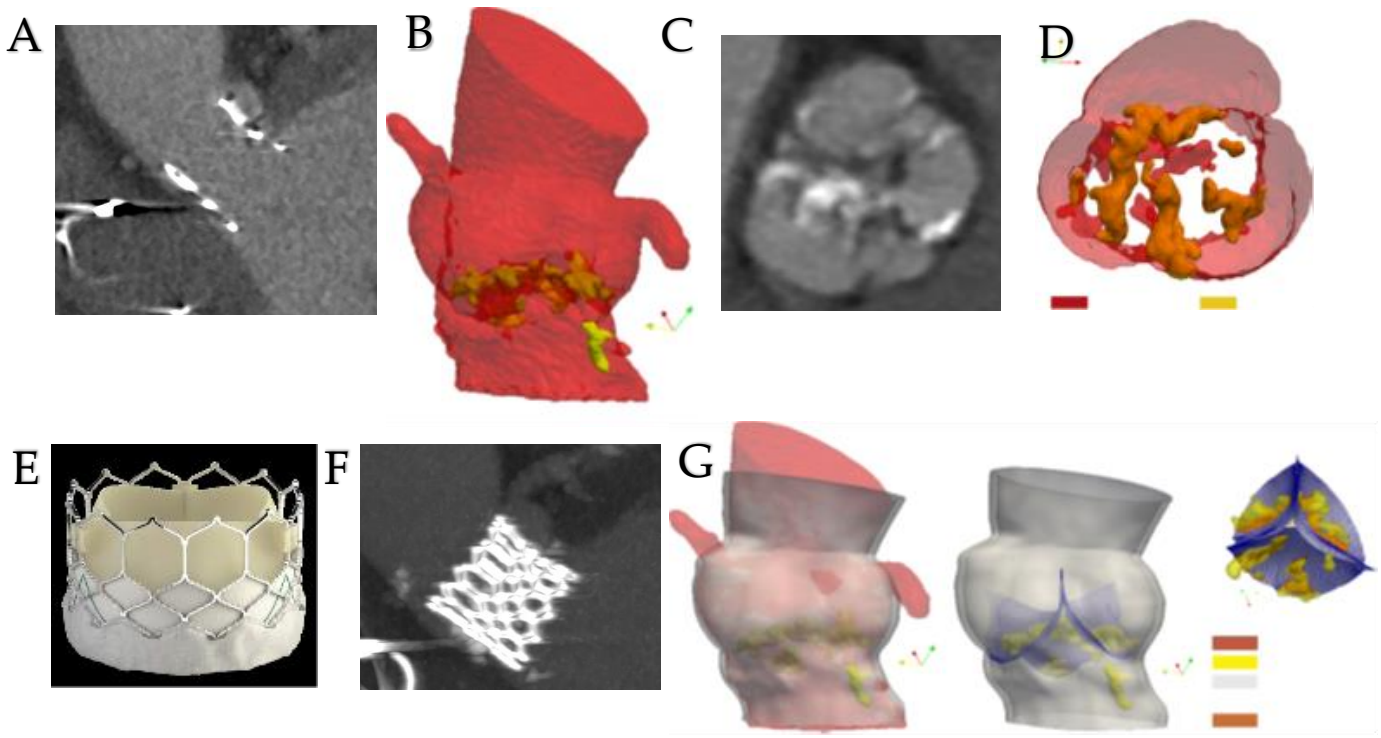


Figure 5. **Up** : with the use of ITK-Snapv 2.4 the data extracted from the CT images (A, C) are processed to highlight the images of the aortic lumen (B, red) and calcium deposits (D, yellow/orange). **Down :** a first generation of balloon-expandable TAVI Sapien (E ; Edwards Lifesciences, Irvine, Calif) is used to treat severe AVS (F). **G** : aortic lumen morphology as well as the calcium conglomerates are extracted with the use of STL files. **Left** : the lumen of the aortic root (red) and the calcifications (yellow) are superimposed to the aortic wall model (gray). **Center** : the enclosed native leaflets (blue mesh) correspond perfectly to the real leaflets with calcifications obtained by processing CT images (A, C). **Right** : The top view is shown.Abbreviations : AVS, aortic valve stenosis ; CT, computed tomography ; STL, stereolitographic ; TAVI, transcatheter aortic valve implantation

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

2.3. Analysis Suitable Model

A crucial step concerns the procedure to obtain suitable analysis models both for the native aortic valve, including calcifications affecting the leaflets along with the aortic wall and for the prosthetic device.

2.3.1 Native Aortic Valve Model

In the native aortic valve model, different investigators reported that once the STL file containing the characteristics of the aortic root is obtained, it can be processed and implemented in Matlab (The Math works Inc., Natick, MA, USA). The latter serves as an effective system for defining a set of splines, similar to the cross-sectional profile of the aortic lumen. In this way, the curves obtained are used to automatically generate a volume model of the aortic root wall.

Finite element analysis setup is ensured by importing the model that has been processed in a commonly used software such as Abaqus CAE (Simulia, Dassáult Systems, Providence, RI, USA) or alternatively HyperMesh (Altair Engineering, Troy, Mich). The latter may be used in association with GeoMagic Design (3DSystems, Rock Hill, SC), a computer-aided design software, to purify and generate 3D geometric volume with accurate size and thickness at zero stress. [39-41,50-53,56,72,78]

Several studies demonstrated that the geometric model of the aortic root obtained by processing the STL file represents the fundamental starting point for performing the finite element analysis of TAVI. Antiga et al created the Vascular Modeling Toolkit (VMTK http://www.vmtk.org). This modeling framework was designed for patient-specific computational hemodynamics to be performed in the context of large-scale studies. WMTK exploits the combination of image processing geometric analysis and mesh generation techniques and stresses full automation and high-level interaction. Importantly, image segmentation is performed using inferred deformable models and exploiting the advantage of a different approach for selective initialization of vascular branches, as well as of a strategy for the segmentation of small vessels. Again, the advantage of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

using WMTK is a solid definition of center lines that provides substantial geometric criteria for the automation of surface editing and mesh generation. [78,79]

Several investigators reported good results by processing STL file of calcifications using WMKT to extract a regular tetrahedral mesh. [39-41,50-53,56,72,78,79] Likewise, an efficient, robust procedure for the mesh generation leading to high-quality computational meshes includes the open-source Gmsh software [80] and the alternative framework described by Dillard al in which the entire image-based modeling process is performed on a Cartesian domain where the image is fixed within the domain as an implicit surface. [81] Gmsh software can generate different types of meshes including isotropic tetrahedral meshes, anisotropic tetrahedral meshes, and mixed hexahedral/tetrahedral meshes. Besides Gmsh software proved the crucial advantage to generating multiple layered arterial walls with a variable thickness. Alternatively, the structure developed by Dillard et gets around the need to generate surface meshes that have to adapt to complex geometries and the subsequent need to generate flow meshes adapted to the body. The three determining factors are identified in Cartesian mesh pruning, local mesh refinement, and massive parallelization which are crucial to providing computational efficiency. The efficacy of the framework described by Dillard et al lies in the full picture analysis which revealed two 3D image reconstructions of geometrically dissimilar intracranial aneurysms that require computed flow calculations. [81]

The finite element mesh generated with this procedure is effective for both reproduced aortic wall and native valve leaflets, in order to obtain at the same time a complete and realistic model to perform the simulations. Morganti et al suggested that to include the native geometry of the leaflets, the first step consists in identifying nine reference points : six of them refer to the commissural extremes while the others correspond to the center of the attachment of the basal leaflets. We recently adopted this method in a study comparing two different biomechanical features involving the two different TAVI device models, the self-expanding Medtronic Corevalve and the balloon-expandable Edwards SAPIEN. [40,41] Of note, Xuan et al also revealed that stent and leaflet surfaces were combined using suture lines as a reference point for leaflet orientation. [56]

 doi:10.20944/preprints202204.0304.v1

It is important to highlight that the use of the aforementioned reference points offers the possibility of defining own planes that can guide the distribution of the entire model of the aortic root which ultimately serves to reproduce both the extraction of the leaflets commissures and the attachment lines. [40,41,50,51] The use of ultrasound is important to measure the length of the free margins which appear as a circular arc. Determining the perimeter of the leaflets leads to the construction of the leaflet surface in the open configuration. [40]

The modeling of the aortic wall is meshed with the use of a variable number of tetrahedral elements that take into account both the healthy part and portion occupied by calcium conglomerates. Morganti reported a number between 235,558 and 265,976 tetrahedral elements for the healthy region of the aortic root while the leaflet were discretized using a number between 3212 and 3258 e of shell elements for the healthy part. In cases where calcium agglomerates are present, the leaflets have been discretized with reduced integration for healthy tissue. The discretization for the occurrence of calcified plaques ranged from 342 to 427 shell elements. [40,41]

Xuan et al worked to determine stent and leaflet stresses in a 26-mm first-generation balloon-expandable transcatheter aortic valve. Investigators imported the refined geometries of leaflets, stent, and polyethylene terephthalate into HyperMesh (Altair Engineering, Troy, Mich) to generate TAV mesh with 46,443 total elements. Their study did not require adjunctive discretization for the presence of calcified plaques located in the aortic wall and leaflets because the simulation was not performed in the aortic root and leaflets cluttered by calcifications. [56]

Bianchi et al in the comparison study between Sapien 3 and Corevalve squeezed out the sinuses of Valsalva in Abaqus CAE, while the calcification deposits were processed in MATLAB and subsequently assembled in the AR. In a previous report Bianchi et al [47]., incorporated calcifications in soft tissues to better mimic the morphology of the stenosis. Investigators finally re-meshed the aortic root with tetrahedral elements in Ansys Fluent Meshing to ensure mesh continuity at the interface between the sinus and the leaflets and between calcifications and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

surrounding soft tissues. Mesh size was approximately 1.4 million for SAPIEN cases and 2.5 million for CoreValve cases, as more of the ascending aorta was required for deployment.

In cases of biomechanical evaluations used to compare prosthetic devices, postoperative configuration, and performance, the simplified St. Venant-Kirchhoff properties can be used to model native aortic tissue, leaflets, and calcifications. Several investigators used Young's modulus for the aortic root, for leaflets and calcifications (E, Poisson's ratio ν and density ϱ). [40,82] Xiong et al used a Young' modulus for the native leaflet and they used such a value to model bovine pericardium aortic leaflet. [82] Stradins et al reported that the same value of 8 MPa approximates the stiffer (i.e., circumferential) non-linear behaviour of the human aortic valve. It is important to underline that considering the stiffer curve is reasonable given the greater stiffness recorded in aortic valve stenosis which has stiffer tissues than the average patient. [83]

2.3.2 Prosthesis model and Material Model

Although several devices for TAVI have been described over the 20 years, [39] the two devices used in a large number of patients in clinical practice include the Medtronic Core Valve and the Edwards Lifesciences SAPIEN. While the CoreValve is self-expanding, the Edwards SAPIEN valve is primarily produced of three flexible biological leaflets sutured into an expandable balloon stent.

Several studies reported computational biomodelling studies of SAPIEN first-generation, [42,56] XT [40], and the last SAPIEN 3 [50] prosthesis starting from 3D CT scans of patients who underwent TAVI. Likewise, the same investigators worked on the computational biomodelling studies of Corevalve Medtronic. [41, 42, 50,52]

For example in two independent works, Morganti et al [40] and Nappi et al [50] obtained a faithful geometrical model of SAPIEN XT 26 mm and of SAPIEN 3 using a high-resolution micro-CT scan (Skyscan 1172 with a resolution of 0.17 micron). These stent models were achieved using 84,435 solid elements. Xuan et al [56] obtained a fully expanded first-generation Sapien valve (26 mm) that was conceived under 0 mm Hg pressure with a desktop cone-beam micro-CT scanner (microCT-40

 doi:10.20944/preprints202204.0304.v1

; Scanco MedicalAG, Baseldorf, Switzerland) in different orientations and intensities to discriminate stent and leaflet geometries. The refined geometries of leaflets, stent, and polyethylene terephthalate were then imported into HyperMesh (Altair Engineering, Troy, Mich) to produce TAV mesh with the use of 46,443 total elements. [56]

Generally, the material model for the native aortic tissue is presupposed to be homogeneous and isotropic as described by Capelli et al [45] and Gnyaneshwar et al [84]. Selvadurai [85] and Yeoh et al [86] hypothesized the use of an incompressible reduced polynomial form aimed at reproducing the material behavior and indicating it as a reduced polynomial strain energy, taking into account the material parameters the deviatoric strain invariant, and the deviatoric stretches.

Morganti et al [40] in computational modeling of SAPIEN XT with regards to the material model have chosen a sixth-order polynomial form, finding an unknown material constant. The investigators took as reference for the aortic leaflets and the Valsalva sinuses the data emerged from the studies by Martins et al [73]. and Stradins et al. [83]. These data have been integrated with those produced by Auricchio et al to obtain the final characteristics of the material models. In particular, with regard to the aortic wall and the native valve leaflets, it has been assumed that these have a uniform thickness of 2.5 and 0.5 mm respectively. In observations of the evidence reported by Capelli et al [45] for calcifications, an elastic modulus of 10 MPa, a Poisson ratio of 0.35, and a density of 2000 kg / m^3 were assumed. Again, as for the Von Mises plasticity model with an isotropic hardening, Morganti et al [40] assumed 233 GPa as Young modulus, 0.35 as Poisson coefficient, 414 MPa as yield stress, 933 MPa as ultimate stress, and 45 % come from deformation at the break. [106]

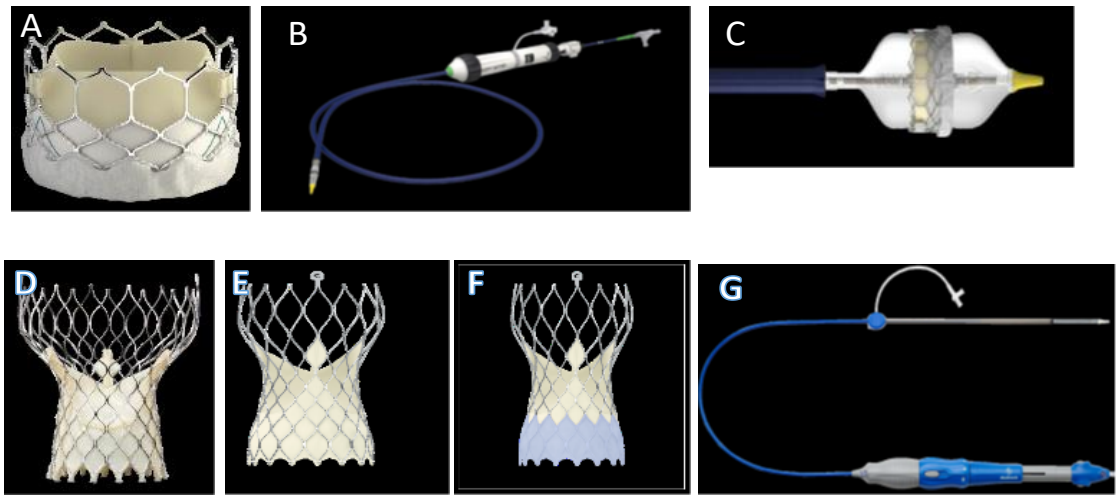
The computational model that evaluates the prosthetic valve leaflets of the SAPIEN device must consider the different factors concerning the constitutive characteristics of bovine pericardium after the fixation process. The leaflets are modeled as an isotropic material and, in particular, an elastic modulus of 8 MPa, a Poisson coefficient of 0.45, and a density of 1100 kg/m3 are used following the evidence reported by Xiong et al. The prosthetic valve is meshed with 6000 quadrilateral shell elements, while a uniform thickness of 0.4 mm is considered. [40, 82, 88,89,90]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

2.3.3 Finite Element analyses

The Finite Element Analyses is a crucial step of computational biomodelling to be applied to the TAVI procedure for biomechanical evaluation. Since TAVI is a complex procedure that is divided into several phases, the simulation must respect rigid steps to be reliable, which are basically two : Stent crimping/deployment and valve mapping/closure.

In the first stage, the prosthetic model is crimped to obtain the catheter diameter which in the transapical approach was usually 24 French (8 mm). Subsequently, the prosthetic prosthesis expands inside the AR. In the aortic root, the device is expanded according to the two most widely used systems: the self and the balloon-expandable method. [3,8,91,92] A third system is represented by mechanical expansion. [93,94] The transapical approach has been replaced by the transfemoral one which is currently more commonly adopted procedure which benefited from the use of small catheter sizes 18-16 and 14 French. [15-17] **Figure 6**



Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

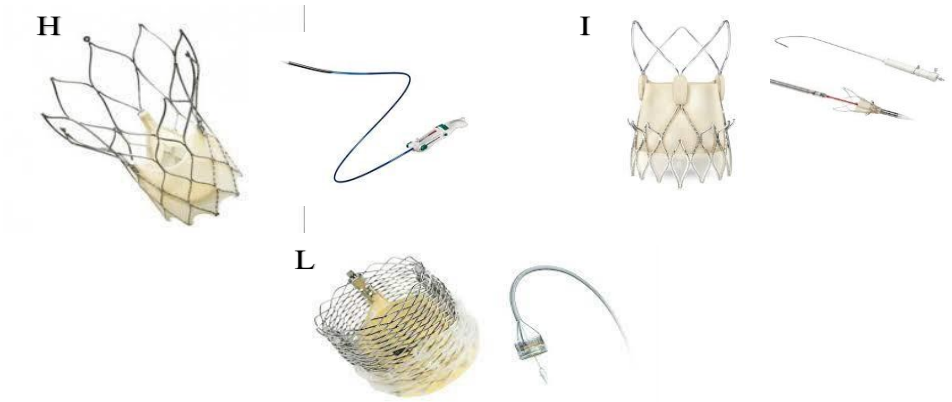


Figure 6. Baloon expandable THV. **(A -C)** The SAPIEN 3 balloon-expandable is constituted by a cobalt-chromium alloy frame valve with bovine pericardium leaflets. A polyethylene terephthalate fabric skirt on the distal section of the frame serves for PVL serves prevention. The device is introduced in the market in the following sizes: 20mm, 23mm, 26mm, and 29mm (**A).** The Commander Delivery System is 14 F expandable introducer sheath compatible for 20-26 mm valves and 16 F expandable introducer sheath compatible for 29mm valves **(B & C). (D-G)** Self Expandable THV. The bioprosthesis is manufactured by suturing 3 valve leaflets and a skirt, made from a single layer of the porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of Nitinol **(D -F).** CoreValve **(D),** Evolut R **(E),** Evolut PRO **(F)** in the following sizes: 20mm, 23mm, 26mm, and 29mm. ©. The loading System. The outer diameter of the catheter is 15 Fr (AccuTrak™ stability layer) and 12 Fr, and the outer diameter of the valve capsule is 18 Fr. The catheter can be used for femoral, subclavian/axillary, or ascending aortic (direct aortic) access sites. **H)** ג The Portico re-sheathable transcatheter aortic valve system (Abbott Structural Heart, St Paul, MN, USA). **I)** *The ACURATE neo (Boston Scientific, Marlborough, MA, USA) self expanding THV. **L)** Lotus mechanically expanded valve (Lotus Valve System (MEV ; Boston Scientific Corp) **H** : Portico valve is designed with large, open cells and intra-annular leaflet placement to preserve flow and access to the coronary arteries after deployment The Portico valve was delivered by a flexible, first-generation Portico Delivery system, which had an 18F outer diameter for the small valves (23 and 25 mm) and a 19F outer diameter for the larger valves (27 and 29 mm). **I** : the ACURATE neo bioprosthesis, consists of a self-expanding nitinol frame with three porcine pericardial leaflets, and a stent body with an outer and inner pericardial skirt. **L** : The MEV is constituted by 3 bovine pericardial tissue valve leaflets and a braided nitinol frame with a polycarbonate-based urethane adaptive seal.

ג From Willson AB et al. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve : first-inhuman experience. J Am Coll Cardiol 2012 [ref 84] ; 60 : 581–86 ; †From Mollmann H, EuroIntervention 2013 ; 9 (suppl) : S107–10.[ref 85] *from Meredith IT, et al. Boston Scientific Lotus valve. EuroIntervention. 2012 ;8(suppl Q) : Q70-Q74 [Ref 86]. Abbreviation. MEV = mechanically expanded valve. THV= Transcatheter Heart Valve

Again, all the numerical analyses are subject to nonlinear concerns involving large deformation and contact. A large part of investigators for this reason used the Abaqus system (solver v6.10 or CAE)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

[40-42,46,50-52,56] to be able to perform analyzes on large deformations. Two points still need to be emphasized. First, quasi-static procedures were used again assuming that inertia forces do not change the solution. Second, kinetic energy monitoring is crucial for which kinetic energy is monitored to ensure that the ratio of kinetic energy to internal energy remains less than 10%.

For example, with regards to the stent crimping and deployment evaluating the procedure for a 26 mm SAPIEN XT implanted with a transapical approach, the cylindrical surface is gradually crimped from an initial diameter of 28 mm to a final diameter of 8 mm. [40] The cylinder is meshed using 2250 4- node surface elements with decreased integration and it is modeled as a rigid material with a density of 7000 kg / m3. In these cases, a frictionless contact must also be considered, which is generally defined between the crimp surface and the stent. After affixing the stent, its deformed configuration is then re-imported into Abaqus CAE, keeping into consideration as inceptive state the tensional state resulting from the crimping analysis. Conversely, to reproduce the stent expansion it is important to keep in consideration that a pure and uniform radial displacement is gradually applied to the node of a rigid cylindrical surface. Note that if a balloon-expandable device is used, it is assumed that the cylindrical surface is represented by the wall of the expanding balloon. Finally, the rigid cylinder is expanded from an initial diameter of 6 mm to a final diameter of 26 mm. Another fundamental point to take in the simulation implies that during the expansion of the stent the axis of the balloon always remains fixed. This hypothesis can be considered valid because it is observed through intraoperative angiographic control that shows a negligible axis rotation and translation. [40-42,46,50-52,56]

The second stage is constituted by the valve mapping and closure in which the prosthetics leaflet is delineated onto the embedded stent ensuring a physiological pressure that is requested to revive the diastolic behaviour of THV implanted. The pivotal study of Auricchio et al [72] offered a substantial contribution to reproducing the realistic features of the prosthetic device thereby evaluating the post-operative performance of implanted THV. Investigators realized that precomputed shifts are assigned to the base of the valve and at the nodes of the commissures of the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

leaflets, in such a way as to obtain a complete configuration of the implanted prosthetic device. [40-42,46,50-52,56]

By respecting these steps it is possible to reproduce the post-operative diastolic features of both the balloon and the self-expandable TAV within the patient-specific model of the aortic root. As reported by Wiggers et al to simulate valve behaviour at the end of the diastolic phase a uniform physiologic pressure is required to apply to the prosthetic leaflet of THV. Furthermore, a frictionless self contact that is settled for the prosthetic valve must be considered. [95] **Figure 7**

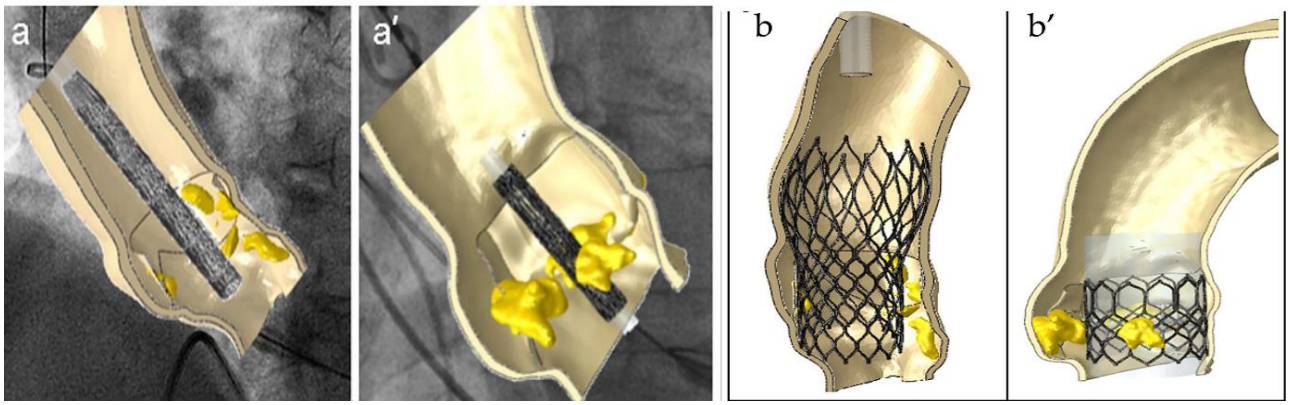


Figure 7. Depict FEA simulations of TAVI in two investigated patients who showed postoperative thrombosis. The positioning (a, a′) and reopening (b, b′) of CoreValve and SAPIEN devices (left and right sides, respectively). Abbreviations in other figures

3. Insight on the use of Biomechanical Evaluation in Predict Paravalvular Aortic Regurgitation

We have learned that the choice of the size and type of the prosthetic device is very important to avoid or at least reduce aortic regurgitation and/or other TAVI complications. [35,37,96] Detain et al. [35] and Delgado et al. [37], first independently reported that the occurrence of aortic regurgitation (AR) was related to incongruence between prosthesis and annulus. Since then, appropriate annular and sizing of the prosthesis has been considered essential to reduce paravalvular aortic regurgitation. Evidence emerged from pivotal RCT in patients who

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

underwent THV implant disclosed that very few TAVI candidates were supported with the anatomic and morphological study on the features of the aortic valve annulus to predict aortic regurgitation after device implant. [2,3,8]

Detain studied 74 patients who underwent TAVI with a balloon-expandable device with all-embracing echocardiographic examinations. The most favorable targets to disclose the occurrence of AR >or=2/4 were greater patient height, larger annulus, and smaller cover index (all $p < 0.002$) while the ejection fraction, severity of stenosis, or prosthesis size were not indicative of the AR-related event. Significantly, AR >or=2/4 was never displayed in patients with aortic annulus <22 mm or with a cover index >8%. The increase in the ability to perform the procedure does not appear to have a statistically significant effect. Although significant improvements were obtained from the first 20 cases where the rate of AR> or = 2/4 was 40% while in the last 54 AR> or = 2/4 it decreased to 15% ($p = 0.02$), however, the former versus the last procedure was an independent predictor for RA recurrence (odds ratio : 2.24; 95% confidence interval : 1.07 to 5.22, $p = 0.03$). [37] One study, reported that use of three-dimensional transoesophageal planimetry of aortic annulus proved that the 'mismatch index' for 3D planimeter annulus area was the only independent predictor of significant aortic regurgitation (odds ratio : 10.614; 95% CI : 1.044-17.21 ; P = 0.04). Three-dimensional transoesophageal planimetry improved the assessment of prosthesis/annulus incongruence and predicts the appearance of significant AR after TAVI as compared to the two-dimensional transoesophageal approach. [97]

The MDCT is the type of imaging by which we have most of the evidence derived for the study of the aortic root. In fact, 4 studies compared the anatomy of the aortic root with the size of the TAVI. Multi-detector row computed tomography was demonstrated to be a very effective tool to enable an accurate sizing of the aortic valve annulus and constitutes a valuable imaging implement to evaluate prosthesis location [96] and deployment after TAVI. Again, MDCT was a better predictor to detect a mismatch between prosthesis area and aortic annulus area [98] as

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

compared to echocardiography, revealing at a pre-and postprocedure examination paravalvular aortic regurgitation (PAVR) ≥2+ in a rate of 20% at 1-month follow-up. [99] In one of the largest TAVI series published to date that checked patients pre and postoperatively with MDCT Katsanos et al found that patients who were managed with TAVI and presented ≥2-mm difference between maximum aortic annulus and nominal prosthesis diameters and depth of the frame into the left ventricular outflow tract of <2 mm were independently associated to PAVR ≥2+ occurrence.

Madukauwa-David et al [100] performed retrospective anatomical measurements post-TAVI in 109 patients with aortic stenosis obtained from the RESOLVE study using 4DCT scans. The investigators assessed the diameter of the aortic root at the level of the annulus, left ventricular outflow tract (LVOT), sinus of Valsalva, sinotubular junction (STJ), and ascending aorta. Again, the height of the STJ and coronary arteries were determined. The major finding of the study proved that, by homogeneously distributing all aortic root dimensions in the cohort, they were susceptible to a statistically significant change between pre-and-post-TAVR conditions ($P < 0.01$). The post-TAVR dimensions had changed significantly from peak systole to end of diastole ($P < 0.01$). Regression models confirmed all measurements of the aortic root in terms of annular diameter disclosing an excellent coefficient of determination ($R2 > 0.95$, $P < 0.001$). Researchers have suggested that there are significant differences between pre-and-post-TAVR affecting the anatomy of the aortic root both at the systolic peak and in the final diastolic part of the cardiac cycle. These findings can help select optimal THV device sizes that are appropriate to anatomical dimensions as geometry varies greatly during the cardiac cycle. [100] Concerns related to the occurrence of PVAR and its worse evolution, are due at least in part to the heterogeneity of the methods for assessing and quantifying PAVR. Moreover, the lack of consistency in the timing of such assessments leads to an obstacle to understanding its accurate prevalence, severity, and effect. [35] Choosing a correct prosthetic size does not seem to be the only way to avoid PVAR but also the complex original morphology of the aortic root, the

 doi:10.20944/preprints202204.0304.v1

location and size of the calcifications are crucial determinants to take into consideration. Again, the occurrence of solid annular calcium deposits that protrude more than 4 mm is a negative predictor of moderate to severe PVAR in undergoing TAVI patients. The morphology of calcium conglomerates is involved in the genesis of PVAR in relation to the size of the annular bulky calcification, which is another predictive factor, unlike adherent calcium which has a "sealant " effect. [101]

Currently, the clinical benefits of computational analysis to guide the TAVI are not well established, and the approach represents the cornerstone of modern transcatheter heart valve therapy. The data that emerged in favor of computational analyzes take into account the recipient of the transcatheter procedure, both the specific structure of the native aortic valve and an accurate evaluation of calcifications. These two parameters can offer a substantial contribution and in association with dynamic fluid assessments, can support and guide device selection.

Many investigators have confirmed the effectiveness of computational analyzes by defining a reliable framework for reproducing the TAVI procedure and predicting any complications. As has been reported in several studies, the distribution of stress is characterized by concentrated spots of higher stress value that are recorded at the points of contact between the stent and the aortic wall. [39-49,50-52,56] We corroborated the evidence of Wang et al. [43], showing that the highest stress values were recorded in the aortic regions close to the calcifications both in self expanded a balloon-expanded THV devices. [50]

Similarly, Morganti et al, [40] in a computational analysis performed on a balloon-expandable device, found major stress levels in the region where the SAPIEN T-stent was most adherent to the aorta wall. Therefore it has been suggested that higher stress values may be related to the greatest adhesion force between the aortic wall and the stent. Likewise, Eker et al [102] firstly revealed that the creation of high levels of stress located in the annular region is not devoid of increased risk of aortic rupture, as a possible early complication of TAVI leading to cardiac

 doi:10.20944/preprints202204.0304.v1

tamponade or nefarious event described among unfavorable occurrence. Kodali et al [103] achieved the same results by studying the high aortic rupture risk, coronary artery occlusion, and PVAR with the FEA method both in retrospectively and prospectively patients (n=3). Of note, the simulation computational analysis revealed that the broad calcified aggregates placed inside the left coronary sinus between the coronary ostium and the aortic annulus were propelled by the stent, leading to the aortic rupture. The most important consideration emerging from this study showed that the expected results from the simulations allowed a correct shared decision-making process once presented to the heart team clinicians. Therefore, engineering evaluation with FEA is recommended for rating patient-specific aortic rupture risk. [103]

Robust evidence suggests that PVAR, rather than aortic rupture (aortic wall or annulus), as an emerged complication of TAVI, is associated with further worsening in late outcomes. The benefits of computational modeling of TAVI apply to high-risk patients, offering a quantitative evaluation of the area of the perivalvular holes, become evident within the first post-operative 5-yers disclosing a survival advantage that tends to increase with time. [9,10] The location of incomplete adherence of the prosthetic stent to the aortic wall modifies the extent of the survival advantage of TAVI. Importantly, Morganti et al suggested that the area of paravalvular holes was proportional to the volume of retrograde perivalvular blood flow and was in accordance with echocardiographic evidence. [40,41]

Auricchio worked on the measured of eccentricity and the stent configuration revealing that eccentricity of the deployed stent substantially affects valve closure and especially the coaptation of leaflets. [104] The evidence presented by Morganti et al indicates that non-symmetric closure is attributed to the elliptical stent configuration leading to the incongruity that one leaflet can close under the other two. Again, although a small central gap may be generated thus causing a regurgitant flow;the geometrical asymmetry of the stent is a crucial determinant of the central gap during diastole and it is related to the choice of the leaflet

 doi:10.20944/preprints202204.0304.v1

material model. The latter has been shown to have a substantial impact on the coaptation values, being able to alter the early and long-term results. [105]

Seven years later Auricchio et al, Bianchi et al [42] evaluated postprocedural complications such as PVAR and related thromboembolic events that have been hampering the TAVI spread procedure in lower-risk patients, receiving the last generation of device. Finite element analysis and computational fluid dynamics analysis were performed in recipients of either Edwards SAPIEN or Medtronic CoreValve. Engineering-based simulation revealed that parametric analyses directly affected positioning and balloon over-expansion, thus suggesting a direct impact on the post-deployment TAVI performance to reach a maximum of 47% in the reduction of the PVAR volume. [42]

Dowling et al [49] used patient-specific computer simulation for TAVI in patients with clinically bicuspid aortic valve (BAV) morphology who were deemed suitable for TAVI procedure and enrolled nine individuals in the study. Computational analysis simulation was effective for 8 patients (89%) who required a change in treatment approach with self expanded TAVR Evolut and Evolut PRO (Medtronic, Minneapolis, Minnesota). The evidence from simulations suggested the occurrence of moderate to PVAR for three recipients after the use of TAV, which were re-discussed in the heart team and considered for SAVR. As for the remaining six patients, the percutaneous treatment strategy was modified. Five patients who received TAVI (83%) with a self-expanding THV have had altered size and/or implantation depth to minimize paravalvular regurgitation and/or conduction disturbance. In one patient, the computed analysis was performed and significant conduction disturbance occurred after TAVI, requiring a permanent pacemaker that was inserted before mechanical intervention. Concerns about PVAR onset were correlated with none to mild recurrence of AV regurgitation in all nine individuals. Note that the patient who required a pre-procedure permanent pacemaker implant with definitive dependent pacing revealed a conduction disturbance classified as a third-degree atrioventricular block. Investigators highlighted the remarkable value of the use of FEA

 doi:10.20944/preprints202204.0304.v1

simulation applied to TAVI in BAV that may predict important clinical outcomes, such as PVAR and conduction disturbance. [49]

Finally, modern platforms to treat structural heart valve disease should entail the use of computational biomodelling, at least in the presence of major clinical or anatomic contraindications, and substantial efforts should be made to integrate the computational biomodelling into MDCT and 3D echocardiography during TAVI procedures avoiding the concern related to a central mild intraprosthetic leak. [39,96-101] Therefore, the scant evidence produced, which offers a comprehensive analysis of the effect of procedural parameters on patient-specific post-TAVR hemodynamics, limits the correct assessment of the effect of the TAV implant depth and balloon over-inflation on anchoring the stent. Ultimately, the occurrence of post-distribution PVL and the risk of thrombus formation remain the true Achilles' heel. A deeper direct analysis of the aforementioned objectives can offer valid help to understand the effect of the choice of the interventional cardiologist on postprocedural complications and help reduce their impact on the basis of patient-specific data. [40-43,50]

4. **Discussion**

4.1 Evidence to Deploying Biomechanical Evaluation and to definitively accept the use of Transcatheter Heart Valve Implantation as a New Paradigm Shift.

Both cardiology and cardiovascular surgery have witnessed an era of consistently evolving change and this new scenario has mainly been driven by the emergence of percutaneous coronary intervention with novel options for the treatment of coronary heart disease. The new endovascular platforms have evolved rapidly and established themselves as vital cogs in the armamentarium available to address structural heart disease. [107] In the past ten years, the innovation has primarily been invested initially in the management of aortic valve stenosis and subsequently pathological mitral valve with the progressive affirmation of transcatheter valve

 doi:10.20944/preprints202204.0304.v1

therapy (TVT). [22,24,61] From the first experimental study by Bonhoeffer who pioneered the transcatheter pulmonary valve implant, [53] the use of the TVT to treat aortic valve stenosis progressed rapidly. In 2010 the first PARTNER (Placement of AoRTic TraNs cathetER Valve Trial) reported a series of high-risk patients who were treated using this novel technique as opposed to conventional aortic valve stenosis surgery. [3] In less than 10 years, the PARTNER III, affirmed the safety and efficacy of the transcatheter aortic valve replacement in low-risk patients. [16] It is conceivable that future generations of transcatheter valves with the advancement of device technology will herald improvements in the hemodynamic profile, longevity, and durability alongside reduced adverse events.

Thomas Kuhn, an American physicist and philosopher, introduced the term "paradigm shift" for the first time in The Structure of Scientific Revolutions in 1962. [108] In this report the author explained how a process can bring about a transition of the worldly view, which has been previously and widely accepted, to a new model because of new emerging evidence. Cardiology and cardiovascular surgery have often faced paradigm shifts because these disciplines are constantly open to a transition that has over time, gradually favored the innovative spirit of those who practice them. We can note that historically, numerous paradigm shifts emerged: coronary bypass grafting, heart transplantation, percutaneous coronary intervention, mechanical and bioprosthetic valves, generations of life-saving drugs for heart failure, and mechanical circulatory support. [109,110] The current summit of these advancements is the emergence of devices used for the replacement of the aortic valve with TVT.

Calcific aortic valve stenosis (AVS) is a pathoanatomic process of aortic valve leaflets that are affected by structural changes sustained by an inflammatory and atherosclerotic process associated with calcium deposition. The morphological changes generated at the level of the cusps alter the function of the valve with consequent reduction in the opening of the leaflets,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

which are variably narrow, during systole. Aortic valve disease causes abnormal hemodynamics and increased mechanical stress of the left ventricle (LV). [111]

Prior to the advent of TAVI, surgical aortic valve replacement (SAVR) was considered the ideal treatment option in patients at risk to severe valve obstruction. However, new platforms for the treatment of structural heart diseases have fueled clinical attention that has shifted towards the use of new less invasive armamentarium represented by THV devices.

The PARTNER Ia study proved superiority of the transcatheter baloon expanded procedure in patients receiving TAVI over those who were managed with optimal medical therapy in short- and medium-term mortality (43.3% in the TAVI group and 68.0% in the standard- therapy group (P <0.001, at 2 years, respectively). [5] As for prohibitive/high risk patients with severe AVS who were suitable to receive a surgical treatment, the use of TAVI revealed the same mortality at 5 years as compared to SAVR (67·8% TAVR cohort vs 62,4% SAVR). Differently, patients who received TAVI disclosed a rate of moderate to severe AVR of 14% as compared to 1% in those receiving SAVR. [9] Not least, evidence from the use of first generation CoreValve Self-Expanding System revealed that 1-year all-cause death rate was higher in patients after SAVR as compared to recipirnts of TAVI. [8]

THVT has proven to be a revolutionary and decisively procedure in the last decade thanks for the achievement of efficacy and safety. Infact, evidence from THVT offered a clear answer to the use of the only life-saving solution for high and extreme surgical risk patients who cannot tolerate the open surgical option due to the presence of significant comorbidities. [112] Given the promising results associated with technological advancement which has undergone very rapid development, the use of TAVI has been approved for the treatment of intermediate risk patients. Although the results reported by the pioneering RCTs suggested increased rates of residual aortic valve regurgitation and more pacemakers implanted in the population intended for the TAVI procedure, however, the use of THVT was directed towards the design of randomized trials involving the intermediate / low surgical risk population. [9,10,13,15-17]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

In the the SURTAVI 84% of patients were managed with the first-generation CoreValve System while 16% of recipints the TAVI has the second generation of Evolut R bioprostheses.This cohort of individuals had an STS score Society for Predicted Risk of Mortality at 4.5±1.6%

At 2 years revealed composite of death from any cause or disabling stroke was higher in SAVR group as compared to TAVI group (14% vs 12,6% respectively). [15] The cheering evidence of non inferiority of TAVI over SAVR recorded for intermediate and high-risk patients offered the favorable points to undertake the randomized PARTNER 3 trial [16] and the multinational randomized clinical Evolut Low Risk Trial Investigators 26 for patients presenting with severe AVS at low risk for death after surgical procedure. [17] In the third series of results reported from the two RCTs, the composite of death from any cause, stroke or re-hospitalization at 1 year was less in TAVI recipients after implantation of the device. Again, investigators found shorter hospitalization rates for individuals undergoing TAVI while there were no significant differences between groups in terms of major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. [16,17]

Certainly a decisive impetus for the success of the large-scale TVT procedure has been linked to the refined technological progress which has seen the use of introducers of reduced diameter and an improvement in the performance of the stent which has proved to be safer and more effective. However, it is important to consider that the results must be confirmed by longer term follow-up.

4.2 Biomechanics Computational Modelling to Give Consistency to The paradigm Shift.

4.2.1 Paravalvular Aortic Regurgitation

Although there has been substantial initial growth in the use of TAVI confirmed by the success of the results, intra- and postprocedural clinical complications have questioned the paradigm shift, questioning the potential expansion of TVT in low-risk patients.

 doi:10.20944/preprints202204.0304.v1

We have learned that post-deployment PVAR, cardiac conduction abnormalities [113,114] (Bagur et al. 2012 ; Van der Boon et al. 2012) and coronary artery occlusion (Ribeiro) are among the most marked immediately recorded disadvantages.[115] Taken together, these complications revealed increased rate of mortality and reoperation. [23, 113-115]

Surely the Achilles heel of the TAVI is constituted by the altered hemodynamics due to the occurrence of the PVAR, in which the emergence of narrow gaps which are exposed to high gradients of dystolic pressure, can lead to an altered function of the platelets which are therefore exposed to a high flow shear stress. This patho-anatomic condition triggers platelet activation, perturbing the aggregation / coagulation balance, with the formation of microemboli. The latter are then expelled at the next systole and can remain trapped and / or deposited in the region of the Valsalva sinuses, which offer a suitable location for typical low shear recirculation areas. Therefore, PVAR may be linked to the deposition of thrombi around the THV device as well as to the potential circulation of thromboembolic clots, which is followed by an increased risk of stroke. Several evidences have reported that thromboembolism is less common than hypo-attenuated thickening of the leaflets, however it is still a fairly common and dangerous phenomenon that required adequate clinical treatment. [116] Another point to consider is the close association of leaflet thrombosis and development of a structural degeneration of the valve incorporated in the device.

Several studies have suggested that the occurrence of PVAR in recipents of TAVI procedure is directly correlated with higher late mortality, cardiac death and repeated hospitalization even in the presence of traces of regurgitation. [117] Five years results from Partner Ib RCT disclosed a rate of 14% of moderate or severe aortic regurgitation in patients who received TAVI as compared to those who were managed with SAVR. This evidence caused an increased risk of mortality at 5 years for patients who developed moderate or severe aortic regurgitation after TAVI. [9]

 doi:10.20944/preprints202204.0304.v1

All the indicators testify that the mortality rate was proportional to the severity of the regurgitation and in this regard Generaux et al [35] reported that even a slight PVAR can lead to a doubling of the mortality rate after 1 year. However, Webb et al [2] pointed out that the progression of PVAR can be unpredictable. Investigators observed that at 2 years, regurgitation increased by ≥ 1 grade in 22.4% of patients, remained unchanged in 46.2% and improved by ≥ 1 grade in 31.5%.

In this context, substantial differences emerged after the installation of balloon-expandable THV device or the use of self expandable THV armamentarium. Two independent studies revealed that recipients of Medtronic CoreValve self-expanding experienced a higher PVL rate and worsening severity than patients who received an expandable Edwards SAPIEN balloon. [50,118] However, substantial improvements have been made in the new devices involving the low profile delivery system and external skirt, thereby improving the sealing of the THV device and promoting more precise valve positioning. A lower rate of PVAR at short-term follow-up has been reported. [119]

Patients who exhibit PVAR post TAVI require clinical and imaging modality evaluation. The quantification of regurgitation is generally determined with the use of echocardiography.

In detail, methods such as transoesophageal echocardiography, cineangiography and haemodynamic measurements are commonly used during the procedure, while transthoracic echocardiography offers substantial support for the evaluation and follow-up of PVAR after TAVI. [120] Above all, the continuous wave echo is the most commonly used method to evaluate the overall hemodynamic performance of the valve, but with the default of not being able to obtain a spatial localization of the leak. The relative consequence is that the aortic regurgitation is quantified as the ratio of reverse flow to direct flow. As report by Hatoum et al [121] the most obvious limit is that the measurement and determination are experimentally. However, a semi-quantitative description of the jets by pulsed wave color doppler can be used to obtain a precise localization and evaluation of the gravity of the PVAR jets.

 doi:10.20944/preprints202204.0304.v1

Concern related to the quantification of PVAR persists after TAVI due to a lack of standardization leading to a challenging diagnosis. In fact, it is often qualitative and different classification schemes are adopted (trace, mild, moderate and severe). [120,122] Several interventional alternatives to reduce paravalvular regurgitation have been put in place and include post-implantation balloon dilation, repositioning, entrapment maneuvers as well as valve-in-valve (ViV) procedure [123]; all of these are not free from an increasing risk of vascular complications. A critical aspect of the procedure is represented by the positioning of the THV device with respect to the patient's aortic annulus which was directly associated with the degree of hemodynamic performance of the TAVI as well as the rate of reintervention. [124]. There is early evidence from Nombela Franco et al [125] and Takagi et al [126] who reported that balloon over-inflation is often used to reduce the degree of PVAR. Investigators revealed the post-balloon decreases regurgitation in the preponderance of patients by at least one degree. [125,126] However, how crucial the post-dilation effect on survival remains elusive. Again, an association with a higher incidence of cerebrovascular events was recorded. [125] The goal of a correctly performed transcatheter procedure necessarily involves minimizing the amount and incidence of PVAR in order to gain improved clinical outcome in the long term.

The development of computational models was identified early as the right bet to study the interaction between TAVI stent and native aortic tissue and predict the performance of the post-procedural device from the point of view of structural dynamics. [41,43,47,127,128] Recently, several studies have substantially quantified the degree of interaction between the device and the implantation site, as a surrogate measure of the PVAR, by measuring the gap between the stent [40,48] or the skirt [129] from native tissue, considering the specific anatomical characteristics of the patient's aortic root. Chang et al reported ideal characteristics that offer better results in terms of PVAR occurrence. [130] We have compared the two most used devices documenting a better performance of the third generation of balloon-expandable device

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

compared to the third generation of self-expandable device in adapting to the dynamics of the aortic root reducing the risk of PVAR. [50]

Similarly, great interest has aroused in the creation of a maximum flow algorithm [46], producing a one-dimensional connected graph capable of representing the flow network based on the size of the gap existing between the stent and the root. aortic. Although in the absence of PVAR the results showed a good correlation, nevertheless the reliability was reduced with the development of models that lacked precision for patients with PVAR recurrence. Significant report has been described by De Jaegere et al. [44] who referred on a large series of computational models that tested the predictability on 60 Medtronic CoreValve deployment cases in which the results were validated through angiographic and echocardiographic measurements. The limit of the work lay in the lack of an adequate description of the reconstruction of the patient's anatomy with respect to the modeling hypotheses. Finally, Mao et al [131] in a recent study evaluated the effect of CoreValve orientation and modeling assumptions, such as skirt shape and stent thickness, on post-deployment hemodynamics. However, the formation of post-TAVI thrombus only involved the generated clots on the valve leaflets following a ViV procedure. Vahidkhah et al analized blood stasis assessing and quantifying idealized ViV models with intra-annular and supra-annular TAVI positions. [132]

4.2.2 Transcatheter Heart Valve Thrombosis

Evidence based on several reports displayed that recipient of TAVI experienced an unclear rate of bioprosthetic valve thrombosis (BPV-TH) and thromboembolic complications of device. Of note that both results from the RCTs and EU Partner Registry are lacking of complete and satisfactory data. As regard PARTNER and CoreValve System randomized clinical trials, the occurrence of cases of BPV-TH has not been revealed. [9,10,25] On the other ends, the EU Partner Registry [133] also revealed very poor data about thromboembolic events in patients who were managed with THV devices. The reported thromboembolic complication rate was

 doi:10.20944/preprints202204.0304.v1

only one case out of 130 patients undergoing TAVI. Latib et al evidenced, from a large number of patients (n=4,266), only 27 cases of BPV-TH thrombosis (0.61%) occurring within a median of 181 days after TAVI procedure. [133]

Importantly, Stortecky et al observed that the risk of BPV-TH was higher in the first 3 months after device implant. In addition, the risk curves were significant testimony for a marked reduction of events in the subsequent months almost matching the curves of the general population.[134] A histopathological analysis from the CoreValve device thrombotic complication, suggested that cloths formation was completed approximately 3 months after the implant of the THV device. [135-139] Makkar et al [140] offered important data using systematically the 4 D computed tomography to prove bioprosthetic valve thrombosis events. 55 patients included in the PORTICO Studio IDE (Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial) revealed the occurrence of BPV-TH at a median of 32 days after valve implantation with a decreased leaflets movement in 40% of recipients. 132 patients included in the Savory study (Subclinical aortic valve thrombosis assessed with 4D CT), and eligible to receive either TAVI or SAVR, or included in RESOLVE (surgical catheter and aortic evaluation Thrombosis of the bioprosthetic valve and its treatment with Anticoagulation), undergoing 4 D computed tomography within 3 months recording a reduced leaflet motion for a rate of 13% of recipients. Of these 14% were treated with TVI while 7% undergoing SAVR with the use of a conventional bioprosthesis. [140,141]

Pache et al [142] corroborated the previous evidence [140,143] on 156 consecutive patients who were managed with TAVI using the SAPIEN 3 (Edwards Lifesciences, Irvine, California). At a median of 5 days after procedure investigators observed by mean of multidetector computed tomography that 10.3% of TAVI recipients disclosed leaflet thickening with hypoattenuation. Although the absence of symptoms was considered a relevant point for a normal clinical evolution, however individuals experienced a higher mean transvalvular gradients and anticoagulant drug therapy led to complete resolution of leaflet thickening. [142] Likewise, in

 doi:10.20944/preprints202204.0304.v1

patients who were treated with dual antiplatelet therapy (DAPT) less frequently than those who were managed with a single antiplatelet drug (37,5% and 50%, respectively) [142] was noted a correlation between increased transvalvular gradient and uncontrolled neointimal proliferation with thickening of the device leaflets. [142,143]

3 recent studies reached significant relevance in the yeld of BPV-TH and thromboembolic events. [136,144,145] Hansson et al [136] monitored patients who received TAVI procedure with the use of balloon-expandable valves (Edwards Sapien XT or Sapien 3 valves) by means of transthoracic or transoesophageal echocardiography and multidetector computed tomography to screen the incidence and predictors of BPV-TH at 1-3 months. The evidence of thrombosis was observed in a rate of 7% of patients with MDCT. 18% of individuals experienced bioprosthetic valve thrombosis events with clinical complications. Cox's multivariate regression analysis revealed that the 2 independent predictors of BPV-TH were related to the use of the TAVI and were the identified in the lack of warfarin administration and larger size of the device measured at 29 mm. [136]

Nührenberg et al [144] studied hypo-attenuated leaflet thickening (HLAT) as a potential precursor of clot formation and thromboembolic events after TAVI. In all cohorts of patients, including those with oral anticoagulation treatment, dual antiplatelet therapy with aspirin and clopidogrel was administered for at least 24 hours before the procedure. In patients who had pre-existing indications for oral anticoagulation treatment aspirin was discontinued, the administration was pursued after TAVI for the rest of the cohort. 18% of TAVI patient's revealed hypo-attenuated leaflet thickening, however lower complication rates were observed in patients receiving oral anticoagulation suggesting that the administration of dual antiplatelet therapy (aspirin and clopidogrel) did not change the occurrence of early HLAT. [144]

GALILEO 4D RCT [145] included 231 patients for antithrombotic strategy assessment, in which long-term anticoagulation was administered, either with the use of rivaroxaban (10 mg) associated with aspirin (75 to 100 mg) once daily or with the administration of dual antiplatelet-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

based strategy with the use of (clopidogrel (75 mg) plus aspirin (75 to 100 mg) once daily. Four-dimensional CT was used after randomization to check all cohorts of individuals. Patients were successfully treated with TAVI with no indication for long-term anticoagulation therapy. The primary endpoint of the study comprehended the percentage of patients who experienced at least one prosthetic valve leaflet with grade 3 or higher motion reduction. Of note, this process substantially involved more than 50% of the leaflet as a follow. 2.1% of patients with rivaroxaban administration revealed at least one prosthetic valve leaflet with grade 3 or higher motion reduction compared to 10.9% in the dual antiplatelet protocol. Thickening of at least one leaflet was recorded in 12.4% of patients in the rivaroxaban cohort compared to 32,4% in which the dual antiplatelet was administered. Lastly, Concerns about the increased risk of death or thromboembolic events and the risk of life-threatening, disabling, or greater bleeding were remarkably higher in patients who received the rivaroxaban administration. [145]

One of the concerns affecting cloths formation after the TAVI procedure is related both to the extent of bulky native valve calcification and its position with respect to the annulus of AV and aortic root, as well as to stent deformation and the size of the patient's annulus. Even more, in these specific morphological features, the role of physiological blood dynamics plays a crucial role has not been fully investigated. [39]

Khalique et al [146] noted that the calcified blocks substantially affect the amount and asymmetry depending on the extent of aortic valve calcification. This condition led to the involvement of all regions of the aortic valve complex in predicting various grades of PVAR from greater than or equal to mild PAVR and post-deployment performance of the device, thereby potentially evolving towards bioprosthetic valve thrombosis of THV device. The preexistent leaflet asymmetry was excluded in favoring PVAR. Quantity of bulky calcification at the level of the junction between annulus and LVOT as well as the occurrence of leaflet calcification independently predict PVAR and post-deployment of TAVI when taking into account multidetector-row computed tomography area cover index. [146]

 doi:10.20944/preprints202204.0304.v1

For this reason, the use of computational biomodeling can lead to predicting both the extent of PVAR and the risk of clots formation. [39-42,50-52] Likewise, the bulky calcification penetrating the aortic annulus may have a different texture thus raising some reflections about the ideal choice of device to implant. [40,41,50,146] So the use of the self and ballon expandable systems prostheses can lead to different geometric alterations of the aortic annulus after the deployment, with a greater or lesser risk of potential disturbance of the blood fluid dynamics that generate clot formation. [40-42,5,]

In this regard, we revealed that both balloon and self-expandable devices were poorly effective in presence of bulky native AV calcifications, and the different degrees of device deformation were studied. Two independent reports based on computational biomodelling suggested that, both Sapien XT and Sapien 3 disclosed high values of the maximal principal stress in the aortic regions close to bulky calcification, resulting in a deformation of the stent that assumed an elliptical shape. [40,52] Accentuated geometric modification with incorrect post-deployment can lead to paravalvular leakage, leaflet mal-coaptation, and hypo-attenuated leaflet thickening. The extreme shape of elliptical deformation is likely to favor subclinical thrombosis due to the presence of residual calcifications that favor hypomobility. [40,52] The SAPIEN Device is highlighted in **Figure 8**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

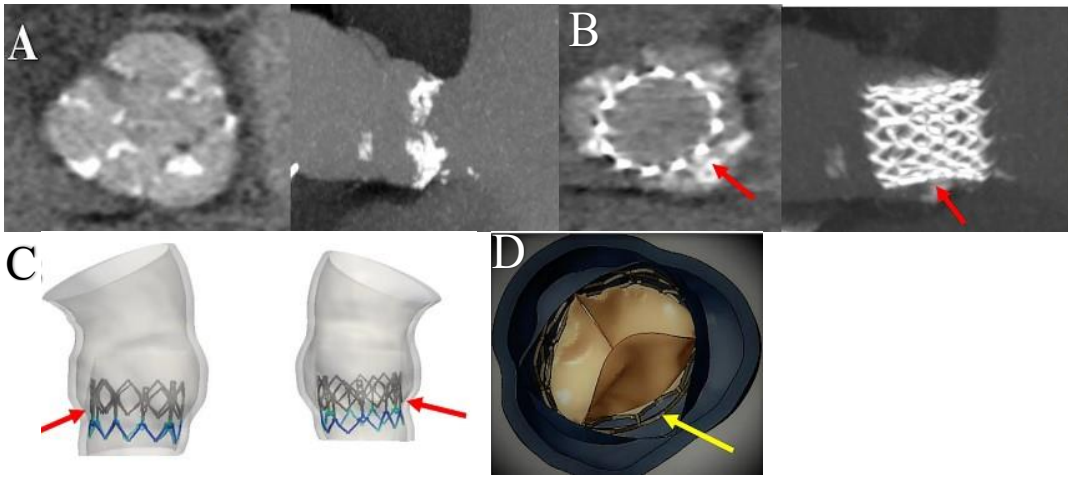


Figure 8. Depict preoperative **(A)** and postoperative **(B)** 3 D CT scan with TAVI thrombosis. **(C)** Biomodeling of a Sapien XT reveal an incomplete deployment (red arrow) of the device with PAVR and thrombotic formation (red arrow). **(D)** The yellow arrow disclose a the distortion of the stent and reduced mobility of the leaflet of the bioprosthesis in correspondence of a PAVR. Abbreviation; PAVR, paravalvular aortic regurgitation. Other abbreviations in previous figures

Again, the Core valve is based on the self-expansion mechanism that may be succumb to the mechanical distortion phenomena. In self-expanding TAVI, the crucial role of positioning in determining valve anchorage is pivotal. The occurrence of non-uniform expansion related to extensive calcifications can lead to prosthetic device deformation that ranges from an increased eccentricity > 10%, resulting in incomplete expansion of the nitinol frame at almost all levels and potentially causing clot formation [41,42,50]

No evidence has demonstrated a statistically significant correlation between the occurrence of moderate PVAR and abnormal flow patterns on the TAV implanted leaflets and in the left main coronary artery that could favor a thrombosis of the THV device and an accelerated progression of the atherosclerotic process. [147] However, several observations suggest that clot formation has been hypothesized could be more directly related to PVAR with the clinical occurrence of a thrombotic embolism. [52, 136,140-145]

An explanation can be offered by the existence of a localized flow at the PVAR level with the development of high-pressure gradients associated with the presence of small tight empty areas. This condition implies that the platelets are subjected to a high flow shear stress.

 doi:10.20944/preprints202204.0304.v1

[41,42,52] This phenomenon, as we have reported, has attracted ever-increasing clinical interest. [41,52]

Bianchi et al [42] evaluated the relationship between PVAR and platelet activation with a computational model, to study the thrombogenic potential of 3 procedural configurations of TAVI, of which 2 were Sapien 3 and 1 was Corevalve Evolute. Investigators calculated the stress accumulation of platelets along particle trajectories in the PVAR region. All the probability density functions in the 3 simulations performed show comparable patterns. For example, in one Sapien 3 26 mm valve, where an over-inflated aortic configuration was exhibited, a major stress accumulation of platelets was evident. This phenomenon can be related to the higher speed that can be recorded in the PVAR jets which leads to a higher flow shear stress. In addition, HS values were observed in agreement with the largest overall regurgitation volumes. The information obtained from the probability density functions notes that the variation in the diameter of PVAR affects the activation potential of platelets. For example, in Corevalve Evolut 29 a reduction in PVAR grade led to a slightly higher thrombogenic potential, as platelets were subjected to more shear stress that was related to their flow through smaller paravalvular spaces. [42] Finally, dynamic fluid has also taught that when the volume of regurgitation is considerably higher, the cause-effect relationship established between PVAR reduction and susceptibility to platelet activation is supported by a more complicated interaction. [41,42,52]

4.2.3 Structural valve degeneration

The term structural valve degeneration SVD implies an acquired anomaly of the valve bioprosthesis due to a substantial deterioration of the flaps and of the structural support that integrates the device. The correlated patho-anatomic consequence is the thickening, calcification, laceration, or rupture of the materials that make up the valve prosthesis. This context of the pathological disorder suggests the development of associated valvular hemodynamic dysfunction, such as the development of stenosis or regurgitation. To date, a

 doi:10.20944/preprints202204.0304.v1

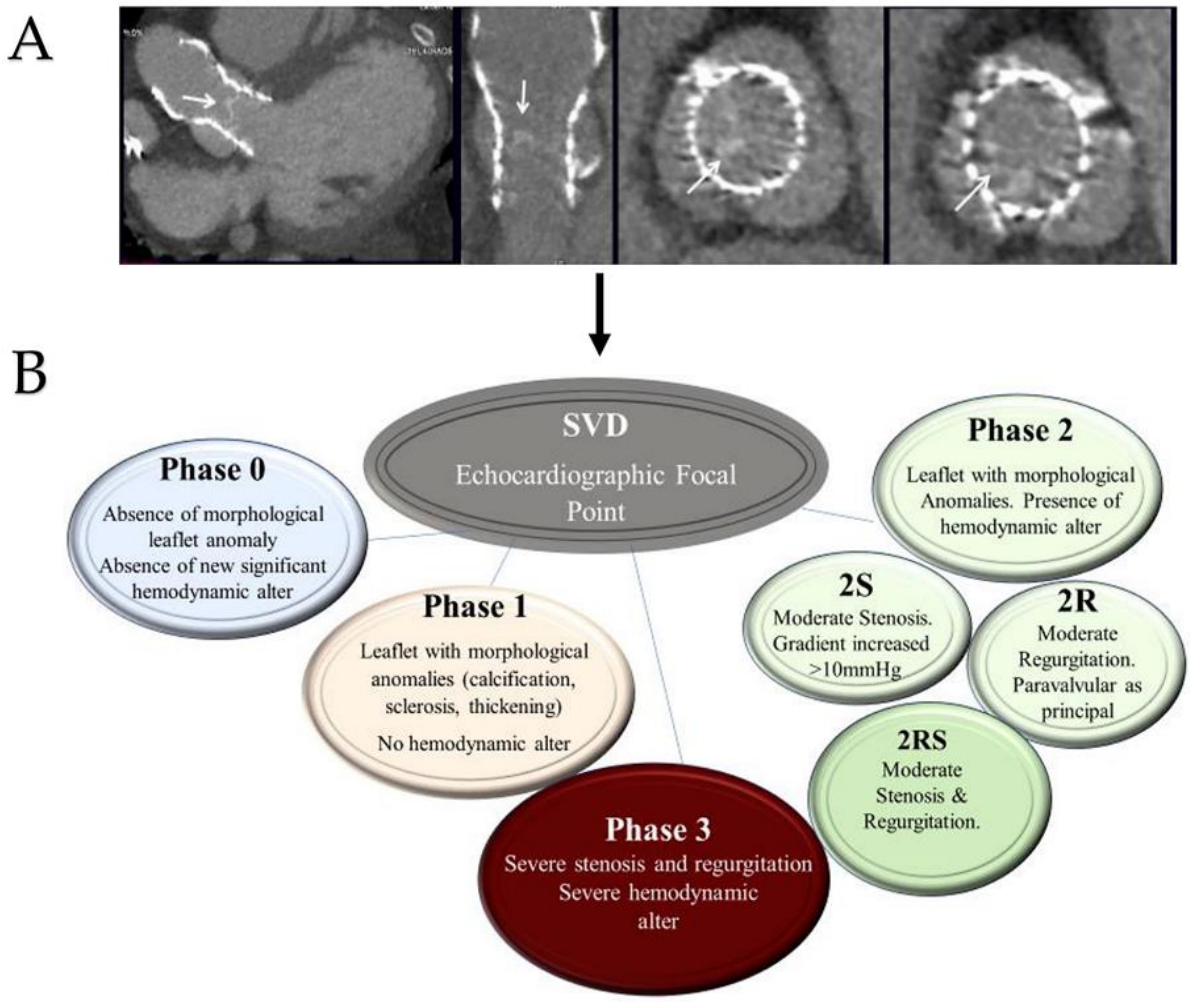
thorough understanding of the precise mechanisms underlying an SVD has not yet been substantially offered. However, the mechanisms that support SVD are multiple, both mechanical and related to fluid dynamics, which are responsible for tissue rupture or thickening over time. [27-33,148-171]

Several factors cause SVD. First of all, a crucial role is provided by the mechanical stress levels associated with both flow anomalies and the occurrence of shear stresses on the surface of the valve leaflets. These two factors are potentially responsible for the progression of SVD leading to the breakdown of the collagen frame of the fibers and the calcification of the tissues. [160,172] Second, other clinical conditions, in which the pathological features of intrinsic structural deterioration of the valve tissue are not detectable, cannot be classified as SVD. However, they deserve to be taken into consideration. SVD may be related to mismatch between prosthesis size and patient size, device malposition, paravalvular regurgitation, and abnormal frame expansion. Likewise, these abnormal situations attributable to the implanted bioprosthesis can lead to early SVD or be considered a cause of its development. The dysfunction involving the prosthesis implanted due to mismatch is difficult to distinguish from a structural degeneration of the valve. Therefore, it is not considered to be an SVD as it exhibits normal leaflet morphology, but instead has a valve area that is relatively small with a high gradient. [27-33; 148-171]

A crucial point that characterizes the difference between the prosthetic mismatch and the SVD is related to the time during which the anomaly is established. The prosthetic maladjustment reveals hemodynamic anomalies of the valve which occur at the moment of implantation of the prosthesis with the manifestation of the patient's hemodynamic deterioration which occurs in conjunction with an increase in gradients and a decrease in the valve area; these conditions that reveal a progressive increase in the patient's clinical conditions on repeated echocardiographic checks. In patients who develop SVD, associated stenosis develops progressively and is seen with the characteristics of a faded lesion during follow-up. Although both prosthetic valve

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

thrombosis and infective endocarditis are not included in the definition of SVD, SVD may be noted despite having recorded therapeutic success. The SVD is currently experiencing a very intense debate due to its potential to involve and therefore influence the TAVI procedure. [148-171] Indeed, since a less invasive transcatheter approach is available for patients presenting with comorbidities and at high risk for conventional surgical strategy, fewer cases of SVD were detected possibly because the deceased patients were not included in the long-term follow-up. Cardiologists believe that SVD is not a reliable criterion for establishing true biological valve durability. They suggested that the actuarial freedom found by re-intervention is inherently lower than the freedom from SVD. [148,149] **Figure 9**



Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 April 2022 doi:10.20944/preprints202204.0304.v1

Figure 9: **A:** Early SVD with calcifications (white arrow) of TAVI in patient receiving self-expanded first generation Corevalve 26 mm (CoreValve, Minneapolis, Minnesota)**. B:** Classification of SVR based on recommendations of the VARC-2 for stent / stentless xenograft. The useful elements to define SVD as valve-related dysfunction were the mean aortic gradient ≥20 mm Hg, the effective orifice area ≤0.9-1.1 cm2, a dimensionless valve index <0.35 m / s and moderate or severe prosthetic regurgitation. Phase 0 displays the absence of morphological leaflet anomaly and absence of hemodynamic alter. Phase 1 discloses early morphological changes without hemodynamic compromise. The morphological alterations typical of stage 1 are also referable to prostheses where the degenerative process is controlled using antithrombotic drugs that reduce the thickening of the leaflet. Phase 2 reveals morphological abnormalities of valve leaflets of SVD associated with hemodynamic dysfunction. The bioprostheses in this phase can manifest as stenosis or regurgitation. The thrombosis is a factor favoring phase 2 leading the stenosis or paravalvular leakage and regurgitation. Phase 2 includes two subcategories, phase 2S and phase 2R. In the evolutive stage of 2S degenerative an increase in the mean transvalvular gradient (≥10 mm Hg) and decrease in the valvular area without leaflet thickening occur. SVD may occur as 2RS form including moderate stenosis and moderate regurgitation. Phase 3 of SVD highlights severe stenosis or severe regurgitation with severe hemodynamic change. Abbreviations: R, regurgitation; SVR, structural valve degeneration; S, stenosis; VARC, Valve Academy Research Consortium

Only the NOTION RCT [31] with 6 years of follow up disclosed SVD rates that were significantly greater after SAVR than TAVI-procedure (24.0% vs. 4.8%; $p < 0.001$). Investigators reported in postprocedural echocardiographic controls a mean gradient of> 20 mm Hg in 22% of patients who received SVD compared to 2.9% for those who were managed with TAVI ($p <0.0001$). This evidence was also corroborated at 3 months postprocedure check where a modified definition of SVD was fixed and a mean gradient increase> 10 mmHg was established (AVR-S 12.4% vs TAVR 1.4%; $p <0.001$). [31]

In figure X an echocardiographic focal point of the SVD of the stent / stentless xenograft is depicted.

On the other end patients who were checked at 5-year follow-up from the PARTNER trial disclosed no structural valve deterioration with preservation of low gradients and increased valve area. [9,10] The results of the two randomized studies are encouraging but a longer follow-up is necessary to confirm and give more solidity in terms of safety and effectiveness to the trans-catheter procedure. [9,10]

The bioprosthesis designed as part of the Sapien THV balloon-expandable consists of bovine pericardium as opposed to the calf pericardium which characterizes the surgically implanted Edwards bioprosthesis. However, it should be noted that the treatment procedure is identical. [172] The use of the TAVR 22 Fr and 24 Fr systems has been adapted to the leaflets of the TAV which are thinner than

 doi:10.20944/preprints202204.0304.v1

surgical bioprostheses. Rapid technological advances have led to the development of delivery systems reduced to 18 Fr before and 4 Fr after for the second generation of Sapien XT and for the third generation Sapien 3 (Edwards Lifesciences, Inc) which accompanied the changes made to the stent in cobalt-chromium and thinner leaflets to obtain a lower crimped TAV profile.

The study by Xuan et al [56] revealed that the major and minor stresses in the Sapien 26 mm valves are located proximally in the annulus, where the stent is deployed and narrowed. Investigators highlighted that maximum and minimum principal stresses were exhibited at the level of TAV leaflets that were attached to the stent located in close contact with the commissures. It is reasonable to suggest that these regions where the peak stress and the highest stress levels occur locally could result in the areas most prone to initiate degeneration. To date, we do not know studies that have shared a comparison on the relative duration of TAVI compared to surgical bioprostheses. Evidence reported from studies on degeneration of surgical bioprostheses suggests that degeneration associated with calcification or tearing of the flaps correlates with areas of high tensile and compressive stresses. [56]

Sun et al [173] performed the first computational biomodeling using FEA on 2 bovine pericardial valves Edwards Lifesciences Inc. The test was performed with quasi-static loading conditions set below 120 mm Hg, with leaflet material properties fixed from those valves and respecting the exact valve geometry 11. The investigators recorded a maximum in the plane stress that ranged from 544.7 kilopascals (kPa) to 663.2 kPa, reliant on the material properties of the leaflet were used. Of note, the degree of stress had different locations. In fact, they revealed that the stresses on the leaflets were greatest near the commissures when inferior near the free edge of the leaflet. In a subsequent study, the authors reported the results of an FEA simulation performed on a 25 mm surgical bioprosthesis, which is the closest dimension to the size of the commonly implanted Sapien Baloon expandable. Again, Xuan et al [56] suggested levels of maximum principal stress for a 26-mm Sapien valve significantly higher than that recorded for a surgical bioprosthesis, offering an explanation due to the difference in the design of the leaflets or a different interaction with the respective frame that constitutes the device. [56] Alavi et al

 doi:10.20944/preprints202204.0304.v1

revealed that the crimping process physically damages TAV leaflets, and may undermine leaflets leading to increased leaflet stress. [174]

Conclusion

TAVI and SAVR are both options that should be seen as part of the treatment armamentarium offered to patients. The use of adjuncts like FEA and MDCT can help steer the decision-making process of the heart team while considering the patients' wishes. Although currently comparable, the long-term effects of TAVI are still uncertain, but advancements are being made at a rapid rate to ensure it remains a pivotal option for treating aortic valve stenosis.

Author Contributions: Conceptualization, F.N.; methodology, F.N, SS.AS, P.N.; software, SS.AS. P.N; validation, F.N, SS.AS, P.N, A.F.; formal analysis, F.N, SS.AS; investigation, F.N, P.N.; data curation, F.N, SS.AS, P.N.; writing—original draft preparation, F.N.; writing—review and editing, F.N, S.S.A.S., P.N, A.F; visualization, F.N, SS.AS.; supervision, F.N, A.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Abbreviations

ACC; American College of Cardiology

AHA; American Heart Association

AR; aortic regurgitation

AVS; aortic valve stenosis

CT; computed tomography

COR; class of recommendation

 doi:10.20944/preprints202204.0304.v1

DLP; Dose Length Product

ESC; European Society of Cardiology

FEA; finite element analysis

HF; heart failure

LOE; level of evidence

LVF; left ventricular function

mGy; microgray

MDCT; Multi-detector row computed tomography

PA; pulmonary artery

PAVR; paravalvular aortic regurgitation

RCT; randomized clinical trial

STL, stereolitographic

SVD; Structural valve degeneration

SAVR; surgical aortic valve replacement

TAVI ; Transcatheter aortic valve implantation

TVT; transcatheter valve therapy

THV; transcatheter heart valve

VARC; Valve Academic Research Consortium

Reference

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis first human case description. Circulation. 2002 ;106 :3006-8.
2. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation : impact on clinical and valve-related outcomes. Circulation. 2009 Jun 16 ;119(23) :3009-16.
3. Leon MB, Smith CR, Mack M, Miller DC, et al. PARTNER Trial Investigators Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 Oct 21 ;363(17) :1597-607.
4. Smith CR, Leon MB, Mack MJ, et al ; PARTNER Trial Investigators Transcatheter versus surgical aortic-valve replacement in high-risk Patients.N Engl J Med. 2011 Jun 9 ;364(23):2187-98
5. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012 ;366 :1696-704.
6. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012 ;366 :1686-95.
7. Falk V. Transcatheter aortic valve replacement indications should not be expanded to lower-risk and younger patients. Circulation. 2014 Dec 23 ;130(25) :2332-42.
8. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a selfexpanding prosthesis. N Engl J Med. 2014 ;370 :1790–8.

9. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1) : a randomised controlled trial. Lancet. 2015 ;385 :2477–84.
10. Kapadia SR, Leon MB, Makkar RR, et al., PARTNER trial investigators. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1) : a randomised controlled trial. Lancet 2015 ;385 :2485–91.
11. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol. 2016 ;67 :2565–74.
12. Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk : systematic review and meta-analysis. BMJ. 2016 ;354 : i5130
13. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate risk patients. N Engl J Med. 2016 ;374 :1609–20.
14. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients : a propensity score analysis. Lancet. 2016 ;387 :2218–25.
15. Reardon MJ, Van Mieghem NM, Popma JJ, et al ; SURTAVI Investigators. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients.N Engl J Med. 2017 Apr 6 ;376(14) :1321-1331.
16. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695–705.
17. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a selfexpanding valve in low-risk patients. N Engl J Med. 2019 ;380 :1706–15.
18. Makkar RR, Thourani VH, Mack MJ, et al ; PARTNER 2 Investigators. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement N Engl J Med. 2020 Jan 29 ;382(9) :799-809.
19. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/ American Heart Association Joint Committee on clinical practice guidelines. J Am Coll Cardiol. 2021 ;77 :450-500
20. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. ESC/EACTS Scientific Document Group ; ESC National Cardiac Societies. Eur Heart J. 2021 Aug 28 : ehab395.

21. Spadaccio C, Fraldi M, Sablayrolles JL, Nappi F.J TAVI in Lower Risk Patients: Revolution or Nonsense? Keep Calm and Select Patients. J Am Coll Cardiol. 2016 Mar 22 ;67(11) :1380-1.
22. Nappi F, Spadaccio C, Sablayrolles JL. Pushing the Limits in Transcatheter Aortic Valve Replacement : High-Volume Center's Effect, Overconfidence, or Something Else ? JACC Cardiovasc Interv 2016 ;9 :2186-8.
23. Nappi F, Spadaccio C, Sablayrolles JL. Delayed prosthesis malposition after transcatheter aortic valve implantation causing coronaries obstruction. Eur J Cardiothorac Surg 2017 ;52 :1227-8.
24. Attias D, Nejjari M, Nappi F et al. How to treat severe symptomatic structural valve deterioration of aortic surgical bioprosthesis : transcatheter valve-in-valve implantation or redo valve surgery ? 2018 Dec 1 ;54(6) :977-985.
25. Reardon MJ, Adams DH, Kleiman NS, et al. 2-year outcomes in patients undergoing surgical or selfexpanding transcatheter aortic valve replacement. J Am Coll Cardiol 2015 ;66 :113–21.
26. Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. Surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis : an updated meta-analysis. Eur Heart J. 2019 ;40 :3143–53.
27. Didier R, Eltchaninoff H, Donzeau-Gouge P, et al. Five-Year Clinical Outcome and Valve Durability After Transcatheter Aortic Valve Replacement in High-Risk Patients. Circulation. 2018 ;138 :2597-607

28. Panico RA, Giannini C, De Carlo M, et al. Long-term results and durability of the CoreValve transcatheter aortic bioprosthesis : outcomes beyond five years. EuroIntervention. 2019 ;14 :1639-47
29. Durand E, Sokoloff A, Urena-Alcazar M, et al. Assessment of Long-Term Structural Deterioration of Transcatheter Aortic Bioprosthetic Valves Using the New European Definition. Circ Cardiovasc Interv. 2019 ;12 : e007597.
30. Mack M, Carroll JD, Thourani V, Vemulapalli S, Squiers J, Manandhar P, et Transcatheter Mitral Valve Therapy in the United States : A Report From the STS-ACC TVT Registry. J Am Coll Cardiol. 2021 Dec 7;78(23):2326-2353.
31. Thyregod HGH, Ihlemann N, Jørgensen TH, et al. Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients. Circulation. 2019 Feb 1
32. Søndergaard L, Ihlemann N, Capodanno D, et al. Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients at Lower Surgical Risk. J Am Coll Cardiol. 2019 Feb 12 ;73(5) :546-553.
33. Zhang XL, Zhang XW, Lan RF, Chen Z, Wang L, Xu W, Xu B. Long-term and Temporal Outcomes of Transcatheter Versus Surgical Aortic-valve Replacement in Severe Aortic Stenosis : A Meta-analysis. Ann Surg. 2021 Mar 1 ;273(3) :459-466
34. Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. J Am Coll Cardiol. 2009 May 19;53(20):1829-36
35. Generaux P, Head S.J, Hahn R., Daneault B, Kodali S.,Williams M.R.,van Mieghem N, et al. Paravalvular leak after transcatheter aortic valve replacement : the new Achilles' heel ? 2013. J.Am.Coll.Cardiol.61(11),1125–1136.
36. Blanke P, Siepe M, Reinöhl J, Zehender M, Beyersdorf F, Schlensak C, Langer M, Pache G. Assessment of aortic annulus dimensions for Edwards SAPIEN Transapical Heart Valve implantation by computed tomography : calculating average diameter using a virtual ring method. Eur J Cardiothorac Surg. 2010 Dec ;38(6):750-8.
37. Détaint D, Lepage L, Himbert D, Brochet E, Messika-Zeitoun D, Iung B, Vahanian A. Determinants of significant paravalvular regurgitation after transcatheter aortic valve : implantation impact of device and annulus discongruence. JACC Cardiovasc Interv. 2009 Sep ;2(9) :821-7.
38. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation : the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012 ;60 :1438–1454.
39. Nappi F, Mazzocchi L, Avtaar Singh SS, et al. Complementary Role of the Computed Biomodelling through Finite Element Analysis and Computed Tomography for Diagnosis of Transcatheter Heart Valve Thrombosis. Biomed Res Int. 2018 Oct 22 ;2018 :1346308.
40. Morganti S., Conti M., Aiello M., et al., 2014. Simulation of transcatheter aortic valve implantation through patient- specific finite element analysis : two clinical cases. J Biomech. 2014 Aug 22 ;47(11):2547-55
41. Morganti S, Brambilla N, Petronio AS et al. Prediction of patient-specific post-operative outcomes of TAVI procedure : The impact of the positioning strategy on valve performance. J Biomech. 2016 Aug 16 ;49(12) :2513-9.
42. Bianchi M, Marom G, Ghosh RP, Rotman OM, Parikh P, Gruberg L, Bluestein D Patient-specific simulation of transcatheter aortic valve replacement : impact of deployment options on paravalvular leakage. Biomech Model Mechanobiol. 2019 Apr ;18(2):435-451.
43. Wang Q, Kodali S, Primiano C, Sun W. Simulations of transcatheter aortic valve implantation : implications for aortic root rupture. Biomech Model Mechanobiol. 2015 Jan ;14(1) :29-38.
44. De Jaegere P et al. Patient-specific computer modeling to predict aortic regurgitation after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2016 Mar 14;9(5):508-12.
45. Capelli C et al. Patient-specific simulations of transcatheter aortic valve stent implantation. Med Biol Eng Comput. 2012 Feb ;50(2) :183-92.

46. Bosmans B, Famaey N, Verhoelst E, Bosmans J, Vander Sloten J. A validated methodology for patient specific computational modeling of self-expandable transcatheter aortic valve implantation. J Biomech. 2016 Sep 6 ;49(13) :2824-2830.
47. Bianchi M, Marom G, Ghosh RP, Fernandez HA, Taylor JR Jr, Slepian MJ, Bluestein D Effect of balloon-expandable transcatheter aortic valve replacement positioning : a patient-specific numerical model. Artif Organs. 2016 Dec ;40(12) : E292-E304.
48. Bosi GM, Capelli C, Hong Cheang M, Delahunty N, Mullen M, Taylor AM, Schievano S. Population-specific material properties of the implantation site for transcatheter aortic valve replacement finite element simulations. J Biomech. 2018 Apr 11;71:236-244.
49. Dowling C, Firoozi S, Brecker SJ. First-in-Human Experience With Patient-Specific Computer Simulation of TAVR in Bicuspid Aortic Valve Morphology. JACC Cardiovasc Interv. 2020 Jan 27 ;13(2) :184-192.
50. Nappi F, Mazzocchi L, Spadaccio C, Attias D, Timofeva I, Macron L, Iervolino A, Morganti S, Auricchio F. CoreValve vs. Sapien 3 Transcatheter Aortic Valve Replacement: A Finite Element Analysis Study. Bioengineering (Basel). 2021 Apr 27 ;8(5) :52
51. Spadaccio C, Mazzocchi L, Timofeva I, Macron L, De Cecco CN, Morganti S, Auricchio F, Nappi F Bioengineering Case Study to Evaluate Complications of Adverse Anatomy of Aortic Root in Transcatheter Aortic Valve Replacement: Combining Biomechanical Modelling with CT imaging.Bioengineering (Basel). 2020 Oct 1 ;7(4):121.
52. Nappi F, Mazzocchi L, Timofeva I, Macron L, Morganti S, Avtaar Singh SS, Attias D, Congedo A, Auricchio F. A Finite Element Analysis Study from 3D CT to Predict Transcatheter Heart Valve Thrombosis. Diagnostics (Basel). 2020 Mar 26;10(4):183.
53. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Transcatheter implantation of a bovine valve in pulmonary position: a lamb study. Circulation. 2000 Aug 15;102(7):813-6.
54. Nappi F, Nenna A, Larobina D, Carotenuto AR, Jarraya M, Spadaccio C, Fraldi M, Chello M, Acar C, Carrel T. Simulating the ideal geometrical and biomechanical parameters ofthe pulmonary autograft to prevent failure in the Ross operation. Interact Cardiovasc Thorac Surg. 2018 Aug 1;27(2):269-276
55. Nappi F, Nenna A, Lemmo F, Chello M, Chachques JC, Acar C, Larobina D. Finite Element Analysis Investigate Pulmonary Autograft Root and Leaflet Stresses to Understand Late Durability of Ross Operation. Biomimetics (Basel). 2020 Aug 3;5(3):37.
56. Xuan Y, Krishnan K, Ye J, Dvir D, Guccione JM, Ge L, et al. Stent and leaflet stresses in a 26-mm first-generation balloon-expandable transcatheter aortic valve. J Thorac Cardiovasc Surg. 2017 May ;153(5) :1065-1073
57. Li K, Sun W. Simulated thin pericardial bioprosthetic valve leaflet deformation under static pressure-only loading conditions : implications for percutaneous valves. Ann Biomed Eng. 2010 ;38 :2690-701
58. Nappi F, Carotenuto AR, Cutolo A, et al. Compliance mismatch and compressive wall stresses drive anomalous remodelling of pulmonary trunks reinforced with Dacron grafts. J Mech Behav Biomed Mater. Oct 2016; 63:287-302.
59. Nappi F, Fraldi M, Spadaccio C, et al. Biomechanics drive histological wall remodeling of neoaortic root : A mathematical model to study the expression levels of ki 67, metalloprotease, and apoptosis transition. J Biomed Mater Res A. Nov 2016;104(11):2785-2793.
60. Wang Q, Sirois E, Sun W. Patient-specific modeling of biomechanical interaction in transcatheter aortic valve deployment. J Biomech. 2012 ;45 : 1965-71.
61. Nappi F, Attias D, Avtaar Singh SS et al. Finite element analysis applied to the transcatheter mitral valve therapy : Studying the present, imagining the future. J Thorac Cardiovasc Surg. 2019 Apr ;157(4) : e149-e151
62. Nappi F, Spadaccio C, Al-Attar N, Acar C. The Ross procedure at the crossroads: lessons from biology: is Dr Ross's dream concluded? Int J Cardiol. 2015 Jan 15 ;178 :37-9.
63. Nataf P, Guettier C, Bourbon A, Nappi F, Lima L, Dorent R, Pavie A, Gandjbakhch I. Influence of arterial allograft preparation techniques on chronic vascular rejection : a histological study. Transplant Proc. 1996 Oct;28(5):2890-2.

64. Nappi F, Carotenuto AR, Avtaar Singh SS, Mihos C, Fraldi M. Euler's Elastica-Based Biomechanics of the Papillary Muscle Approximation in Ischemic Mitral Valve Regurgitation : A Simple 2D Analytical Model. Materials (Basel). 2019 May 9 ;12(9) :1518
65. Rama A, Nappi F, Praschker BG, Gandjbakhch I. Papillary muscle approximation for ischemic mitral valve regurgitation. J Card Surg. 2008 Nov-Dec ;23(6) :733-5.
66. Spadaccio C, Nappi F, De Marco F et al. Implantation of a Poly-L-Lactide GCSF-Functionalized Scaffold in a Model of Chronic Myocardial Infarction. J Cardiovasc Transl Res . 2017 Feb;10(1):47-65
67. Spadaccio C, Nappi F, De Marco F, et al.. Preliminary In Vivo Evaluation of a Hybrid Armored Vascular Graft Combining Electrospinning and Additive Manufacturing Techniques Drug Target Insights. 2016 Feb 28;10(Suppl 1):1-7.
68. Nappi F, Carotenuto AR, Di Vito D, Spadaccio C, Acar C, Fraldi M. Stress-shielding, growth and remodeling of pulmonary artery reinforced with copolymer scaffold and transposed into aortic position. Biomech Model Mechanobiol. 2016 Oct;15(5):1141-57
69. Kunzelman KS, Cochran RP, Chuong C, Ring WS, Verrier ED, Eberhart RD. Finite element analysis of the mitral valve. Journal of Heart Valve Disease 1993; 2 :326–340.
70. Smuts AN, Blaine DC, Scheffer C, Weich H, Doubell AF, Dellimore KH. Application of finite element analysis to the design of tissue leaflets for a percutaneous aortic valve. J Mech Behav Biomed Mater. 2011 Jan;4(1):85-98.
71. Sun W, Li K, Sirois E. Simulated elliptical bioprosthetic valve deformation: implications for asymmetric transcatheter valve deployment. J Biomech. 2010 Dec 1;43(16):3085-90
72. Auricchio, F., Conti, M., Morganti, S., Reali, A. Simulation of transcatheter aortic valve implantation: a patient-specific finite element approach. Comput Methods Biomech Biomed Engin. 2014;17(12):1347-57.
73. Martin C, Sun W. Comparison of transcatheter aortic valve and surgical bioprosthetic valve durability: a fatigue simulation study. J Biomech. 2015 ;48: 3026-34
74. Formosa A, Santos DM, Marcuzzi D, Common AA, Prabhudesai V. Low Contrast Dose Catheter-Directed CT Angiography (CCTA). Cardiovasc Intervent Radiol. 2016 Apr;39(4):606-10
75. Raby J, Newton JD, Dawkins S, Lewis AJM. Cardiovascular magnetic resonance facilitates entirely contrast-free transcatheter aortic valve implantation: case report. Eur Heart J Case Rep. 2021 Sep 28;5(12): ytab378
76. Bittner DO, Arnold M, Klinghammer L, Schuhbaeck A, Hell MM, Muschiol G, Gauss S, Lell M, Uder M, Hoffmann U, Achenbach S, Marwan M. Contrast volume reduction using third generation dual source computed tomography for the evaluation of patients prior to transcatheter aortic valve implantation. Eur Radiol. 2016 Dec;26(12):4497-4504.
77. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 2006 Jul 1;31(3):1116-28.
78. Antiga L, Piccinelli M, Botti L, Ene Iordache B, Remuzzi A, Steinman DA. An image-based modeling framework for patient-specific computational hemodynamics. Med Biol Eng Comput. 2008 Nov ;46(11) :1097-112.
79. Piccinelli M, Veneziani A, Steinman DA, Remuzzi A, Antiga A framework for geometric analysis of vascular structures: application to cerebral aneurysms. L.IEEE Trans Med Imaging. 2009 Aug;28(8):1141-55
80. Marchandise E, Geuzaine C, Remacle JF Cardiovascular and lung mesh generation based on centerlines. Int J Numer Method Biomed Eng. 2013 Jun ;29(6) :665-82.
81. Dillard SI, Mousel JA, Shrestha L, Raghavan ML, Vigmostad SC From medical images to flow computations without user-generated meshes. Int J Numer Method Biomed Eng. 2014 Oct ;30(10) :1057-83.
82. Xiong FL, Goetz WA, Chong CK, Chua YL, Pfeifer S, Wintermantel E, Yeo JH Finite element investigation of stentless pericardial aortic valves: relevance of leaflet geometry. Ann Biomed Eng. 2010 May ;38(5):1908-18.

83. Stradins P, Lacis R, Ozolanta I, Purina B, Ose V, Feldmane L, Kasyanov V. Comparison of biomechanical and structural properties between human aortic and pulmonary valve. Eur J Cardiothorac Surg. 2004 Sep;26(3):634-9.
84. Gnyaneshwar R, Kumar RK, Balakrishnan KR. Dynamic analysis of the aortic valve using a finite element model. Ann Thorac Surg. 2002 Apr;73(4):1122-9.
85. Selvadurai, A.P.S. Deflections of a rubber membrane. J. Mech. Phys. Solids. 2006. 54 (6), 1093–1119.
86. Yeoh O.H. Some forms of the strain energy function for rubber. 1993. Rubber Chem. Technol.66,754–771
87. Auricchio, F. Ferrara A., Morganti S. Comparison and critical analysis of invariant-based models with respect to their ability in fitting human aortic valve data. 2012c. Ann. Solid Struct. Mech.4(1–2), 1–14.
88. Hanlon JG, Suggit RW, Love JW. Pre-use intraoperative testing of autologous tissue for valvular surgery: a proof-of-concept study. J Heart Valve Dis. 1999 Nov;8(6):614-23; discussion 623-4
89. Lee JM, Haberer SA, Boughner DR. The bovine pericardial xenograft: I. Effect of fixation in aldehydes without constraint on the tensile viscoelastic properties of bovine pericardium. J Biomed Mater Res. 1989 May;23(5):457-75.
90. Trowbridge, E.A, Black, M.M, Daniel, C.L. The mechanical response of glutaraldehyde fixed bovine pericardium to uniaxial load., 2011. J.Mater.Sci.20, 114–140
91. Willson AB, Rodés-Cabau J, Wood DA, Leipsic J, Cheung A, Toggweiler S, Binder RK, Freeman et al. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. J Am Coll Cardiol. 2012 Aug 14;60(7):581-6.
92. Möllmann H, Diemert P, Grube E, Baldus S, Kempfert J, Abizaid A. Symetis ACURATE TF™ aortic bioprosthesis. EuroIntervention. 2013 Sep 10;9 Suppl: S107-10
93. Meredith IT, Hood KL, Haratani N, Allocco DJ, Dawkins KD. Boston Scientific Lotus valve. EuroIntervention. 2012 Sep;8
94. Feldman TE, Reardon MJ, Rajagopal V, et al. Effect of Mechanically Expanded vs Self-Expanding Transcatheter Aortic Valve Replacement on Mortality and Major Adverse Clinical Events in High-Risk Patients Wit50,52h Aortic Stenosis: The REPRISE III Randomized Clinical Trial.JAMA. 2018 Jan 2;319(1):27-37
95. Wiggers, C.J. ,1952. Circulatory Dynamics: Physiological Studies. Grune & Stratton, New York, vol.4.
96. Delgado V, Ng AC, van de Veire NR, van der Kley F, Schuijf JD, Tops LF, et al. Transcatheter aortic valve implantation: role of multi-detector row computed tomography to evaluate prosthesis positioning and deployment in relation to valve function. Eur Heart J. 2010 May;31(9):1114-23.
97. Santos N, de Agustín JA, Almería C, Gonçalves A, Marcos-Alberca P, Fernández-Golfín C, at al. Prosthesis/annulus discongruence assessed by three-dimensional transoesophageal echocardiography: a predictor of significant paravalvular aortic regurgitation after transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging. 2012 Nov;13(11):931-7
98. Pontone G, Andreini D, Bartorelli AL, Bertella E, Cortinovis S, Mushtaq S, Annoni A, et al. Aortic annulus area assessment by multidetector computed tomography for predicting paravalvular regurgitation in patients undergoing balloon-expandable transcatheter aortic valve implantation: a comparison with transthoracic and transoesophageal echocardiography. Am Heart J. 2012 Oct;164(4):576-84
99. Katsanos S, Ewe SH, Debonnaire P, van der Kley F, de Weger A, Palmen M, Scholte AJ, et al. Multidetector row computed tomography parameters associated with paravalvular regurgitation after transcatheter aortic valve implantation. Am J Cardiol. 2013 Dec 1;112(11):1800-6.
100. Madukauwa-David ID, Midha PA, Sharma R, McLain K, Mitra R, Crawford K, Yoon SH, et al. Characterization of aortic root geometry in transcatheter aortic valve replacement patients. Catheter Cardiovasc Interv. 2019 Jan 1;93(1):134-140.
101. Feuchtner G, Plank F, Bartel T, Mueller S, Leipsic J, Schachner T, Müller L, et al. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. Ann Thorac Surg. 2013 Nov;96(5):1574-80.
102. Eker A, Sozzi FB, Civaia F, Bourlon F. Aortic annulus rupture during transcatheter aortic valve implantation: safe aortic root replacement. Eur J Cardiothorac Surg. 2012 May;41(5):1205.

103. Wang Q, Kodali S, Primiano C, Sun W. Simulations of transcatheter aortic valve implantation: implications for aortic root rupture. Biomech Model Mechanobiol. 2015 Jan;14(1):29
104. Auricchio, F., Conti, M., Morganti, S., Totaro, P., A computational tool to support pre-operative planning of stentless aortic valve implant. 2011. Med.Eng. Phys.33(10),1183–1192
105. Auricchio, F. Conti, M., Ferrara, A., Morganti, S., Reali, A., Patient-specific simulation of a stentless aortic valve implant: the impact of fibres on leaflet performance. 2012b Comput. Methods Biomech. Biomed. Eng., doi: http://dx.doi.org/ 10.1080/10255842.2012.681645
106. Morlacchi S, Colleoni SG, Cárdenes R, Chiastra C, Diez JL, Larrabide I, Migliavacca F. Patient-specific simulations of stenting procedures in coronary bifurcations: two clinical cases. Med Eng Phys. 2013 Sep;35(9):1272-81
107. Grover A, Gorman K, Dall TM, Jonas R, Lytle B, Shemin R, et al. Shortage of Cardiothoracic Surgeons Is Likely by 2020. Circulation. 2009 ;120(6) :488-94.
108. Kuhn TS. The Structure of Scientific Revolutions. The American Historical Review. 1963 ;68(3) :700-1.
109. Holmes DR, Jr., Firth BG, Wood DL. Paradigm shifts in cardiovascular medicine. Journal of the American College of Cardiology. 2004 ;43(4) :507-12.
110. Sacks CA, Jarcho JA, Curfman GD. Paradigm shifts in heart-failure therapy--a timeline. The New England journal of medicine. 2014 ;371(11) :989-91.
111. Kanwar A, Thaden JJ, Nkomo VT. Management of patients with aortic valve stenosis. Mayo Clin Proc 2018. 93:488–508.
112. Pilgrim T, Windecker S. Transcatheter aortic valve replacement: lessons gained from extreme-risk patients. J Am Coll Cardiol. 2015 Sep 22;66(12):1335-8
113. Bagur R, Rodés-Cabau J, Gurvitch R, Dumont É, Velianou JL, Manazzoni J, Toggweiler S, et al. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. JACC Cardiovasc Interv. 2012 May;5(5):540-551
114. Van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, Serruys PW et al. New conduction abnormalities after TAVI—frequency and causes. Nat Rev Cardiol Nat Rev Cardiol 2012 May 1;9(8):454-63.
115. Ribeiro HB et al. (2013) Coronary obstruction following transcatheter aortic valve implantation: a systematic review. JACC Cardiovasc Interv 6:452–461. 10.1016/j.jcin.2012.11.014 [PubMed: 23602458]
116. Scotten LN, Siegel R (2014) Thrombogenic potential of transcatheter aortic valve implantation with trivial paravalvular leakage. Ann Transl Med 2:43 10.3978/jissn.2305-5839.2014.05.04 [PubMed: 25333018]
117. Maisano F, Taramasso M, Nietlispach F (2015) Prognostic influence of paravalvular leak following TAVI: is aortic regurgitation an active incremental risk factor or just a mere indicator? Eur Heart J 36:413–415. 10.1093/eurheartj/ehu410 [PubMed: 25336227]
118. Gilbert ON et al. (2018) Comparison of paravalvular aortic leak characteristics in the Medtronic CoreValve versus Edwards Sapien Valve: Paravalvular aortic leak characteristics. Catheter Cardiovasc Interv. 10.1002/ccd.27643
119. Still S, Szerlip M, Mack M (2018) TAVR Vs. SAVR in intermediate-risk patients: what influences our choice of therapy. Curr Cardiol Rep 20:82 10.1007/s11886-018-1026-3 [PubMed: 30094642]
120. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ (2015) Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. JACC Cardiovasc Imag 8:340–360. 10.1016/j.jcmg.2015.01.008
121. Hatoum H, Yousefi A, Lilly S, Maureira P, Crestanello J, Dasi LP (2018) An in-vitro evaluation of turbulence after transcatheter aortic valve implantation. J Thorac Cardiovasc Surg 1:1 10.1016/j.jtcvs.2018.05.042
122. Abdelghani M, Soliman OII, Schultz C, Vahanian A, Serruys PW (2016) Adjudicating paravalvular leaks of transcatheter aortic valves: a critical appraisal. Eur Heart J 37:2627–2644. 10.1093/eurheartj/ehw115 [PubMed: 27075871]

123. Eggebrecht H, Doss M, Schmermund A, Nowak B, Krissel J, Voigtländer T (2012) Interventional options for severe aortic regurgitation after transcatheter aortic valve implantation: balloons, snares, valve-in-valve. Clin Res Cardiol 101:503–507. 10.1007/s00392-012-0434-4 [PubMed: 22476821]
124. Dvir D et al. (2012) Multicenter evaluation of Edwards SAPIEN positioning during transcatheter aortic valve implantation with correlates for device movement during final deployment. JACC Cardiovasc Interv 5:563–570. 10.1016/j.jcin.2012.03.005 [PubMed: 22625196]
125. Nombela-Franco L et al. (2012) Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. JACC Cardiovasc Interv 5:499–512. 10.1016/j.jcin.2012.02.010 [PubMed: 22625188]
126. Takagi K et al. (2011) Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. Catheter Cardiovasc Interve 78:432–443. 10.1002/ccd.23003
127. McGee OM, Gunning PS, McNamara A, McNamara LM (2018) The impact of implantation depth of the Lotus™ valve on mechanical stress in close proximity to the bundle of His. Biomech Model Mechanobiol 1:1 10.1007/s10237-018-1069-9
128. Sturla F et al. (2016) Impact of different aortic valve calcification patterns on the outcome of Transcatheter Aortic Valve Implantation: a finite element study. Journal of biomechanics 1:1 10.1016/j.jbiomech.2016.03.036
129. Schultz C et al. (2016) Patient-specific image-based computer simulation for the prediction of valve morphology and calcium displacement after TAVI with the Medtronic CoreValve and the Edwards SAPIEN valve. EuroIntervention 11:1044–1052. 10.4244/eijv11i9a212 [PubMed: 26788707]
130. Chang J, Rong-Hui L, Sheng-Ping Z, Li-Zhen W, Yu-Bo F (2018) Effect of stent designs on the paravalvular regurgitation of transcatheter aortic valve implantation. Int J Comput Methods. 10.1142/s0219876218420070
131. Mao W, Wang Q, Kodali S, Sun W (2018) Numerical parametric study of paravalvular leak following a transcatheter aortic valve deployment into a patient-specific aortic root. J Biomech Eng 140:101007 10.1115/1.4040457
132. Vahidkhah K, Azadani AN (2017) Supra-annular Valve-in-Valve implantation reduces blood stasis on the transcatheter aortic valve leaflets. J Biomech 58:114–122. 10.1016/j.jbiomech.2017.04.020 [PubMed: 28511838
133. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv 2015 ;8 : e001779.
134. Stortecky S, Windecker S. Stroke: an infrequent but devastating complication in cardiovascular interventions. Circulation 2012 ;126 :2921–4.
135. Leetmaa T, Hansson NC, Leipsic J, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. Circ Cardiovasc Interv 2015 ;8: e001596.
136. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic heart valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol 2016 ;68 :2059–69.
137. Wolberg AS, Aleman MM, Leiderman K, et al. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg 2012 ;114 :275–85.
138. Turbill P, Beugeling T, Poot AA. Proteins involved in the Vroman effect during exposure of human blood plasma to glass and polyethylene. Biomaterials 1996 ;17 :1279–87.
139. Noble S, Asgar A, Cartier R, et al. Anatomopathological analysis after CoreValve Revalving system implantation. EuroIntervention 2009 ;5: 78–85.
140. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015 ;373: 2015–24.
141. Chakravarty T, Søndergaard L, Friedman J, et al; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017 Jun 17 ;389(10087) :2383-2392.

142. Pache G, Schoechlin S, Blanke P, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J 2016 ;37 :2263–71.
143. Vollema EM, Kong WKF, Katsanos S, et al. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. Eur Heart J. 2017 Apr 21 ;38(16):1207-1217.
144. . Nührenberg TG, Hromek J, Kille A, et al. Impact of On-Clopidogrel Platelet Reactivity on Incidence of Hypoattenuated Leaflet Thickening After Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2019 Jan 14 ;12(1) :12-18.
145. De Backer O, Dangas GD, Jilaihawi H, et al. GALILEO-4D Investigators. Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement. N Engl J Med. 2020 Jan 9 ;382(2) :130-13
146. Khalique OK, Hahn RT, Gada H, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2014 Aug;7(8):885-94.
147. Couture EL, Lepage S, Masson J-B, Daneault B (2017) Very late transcatheter heart valve thrombosis. World J Cardiol 9:196–199. 10.4330/wjc. v9.i2.196 [PubMed: 28289535]
148. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016 ;17 :589–590.
149. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2017 ;52 :408–417.
150. Zilberszac R, Gabriel H, Schemper M, et al. Outcome of combined stenotic and regurgitant aortic valve disease. J Am Coll Cardiol. 2013 ;61 :1489–1495.
151. Masters RG, Walley VM, Pipe AL, et al. Long-term experience with the Ionescu-Shiley pericardial valve. Ann Thorac Surg. 1995 ;60(2 Suppl): S288–S291
152. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. Circulation. 2001 ;103 :1535–1541.
153. Wang M, Furnary AP, Li HF, et al. Bioprosthetic aortic valve durability: a meta-regression of published studies. Ann Thorac Surg. 2017 ;104 :1080–1087.
154. Foroutan F, Guyatt GH, O'Brien K, et al. Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. BMJ. 2016 ;354: i5065.
155. Nappi F, Nenna A, Petitti T, Spadaccio C, Gambardella I, Lusini M, Chello M, Acar C. Long-term outcome of cryopreserved allograft for aortic valve replacement. J Thorac Cardiovasc Surg 2018 ;156 :1357-1365.e1356.
156. Fukushima S, Tesar PJ, Pearse B, et al. Long-term clinical outcomes after aortic valve replacement using cryopreserved aortic allograft. J Thorac Cardiovasc Surg 2014 ;148 :65-72. e62.
157. Arabkhani B, Bekkers JA, Andrinopoulou ER, et al. Allografts in aortic position: Insights from a 27-year, single-center prospective study. J Thorac Cardiovasc Surg 2016 ;152 :1572-1579.e1573.
158. David TE, Feindel CM, Bos J, et al. Aortic valve replacement with Toronto SPV bioprosthesis: optimal patient survival but suboptimal valve durability. J Thorac Cardiovasc Surg. 2008 ;135 :19–24.
159. Schaefer A, Dickow J, Schoen G, et al. Stentless vs stented bioprosthesis for aortic valve replacement: A case matched comparison of long-term follow-up and subgroup analysis of patients with native valve endocarditis. PLoS One. 2018 Jan 16 ;13(1) : e0191171
160. Nishida T, Tominaga R. A look at recent improvements in the durability of tissue valves. Gen Thorac Cardiovasc Surg. 2013 ;61 :182–190.

161. Garrido-Olivares L, Maganti M, Armstrong S, David T. Aortic valve replacement with Hancock II bioprosthesis with and without replacement of the ascending aorta. Ann Thorac Surg 2011 ;92 :541-547.
162. David TE, Armstrong S, Maganti M. Hancock II bioprosthesis for aortic valve replacement: the gold standard of bioprosthetic valves durability? Ann Thorac Surg. 2010 ;90 :775–781.
163. Glaser N, Franco-Cereceda A, Sartipy U Late survival after aortic valve replacement with the perimount versus the mosaic bioprosthesis. Ann Thorac Surg. 2014 Apr ;97(4) :1314-20
164. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, et al. Very long-term outcomes of the Carpentier-Edwards Perimount valve in aortic position. Ann Thorac Surg 2015 ;99 :831-837.
165. Johnston DR, Soltesz EG, Vakil N, et al. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. Ann Thorac Surg 2015 ;99 :1239-1247.
166. Senage T, Le Tourneau T, Foucher Y, et al. Early structural valve deterioration of Mitroflow aortic bioprosthesis: mode, incidence, and impact on outcome in a large cohort of patients. Circulation 2014 ;130 :2012-2020.
167. Goldman S, Cheung A, Bavaria JE, et al. Midterm, multicenter clinical and hemodynamic results for the Trifecta aortic pericardial valve. J Thorac Cardiovasc Surg 2017 ;153 :561-569.e562.
168. Kalra A, Rehman H, Ramchandani M, et al Early Trifecta valve failure: Report of a cluster of cases from a tertiary care referral center. J Thorac Cardiovasc Surg 2017 ;154 :1235-1240
169. Fischlein T, Meuris B, Hakim-Meibodi K, et al. The sutureless aortic valve at 1 year: A large multicenter cohort study. J Thorac Cardiovasc Surg 2016 ;151 :1617-1626.e1614.
170. Kocher AA, Laufer G, Haverich A, et al. One-year outcomes of the Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial: a prospective multicenter study of rapid-deployment aortic valve replacement with the EDWARDS INTUITY Valve System. J Thorac Cardiovasc Surg 2013 ;145 :110-115; discussion 115-116.
171. Durand E, Tron C, Eltchaninoff H. Emergency Transcatheter Aortic Valve Implantation for Acute and Early Failure of Sutureless Perceval Aortic Valve. Can J Cardiol 2015 ;31: 1204.e1213-1205.
172. Tseng E, Wisneski A, Azadani A, Ge L. Engineering perspective on transcatheter aortic valve implantation. Interv Cardiol. 2013 ;5 :53-70.
173. Sun W, Abad A, Sacks MS. Simulated bioprosthetic heart valve deformation under quasi-static loading. J Biomech Eng. 2005; 127:905-14.
174. Alavi SH, Groves EM, Kheradvar A. The effects of transcatheter valve crimping on pericardial leaflets. Ann Thorac Surg. 2014 ;97 :1260-6.

 doi:10.20944/preprints202204.0304.v1