

**First-in-human experience with patient-specific computer simulation of transcatheter aortic valve replacement in bicuspid aortic valve morphology**

**Brief Title:** Dowling et al. Computer simulation of TAVR in BAV.

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## Structured Abstract

**Objectives:** To prospectively evaluate the clinical utility of patient-specific computer simulation of transcatheter aortic valve replacement (TAVR) in bicuspid aortic valve (BAV) morphology.

**Background:** Patient-specific computer simulation of TAVR in BAV may predict important clinical outcomes, such as paravalvular regurgitation and conduction disturbance.

**Methods:** Between May 2018 and April 2019, all patients who were referred for TAVR who had BAV identified on workup computed tomography imaging, prospectively underwent patient-specific computer simulation with a self-expanding transcatheter heart valve (THV) using TAVIguide technology (FEops, Ghent, Belgium).

**Results:** Nine patients were included in the study. Sievers Classification was Type 0 (n=2) and Type 1 (n=7). The simulations altered the treatment strategy in eight patients (89%). The simulations suggested moderate-to-severe paravalvular regurgitation in three patients and they were referred for consideration of surgery. The remaining six patients underwent TAVR with a self-expanding THV. Five of these patients (83%) had their THV size and/or implant depth altered to minimise paravalvular regurgitation and/or conduction disturbance. In one patient, simulations suggested significant conduction disturbance after TAVR and a permanent pacemaker (PPM) was implanted prior to the procedure. Following treatment, all nine patients had none-to-mild paravalvular regurgitation. The patient in whom a pre-procedure PPM had been implanted became pacing dependent with underlying third-degree atrioventricular block.

Conclusions: Patient-specific computer simulation of TAVR in BAV can be used to identify patients in whom TAVR may be associated with an unfavourable clinical outcome. Patient-specific computer simulation may be useful to guide THV sizing and positioning for potential favourable clinical outcomes.

### **Keywords**

Aortic Valve Stenosis

Bicuspid Aortic Valve

Computer Simulation

Finite Element Analysis

Heart Valve Prosthesis Implantation

Transcatheter Aortic Valve Replacement

### **Condensed Abstract**

Between May 2018 and April 2019, nine patients prospectively underwent patient-specific computer simulation of transcatheter aortic valve replacement (TAVR) in bicuspid aortic valve using TAVIguide technology (FEops, Ghent, Belgium). The computer simulations altered the treatment strategy in eight patients (89%). The computer simulations suggested moderate-to-severe paravalvular regurgitation in three patients and they were referred for consideration of surgery. The remaining six patients underwent TAVR with a self-expanding THV. Five of these patients (83%) had their THV size and/or implant depth altered to minimise paravalvular regurgitation and/or conduction disturbance. Following treatment, all nine patients had none-to-mild paravalvular regurgitation.

### **Short Summarising Tweet**

See how computer simulation may be used to risk-stratify and optimize procedural outcomes for TAVR in bicuspid patients. Learn more in the latest issue of #JACCINT. [fal.cn/XXXX](http://fal.cn/XXXX)

## **Abbreviations List**

3D 3-Dimensional

BAV Bicuspid Aortic Valve

CPMax Maximum Contact Pressure

CPI Contact Pressure Index

MDCT Multidetector Computed Tomography

PPM Permanent Pacemaker

TAVR Transcatheter Aortic Valve Replacement

THV Transcatheter Heart Valve

## **Introduction**

Transcatheter aortic valve replacement (TAVR) has been demonstrated in a number of clinical trials to be a viable treatment option for patients with symptomatic severe aortic stenosis who are at low risk for surgery (1-4). However, the majority of younger low-risk patients will have congenitally bicuspid valves (5), and this patient subgroup has been excluded from all trials comparing TAVR and surgery.

While outcomes of TAVR in bicuspid aortic valve (BAV) have improved with increased operator experience and newer-generation devices (6), we are still some way off the very high standards set by surgical aortic valve replacement, when it comes to important clinical end points such as permanent pacemaker and paravalvular regurgitation.

As TAVR begins to move into a younger, lower-risk patient cohort, it is important that clinicians acknowledge the inherent limitations of the technology and identify patients who, on an anatomical basis, may not be suitable for TAVR. Furthermore, for patients who are undergoing TAVR, efforts should be made to optimise transcatheter heart valve (THV) sizing and positioning, in order to minimise paravalvular regurgitation and conduction disturbance. Patient-specific computer simulation is an attractive solution to both of these challenges faced by TAVR in BAV.

In this study we wish to describe our early experience with patient-specific computer simulation of TAVR in BAV, in order to evaluate its clinical utility in BAV patients who are being considered for TAVR.

## **Methods**

A prospective, single-centre study was performed on all patients who were referred for TAVR and had BAV identified on cardiac multidetector computed tomography (MDCT) imaging. The study protocol was approved by a local research ethics committee and confidentiality advisory group.

### BAV Classification

Multiphase electrocardiographic-gated cardiac MDCT imaging was used to create aortic valve perpendicular plane and three-dimensional (3D) reconstructions using 3Mensio Structural Heart version 9.1 (Pie Medical Imaging, Maastricht, Netherlands). BAV was classified by the TAVR operators using both the Sievers system (7) and the TAVR-directed BAV imaging morphological classification (8). The aortic annulus dimensions were then recorded.

### Computer Simulation

Patient-specific computer simulation was performed using TAVIguide technology (FEops NV, Belgium Ghent) (Central Illustration). The methods have been described previously (9-11). In brief, patient-specific finite element models of the aortic root were constructed from pre-procedural MDCT imaging. The aortic wall, leaflets and calcium were modelled with differing mechanical properties.

An appropriately sized THV was selected from the self-expanding Evolut R and Evolut PRO family of self-expanding THVs, based on the perimeter-derived aortic annular assessment. Finite element models of the THV were positioned within the aortic root model and finite element analysis performed, targeting a 0 mm (annular), 4 mm (standard) and in select cases an 8 mm (deep) implant depth. Further simulations were then performed with an “undersized” THV. This process was guided by the TAVR operators in order to answer their

clinical queries regarding predicted paravalvular regurgitation and conduction disturbance with differing THV sizes and positions.

The blood domain was extracted from the finite element analysis output and computational fluid dynamics performed. Predicted paravalvular regurgitation was then recorded in the left ventricular outflow tract.

In patients whose MDCT scan had adequate right-sided contrast enhancement, the membranous septum was then located and an area immediately inferior to this anatomical structure was identified. The predicted maximum pressure exerted by the THV on the region of interest (maximum contact pressure [CPMax]) and the predicted percentage of this area subject to pressure by the THV (contact pressure index [CPI]) were then recorded.

#### Paravalvular regurgitation assessment

Peri-procedural cineangiography, transoesophageal and transthoracic echocardiography were reviewed and paravalvular regurgitation graded using a 5-class grading system (12). Peri-procedural electrocardiograms were reviewed, and major conduction abnormalities defined as the development of either new left bundle branch block, Mobitz Type II second-degree atrioventricular block or third-degree atrioventricular block.

#### Statistical Analysis

Continuous variables were summarised as mean  $\pm$  SD and categorical variables as counts and percentages. Continuous variables were compared using a paired Student's t-test, with a two-sided p value  $<0.05$  considered statistically significant.

#### **Results**



Between May 2018 and April 2019, a total of nine patients who were referred for TAVR had BAV identified on workup MDCT imaging. Patients were elderly (mean age  $79.1 \pm 6.9$  years) and at increased risk for surgery (Society of Thoracic Surgeons Predicted Risk of Mortality  $4.7 \pm 3.2\%$ ). Furthermore, the majority (67%) of patients required urgent inpatient treatment for their aortic valve disease, including two patients who had required an emergency balloon aortic valvuloplasty to be performed prior to their MDCT scans. A significant minority (33%) of patients had a left ventricular ejection fraction  $<20\%$ .

#### MDCT analysis

Aortic valve perpendicular plane and 3D reconstructions are presented in Figure 1. The majority of patients (78%) had Sievers Type 1 morphology and the remaining patients had Sievers Type 0 morphology. Using the TAVR-directed BAV imaging morphological classification, the most common leaflet morphology was tricommissural (44%), followed by bicommissural raphe-type (33%) and then bicommissural non raphe-type (22%). The average aortic annulus perimeter-derived diameter was  $26.8 \pm 2.7$  mm.

#### Computer Simulation

Patient-specific computer simulation of the manufacturer-recommended THV size, implanted at a standard implant depth are presented in Figure 2. Based on a previously defined cut-off of  $16.25$  mL/sec (10), the computer simulations suggested that three patients would develop moderate-to-severe paravalvular regurgitation after TAVR. Conduction disturbance modelling was feasible in five patients. Based on previously defined cut-offs of a  $CP_{Max} >0.39$  MPa and a  $CPI >0.14$  (11), the computer simulations suggested that four patients would develop significant conduction disturbance after TAVR.

A further 43 additional simulations were then performed (an average of 4.8 additional simulations per patient) in order to identify an optimal THV size and implant depth for each patient's specific anatomical characteristics, with the aim of minimising predicted paravalvular regurgitation and/or conduction disturbance. The TAVR operators were particularly interested in the computer simulation output of a "downsized" THV implanted at an annular implant depth, in order to assess the possibility of supra-annular sealing with the THV.

Predicted paravalvular regurgitation was similar between a standard and annular implant depth ( $20.0 \pm 24.4$  versus  $15.1 \pm 14.7$  mL/sec,  $P=0.15$ ) but was higher when comparing a manufacturer-recommended and "downsized" THV size ( $16.4 \pm 18.3$  versus  $24.5 \pm 32.0$  mL/sec). CPMax was similar between both a standard and an annular implant depth ( $0.62 \pm 0.39$  versus  $0.63 \pm 0.66$  MPa,  $P=0.96$ ) and between a manufacturer-recommended and "downsized" THV size ( $0.70 \pm 0.52$  versus  $0.87 \pm 1.06$  MPa,  $P=0.18$ ). CPI was lower with an annular implant depth when compared with a standard implant depth ( $0.10 \pm 0.08$  versus  $0.19 \pm 0.12$ ,  $P=0.01$ ) but was similar when comparing a manufacturer-recommended and a "downsized" THV size ( $0.22 \pm 0.14$  versus  $0.18 \pm 0.15$ ,  $P=0.08$ ).

### Heart Team Discussions

Following discussion in the Heart Team meeting, the six patients in whom the computer simulations predicted none-to-mild paravalvular regurgitation with a self-expanding THV were recommended TAVR with a self-expanding THV. The Heart team recommended consideration for surgical aortic valve replacement for the three patients in whom the computer simulations predicted moderate-to-severe paravalvular regurgitation with a self-expanding prosthesis.

### Procedural Optimisation

For each of the six patients undergoing TAVR with a self-expanding prosthesis, operators reviewed multiple computer simulations of differing THV prosthesis sizes and implant depths, in order to identify an optimal THV prosthesis size and implant depth to minimise paravalvular regurgitation and/or conduction disturbance. After reviewing these simulations, the planned THV size and/or implant depth was altered in five of these patients (83%) (Figure 3). Specifically, the THV size was downsized in three patients, positioned at an annular implant depth in three patients and positioned at a deep implant depth in one patient.

For the patient in whom a deep implant was required to minimise paravalvular regurgitation, a permanent pacemaker (PPM) was implanted prior to the TAVR procedure, as the patient also had pre-existing first-degree heart block and left bundle branch block.

#### Patient Outcomes

All patients in whom TAVR with a self-expanding prosthesis had been recommended by the Heart Team underwent successful implantation with an Evolut R or Evolut PRO THV. The three patients in whom computer simulation suggested moderate-to-severe paravalvular regurgitation with a self-expanding THV underwent formal surgical and intensive care physician reviews. Following these reviews, two of these patients were felt to be suitable for surgery and underwent successful operations with Carpentier-Edwards PERIMOUNT Magna Ease aortic valve bioprostheses (Edwards Lifesciences, Irvine, CA). The third patient was deemed to be too high risk for surgery and was successfully treated with a SAPIEN 3 THV (Edwards Lifesciences).

All nine patients had device success and early safety, as defined by the Valve Academic Research Consortium-2 criteria (13). Post-procedural transthoracic echocardiography demonstrated no paravalvular regurgitation in three patients (33%), trace paravalvular

regurgitation in two patients (22%) and mild paravalvular regurgitation in 4 patients (44%). The mean aortic valve gradient was  $9.4 \pm 2.2$  mm Hg.

The patient in whom a PPM had been implanted prior to TAVR became long-term pacing dependent with underlying third-degree atrioventricular block. No other patient required post-procedural insertion of a PPM. The patient in whom conduction disturbance modelling predicted a favourable clinical outcome did not develop any major conduction disturbance.

#### Post-Procedural MDCT Imaging

Post-procedural MDCT imaging was performed in one patient. This demonstrated strong visual agreement between the finite element analysis simulation and post-procedural imaging (Figure 4).

### **Discussion**

TAVR is increasingly being used to treat younger, lower-risk patient cohorts, with encouraging outcomes in a number of clinical trials (1-4). Nonetheless, TAVR has been associated with a higher incidence of paravalvular regurgitation, new left bundle branch block and new PPM requirement, when compared with surgery (1-3), and these three patient subgroups all have poorer long-term prognosis after TAVR (14-18).

Furthermore, all randomised trials to date have excluded patients with BAV and therefore in the absence of any definitive evidence directly comparing TAVR and surgery, careful patient-selection by the Heart Team based on clinical and anatomical factors must remain paramount. One potential solution for identifying patients whose anatomy may not be suitable for TAVR, is patient-specific computer simulation. This technology has been well-

validated in the trileaflet cohort (9-11) with encouraging early validation in BAV patients (19-21).

With this as a background, we have described here our early experience with the usage of patient-specific computer simulation to guide treatment decisions on a small cohort of BAV patients being considered for TAVR. The patients studied represent an unselected patient cohort and many patients had high-risk clinical and anatomical features for both percutaneous and surgical aortic valve intervention. Indeed, the majority of patients required urgent inpatient treatment, demonstrating the feasibility of this technology within the workflows of a busy clinical unit.

On the basis of computer simulation, we were able to identify three patients in whom TAVR with a self-expanding prosthesis would be predicted to result in moderate-to-severe paravalvular regurgitation. After discussion in our Heart Team meeting, and following formal surgical and intensive care physician reviews, two of these patients underwent surgical treatment and the third patient underwent TAVR with a balloon-expandable THV. In the remaining six patients, computer simulations suggested only none-to-mild paravalvular regurgitation with a self-expanding THV and in these patients, additional computer simulations were used to identify an optimal THV size and implant depth for each patient's specific anatomical characteristics, in order to minimise predicted paravalvular regurgitation and/or conduction disturbance. Interestingly, we found that the optimal THV size and position differed from the manufacturer recommendations in the majority (83%) of patients.

Through this process of careful patient selection and procedural optimisation, we demonstrated favourable clinical outcomes in all nine patients. In particular, no patient developed moderate-to-severe paravalvular regurgitation.

Overall, the computer simulations altered either the treatment modality or procedural aspects in 89% of patients. These observations illustrate that computer simulation might have

a role in altering the treatment approach in the majority of patients. It is plausible, therefore, that the usage of computer simulation might be associated with improved clinical outcomes, when compared with the current standard of care. However, these observations should be considered hypothesis generating and do not prove that patient-specific computer simulation improves clinical outcomes. A randomised trial will be required to definitively address this question.

Optimal THV sizing and positioning in BAV is an area of intense interest amongst TAVR operators. Strategies include annular, supra-annular and balloon-sizing methods (22-24). Recently, insights from post-procedural CT scans, obtained through the BAVARD registry, have suggested that the majority (66.3%) of BAV patients have discordance between the annular and supra-annular structures (25). Interestingly, we found that in 50% of patients, computer simulations suggested an optimal THV that was smaller in size than a THV based purely on aortic annular dimensions.

In this study, we used patient-specific computer simulation in all patients with BAV. However, due to time and financial constraints, the usage of this technology may not be feasible in all patients and in such cases its usage could potentially be limited to patients with high-risk features for paravalvular regurgitation such as aortopathy, heavy calcification, Sievers Type 1 BAV with a calcified raphe, and large aortic annular dimensions. Its usage could also be considered for patients with impaired left ventricular systolic function who may not tolerate paravalvular regurgitation, and for patients with pre-existing conduction disturbance. The attractiveness of patient-specific computer simulation for mainstream clinical usage could be increased through limiting the number of simulations performed in each patient, thus reducing overall computer processing time. Finally, usage of this technology may be of particular assistance to low-volume TAVR in BAV operators.

Moving forward, patient-specific computer simulation may have a role in a number of other challenging TAVR scenarios. Such clinical situations may include patients with heavily calcified trileaflet aortic valve disease, left ventricular outflow tract calcium spurs, aortic annulus dimensions on the borderline of THV sizing algorithms and anatomical characteristics which place the patient at risk for coronary obstruction.

## Limitations

This was a small study and further prospective evaluation will be required to further define the role of this technology amongst the bicuspid cohort.

The favourable clinical outcomes reported in this study could potentially be attributed to improvements in THV technology and increased operator experience treating BAV.

The Lotus THV (Boston Scientific Corporation, Marlborough, MA) has been recently demonstrated to have favourable clinical outcomes in bicuspid anatomy (26). While the computer simulations can model this THV, we did not perform simulations with this THV as it was not commercially available during the time frame of this study.

The SAPIEN 3 THV has recently been reported to be associated with favourable clinical outcomes in bicuspid anatomy (27). The computer simulations cannot currently simulate the SAPIEN 3 THV and would be improved by the addition of this prosthesis. Furthermore, it is possible that the patients treated with surgery in this study may have had favourable clinical outcomes with the SAPIEN 3 THV.

## Conclusions

Patient-specific computer simulation of TAVR in BAV can be used to identify patients in whom TAVR may be associated with an unfavourable clinical outcome. Patient-specific computer simulation may be useful to guide THV sizing and positioning for potential favourable clinical outcomes.



## **Clinical Perspectives**

**What's known?** Patient-specific computer simulation has been demonstrated in retrospective studies to be predictive for the development of paravalvular regurgitation and conduction disturbance after TAVR.

**What's new?** Patient-specific computer simulation was used in a prospective cohort of bicuspid patients to guide treatment decisions and to optimize transcatheter heart valve sizing and positioning.

**What's next?** Randomized trials evaluating patient-specific computer simulation of TAVR in bicuspid aortic valve could be considered.

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## Figure Titles and Legends

Central Illustration. Patient-specific computer simulation. Cardiac MDCT imaging is used to create a finite element model of the aortic root. A finite element model of the THV is positioned within the aortic root model and finite element analysis then performed in order to simulate the interaction between the THV and the native anatomy. The blood domain is extracted from the finite element analysis output and computational fluid dynamics performed in order to simulate paravalvular regurgitation. The pressure exerted by the THV on the native anatomy is recorded in order to simulate conduction disturbance.

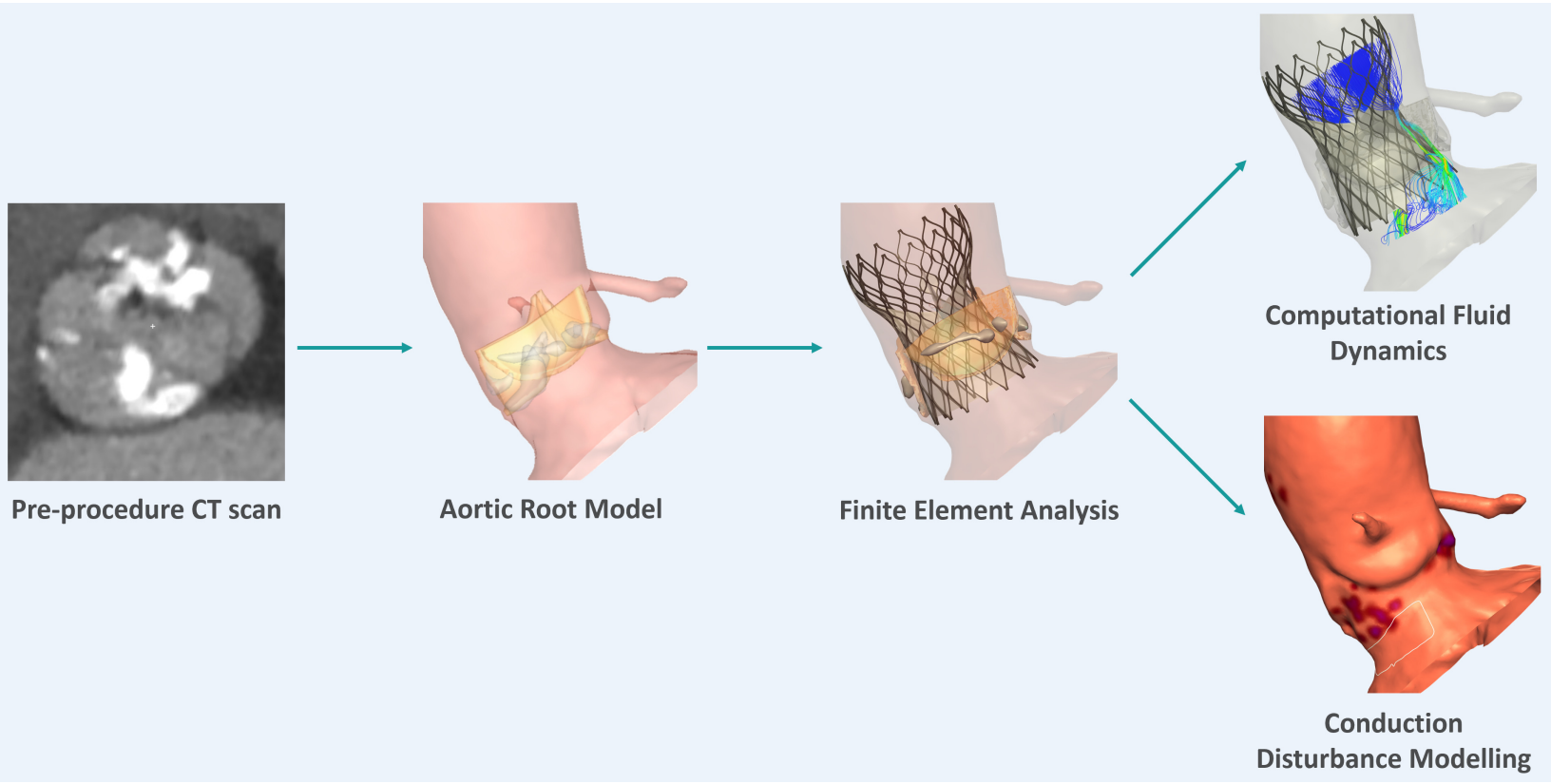
Figure 1. Aortic valve perpendicular plane and 3D reconstructions. Patients 1 and 8 have Sievers Type 0 morphology and the remaining patients have Sievers Type 1 morphology. Patients 4-7 have tricommissural morphology, patients 2, 3 and 9 have bicommissural raphe-type morphology and the remaining patients have bicommissural non-raphe type morphology.

Figure 2. Patient-specific computer simulation of the manufacturer-recommended THV positioned at a standard implant depth. (A) Paravalvular regurgitation simulation. (B) Conduction disturbance modelling. Values highlighted in green indicate a favourable predicted clinical outcome and values highlighted in red indicate an unfavourable predicted clinical outcome.

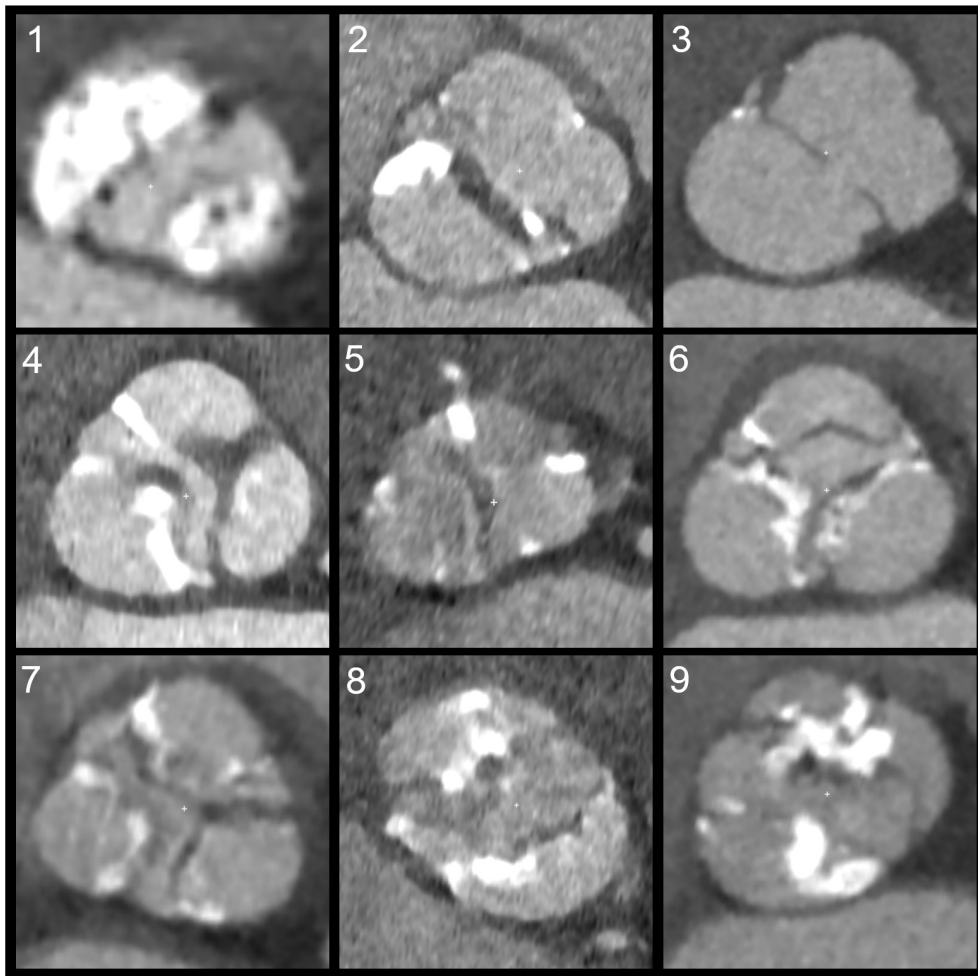
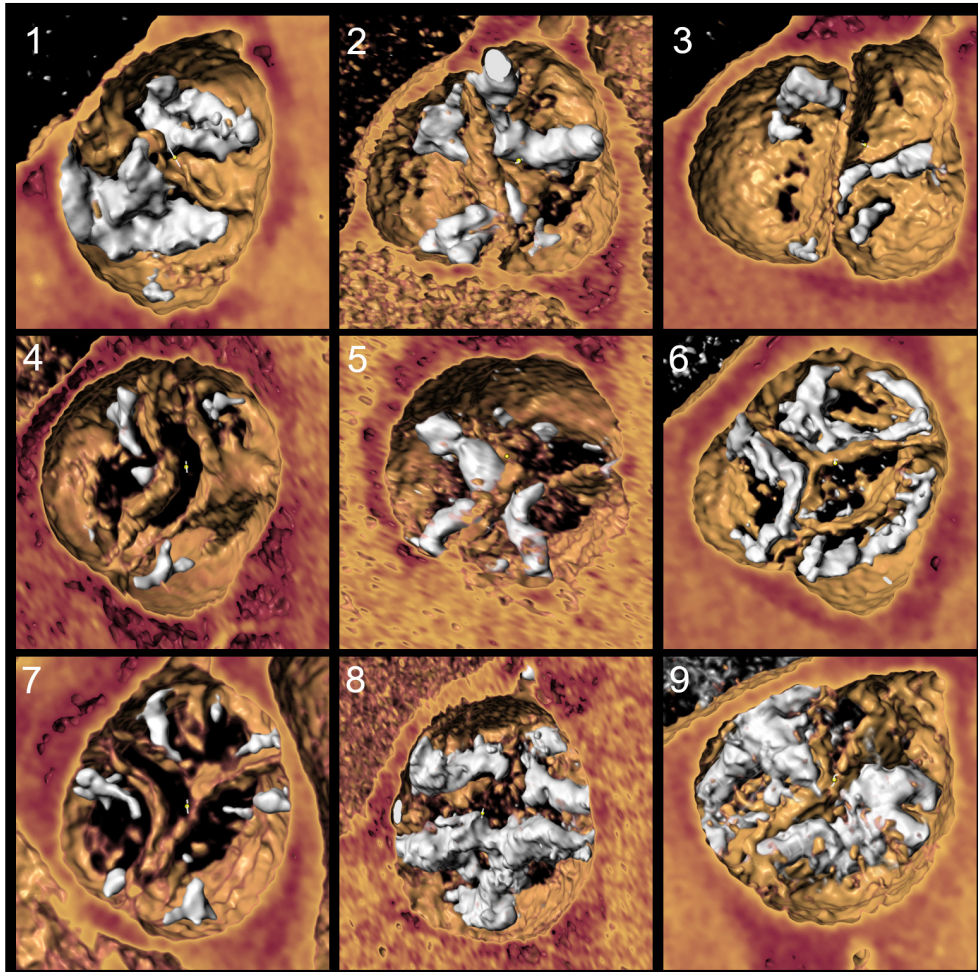
Figure 3. TAVR patients in whom the size and/or position of their THV was altered based on the computer simulation output. Simulations predicted that Patient 1 would have a favourable outcome with a “downsized” 26 mm Evolut PRO THV implanted at an annular implant depth. Patient 2 was predicted to have less paravalvular regurgitation with a “downsized” 29 mm

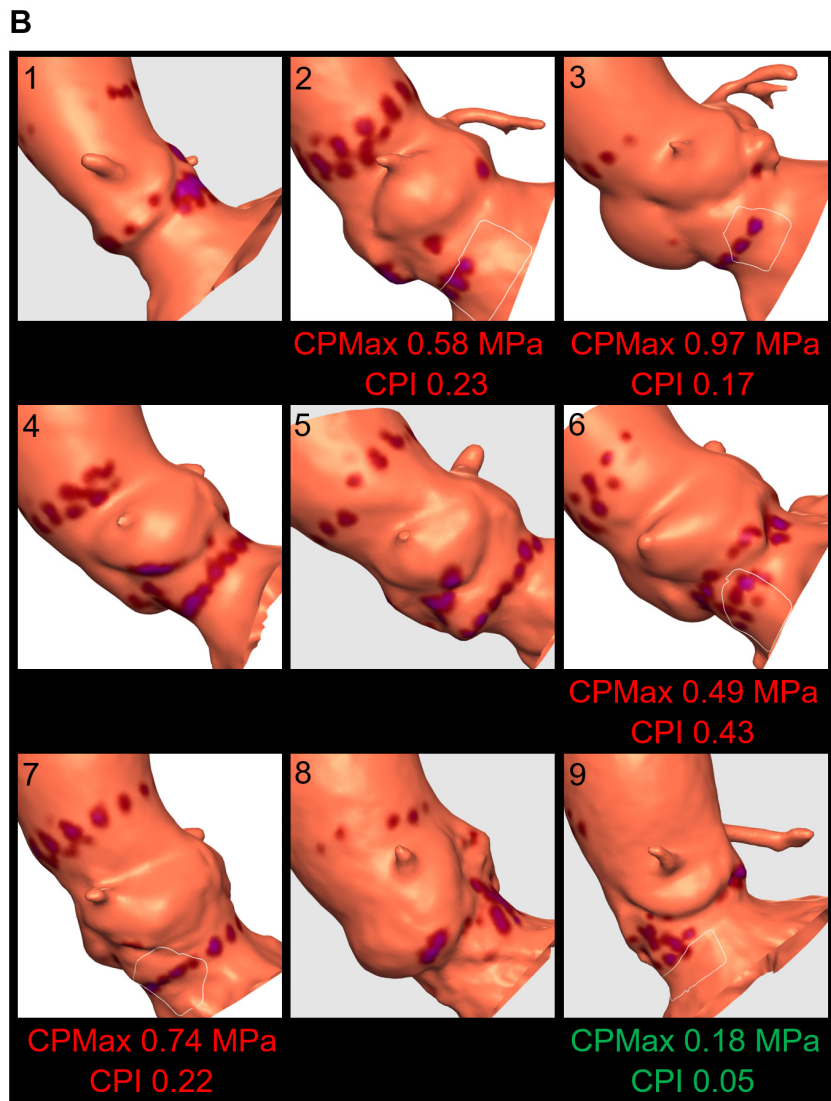
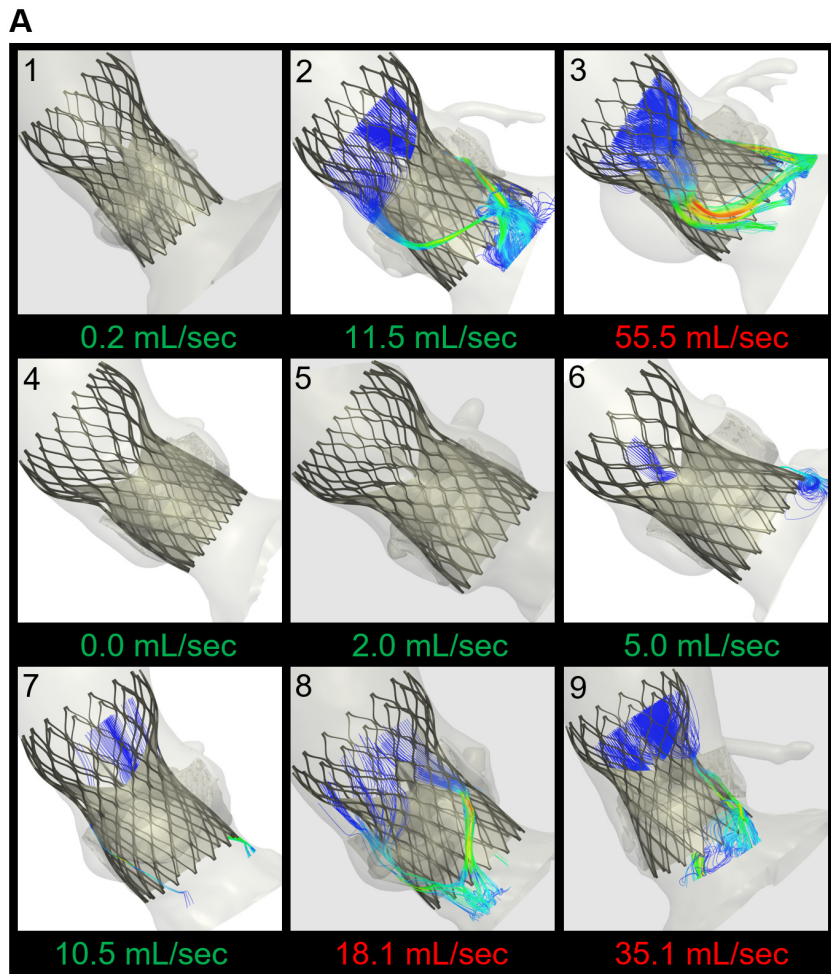
Evolut PRO THV implanted at an annular implant depth. Patient 4 was predicted to have only minimal paravalvular regurgitation when the THV was positioned at an annular implant depth. Patient 6 was predicted to have less paravalvular regurgitation with a “downsized” 29 mm Evolut PRO THV implanted at a standard implant depth. Patient 7 was predicted to have less paravalvular regurgitation with a 34 mm Evolut R THV positioned at a deep implant depth. Arrows mark the nadirs of the non-coronary cusps.

Figure 4. Comparison between finite element analysis simulation and post-procedural MDCT imaging. There is strong visual agreement between the predicted (A-B) and actual THV frame morphology (C-D) as demonstrated by the overlay (E-F). In particular, the elliptical shape of the THV has been correctly modelled.

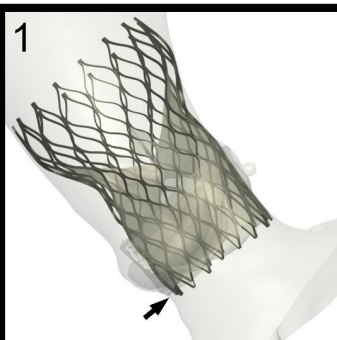




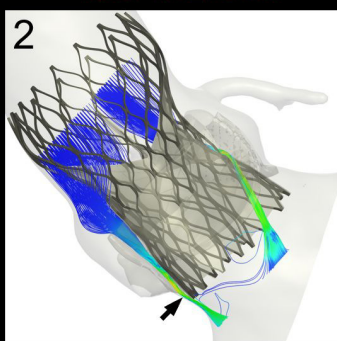
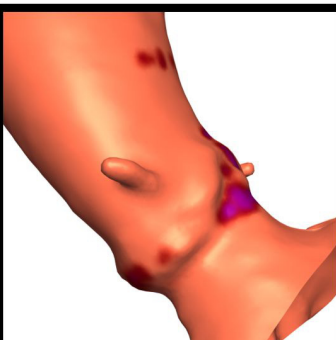
**A****B**



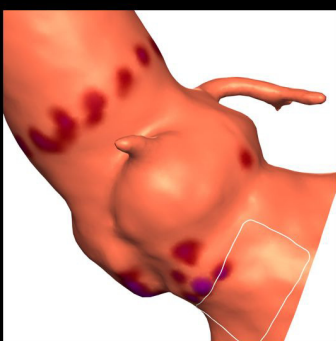




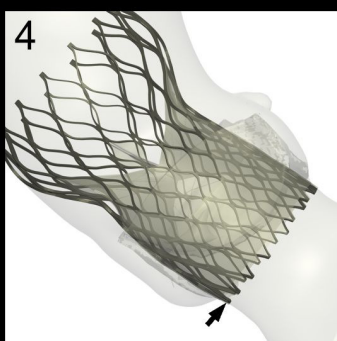
0.3 mL/sec



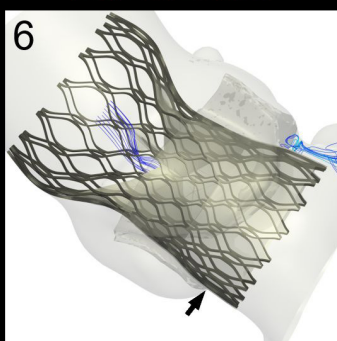
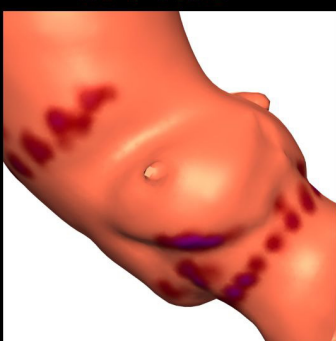
9.8 mL/sec



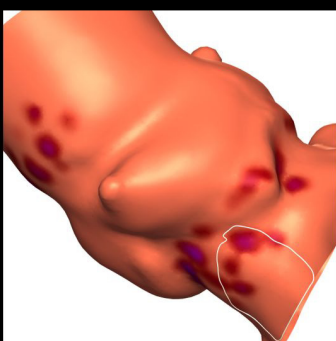
CPMax 0.37 MPa  
CPI 0.03



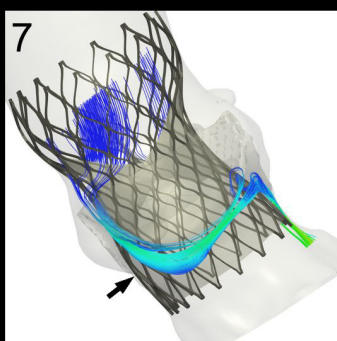
2.9 mL/sec



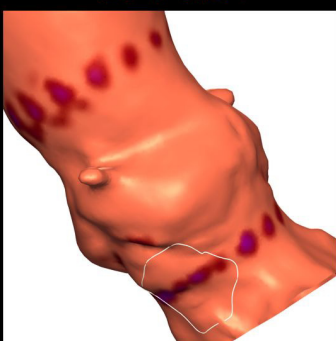
3.8 mL/sec



CPMax 0.32 MPa  
CPI 0.31



8.7 mL/sec



CPMax 0.82 MPa  
CPI 0.34

