Redo-TAVI with the **SAPIEN 3** valve in degenerated calcified CoreValve/Evolut explants

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BACKGROUND: Redo-transcatheter aortic valve implantation (TAVI) is the treatment of choice for failed transcatheter aortic valves. Currently, implantation of a SAPIEN 3 (S3) is indicated for redo-TAVI in degenerated CoreValve/ Evolut (CV/EV) transcatheter aortic valves (TAVs) but is not well understood.

AIMS: We aimed to evaluate S3 function following implantation in explanted calcified CV/EV TAVs and to assess the impact of CV/EV pathology on redo-TAVI outcomes.

METHODS: *Ex vivo* hydrodynamic testing was performed per the International Organization for Standardization (ISO) 5840-3 standard on 4 S3 TAVs implanted at node 5 in calcified CV/EV explants. The mean gradient (MG), effective orifice area (EOA), peak velocity, regurgitant fraction (RF), geometric orifice area (GOA), leaflet overhang, leaflet pinwheeling, neoskirt height, and frame deformation were evaluated.

RESULTS: CV/EV explants were calcified and stenotic. Following S3 implantation, the MG and peak velocity decreased. As per the ISO standard, all S3 implants showed adequate EOA, and 3 out of 4 had an RF within the accepted value (<20%). CV/EV leaflet overhang ranged from 25-37%. Calcified leaflets remained stationary throughout the cardiac cycle (difference <9%) and were not pinned in a manner that constrained S3 systolic flow or appeared to prevent selective frame cannulation. The downstream CV/EV GOA was larger than the upstream S3 GOA during systole. S3 frame underexpansion was seen, resulting in leaflet pinwheeling (range 13-30%). Above the neoskirt, calcium protrusion was observed in contact with the S3 leaflets.

CONCLUSIONS: S3 implantation at node 5 in calcified CV/EV valves resulted in satisfactory hydrodynamic performance in most configurations tested with stable leaflet overhang throughout the cardiac cycle. The long-term implications of S3 underexpansion, leaflet pinwheeling, and calcium protrusion require future studies.

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ranscatheter aortic valve implantation (TAVI) has been shown to be an effective therapy for patients with severe symptomatic aortic stenosis (AS) irrespective of surgical risk^{1,2}. As TAVI is progressively utilised in lowerrisk patients with the potential for longevity, transcatheter aortic valve (TAV) durability and the need for reintervention have become increasingly relevant³⁻⁷. A subset of younger, low-risk patients that are undergoing TAVI will eventually require repeat interventions due to structural valve deterioration (SVD), non-SVD, and/or other failure mechanisms.

Redo-TAVI has emerged as a viable therapeutic option for patients with a failed TAV. Redo-TAVI serves as a minimally invasive alternative to surgical TAV explant, which has been shown to be associated with high morbidity and mortality due to patient risk factors and technical challenges such as valve adherence, tissue ingrowth, and damage to surrounding structures⁸⁻¹¹. However, redo-TAVI has many complexities and potential pitfalls. This procedure may not be feasible in all patients due to the risk of coronary obstruction and impaired coronary access, which requires careful consideration in procedural planning with respect to device combinations¹²⁻¹⁸.

While clinical experience with redo-TAVI continues to grow, many critical knowledge gaps remain. Ex vivo bench testing can provide important insights when clinical experience is limited14,19-21. A recent study evaluated redo-TAVI for the self-expanding Evolut R (Medtronic) TAV following implantation of a balloon-expandable SAPIEN 3 (S3 [Edwards Lifesciences]) TAV¹⁹. The neoskirt height, leaflet overhang, Evolut R frame expansion, and S3 hydrodynamic performance were evaluated at different S3 implant depths. However, like all redo-TAVI bench testing to date, brand new index TAVs were used, thus, not accounting for the potential effect of index TAV leaflet degeneration and calcification on redo-TAVI. Given the features of TAV degeneration, such as leaflet thickening, stiffening and calcium nodule formation²²⁻²⁴, consideration of these pathological features in bench models is key to further inform clinical practice regarding redo-TAVI. Therefore, this ex vivo benchtop study aimed to evaluate the functional performance of the S3 TAV following implantation within degenerated calcified CoreValve/Evolut (CV/EV) TAVs.

Methods

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COREVALVE/EVOLUT TAVI EXPLANTS

A total of 4 CV/EV explants were used in this study as index TAVs: 23 mm Evolut R, 29 mm CoreValve, 29 mm Evolut PRO, and 34 mm Evolut R (all Medtronic devices). Two explants were obtained from the international, multicentre EXPLANT THV registry at St. Paul's Hospital (Vancouver, BC, Canada), with their study approved by the Providence Health Care Research Ethics Board. The remaining 2 TAV explants were acquired from clinical institutions and approved by local institutional review boards. Surgical explantation

Impact on daily practice

Implantation of a SAPIEN 3 is indicated for redotranscatheter aortic valve implantation (TAVI) in the setting of degenerated transcatheter aortic valves (TAVs) but has never been modelled in failed calcified CoreValve/Evolut TAVs. Redo-TAVI with the SAPIEN 3 outflow at node 5 of the degenerated calcified CoreValve/Evolut led to favourable haemodynamics in 3 of the 4 configurations tested, stable leaflet overhang, acceptable neoskirt heights, SAPIEN 3 underexpansion and pinwheeling, and some instances of index TAV calcium touching the SAPIEN 3 leaflets.

occurred for clinical indications as determined by local Heart Teams. Clinical and patient characteristics were obtained from each clinical institution, when available. This bench study did not involve animal participants. Additional details can be found in Supplementary Appendix 1.

SAPIEN 3 IN COREVALVE/EVOLUT REDO-TAVI

Redo-TAVI was performed on the bench using new S3 TAVs in the following combinations: 20 mm S3 within the 23 mm Evolut R, 26 mm S3 within the 29 mm CV, 26 mm S3 within the 29 mm Evolut PRO, and 29 mm S3 within the 34 mm Evolut R. The S3 TAVs were implanted with their outflow at CV/EV node 5 (Figure 1A). Implant depth was chosen on the basis of prior bench testing and computed tomography (CT)-based simulation studies that evaluated the feasibility of coronary access at implantation depths between nodes 4-6 of the index CV/EV12,18,19,25. The S3 TAVs were implanted under fluoroscopy (ARTIS icono biplane C-arm system [Siemens Healthineers]) into the CV/EV TAVs using the manufacturer's standard delivery systems at a nominal volume. Balloon preand post-dilatation were not performed.

HYDRODYNAMIC BENCH TESTING

The HDTi-6000 heart valve pulse duplicator system (BDC Laboratories) was used to assess hydrodynamic performance before and after redo-TAVI in accordance with ISO 5840-3:2021 guidelines for in vitro pulsatile flow testing for heart valve substitutes implanted by transcatheter techniques (Figure 1B). The mean gradient (MG; mmHg), effective orifice area (EOA; cm²), peak velocity (m/s), and regurgitant fraction (RF; %) were quantified. An RF of >20% is considered significant in accordance with ISO guidelines. The EOA was derived from the continuity equation²⁶. Additional details can be found in Supplementary Appendix 1.

MULTIMODALITY IMAGING ANALYSIS

Micro-CT imaging was used for calcium quantification of the index CV/EV leaflets, as previously described²². Briefly,

Abbreviations										
AS	aortic stenosis	GOA	geometric orifice area	SVD	structural valve deterioration					
CT	computed tomography	MG	mean gradient	TAV	transcatheter aortic valve					
CV/EV	CoreValve/Evolut	RF	regurgitant fraction	TAVI	transcatheter aortic valve implantation					
EOA	effective orifice area	S 3	SAPIEN 3							



Figure 1. *Study methodology. A) Redo-TAVI with S3 outflow at node 5 (orange arrow) of CV/EV; (B) pulse duplicator; (C) microcomputed tomography imaging; (D) degree of leaflet overhang (%) of the stenotic CV/EV leaflets following S3 implant; (E) GOA of S3 and CV/EV; (F) S3 leaflet pinwheeling; (G) CV/EV frame nodes and S3 frame heights; (H) neoskirt height. CV/ EV: CoreValve/Evolut; EOA: effective orifice area; L: leaflet; MG: mean gradient; RF: regurgitant fraction; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

calcification distribution on the CV/EV leaflets was assessed using volume measurement of the three-dimensionally (3D) reconstructed explanted TAVs. As shown in **Figure 1C**, segmentation and 3D reconstruction of the CV/EV frame (purple), leaflets (blue) and calcium burden (yellow) were performed in Mimics software, version 25.0 (Materialise). Calcium distribution analysis was performed in 3-matic software, version 17.0 (Materialise). Additional imaging details can be found in **Supplementary Appendix 1**.

LEAFLET FUNCTION ANALYSIS

COREVALVE/EVOLUT NEOSKIRT HEIGHT

The neoskirt height was defined as the distance from the CV/EV frame inflow to the pinned leaflet height at the S3 frame outflow¹⁹ (Figure 1H). Neoskirt height was measured by fluoroscopy at the level of the S3 outflow following visual confirmation that the degenerated index leaflets were subjected to overhang and not pinned in a manner that extended the functional neoskirt above the S3 frame outflow. Neoskirt values were derived from averaging 4 height measurements per redo-TAVI combination using the DICOM viewer software, version 3.9.5 (MicroDicom).

COREVALVE/EVOLUT LEAFLET OVERHANG

As shown in **Figure 1D**, leaflet overhang was defined as the percentage of orifice obstruction at the level of the index CV/ EV commissure pad region (leaflet outflow) due to inward flexing of the unpinned portion of the CV/EV leaflets¹⁹ (Supplementary Appendix 1).

COREVALVE/EVOLUT AND SAPIEN 3 GEOMETRIC ORIFICE AREA

As shown in Figure 1E, the CV/EV geometric orifice area (GOA; blue) and S3 GOA (green) following redo-TAVI were measured and averaged from 3 still-frame systolic images

obtained from the high-speed videos using ImageJ software (ImageJ). The CV/EV GOA was compared to the S3 GOA at systole.

SAPIEN 3 PINWHEELING

Pinwheeling, defined as twisting of the TAV leaflet's free edge as a consequence of redundant leaflet tissue was assessed for the S3²⁷. As shown in **Figure 1F**, pinwheeling – expressed as a percentage – was determined by tracing the contour of the length of the actual leaflet's free edge (L_{actual}) from the frame to the coaptation centre compared to the ideal configuration for the leaflet's free edge (straight line; L_{ideal}) (**Supplementary Appendix 1**). Since pinwheeling might be difficult to measure in cases where major leaflet redundancy leads to a phenomenon of localised malcoaptation, regions where the leaflets' free edges failed to achieve full coaptation along their length were manually traced from images captured during diastole.

FRAME DEFORMATION ANALYSIS

As shown in **Figure 1G**, micro-CT imaging performed before and after redo-TAVI was used for measuring the CV/EV perimeter-derived outer frame diameter in each of the 11 frame node levels from inflow to outflow (nodes 0-10). Similarly, the S3 area-derived outer frame diameter was measured at the 8 frame heights from inflow to outflow (heights 0-7) following redo-TAVI. Diameter measurements were originally taken mid-strut followed by the addition of the frame thickness to obtain the outer frame diameter values. The reference S3 frame diameter before redo-TAVI was the nominal frame diameter per the instructions for use, which was assumed to be constant across the frame height. The change in radius for the CV/EV TAVs following redo-TAVI was also quantified.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation or median with interquartile range (IQR). Statistics were performed using Minitab software, version 20.1.3 (Minitab). Due to the small sample size, statistical comparisons between redo-TAVI configurations were not performed.

Results

COREVALVE/EVOLUT EXPLANTS CHARACTERISTICS

Clinical characteristics of the 4 CV/EV explants are provided in **Supplementary Table 1**. The median patient age at explant was 67 years (IQR 53-72 years), and 50% were female. The median time from index TAVI to explant was 4 years and 5 months (IQR 3 years and 1 month-4 years and 11 months). The degenerative mechanism responsible for explant in all cases was SVD, causing AS in 3 cases and mixed stenosis and concomitant regurgitation in 1 case.

Figure 2 and **Supplementary Table 1** show the calcium burden, leaflet thickness, morphological appearance, and leaflet kinematics of the 4 CV/EV explants before redo-TAVI. Leaflet kinematics were abnormal in all explants (**Moving image 1**), and all explants were found to have leaflet calcification by micro-CT quantification (median 413 mm³ [IQR 120-597 mm³]). **Table 1** shows the hydrodynamic performance of the CV/EV explants. *Ex vivo* MG, EOA and peak velocity median values were 48.9 mmHg (IQR 34.9-71.5 mmHg), 0.84 cm² (IQR 0.70-1.04 cm²) and 4.8 m/s (IQR 4.0-5.9 m/s), respectively.

SAPIEN 3 IN COREVALVE/EVOLUT HYDRODYNAMIC PERFORMANCE

Table 1 and **Figure 3** show the hydrodynamic performance and morphological appearance of the 4 redo-TAVI combinations. Following S3 implantation within the CV/EV at node 5 position, adequate S3 hydrodynamic function was achieved for 3 of the 4 redo-TAVI combinations per the ISO 5840-3 standard. The 29 mm S3 in 34 mm EV configuration showed an RF of 25.8%, above the 20% cutoff point defined by the standard. Further testing of this configuration was conducted by adding silicone sealant to the exterior surface of the 29 mm S3 to prevent inter-TAV leakage. Hydrodynamic retesting resulted in an RF of 21.7%, confirming the major contribution of central regurgitation to the high RF initially observed. The S3 in CV/EV redo-TAVI leaflet kinematics are presented in **Moving image 2**.

Hydrodynamic testing following redo-TAVI resulted in median MG, EOA and peak velocity measurements of 9.9 mmHg (IQR 7.6-23.9 mmHg), 2.1 cm² (IQR 1.4-2.4 cm²) and 1.9 m/s (IQR 1.7-3.0 m/s), respectively (Figure 3B, Table 1). As expected, the highest MG/peak velocity and smallest EOA were noted for the 20 mm S3 in 23 mm EV redo-TAVI combination.

REDO-TAVI LEAFLET MEASUREMENTS

As shown in **Table 2** and **Figure 3C**, the S3 in CV/EV redo-TAVI at node 5 position resulted in neoskirt heights ranging between 19.9-24.0 mm. The lowest neoskirt value was measured for the 20 mm S3 in 23 mm EV combination (19.9 mm), and the highest neoskirt was noted for the 26 mm S3 in 29 mm EV combination (24.0 mm). Of note, despite leaflet rigidity due to calcification, the neoskirt was not found to extend above the S3 frame. **Table 2** shows the degree of CV/EV leaflet overhang during diastole and systole. Leaflet overhang ranged from 24.8% to 37.3% across the 4 redo-TAVI combinations (**Figure 3B**). Overall, index CV/EV leaflets were pinned open and remained stationary throughout the cardiac cycle, with a difference <9% in leaflet overhang between diastole and systole.

Index CV/EV GOA and S3 GOA were quantified for the 4 redo-TAVI combinations (**Table 2**). The CV/EV GOA ranged from 3.2 cm² to 5.3 cm² across the 4 test combinations, while the S3 GOA ranged between 2.8 cm² and 4.2 cm². As shown in **Figure 4A**, during systole, the downstream opening orifice area (CV/EV GOA) was always larger than the upstream orifice area (S3 GOA), demonstrating that S3 systolic flow is not constrained by the overhanging leaflets. S3 EOA values are also presented in **Figure 4A**; however, directly comparing GOA to EOA measurements is inaccurate, because the former only considers the physical dimensions of the orifice, while the latter accounts for fluid flow characteristics.

As shown in **Table 2**, S3 implanted within CV/EV resulted in average S3 pinwheeling values ranging from 12.5-29.8%. The largest degree of pinwheeling was noted for the 26 mm S3 in 29 mm EV combination. **Supplementary Table 2** shows the degree of pinwheeling for each pair of S3 leaflets. Pinwheeling also resulted in deficits in free-edge coaptation



Figure 2. Appearance, hydrodynamics and calcium of degenerated Core Valve/Evolut. A) Gross pathology of the explanted calcified CV/EV used in the study. B) Images of explants during systolic opening prior to redo-TAVI with corresponding MG and EOA. C) Micro-CT of explants (calcification=yellow) with calcium volume per valve. CT: computed tomography; CV/EV: CoreValve/Evolut; EOA: effective orifice area; MG: mean gradient; TAVI: transcatheter aortic valve implantation

Table 1. Hydrodynamic performance before and after redo-TAVI.

	Mean gradient, mmHg			EOA, cm²		Peak vel	ocity, m/s	Regurgitant fraction, %		
	Index CV/EV	Redo-TAVI	Index CV/EV	Redo-TAVI	ISO accepted	Index CV/EV	Redo- TAVI	Redo-TAVI	ISO accepted	
VALVE 1 20 mm S3 in 23 mm Evolut R	56.3±0.3	28.5±0.2	0.82±0.01	1.17±0.00	0.95	5.0±0.0	3.4±0.0	7.9±0.6		
VALVE 2 26 mm S3 in 29 mm CoreValve	32.7±0.2	9.5±0.1	1.10±0.00	2.16±0.02	1.60	3.8±0.0	1.9±0.0	18.9±0.4	20	
VALVE 3 26 mm S3 in 29 mm Evolut PRO	41.4±0.4	10.2±0.1	0.85±0.00	2.08±0.01	1.60	4.6±0.0	1.9±0.0	12.3±0.4	20	
VALVE 4 29 mm S3 in 34 mm Evolut R	76.6±0.4	7.0±0.1	0.66±0.00	2.54±0.02	2.10	6.2±0.1	1.6±0.0	25.8±0.3*		

Data presented as mean±standard deviation. *Subsequent hydrodynamic testing determined that central AR caused 21.7% of the total regurgitant fraction. AR: aortic regurgitation; CV/EV: CoreValve/Evolut; EOA: effective orifice area; ISO: International Organization for Standardization; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation

along the leaflet length. **Supplementary Figure 1** shows these areas highlighted in red where the free edges of each pair of leaflets did not meet.

COREVALVE/EVOLUT FRAME DEFORMATION FOLLOWING REDO-TAVI

Figure 4B presents the CV/EV outer frame diameter measurements at each node level before and after redo-TAVI. CV/EV frame expansion following redo-TAVI occurred more frequently closer to the waist and the functional leaflet region (nodes 4-7), and to a lesser extent at the inflow and outflow regions. CV/EV frame diameter measurements at each node level and change in radius following redo-TAVI are presented in **Supplementary Table 3**. The change in CV/EV radius was up to 1.7 mm across the tested combinations.

SAPIEN 3 FRAME EXPANSION FOLLOWING REDO-TAVI

Following redo-TAVI, S3 frame underexpansion was systematically observed to varying degrees along the frame height. Figure 4C shows the observed S3 frame diameter values compared to theoretical nominal expansion. In the case of the 20 mm S3 in 23 mm EV combination, the S3 showed a trumpet-like, "flared" frame geometry, with the highest frame underexpansion at the inflow and the lowest underexpansion at the outflow. In contrast, 2 of the remaining redo-TAVI combinations (valves 2 and 4) showed a funnel-like, "tapered" frame geometry, with the lowest frame underexpansion at the inflow and the highest underexpansion at the outflow, especially for the 29 mm S3 in 34 mm EV combination. The high S3 frame underexpansion observed for the 29 mm S3 in 34 mm EV combination appeared to have contributed to the high RF quantified for this configuration. The remaining redo-TAVI combination (valve 3) displayed a "dumbbell" geometry, with the midportion showing the highest degree of underexpansion. S3 frame underexpansion and degree of leaflet pinwheeling appears to be affected by redo-TAVI sizing and calcium location.

CALCIFICATION PATTERNS AND PROTRUSION

Calcification was observable on both the outflow and inflow surfaces of the CV/EV TAVs and protruded from the inflow and outflow surfaces (Figure 5A). During hydrodynamic testing, CV/EV leaflet calcium protrusion from the inflow side through the S3 frame was observed for the 29 mm S3 in 34 mm EV combination, and to a lesser extent for the 26 mm S3 in 29 mm EV combination (Figure 5B). During systole, this calcification could be seen in contact with the S3 leaflets (Moving image 3). As shown in Figure 5A, this finding is in line with the substantial calcium burden and location identified by micro-CT at the inflow side of the 34 mm and 29 mm EV TAVs, which was deflected during redo-TAVI.

FRAME CANNULATION NEEDED FOR POTENTIAL CORONARY ACCESS FOLLOWING REDO-TAVI

Visually, *ex vivo* frame cannulation, which would be needed for coronary access, did not appear to be prevented by the positioning of the calcified CV/EV leaflets for all redo-TAVI combinations with the S3 outflow at node 5 (Supplementary Figure 2A). Supplementary Figure 2B shows modelling of catheter access for the 20 mm S3 in 23 mm EV and the 29 mm S3 in 34 mm EV redo-TAVI combinations.

Discussion

Redo-TAVI is an increasingly common procedure, and the assessment of its feasibility plays a central role in the lifetime management of patients with AS. However, clinical evidence remains limited, and bench testing can provide valuable insight to help fill this knowledge gap^{21,28-30}. In the context of redo-TAVI with an S3 for a failed calcified CV/EV, this study provides the following key insights: first, node 5 positioning of the S3 outflow within a stenotic calcified CV/EV resulted in favourable hydrodynamics in 3 of the 4 configurations tested. Second, leaflet overhang – which was originally described in pristine valves – was also observed in degenerated calcified samples but remained stable throughout the cardiac cycle. In the current short-term hydrodynamic testing, this



Figure 3. *Redo-TAVI with SAPIEN 3 in CoreValve/Evolut at node 5. A) Appearance of redo-TAVI combinations following S3 implant from the outflow perspective. B) Following redo-TAVI, images of confirmed leaflet opening (systole) and closing (diastole) during hydrodynamic testing with resulting EOA, MG, leaflet overhang and S3 pinwheeling. C) Fluoroscopy of redo-TAVI configuration noting neoskirt heights. EOA: effective orifice area; MG: mean gradient; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation*

	Nenskirt	Index CV/	EV leaflet ov	erhang, %	Index CV/FV	S3 G0A.	S3 pinwheeling, %			
	height, mm	Diastole	Systole	Difference	GOA, cm ²	cm ²				
VALVE 1 20 mm S3 in 23 mm Evolut R	19.9±0.1	35.2±0.6	35.7±0.4	1.4	3.22±0.03	2.81±0.02	16.1±5.7			
VALVE 2 26 mm 3 in 29 mm CoreValve	20.5±0.4	37.3±0.8	34.6±0.2	7.5	4.08±0.02	3.67±0.05	14.3±10.5			
VALVE 3 26 mm S3 in 29 mm Evolut PRO	24.0±0.5	25.1±1.0	24.8±1.4	1.2	5.11±0.05	3.76±0.01	29.8±9.3			
VALVE 4 29 mm S3 in 34 mm Evolut R	22.5±0.3	28.9±0.3	31.5±0.6	8.6	5.26±0.02	4.19±0.04	12.5±3.6			
Data presented as mean±standard deviation. CV/EV: CoreValve/Evolut; GOA: geometric orifice area; S3: SAPIEN 3; TAVI: transcatheter aortic valve										

Table 2. Neoskirt height,	leaflet overhang	geometric orifice area, an	d pinwheeling f	following redo-TAVI
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phenomenon did not seem to have a significant impact on S3 hydrodynamic performance, since all combinations exhibited an EOA above the ISO-defined cutoff points and the GOA of CV/EV TAVs with overhanging leaflets always exceeded the GOA of S3 valves. Further, the ability to cannulate the frame on the bench did not appear to be affected by leaflet overhang. Third, considerable S3 frame underexpansion and leaflet pinwheeling were observed and may be affected by TAV sizing and calcium location. Fourth, in highly calcified CV/EV, calcium nodules from the inflow side can protrude through the S3 open cells and make contact with the S3 leaflets during systole. Fifth, we observed different patterns of S3 frame underexpansion geometry across the considered valves assessed.

The present study addresses some of the limitations of previous bench work on redo-TAVI with S3 in CV/EV¹⁹. Indeed, in the prior analysis, brand new CV/EV TAVs were used, which did not reproduce the challenges and outcomes of calcified stenotic CV/EV TAVs. Therefore, the present analysis offers a thorough examination of redo-TAVI in calcified CV/EV TAVs, assessing hydrodynamics, leaflet displacement and kinematics, frame deformation and expansion, and the impact of leaflet displacement and calcium burden on redo-TAVI functional outcomes.

The index TAVs used in our study demonstrated overt SVD consistent with previously documented modes of TAV degeneration, resulting in stenosis or mixed stenosis and regurgitation. These valves, while a selected subset, provide insight into the challenges faced in the setting of redo-TAVI across the different ranges of size combinations. Two of the 4 redo-TAVI combinations tested demonstrated overall satisfactory hydrodynamic performance per the ISO 5840-3 standard and clinical guidelines. However, the 29 mm S3 in 34 mm EV combination exhibited suboptimal RF, and the 20 mm S3 in 23 mm EV configuration showed a residual MG >20 mmHg. Interestingly, the 20 mm S3 in 23 mm EV combination also demonstrated a residual MG >20 mmHg when pristine valves were used¹⁹.

These suboptimal results serve to highlight important clinical considerations for redo-TAVI. In the case of the high RF for the

29 mm S3 in 34 mm EV redo-TAVI, it was found that central leakage was the major contributor to the total RF initially observed. This was very likely secondary to S3 underexpansion, which was highest in this redo-TAVI combination, although it was observed in all redo-TAVI combinations. This observation is of utmost importance since the present study used a widely clinically accepted S3 sizing strategy of using an S3 that is one size smaller than the index CV/EV²⁵ and provides a comparison to previous bench studies using new TAVs and the same sizing strategy¹⁹. However, our findings underline the importance of TAV sizing based on the in vivo CT-based internal diameter of the index TAV, which may result in a smaller S3 implant with improved expansion and a potential reduction in the RF. This is in line with emerging data¹³ and recent expert consensus from the freshly released Redo TAV app (KRUTSCH). Future redo-TAVI bench studies should consider the use of novel models that allow CT sizing. Our findings may also prove valuable for clinical studies on CT sizing. For example, current CT sizing does not incorporate aspects of TAV degeneration that may impact the internal diameter or the expansion of the index TAV. With respect to the high residual MG seen in the 20 mm S3 in 23 mm Evolut R configuration, this is in line with known complications of higher gradients in smaller TAVs, particularly when underexpanded, including the observation of gradients over 20 mmHg in the settings of index TAVI, valve-in-valve, and redo-TAVI with small S3 TAVs^{15,31,32}. Thus, these findings bring important focus on the importance of optimising TAV type and size selection at the time of the index TAVI procedure in order to maximise the chances of successful redo-TAVI. Indeed, when considering the lifetime management of young patients, it is critical to consider the potential need for a subsequent intervention at the time of the index TAVI procedure.

We previously showed that the presence of calcification on the surface of failed TAVs provides insights into the underlying mechanisms of valve degeneration²². The current analysis now unveils a potential functional consequence of this in the context of redo-TAVI: protrusion of calcium from the inflow and outflow surfaces can interact with the second TAV. This can impact redo-TAVI functional outcomes



Figure 4. CoreValve/Evolut and SAPIEN 3 orifice areas and frame deformation. A) Comparison of CV/EV GOA, S3 GOA and S3 EOA. B) CV/EV frame deformation at nodes 0 to 10 comparing frame diameter before (yellow) and after (blue) redo-TAVI. C) S3 frame expansion comparing observed S3 frame diameter at node heights 0 to 7 at nominal state (yellow) and after redo-TAVI (blue). The data points shown correspond to frame diameter values following redo-TAVI. CV/EV: CoreValve/Evolut; EOA: effective orifice area; GOA: geometric orifice area; S3: SAPIEN 3; TAVI: transcatheter aortic valve implantation

in two potential ways. First, outflow surface calcium can become pinned between the two TAVs during redo-TAVI and thus, as a component of leaflet thickening, impact S3 expansion, as observed. Second, inflow surface calcium can be displaced through the S3 frame, leading to contact with the S3 leaflets during systole, as was seen in 2 of the 4 redo-TAVI configurations tested. The significant calcium burden identified by micro-CT imaging on the inflow side of explanted TAVs suggests a potential link between calcium location and the observed protrusion phenomenon. Moreover, future studies will need to consider how to characterise valve degeneration, including leaflet thickening and calcification



Figure 5. Core Valve/Evolut calcification patterns and protrusion following redo-TAVI. A) CV/EV micro-CT showing patterns of inflow and outflow calcification protrusions from the surface of the TAV leaflet. B) Images from hydrodynamic testing showing protruding calcification from degenerated CV/EV in contact with the implanted S3 and high-resolution gross pathology images of areas of protrusion. The yellow arrowheads denote protruding calcification. CT: computed tomography; CV/EV: CoreValve/ Evolut; S3: SAPIEN 3; TAV: transcatheter aortic valve; TAVI: transcatheter aortic valve implantation

patterns, clinically in redo-TAVI. Indeed, even if the long-term consequences of repeated contact/friction with the calcium nodules are unknown, procedural planning to optimise sizing and minimise the risk of potential complications associated with calcium protrusion may be necessary. This is also important when considering post-dilatation. While post-dilatation could improve S3 expansion, CV/EV deformation, and pinwheeling, there are potential concerns of damage to the S3 leaflets from protruding calcium, and further S3 expansion has implications for coronary flow obstruction and the extent and stability of leaflet overhang. In the current study, post-dilatation was not performed, and this may have resulted in the notable S3 underexpansion, associated pinwheeling, and high RF observed in the 29 mm S3 in 34 mm EV configuration. Notably, S3 pinwheeling in the setting of considerable central leakage can be lower than expected, given the lack of central coaptation, which impacts the assessment of the length of the actual leaflet's free edge (L_{actual}). This can also be impacted by differences in the extent of coaptation along the length of the free edges of leaflet pairs, as leaflet redundancy is taken up by flexion of the leaflet in an axis that pinwheeling measurements are not able to assess. We highlight this in Supplementary Figure 1. Our findings regarding pinwheeling also suggest that factors such as differences in calcification volume and pattern may impact the extent of pinwheeling, likely related to differences in expansion geometry and central coaptation location.

Importantly, leaflet overhang, originally described on the bench using new TAVs19, was still present in degenerated TAVs, although to a slightly lesser degree in some combinations. Furthermore, we showed that, in the presence of calcified leaflets, leaflet overhang is stable throughout the cardiac cycle with minimal difference between systole and diastole. While requiring more study, this may have implications for flow dynamics in the sinus, as an overhanging leaflet - whether stable or not - may contribute to turbulent flow, but how and the relative magnitude by which stable or unstable leaflet overhang impacts flow are unknown. The persistence of the leaflet overhang phenomenon in the presence of calcified leaflets has important clinical implications when considering redo-TAVI planning. Indeed, here we showed that leaflet overhang and neoskirt height findings are consistent: as the leaflets overhung and were not pinned straight or deflected outwards, the neoskirt was not found to extend above the S3 frame outflow. This is critical, since the neoskirt height is a key consideration for coronary access and assessment of risk of coronary obstruction. Thus, the fact that, on the bench, the neoskirt height can still be predicted by the level of the S3 outflow offers some reassuring elements in terms of the clinical predictability of procedural results. Current investigations have primarily focused on how leaflet overhang impacts the acute hydrodynamic function of redo-TAVI. However, future studies should explore other aspects of leaflet overhang and its effect on longer-term redo-TAVI outcomes, including evaluating how leaflet overhang and hydrodynamic function may change with implantation at higher or lower node positions. However, performing this in explants will always remain a significant challenge since implants in a degenerated CV/EV generally cause damage to the leaflets that preclude multiple S3 deployments.

Despite leaflet thickening and stiffness, and given the presence of leaflet overhang, we observed that these did not later prevent, at least on the bench, the ability to selectively cannulate the index TAV frame. This is of importance when considering the high prevalence of concomitant coronary artery disease in patients undergoing TAVI, especially when long-term survival is anticipated. However, given the patient-to-patient anatomical variation in aortic root dimensions, coronary height, and inconsistent rate of commissural alignment, selective coronary engagement might still remain extremely challenging in some cases, and further studies are required to better understand this issue.

Finally, we found that depending on the index TAV size and type, S3 frame expansion could follow several patterns. The smallest combination exhibited a "flared" frame geometry; 2 samples, particularly the largest configuration, displayed a "tapered" frame geometry, while one sample had a "dumbbell" geometry. This is of interest since S3 frame deformation has been shown to potentially impact outcomes such as risk for leaflet thrombosis³³. While the current sample size does not allow for further characterisation of this phenomenon, future studies will need to look at the impact of parameters like degenerative changes of the index TAV or redo-TAVI sizing on patterns of expansion following redo-TAVI.

Limitations

There are limitations to be considered in this analysis. First, the ex vivo bench-testing setup may not reflect physiological conditions in clinical practice including the challenges of frame cannulation to achieve coronary access. In vivo expansion of the index and second TAVs may vary compared with a bench model, and the CV/EV holder used may not reflect patient anatomy but was in accordance with ISO 5840-3 guidance. Second, this is a limited redo-TAVI population which does not reflect all pathologies, patterns of calcification, size combinations, etc., but does reflect common challenges for failed CV/EV TAVs. Further, irreversible S3 frame deformation, risk of explanted CV/ EV leaflet damage/tear during S3 removal, and CV/EV explant availability limited the assessment of additional redo-TAVI implant depth configurations. Third, sizing the S3 was based on recommendations of downsizing that did not consider CT sizing. Fourth, no balloon pre- or postdilatation was performed, which may have impacted S3 frame expansion, CV/EV frame deformation, and S3 hydrodynamic performance. This gives insight into the standard nominal S3 deployment - a conservative approach that is used in clinical settings where the risk of coronary obstruction precludes the use of post-dilatation, which would further expand the CV/EV frame and increase the risk. However, this approach does not reflect the best-case scenario, where S3 nominal expansion can be achieved and where improved valve function could be expected. However, as mentioned earlier, it is also possible that aggressive post-dilatation could result in damage to the S3 leaflets from the calcium protrusion, and the issue of pre-/post-dilatation would warrant a full-scale future study considering method variations and outcomes of pre-/post-dilatation. Indeed, although 3 out of 4 redo-TAVI configurations had adequate hydrodynamic performance immediately after the procedure, S3 underexpansion, leaflet pinwheeling and calcium protrusion may have important longer-term clinical implications that were out of the scope of this study. While this study provides highly valuable insights, further validation using real-world clinical data on redo-TAVI is necessary.



Conclusions

Redo-TAVI with the S3 outflow at node 5 of a calcified stenotic CV/EV resulted in adequate systolic hydrodynamic performance (EOA, MG, velocity) per the ISO standard in all combinations tested, while 3 out of 4 combinations had an

RF within the accepted ISO range (RF <20%). On the bench, leaflet overhang did not seem to have a significant impact on S3 short-term hydrodynamic performance. CV/EV leaflets remained open and stationary throughout the cardiac cycle and were not pinned in a manner that constrained S3 systolic

flow or appeared to prevent selective frame cannulation on the bench. S3 frame underexpansion and leaflet pinwheeling, however, were observed. Overall, our findings contribute to the understanding of redo-TAVI in the context of failed CV/ EV TAVs, offering valuable insights into patient selection, procedural planning with routine use of *in vivo* CT sizing, and optimisation of TAV performance. Further research and clinical studies are warranted to validate our findings and refine treatment strategies for patients requiring redo-TAVI, particularly in cases of valve degeneration and calcification.

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Supplementary data

Supplementary Appendix 1. Supplementary methods.

Supplementary Table 1. Characteristics of the four calcified transcatheter aortic valve explants.

Supplementary Table 2. SAPIEN 3 pinwheeling by leaflet pair. Supplementary Table 3. CoreValve/Evolut frame diameter and change in frame radius following redo-TAVI.

Supplementary Figure 1. SAPIEN 3 coaptation deficit following redo-TAVI.

Supplementary Figure 2. Feasibility of frame cannulation needed for coronary access following redo-TAVI.

Moving image 1. Baseline CoreValve/Evolut explant function. Visualisation of valve kinematics during baseline hydrodynamic testing of explanted calcified CoreValve and Evolut TAVs.

Moving image 2. Hydrodynamic evaluation following redo-TAVI. Visualisation of valve kinematics, pinwheeling, and leaflet overhang following S3 in CV/EV redo-TAVI.

Moving image 3. Calcium protrusion. Visualisation of S3 leaflet contact with protruding CV/EV calcification following redo-TAVI.

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-24-00619



Supplementary data Supplementary Appendix 1. Supplementary methods. CoreValve/Evolut TAVI explants

The 4 CV/EV explants had intact leaflets, were visually calcified and stenotic, and were suitable for ex vivo hydrodynamic testing. Explants were collected in buffered aldehyde fixative at sites after explant and stored at controlled room temperature. Prior to hydrodynamic testing, samples were all transitioned to 0.2% buffered isotonic glutaraldehyde solution before being placed in the test medium providing significant washout prior to data collection.

Hydrodynamic bench testing

Initially, the index CV/EV explants were placed in a holder fabricated from silicone with a durometer scale Shore A hardness of 40 ± 5 . The holder dimensions and compliance were chosen in accordance to ISO 5840-3:2021²⁶. Holder inner diameters were representative of the upper limit of the indicated patient annular range per manufacturer's instructions for use (IFU). The 23 mm Evolut R, 29 mm CoreValve, 29 mm Evolut PRO, and 34 mm Evolut R were placed in 20 mm, 26 mm, and 30 mm diameter holders, respectively. Each CV/EV explant was sutured at 6 equidistant locations around the circumference of the frame inflow to the holder to prevent migration. The HDTi-6000 pulse duplicator was fitted with a custom 3D printed test chamber to secure the holders in the tester and measure the aortic and ventricular pressures at 2.5 cm from the inflow and outflow of the TAV.

Following S3 implantation within CV/EV, silicone (Silicone Plastique® Part A and B, Culinart Inc., SKU: SP-001; Cure Time: 60-75 minutes) was applied between the CV/EV and the holder to eliminate paravalvular leakage at the index TAV/holder interface. This allowed accurate quantification of total regurgitation fraction (RF), inclusive of central S3 leakage and inter-TAV leakage. In one instance, additional silicone was added between the S3 and the CV/EV frames at the inflow to further assess the cause of a high RF, and to differentiate inter-TAV from S3 central leakage.

The test medium used in the hydrodynamic testing was a 37 ± 2 °C buffered saline solution (0.9 ± 0.2 % sodium chloride). Hydrodynamic measurements were based on average results taken

from >10 consecutive cardiac cycles. Pulsatile flow performance was tested at a nominal rate of 70 ± 1 beats per minute, systolic duration of 35 ± 5 %, mean aortic pressure of 100 ± 2 mmHg, and a cardiac output of 5.0 ± 0.1 L/min.

Multimodality imaging analysis

Multimodality imaging was performed including high-resolution photography with a Nikon D5100 and a digital microscope (VHX-7000, Keyence, US), fluoroscopy at 0 and 90 degree orientation using the ARTIS icono biplane C-arm system (Siemens Healthineers, Germany), high-speed video recordings with 1280×1024 resolution from the outflow TAV surface (HDTi-6000 vision cameras, BDC Laboratories, US), endoscopic imaging with a 4mm camera (iPLEX RT, Olympus, US), and high-resolution micro-computed tomography (micro-CT) imaging (North Star Imaging X5000, US).

High-resolution photography was also utilized to document calcium protrusion and ability for potential selective frame cannulation with coronary catheters. Frame cannulation was performed on the bench by an interventional cardiologist with JR 4.0 and JL 3.5 guide catheters (Medtronic, US). The interventionalist was restricted to angles pre-designated to be representative of those that would be likely to be achieved clinically to provide ex vivo insight to impact of EV/CV leaflet position on the potential to cannulate the EV/CV frame.

Leaflet function analysis

CoreValve/Evolut leaflet overhang

$$Leaflet Overhang (\%) = \left(\frac{CV/EV \text{ orifice area} - CV/EV \text{ leaflet overhang area}}{CV/EV \text{ orifice area}}\right) \times 100$$

The CV/EV orifice area (yellow) was determined by tracing the outer boundary of the index TAV orifice at the commissure pad region height. The area was calculated by planimetry expressed in pixels using ImageJ software. Similarly, the leaflet overhang area (orange) was calculated by tracing the unpinned CV/EV leaflet free edge. Percent leaflet overhang was measured from images taken from hydrodynamic testing during the diastolic and systolic phases from three cardiac cycles. Variation of leaflet overhang across diastole and systole was expressed as percentage difference:

$$\frac{|\Delta Leaflet Overhang|}{\left[\frac{\Sigma Leaflet Overhang}{2}\right]} \times 100$$

SAPIEN 3 pin-wheeling:

$$Pin Wheeling = \frac{(L_{actual} - L_{ideal})}{L_{ideal}} \times 100$$

Pin-wheeling was averaged from 3 still frame images selected at diastole using ImageJ software. Pin-wheeling was calculated as an average of the 3 leaflets as well as for each leaflet pair.

	VALVE 1	VALVE 2	VALVE 3	VALVE 4
Model	Evolut R	CoreValve	Evolut PRO	Evolut R
Size	23mm	29mm	29mm	34mm
Degenerative mechanism	SVD (AS)	SVD (AS)	SVD (AS and central AR)	SVD (AS)
Sex	Female	Female	Male	Male
Age at the time of explant (years)	63	73	50	71
Time from implant to explant	4 years 3 months	4 years 9 months	2 years 9 months	5 years 1 month
Total calcium volume (mm ³)	77.9	246.8	448.5	603.0
L1 calcium volume	26.8	104.5	193.1	244.4
L2 calcium volume	26.6	88.0	97.4	181.0
L3 calcium volume	24.6	54.3	158.0	177.6
Average leaflet thickness (mm)	0.85	1.34	1.32	1.79
L1 thickness	0.87	1.40	1.31	1.91
L2 thickness	0.81	1.42	1.13	1.72
L3 thickness	0.88	1.20	1.53	1.73
S3 size implanted	20mm	26mm	26mm	29mm

Supplementary Table 1. Characteristics of the four calcified transcatheter aortic valve explants.

SVD denotes structural valve deterioration, AS aortic stenosis, AR aortic regurgitation, L leaflet and S3 SAPIEN 3.

	L1-L2 Pin-Wheeling (%)	L2-L3 Pin-Wheeling (%)	L3-L1 Pin-Wheeling (%)
VALVE 1 20mm S3 in 23mm Evolut R	22.8 ± 1.6	10.0 ± 1.5	15.4 ± 1.1
VALVE 2 26mm 3 in 29mm CoreValve	1.3 ± 0.0	16.3 ± 0.2	25.3 ± 0.3
VALVE 3 26mm S3 in 29mm Evolut PRO	36.4 ± 6.8	34.5 ± 1.6	18.4 ± 2.1
VALVE 4 29mm S3 in 34mm Evolut R	15.8 ± 1.0	13.1 ± 2.8	8.7 ± 2.3

Supplementary Table 2. SAPIEN 3 pinwheeling by leaflet pair.

Data presented as mean \pm standard deviation. L denotes leaflet and S3 SAPIEN 3.

	Node 0		Node 0 Node 1 Node 2		e 2	Node 3		Node 4		Node 5		Node 6		Node 7		
	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	∆ Radius (mm)	Diameter (mm)	Δ Radius (mm)
VALVE 1 20mm S3 in 23mm Evolut R	19.7	-0.4	19.9	-0.1	20.5	0.3	21.2	0.9	21.5	1.2	23.3	0.9	27.7	0.4	32.6	0.1
VALVE 2 26mm S3 in 29mm CoreValve	26.8	-0.4	26.2	-0.1	25.7	0.1	25.4	0.4	25.1	0.7	24.4	0.8	24.9	0.5	28.5	0.3
VALVE 3 26mm S3 in 29mm Evolut PRO	28.7	0.0	27.1	-0.1	26.2	-0.1	25.6	0.4	25.6	0.9	25.8	1.2	25.7	1.0	27.5	0.7
VALVE 4 29mm S3 in 34mm Evolut R	32.5	-0.7	30.3	-0.2	28.7	0.3	27.6	1.0	27.4	1.7	26.9	1.7	26.1	1.0	27.6	0.4

Supplementary Table 3. CoreValve/Evolut frame diameter and change in frame radius following redo-TAVI.

CoreValve/Evolut micro-CT perimeter-derived outer frame diameter for frame nodes 0-7. S3 denotes SAPIEN 3.



Supplementary Figure 1. SAPIEN 3 coaptation deficit following redo-TAVI.



Supplementary Figure 2. Feasibility of frame cannulation needed for coronary access following redo-TAVI. A. Gross visualization of areas for frame cannulation needed for coronary access following S3 implant. B. Modelling of catheter access.