Early safety and feasibility of a first-in-class biomimetic transcatheter aortic valve - DurAVR

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Abstract

Background: TAVI is a widely accepted treatment for patients with severe aortic stenosis (AS). Despite the adoption of diverse therapies, opportunities remain to develop technologies tailored to provide optimal acute and potential long-term benefits, particularly around haemodynamics, flow and durability.

Aims: We aimed to evaluate the safety and feasibility of the DurAVR transcatheter heart valve (THV), a first-in-class biomimetic valve, in the treatment of patients with symptomatic severe AS.

Methods: This was a first-in-human (FIH), prospective, non-randomised, single-arm, single-centre study. Patients with severe, symptomatic AS of any surgical risk and who were eligible for the DurAVR THV prosthesis were recruited; they were assessed at baseline, 30 days, 6 months, and 1 year post-procedure for implant success, haemodynamic performance, and safety.

Results: Thirteen patients (73.9±6.4 years old, 77% female) were enrolled. The DurAVR THV was successfully implanted in 100% of cases with no device-related complications. One access site complication, one permanent pacemaker implantation, and one case of moderate aortic regurgitation occurred. Otherwise, no deaths, stroke, bleeding, reinterventions, or myocardial infarction were reported during any of the follow-up visits. Despite a mean annulus size of 22.95±1.09 mm, favourable haemodynamic results were observed at 30 days (effective orifice area [EOA] 2.00±0.17 cm^2, and mean pressure gradient [MPG] 9.02±2.68 mmHg) and were sustained at 1 year (EOA 1.96±0.11 cm^2, MPG 8.82±1.38 mmHg), resulting in zero patients with any degree of prosthesis-patient mismatch. Additionally, new valve performance measures derived from cardiovascular magnetic resonance displayed restoration of laminar flow, consistent with a predisease state, in conjunction with a mean coaptation length of 8.3±1.7 mm.

Conclusions: Preliminary results from the FIH study with DurAVR THV demonstrate a good safety profile with promising haemodynamic performance sustained at 1 year and restoration of near-normal flow dynamics. Further clinical investigation is warranted to evaluate how DurAVR THV may play a role in addressing the challenge of lifetime management in AS patients.

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Abbreviations

CMR	cardiovascular magnetic resonance
DVI	Doppler velocity index
EOA	effective orifice area
FD	flow displacement
FRR	flow reversal ratio
HALT	hypoattenuated leaflet thickening
iEOA	indexed effective orifice area
MPG	mean pressure gradient
PPI	permanent pacemaker implantation
PVL	paravalvular leak
TF	transfemoral
THV	transcatheter heart valve
TOE	transoesophageal echocardiogram
TTE	transthoracic echocardiogram

Introduction

Transcatheter aortic valve implantation (TAVI) has seen a significant evolution since it was first used in 2002, to today, where it has become an acceptable option for younger patients with lower surgical risk[1-3]. This transformation was primarily driven by the optimisation of the overall procedure, ease of use, size of delivery systems, reduction in residual paravalvular leak and the need for permanent pacemakers after implantation[4,5]. These incremental design advances have contributed to improved patient outcomes and the subsequent rapid adoption of TAVI globally[5-7].

Despite these advances, achieving ideal haemodynamic performance with current TAVI devices remains a significant clinical concern[8,9]. Considerable opportunity exists to challenge the current paradigm of incremental design improvement, in pursuit of true valve design innovation, with the goals of restoring haemodynamic performance and exercise capability to a predisease state. Advanced multimodality imaging, particularly cardiovascular magnetic resonance (CMR), plays an increasingly important role in our understanding of aortic stenosis (AS) and in the clinical evaluation of haemodynamic parameters such as aortic flow patterns, which could become potential therapeutic targets as they may impact patient outcomes[10,11].

The DurAVR transcatheter heart valve (THV) (Anteris Technologies), a first-in-class biomimetic valve, is designed to mimic the performance of a healthy native aortic valve. Traditional bioprosthetic aortic valves comprise 3 separate pieces of flat tissue sutured together, which hinder a complete valve opening and, thus, result in smaller orifice areas and are potentially linked with abnormal flow patterns[8,10]. In contrast, the DurAVR THV is manufactured by moulding a single piece of tissue into the shape of a native aortic valve, facilitating a larger orifice area and near-normal flow patterns. This novel valve design, combined with the proprietary ADAPT (Anteris Technologies) tissue engineering anticalcification process, is mounted on a short-frame, balloon-expandable platform with large open-cell geometry for coronary access **(Central illustration A)**. The objective of this first-in-human (FIH) study was to evaluate the safety and feasibility of the DurAVR THV in the treatment of patients with symptomatic severe AS and to better understand the differentiating impact of its unique biomimetic design.

Methods

STUDY DESIGN

This was a prospective, single-arm, single-centre, FIH study (ClinicalTrials.gov: NCT05182307). The study protocol was approved by the local ethics committee of Tbilisi Heart and Vascular Clinic, Tbilisi, Georgia, and required informed consent of all subjects for treatment with an investigational device and confirmation of their participation in follow-up for one year.

PATIENT POPULATION

A total of 25 patients with severe, symptomatic AS of any surgical risk were screened for the study between November 2021 and May 2022. Of these, 12 patients were excluded leaving 13 patients in the study. Inclusion and exclusion criteria for participation in the study, in addition to screen failure rationale, are provided in **Supplementary Appendix 1** and **Supplementary Appendix 2**. Eligibility of participants for delivery of the DurAVR THV prosthesis was determined by the study's Heart Team. Healthy controls were recruited from Dr Pankaj Garg's research study in Sheffield, UK, for a subanalysis. All participants gave informed consent for CMR imaging. This subanalysis was approved by the local ethics committee (18/NE/0186).

DEVICE DESCRIPTION

The Anteris DurAVR THV system is composed of the DurAVR THV and the ComASUR transfemoral (TF) delivery system (Anteris Technologies). The DurAVR THV comprises a balloon-expandable frame surrounding a single piece of bovine pericardial tissue moulded into a trileaflet valve to mimic the performance of a healthy native aortic valve. The bovine pericardium is treated with the proprietary ADAPT tissue engineering process. Compared to other biological materials used for cusp replacement, the ADAPT-treated bovine pericardium shows improved mechanical properties, like elasticity and strength, similar to healthy native aortic leaflets[12]. The single-piece structure aims at replicating the native valve tissue continuity and reduces the number of stitches needed in the manufacturing process, thus, leaving fewer potential sites for calcification initiation[13,14]. The ADAPT tissue engineering process is a platform technology developed to mitigate bioprosthetic calcification, which impacts valve durability. It is based on a multifactorial approach where all known antigens (phospholipids, cells and cell remnants, nucleic acids, alpha-gal) and process chemistry (crosslinking and storage), responsible for the inflammatory response leading to calcification, are addressed[15]. The balloon-expandable frame features large, open-cell geometry and radiopaque markers to facilitate valve rotation and achieve commissural alignment to the native aortic valve for improved haemodynamic performance and coronary access. The valve also includes a polyethylene terephthalate (PET) skirt to reduce potential paravalvular leakage (PVL) **(Central illustration A)**. The valve

CENTRAL ILLUSTRATION The DurAVR THV system: features, haemodynamic results and aortic flow characteristics.
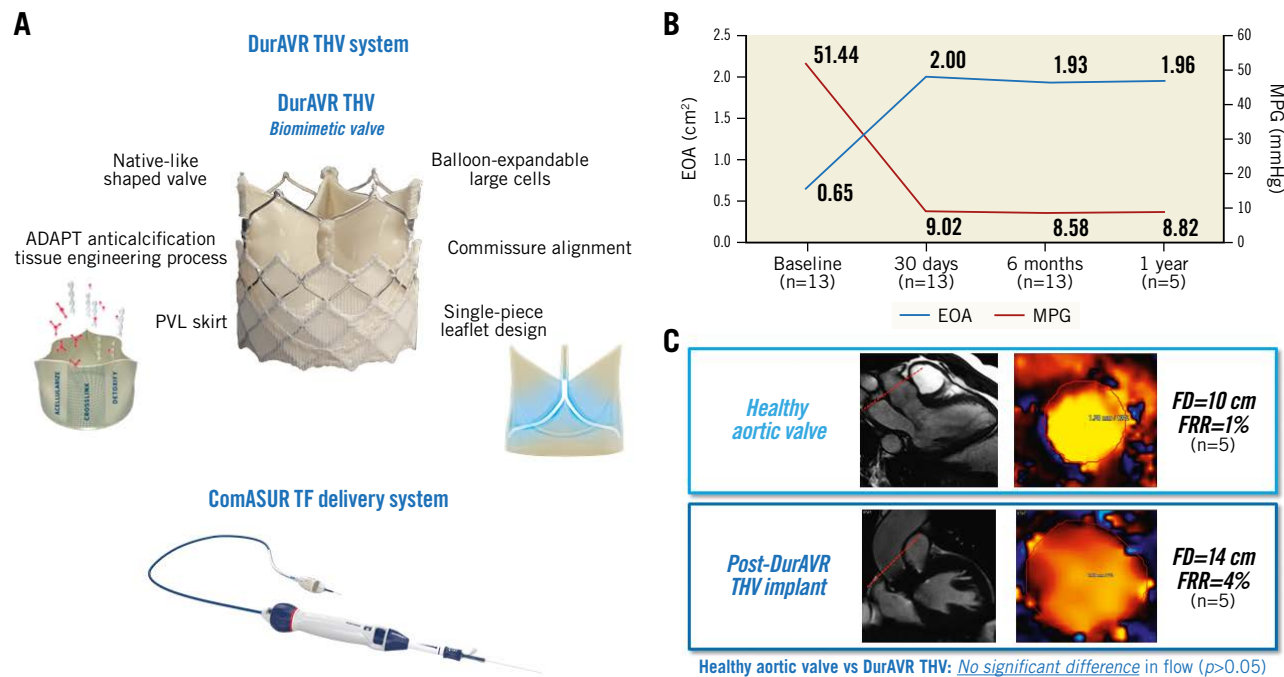
A) DurAVR THV system: DurAVR THV and ComASUR TF delivery system. B) Aortic valve haemodynamics: EOA and MPG at baseline, 30 days, 6 months, and 1 year post-procedure demonstrating favourable and sustained haemodynamic performance despite a mean annulus size of 22.95 mm and an aortic valve area of 409.22 mm². C) Two-dimensional CMR at 6 months showing no significant difference in aortic flow characteristics between a healthy aortic valve and a DurAVR THV (p>0.05 for both FD and FRR), thus demonstrating restoration of laminar aortic flow post-DurAVR THV implantation. CMR: cardiac magnetic resonance; EOA: effective orifice area; FD: flow displacement; FRR: flow reversal ratio; MPG: mean pressure gradient; PVL: paravalvular leak; TF: transfemoral; THV: transcatheter heart valve

is currently available in 1 size and was used in our study for the treatment of native aortic annuli with an area-derived diameter of 21 to 25 mm. The DurAVR THV is directly crimped onto a balloon-expandable catheter and delivered transfemorally via the ComASUR TF delivery system.

IMPLANT PROCEDURE

Given the FIH nature of this study, all procedures were performed using general anaesthesia and transoesophageal echocardiographic (TOE) guidance. For peripheral access cases, the ComASUR TF delivery system was used. A 22 Fr Gore DrySeal delivery sheath (W.L. Gore & Associates) − compatible with the expandable 14 Fr sheath currently in development − was introduced into the vasculature and a Safari wire (Boston Scientific) was placed in the left ventricle. Balloon aortic valvuloplasty (BAV) was performed with rapid ventricular pacing in all cases prior to valve implantation. The DurAVR THV was deployed under fluoroscopic guidance after assessment of its position in the proper anatomical location. Appropriate valve expansion, haemodynamic function, and the presence of paravalvular leaks and central aortic regurgitation were then assessed via TOE. European guidelines for anticoagulation management in valvular heart disease were followed, with all patients receiving low-dose acetylsalicylic acid (100 mg) post-TAVI or dual antiplatelet therapy, as needed.[6]

STUDY ASSESSMENTS AND PRIMARY ENDPOINTS

Patients were assessed at baseline, and again at 30 days, 6 months, and 1 year post-procedure. Visits included medical, echocardiographic, cardiac computed tomography (CT) and CMR assessments, the Kansas City Cardiomyopathy Questionnaire (KCCQ) and a 6-minute walk test (6MWT). Primary performance endpoints were the correct positioning of a single DurAVR THV into the proper anatomical location and postoperative haemodynamic performance; safety endpoints were all-cause mortality, myocardial infarction, disabling stroke, and life-threatening bleeding at 30-day and 1-year follow-up. Study endpoints were defined according to the Valve Academic Research Consortium (VARC)-3 guidelines[16].

ECHOCARDIOGRAPHY

All echocardiograms were performed according to the American Society of Echocardiography guidelines for transthoracic echocardiogram (TTE) examination[17]. The grading of aortic stenosis was performed using mean gradients and peak velocities, as well as the

dimensionless index. The effective orifice area (EOA) was calculated by the continuity equation[18].

CARDIOVASCULAR MAGNETIC RESONANCE

CMR acquisition was performed on a 3.0T Ingenia (Philips). Balanced, steady-state, free precession, end-expiratory breath-hold cine images were acquired for the 2-, 3- and 4-chamber long-axis views and a stack of short-axis images, as per the standardised protocols[19]. Two-dimensional phase-contrast velocity-encoded flow with 30 frames per RR interval was acquired in the ascending aorta at an orthogonal plane just above the sinotubular junction and at the mid-level of the main pulmonary artery.

CARDIAC MAGNETIC RESONANCE IMAGE ANALYSIS

All CMR image analyses were performed at a core laboratory using commercial research software MASS (version 2022 EXP; Leiden University Medical Center). Peak systolic flow displacement (FD), a marker of flow eccentricity, was calculated as the distance between the vessel centreline and the centre of the eccentric flow. It was normalised for overall vessel size at the peak systolic phase[11] and is presented as a percentage in this paper. Peak systolic flow reversal ratio (FRR) was calculated as previously described in the literature[20].

STATISTICAL ANALYSIS

This is a FIH feasibility study, and thus, primary endpoints are not powered for statistical differences to historical controls. The sample size allowed investigators to make a qualitative assessment of the safety of DurAVR THV in the population studied. Study endpoints, including baseline characteristics, procedural details and clinical outcomes, are presented as percentage for categorical variables and mean±standard deviation for continuous variables without formal statistical testing.

Results

BASELINE PATIENT CHARACTERISTICS

A total of 13 patients were enrolled in the study. Baseline characteristics of the intention-to-treat (ITT) population are provided in **Table 1**. The mean age was 73.9±6.4 years, and 10 (77%) were female. Overall, patients had a mean Society of Thoracic Surgeons (STS) score of 2.3±1.1%. Prior to procedures, 11 patients (85%) were in New York Heart Association (NYHA) Functional Class II, and 2 (15%) were in NYHA Class III. Additionally, the mean aortic annulus systolic diameter by computed tomography angiography (CTA) was 22.95±1.09 mm. Several challenging anatomies were treated in this FIH study, including patients with severe annular calcium, extreme leaflet calcium, type 1 bicuspid aortic valve morphology, and severe left ventricular outflow tract (LVOT) calcium.

PROCEDURAL CHARACTERISTICS AND CLINICAL ENDPOINTS

A single DurAVR THV was successfully implanted in each of the 13 patients enrolled in the study (100% success). Procedural

characteristics and details are shown in **Table 2**. The first cohort of 5 patients enrolled in November 2021 underwent a TAVI procedure with a direct aortic approach. The second cohort of 8 patients was enrolled in May 2022 after development of the ComASUR TF delivery system. The vascular access was transfemoral in 7 cases and transcarotid in 1 case. There were no device-related complications, need for a second TAVI device, nor conversions to open heart surgery. One access site complication (thrombosis of the external iliac artery and common femoral artery secondary to the access site closure) occurred. The patient underwent vascular surgery on postoperative day 1 and the event was resolved with a favourable outcome. In addition, 1 new permanent pacemaker was implanted as a precautionary measure on postoperative day 6 in a patient with pre-existing right bundle branch block (QRS duration 144 ms prior to DurAVR THV implant) and left anterior fascicular block.

The study safety endpoints are provided in **Table 3**. No deaths, myocardial infarction, stroke, minor or life-threatening bleeding occurred during any of the follow-up timepoints of 30 days, 6 months and 1 year. There were no device-related complications, reoperation or reinterventions reported or changes in QRS and PR intervals observed throughout follow-up, apart from the patient who was implanted with the permanent pacemaker. Additionally, no neurological dysfunction or acute kidney injury were recorded. Outcomes for the 6MWT showed improvement from baseline with a 31% increase in the average walked distance at 1 year. Moreover, the KCCQ score was 20.4 points higher at 6 months (n=13) and 22.9 points higher at 1-year (n=5) follow-up compared to baseline, demonstrating continuous improvement in exercise capacity and quality of life.

Echocardiography results demonstrate a robust and consistent haemodynamic performance up to 1-year follow-up **(Table 4)**. Despite a small mean annulus diameter (22.95±1.09 mm on baseline CT), TTE at 30 days post-procedure showed a mean EOA of 2.00±0.17 cm², mean indexed effective orifice area (iEOA) of 1.14±0.15 cm²/m², mean pressure gradient (MPG) of 9.02±2.68 mmHg, and mean Doppler velocity index (DVI) of 0.53±0.10. The echo assessment at 6 months (n=13) confirmed sustained performance with a mean EOA of 1.93±0.15 cm² (mean iEOA 1.10±0.18 cm²/m²), mean MPG of 8.58±2.04 mmHg and mean DVI of 0.55±0.10. The one-year results on the first five patients reported a mean EOA of 1.96±0.11 cm² (mean iEOA 1.11±0.07 cm²/m²), mean MPG of 8.82±1.38 mmHg, and mean DVI of 0.54±0.05, further strengthening these findings **(Central illustration B)**. In addition, no moderate or severe prothesis-patient mismatch (PPM) was observed **(Table 4)**[21].

There was one case of moderate central aortic regurgitation (AR) secondary to balloon overexpansion of the proximal valve frame in the first case of the second patient cohort (immediately addressed prior to the following cases) that remained unchanged at 6-month follow-up. For the entire cohort, at 30 days, 6 months and 1 year, there was no moderate or severe PVL. At 30 days, 5 cases

Table 1. Patient baseline characteristics.

Characteristics		n=13
Age, years		73.9±6.4
Gender, female		10 (77)
Society of Thoracic Surgeons score, %		2.3±1.1
EuroSCORE II, %		1.5±0.7
New York Heart Association Functional Class	I	0 (0)
	II	11 (85)
	III	2 (15)
	IV	0 (0)
Medical history and previous cardiovascular interventions	Coronary artery disease	9 (69)
	Aortic valve insufficiency (mild to moderate)	9 (69)
	History of conduction disturbances	6 (46)
	Mitral valve insufficiency	5 (38)
	Smoker (former or current)	4 (31)
	Previous myocardial infarction	3 (23)
	Diabetes	3 (23)
	Tricuspid valve insufficiency	3 (23)
	Obesity	2 (15)
	Cerebrovascular disease	0 (0)
	Chronic obstructive pulmonary disease	0 (0)
	Percutaneous coronary intervention	8 (62)
	Coronary artery bypass grafting	2 (15)
	Permanent pacemaker implant	1 (8)
Computed tomography data		
Aortic root analysis	Left ventricular outflow tract diameter, mm	23.18±1.81 [20.7, 26.6]
Annulus valve analysis	Perimeter, mm	72.58±3.49 [67.9, 78.4]
	Perimeter-derived diameter, mm	23.09±1.11 [21.6, 24.9]
	Aortic area, mm^2	409.22±38.47 [355.2, 479.6]
	Area-derived diameter, mm	22.95±1.09 [21.3, 24.5]
	Minimum diameter, mm	20.54±1.13 [17.8, 22.7]
	Maximum diameter, mm	25.38±1.34 [23.5, 28]
	Eccentricity	0.19±0.05 [0.14, 0.28]
Sinus of Valsalva diameter	Left, mm	30.50±1.18 [28.5, 33.1]
	Right, mm	29.26±1.71 [26.4, 33.0]
	Non-coronary, mm	30.85±2.36 [27.3, 35.2]
Height of coronary ostia	Left, mm	13.99±2.68 [9.1, 19.1]
	Right, mm	18.06±3.49 [12.1, 23.5]
Sinotubular junction diameter, mm		27.81±2.74 [23.9, 32.7]
Sinotubular junction height, mm		20.00±1.79 [18.5, 24.3]
Ascending aorta diameter, mm		34.41±4.53 [27.4, 42.3]
Data are presented as n (%) or mean±standard deviation [min, max]. EuroSCORE: European System for Cardiac Operative Risk Evaluation		

had none/trace PVL, while at 6 months, PVL was none/trace in 7 cases. For the first 5 patients who completed their 1-year assessment, 2 had mild PVL and 3 had none/trace.

The postprocedural CT results at 30 days confirmed normal leaflet mobility and no calcifications. CT images showed the DurAVR THV in the same position as at implant and no frame deformation. There was one case of hypoattenuated leaflet thickening (HALT) limited to the base and one case of 50-75% HALT on the right cusp. None of these subclinical findings led to changes in haemodynamics and/or symptoms. Both patients started oral anticoagulation therapy, which resulted in the complete resolution of the 50-75% HALT, while the other remained unchanged.

NEW PARAMETERS FOR PERFORMANCE ASSESSMENT OF THE DURAVR THV BIOMIMETIC VALVE

The unique leaflet design and performance of DurAVR THV was evaluated in multiple modalities. Intraoperative TOEs revealed a mean leaflet coaptation length of 8.3±1.8 mm; CT scan results at 30 days were consistent with these findings and visually displayed the unique leaflet design *in vivo* **(Figure 1A)**.

The TTE at 30 days displayed consistent laminar flow throughout the valve **(Figure 1B)**. In addition, the first 5 patients underwent CMR which incorporated two-dimensional phase contrast at the level of the ascending aorta at 6 months to investigate the aortic flow physiology post-DurAVR THV implantation. Aortic flow characteristics were assessed through the measurement of aortic FD and aortic systolic

Table 2. Procedural characteristics.

Parameters		n=13
Approach	Transfemoral	7 (54)
	Transaortic	5 (38)
	Transcarotid	1 (8)
General anaesthesia		13 (100)
Predilatation		13 (100)
Post-dilatation		10 (77)
Contrast media, ml		105±32
Fluoroscopy time, mm:ss		19:54±06:24 [09:19, 33:01]
DurAVR THV implant time, hh:mm		0:18±0:10 [0:07; 0:46]
DurAVR THV implant success*		13 (100)
Coaptation length (intraprocedural TOE), mm		8.3±1.8 [6.0, 11.1]
Postoperative transthoracic echocardiography		
Mean pressure gradient, mmHg		8.34±1.74 [6.00, 11.00]
Effective orifice area, cm²		2.12±0.29 [1.83, 2.71]
Major paravalvular leak (moderate or severe)		0 (0)
Major aortic regurgitation (moderate or severe)		0 (0)
Data are presented as n (%) or mean±SD [min, max]. *One single DurAVR THV implanted with no device-related complications nor conversion to open heart surgery. SD: standard deviation; THV: transcatheter heart valve; TOE: transoesophageal echocardiography		

FRR. The average FD was 14±10 cm while the average FRR was 4±6%. The results of the first 5 patients who received the DurAVR THV were compared with those of 5 age/height/weight-matched controls with healthy native aortic valves (**Central illustration C**). Characteristics of the healthy controls and their comparison to the DurAVR THV group are provided in **Supplementary Appendix 3**. DurAVR THV recipients had comparable flow displacement (14±10 cm vs 10±5 cm; p=0.453) and minimal flow reversal ratio (4±6% vs 1±1%; p=0.328) to the controls. Together these results, in conjunction with the echocardiographic findings at 30 days, indicate that the novel leaflet design of DurAVR THV restores laminar aortic flow.

Discussion

In this study we report the first clinical use of the novel biomimetic DurAVR THV. High implant success with a good safety profile was demonstrated. In this small sample size, none of the safety endpoints (mortality for any cause, myocardial infarction, disabling stroke, and life-threatening bleeding) occurred. One case of permanent pacemaker implantation (PPI) was reported in a patient with pre-existing conduction disturbances. Of note, no increase in the QRS interval from baseline was observed in the remaining patients throughout the study. The 30-day TTE showed 1 case of moderate central AR secondary to balloon overexpansion that remained unchanged up to the 6-month follow-up. Considering this is an FIH study, we chose to perform pre-BAV in all cases and elected to be conservative in our implant strategy, undersizing at first and then

Table 3. Cumulative events at 30-day, 6-month and 1-year follow-up.

Event	30-day follow-up n=13	6-month follow-up n=13	1-year follow-up n=5
Primary safety endpoints			
All-cause mortality	0 (0)	0 (0)	0 (0)
Myocardial infarction	0 (0)	0 (0)	0 (0)
Disabling stroke	0 (0)	0 (0)	0 (0)
Life-threatening bleeding	0 (0)	0 (0)	0 (0)
VARC-3 endpoints*			
Valve-related mortality	0 (0)	0 (0)	0 (0)
All strokes	0 (0)	0 (0)	0 (0)
Neurological dysfunctions	0 (0)	0 (0)	0 (0)
All bleeding	0 (0)	0 (0)	0 (0)
Major vascular complications	1 (7.69)	0 (0)	0 (0)
Minor vascular complications	0 (0)	0 (0)	0 (0)
Cardiac complications	0 (0)	0 (0)	0 (0)
Permanent pacemaker implant	1 (7.69)	0 (0)	0 (0)
Bioprosthetic valve dysfunction	0 (0)	0 (0)	0 (0)
Structural valve deterioration	0 (0)	0 (0)	0 (0)
Reoperations/reinterventions on the study valve	0 (0)	0 (0)	0 (0)
Acute kidney injury	0 (0)	0 (0)	0 (0)
Major paravalvular leak (moderate or severe)	0 (0)	0 (0)	0 (0)
Major aortic regurgitation (moderate or severe)	1 (7.69)	1 (7.69)	0 (0)
Values are n (%). *Study endpoints are defined according to the VARC-3 guidelines[16]. VARC: Valve Academic Research Consortium			

Table 4. Clinical and haemodynamic results at baseline, 30-day, 6-month and 1-year follow-up.

	Baseline	30 days	6 months	1 year
NYHA Class	**n=13**	**n=13**	**n=13**	**n=5**
NYHA I	0 (0)	2 (15.4)	4 (30.8)	2 (40.0)
NYHA II	11 (84.6)	9 (69.2)	9 (69.2)	3 (60.0)
NYHA III	2 (15.4)	2 (15.4)	0 (0)	0 (0)
NYHA IV	0 (0)	0 (0)	0 (0)	0 (0)
6-minute walk test (6MWT)	**n=13**	**n=13**	**n=12***	**n=4***
Total walked distance, m	230.9±45.7	278.2±59.3	306.0±52.8	323.5±48.1
KCCQ	**n=13**	**n=13**	**n=13**	**n=5**
Overall summary score	37.8±8.4	52.8±9.7	58.2±14.1	67.8±18.8
Electrocardiogram results	**n=13**	**n=13**	**n=13**	**n=5**
PR interval, ms	172.7±44.9	176.6±41.5	184.6±50.5	184.4±46.0
QRS interval, ms	107.2±23.9	107.5±22.0	111.5±25.2	108.4±24.3
Haemodynamic results	**n=13**	**n=13**	**n=13**	**n=5**
Effective orifice area, cm^2	0.65±0.20	2.00±0.20	1.93±0.12	1.96±0.10
Indexed effective orifice area, cm^2/m^2	0.37±0.10	1.14±0.20	1.10±0.20	1.11±0.10
Mean pressure gradient, mmHg	51.44±18.3	9.02±2.7	8.58±2.0	8.82±1.4
Peak pressure gradient, mmHg	85.48±29.9	18.66±5.67	16.58±4.3	18.06±3.3
Doppler velocity index	0.20±0.00	0.53±0.10	0.55±0.10	0.54±0.10
Left ventricular ejection fraction, %	57.0±7.3	59.0±11.5	59.0±12.0	56.0±9.5
Moderate prosthesis-patient mismatch	N/A	0 (0)	0 (0)	0 (0)
Severe prosthesis-patient mismatch	N/A	0 (0)	0 (0)	0 (0)

Data are presented as n (%) or mean±SD. *One patient unable to complete the 6MWT at 6 months and 1 year due to hip replacement. KCCQ: Kansas City Cardiomyopathy Questionnaire; N/A: not applicable; NYHA: New York Heart Association; SD: standard deviation
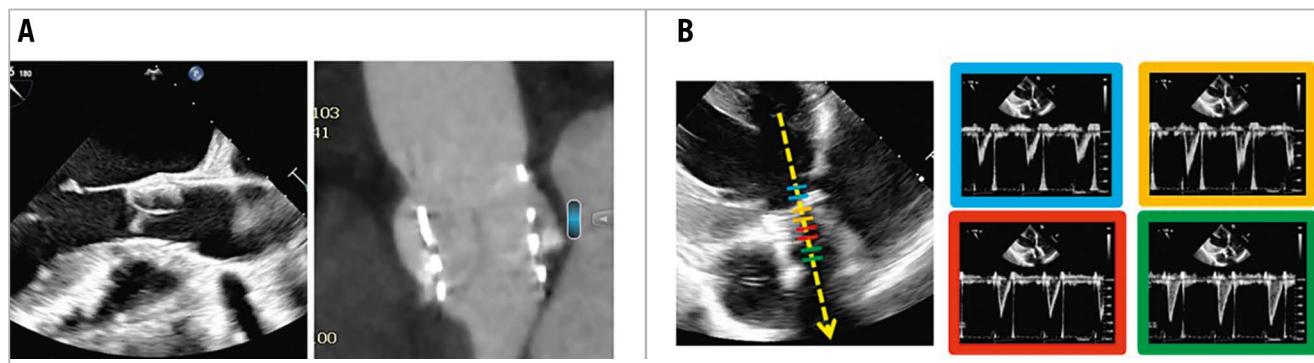
Figure 1. DurAVR THV is the first AVR shown to restore normal aortic blood flow. A) Intraoperative TOE (left) and 30-day CT scan (right) displaying the DurAVR THV leaflet coaptation length. B) 30-day TTE, showing consistent laminar flow throughout the valve. AVR: aortic valve replacement; CT: computed tomography; TOE: transoesophageal echocardiography; THV: transcatheter heart valve; TTE: transthoracic echocardiography

adding volume. In 77% of the cases, we also performed post-dilatation. Moving to larger clinical studies, we expect lower pre- and post-dilation rates, similar to other balloon-expandable THVs[22].

The DurAVR THV displayed an excellent haemodynamic performance up to 1-year follow-up despite a small mean patient annulus size. Contemporary data from clinical studies with commercially available TAVI technologies in the US showed a smaller EOA in patients with a similar baseline native aortic valve area or native annular diameter[23]. While DurAVR THV showed a mean EOA of 2.00±0.17 cm^2 at 30 days, in a study by Hahn et al[23], a mean EOA of 1.58±0.33 cm^2 was reported for the SAPIEN 3 (Edwards Lifesciences) group (native aortic valve area

385-439 mm^2) and a mean EOA of 1.82±0.43 cm^2 was reported for the Evolut R (Medtronic) group (native annular diameter >22.3 to ≤23.3 mm). We believe the favourable haemodynamic findings in our study are the result of the biomimetic design of DurAVR THV and the long coaptation length, which allow for a larger EOA.

The restoration of near-normal haemodynamics likely contributed to improved exercise capacity, measured by the 6MWT, and improved quality of life, assessed through the KCCQ. This is particularly relevant with the current change in guidelines, with TAVI now recommended in younger and low-risk patients who are expected to have an active lifestyle[6,7].

Previous observational studies using four-dimensional (4D) flow CMR to quantify aortic flow haemodynamics have demonstrated that TAVI devices have a greater degree of flow eccentricity than surgical aortic valve replacement (SAVR)[10], potentially leading to increased wall shear stress, arterial stiffness, and aortic root dilatation[24,25], which is an undesirable clinical outcome if TAVI was to be considered in younger cohort of patients. More recently, a large observational study also confirmed that systolic flow reversal is independently associated with ascending aorta dilatation even without any significant gradient across the aortic valve[26]. Our CMR substudy reported for the first time restoration of aortic flow eccentricity and systolic flow reversal ratio. Collectively, our data indicate that the novel leaflet design of the DurAVR THV restores ascending aortic flow patterns. This physiological advantage may have potential clinical benefits in reducing the risk of aortic dilatation and remodelling and ameliorating the potential increased aortic stiffness seen after SAVR[27]. Additional studies are warranted to investigate the prognostic importance of restoration of normal aortic flow on durability, myocardial recovery, and myocardial remodelling.

Study limitations

This study is not without limitations, given this is a first-in-human experience, with a small sample size and no comparator arm. Thus, the current study provides insights for future trials with larger populations and adequate power to validate clinical outcomes. Moreover, this study was not statistically powered for clinical endpoints at each follow-up timepoint and, therefore, results should be interpreted with caution and considered hypothesis-generating only. Given the length of follow-up, the study was not intended to prove the durability of the DurAVR THV System.

Conclusions

The DurAVR THV FIH study provides encouraging echo and CMR evidence of near-normal haemodynamics and normalised flow characteristics associated with its unique native-like properties at 1-year follow-up. The preliminary observations provided here will serve as a basis for future powered clinical trials to gain a better understanding of how the acute benefits of a biomimetic design (haemodynamics and normalised flow) impact on quality of life, durability, myocardial recovery, myocardial remodelling and aortopathies in the long-term treatment of AS.

Impact on daily practice

At 1-year follow-up, the DurAVR THV FIH study provides encouraging echo and CMR evidence of improved haemodynamics and normalised flow characteristics associated with its unique single-piece leaflet design. These findings demonstrate that valve leaflet design appears to play a significant role in acute haemodynamic benefits (EOA and MPG), as well as aortic flow patterns (laminar flow), leading to potential short- and long-term favourable clinical implications. Additional studies and further direct comparisons with other commercial TAVI systems will establish the clinical value of this new and highly differentiated TAVI device.

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Conflict of interest statement

S.K. Kodali is a consultant for Anteris Technologies, TRiCares, TriFlo Cardiovascular, xDot Medical, Micro Interventional Devices, Supira Medical, Adona Medical, Tioga Cardiovascular, HVR Cardio, and Moray Medical; serves on the scientific advisory boards for Dura Biotech, Thubrikar Aortic Valve, Philips, Medtronic, Boston Scientific, and Abbott Laboratories; and has received institutional research funding from Edwards Lifesciences, Medtronic, Abbott Vascular, Boston Scientific, and JenaValve Technology. P. Sorajja serves on the advisory boards of 4C Medical Technologies, Abbott Structural (Global Valve Masters, Global Complexity Score, Tricuspid Advisory Board), Boston Scientific SHV Strategic Advisory Board, Medtronic Structural Advisory Board, and VDyne; has received consulting fees from 4C Medical Technologies, Anteris Technologies, Abbott Structural, Boston Scientific, Edwards Lifesciences, Evolution Medical Technologies, Foldax, GLG, Medtronic, Philips, Siemens, Shifamed, W.L. Gore, VDyne, and xDot Medical; and served as member of REPAIR MR Steering Committee, EXPAND Steering Committee, W.L. Gore Pipeline Executive Committee, SUMMIT Steering Committee, TRILUMINATE Steering Committee, TRILUMINATE Eligibility Committee for Anatomy, G4 Adverse Leaflet Events Committee, Neovasc Executive Steering Committee; National or Global Principal Investigator for TRILUMINATE Pivotal US Trial, SUMMIT MAC Pivotal Trial, EXPAND EFS and Pivotal US Trial, HighLife (USA) EFS, VDyne EFS, SOAR EFS and AMEND EFS. C.U. Medori is the CMO at Anteris Technologies; received grants/research support

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Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria of the DurAVR THV study.

Supplementary Appendix 2. Patient enrolment flowchart.

Supplementary Appendix 3. Study cohort with aortic flow characteristics on cardiac MRI.

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Supplementary data

Supplementary Appendix 1. Inclusion and exclusion criteria of the DurAVR THV study.

Inclusion criteria

Subjects are eligible for entry in this study if <u>ALL</u> the following conditions are met:
1. Symptomatic, severe aortic stenosis*

2. Preprocedural required measurements: aortic annulus diameter 21-25 mm and minimum access vessel diameter of 5.5 mm via TTE and CT

3. Anatomy appropriate to accommodate safe placement of DurAVR™ THV (Preprocedural measurements by TTE and CT required: aortic annulus diameter 21-25 mm by CT, minimum access vessel diameter of 5.5 mm)

4. Understands the study requirements and the treatment procedures and provides written informed consent

5. Subject agrees to complete all required scheduled follow-up visits

*Critical aortic valve area defined as an initial aortic valve area of ≤ 1.0 cm^2 OR aortic valve area index < 0.6 cm^2/m^2 AND, in presence of left ventricular function (LVEF $> 40\%$):
    a.   Mean gradient $\geq$40mmHg OR
    b.   Vmax$\geq$ 4m/sec OR
    c.   DVI ≤ 0.25

Exclusion criteria

Subjects are eligible for entry in this study if <u>NONE</u> of the following conditions are met:
Anatomical
1. Anatomy precluding safe placement of DurAVR™ THV
2. Pre-existing prosthetic heart valve in any position
3. Congenital unicuspid or bicuspid aortic valve with no raphe (Sievers classification type 0)
4. Severe aortic regurgitation
5. Severe mitral or severe tricuspid regurgitation requiring intervention.
6. Moderate to severe mitral stenosis
7. Hypertrophic obstructive cardiomyopathy
8. Echocardiographic evidence of intracardiac mass, thrombus or vegetation requiring treatment.
9. Severe basal septal hypertrophy with outflow gradient

Clinical
10. Evidence of an acute myocardial infarction $\leq$ 30 days before the intended treatment
11. Determined inoperable/ineligible for surgery by the Heart Team
12. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure
13. Blood dyscrasias as defined: leukopenia (WBC < 1000 mm^3), thrombocytopenia (platelet count $<50,000$ cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states
14. Untreated clinically significant Coronary Artery Disease (CAD) requiring revascularization
15. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
16. Need for emergency surgery for any reason
17. Ventricular dysfunction with LVEF$\leq$40% as measured by resting echocardiogram
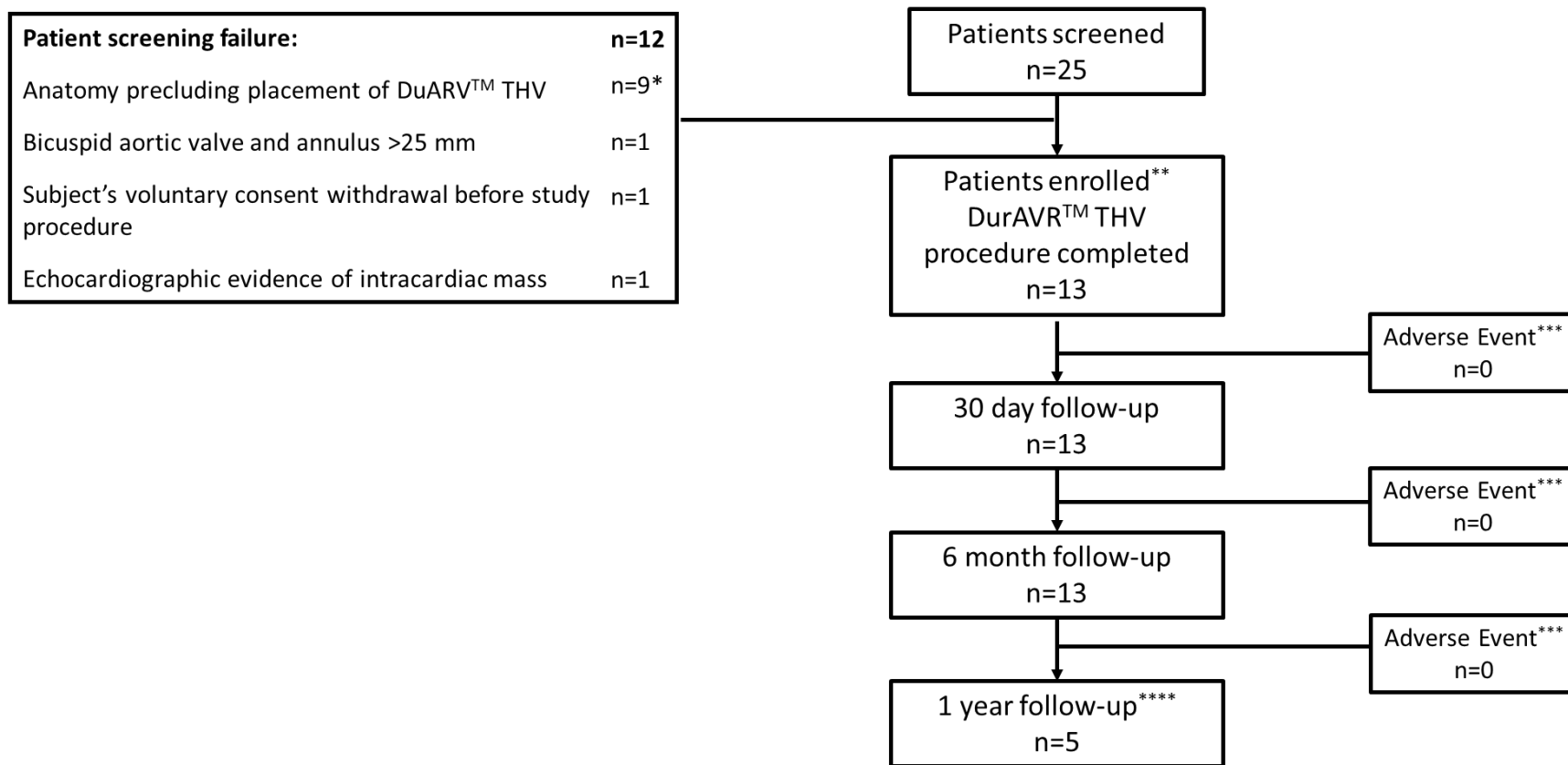
18. Recent (within 6 months) CVA or TIA
19. Symptomatic carotid or vertebral artery disease
20. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min
21. GI bleeding within the past 3 months
22. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated: aspirin, heparin, nitinol (titanium or nickel), ticlopidine and clopidogrel, contrast media
23. Ongoing sepsis, including active endocarditis (Duke Criteria)
24. Subject refuses a blood transfusion
25. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions
26. Other medical, social or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent
27. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with following visits).
28. Currently participating in an investigational drug or another investigational device trial
29. Subject belongs to a vulnerable population

Abbreviations: CAD, coronary artery disease; CT, computed tomography; CVA, cerebrovascular accident; GI, gastrointestinal; LVEF, left ventricular ejection fraction; THV, transcatheter heart valve; TIA, transient ischemic attack; TTE, transthoracic echocardiogram.

Supplementary Appendix 2. Patient enrolment flowchart.

Patient screening failure:	n=12
Anatomy precluding placement of DuARV™ THV	n=9*
Bicuspid aortic valve and annulus >25 mm	n=1
Subject's voluntary consent withdrawal before study procedure	n=1
Echocardiographic evidence of intracardiac mass	n=1

Patients screened
n=25

Patients enrolled**
DurAVR™ THV
procedure completed
n=13

Adverse Event***
n=0

30 day follow-up
n=13

Adverse Event***
n=0

6 month follow-up
n=13

Adverse Event***
n=0

1 year follow-up****
n=5

*7 patients had annulus outside of the criteria range, 1 patient was unsuitable for peripheral access, and 1 pre-existing coronary stent position precluding safe placement of the DurAVR™ THV
**Point of enrolment: A subject will be considered enrolled into the study once informed consent is obtained, all inclusion and no exclusion criteria are met, and the implant of DurAVR™ THV is initiated. The DurAVR™ THV implant is considered initiated when the subject is laying on the table in the hybrid operating room/catheterization lab, is sedated, and the DurAVR™ THV System device package is open.
***No subjects died or exited the study prior to study completion
****To date

Supplementary Appendix 3. Study cohort with aortic flow characteristics on cardiac MRI.

	Healthy control	DurAVR™ THV	Healthy Control vs DurAVR™ THV
	n=5	n=5	P-value
Clinical characteristics			
Age, years	60±15	73±9	0.115
Height, cm	169±10	162±9	0.315
Weight, kg	75±7	69±8	0.220
Aortic Systolic Flow characteristics			
Aortic Forward Flow, ml	66±24	71±26	0.760
Aortic Regurgitation, ml	2±2	8±6	0.087
Aortic flow displacement (FD), cm	10±5	14±10	0.453
Aortic flow reversal ratio (FFR), %	1±1	4±6	0.328

Data presented as n or mean±SD