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Non-implant valve repair for calcific aortic stenosis: the Leaflex study

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Introduction

Senile calcific aortic stenosis (AS) is a multifactorial degenerative disease which results in calcification of the aortic valve leaflets. A bridging pattern of calcium involving both the centre and bases of the leaflets is typical and causes progressive restriction of valve opening, yielding the clinical syndrome of symptomatic AS. The Leaflex™ device (Pi-Cardia, Rehovot, Israel) is designed to score calcium deposits on the aortic surface of calcified aortic valve leaflets. The scoring lines aim to segment restrictive deposits and thereby increase mobility, reducing the severity of AS without implantation of a bioprosthetic valve. The device has undergone extensive bench testing in a reconstructed excised human stenotic aortic valve model[1] and was also tested intraoperatively[2]. The aim of this first-in-human study was to evaluate the safety, feasibility, and performance of aortic valve repair with the transfemoral Leaflex device.

Methods

We conducted a single-arm prospective first-in-man evaluation of the Leaflex device in six centres in Europe and Israel **(Supplementary Appendix 1)**. Patients undergoing transcatheter aortic valve implantation (TAVI) for treatment of symptomatic severe AS were considered for the study. Eligibility criteria, an example computed tomography (CT) scan, and core labs are provided in **Supplementary Appendix 2** and **Supplementary Figure 1**.

The scoring procedure is shown in **Figure 1** and **Moving image 1**. The device components are described in **Supplementary Appendix 3** and illustrated in **Supplementary Figure 2**. The Leaflex intervention was performed during the index TAVI procedure. General anaesthesia (GA) was recommended due to the requirement for transoesophageal echocardiography assessment of the acute performance of the system. A SENTINEL™ embolic protection device (Boston Scientific, Marlborough, MA, USA) was inserted from the right radial artery, as per recommendation. Femoral access was achieved through a 16 Fr arterial sheath in standard fashion. A stiff guidewire was placed in the left ventricle and the Leaflex system was introduced across the aortic valve. Following unsheathing and positioning of the device, scoring was performed with the intention of creating multiple scoring lines in

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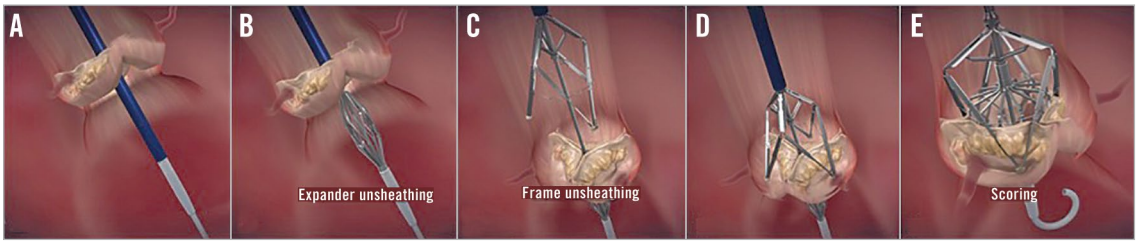

Figure 1. *Mechanism of action. Scoring steps – Leaflex insertion and valve crossing (A), expander unsheathing below valve (B), frame unsheathing above valve (C), frame landing on valve (D), scoring (E).*

different locations across the valve leaflets. Echocardiographic and valve haemodynamic measurements were performed before and after the Leaflex procedure. On completion of the Leaflex procedure, a standard TAVI was performed. Sheath removal and femoral closure was carried out as per standard procedure and patients were monitored in hospital for at least 24 hours. Clinical follow-up was mandated at one and three months. Post-procedural anticoagulation therapy was at the operator's discretion. Endpoints, definitions and statistical analysis are described in **Supplementary Appendix 4** and **Supplementary Appendix 5**.

The study protocol was approved by national regulatory authorities and local ethics committees, and all patients signed written informed consent for study participation.

Results

Sixteen patients were enrolled from May 2018 to April 2019. Demographics and baseline echocardiographic findings are shown in **Supplementary Table 1**. Fifteen procedures were performed under GA. The Leaflex procedure was followed by TAVI in 15 patients. In one patient, a guidewire perforation occurred, requiring surgical repair without subsequent TAVI.

In the first four cases, less than full expansion of the device with incomplete leaflet scoring was observed. This was caused by high friction forces between the internal shafts of the delivery system and required a design modification. Thereafter, successful scoring was achieved in all but one case, where initially the device could not be positioned on the valve due to anatomical reasons and had mechanical failure after resheathing.

We report echocardiographic and haemodynamic results in the patient cohort treated with the modified device, where scoring was performed as intended (N=11) **(Table 1)**. In these cases, the mean aortic valve area (AVA) increased from 0.7±0.1 cm^2 to 1.2±0.3 cm^2 (p<0.001). Invasive measurements showed a relevant reduction of peak-to-peak pressure gradient (51±29 mmHg to 21±23 mmHg, p<0.001). Structural valve damage was not observed, and there was only one case with echocardiographically severe aortic regurgitation (AR), but none with haemodynamic effects **(Supplementary Table 2, Supplementary Table 3)**. **Figure 2** shows an example of the haemodynamic improvement and planimetry before and after a successful procedure. The median Leaflex procedure time (device insertion to removal) was 23 minutes.

Table 1. Core lab-validated echocardiographic measurements and invasive pressure measurements.

Echocardiography and haemodynamic measurements N=11	Pre (Mean±SD)	Post (Mean±SD)
Aortic valve area, cm^2	0.7±0.1	1.2±0.3*
Mean pressure gradient, mmHg	33±13	17±10*
Peak-to-peak pressure gradient, mmHg	51±29	21±23*
*Pre vs post: p<0.001.		

In three patients, balloon aortic valvuloplasty (BAV) was performed post TAVI for bioprosthesis optimisation. Moderate paravalvular leak (PVL) post TAVI was observed in two patients. Four patients received new permanent pacemaker implantation following TAVI (days 0, 2, 4 and 86 post procedure). In two of these patients a new conduction disturbance occurred after the Leaflex procedure.

One patient suffered a wire-related ventricular perforation. This occurred following uneventful positioning and three complete scorings. Pericardiocentesis and fluid resuscitation was instigated. The patient underwent emergency sternotomy with surgical repair of perforation/tear in the left ventricle (LV).

There were two disabling strokes, both attributed to prolonged procedures with protracted periods of hypotension due to complications. The first patient suffered a stroke after surgical conversion following LV guidewire perforation. The second patient had a prolonged procedure, with a period of hypotension caused by a failure in the external (sheathing) tube which prevented sheathing of the frame. It was eventually sheathed by the introducer and successfully removed. One patient died of an unrelated syndrome with diarrhoea and fever 16 days post procedure, after initial successful discharge from hospital.

Discussion

This study confirms that, among patients with severe calcific AS, the Leaflex procedure is feasible and leaflet scoring can improve valve haemodynamics and increase AVA. In most cases, treatment with the Leaflex led to a change of AS classification from severe to moderate.

In the current study, the modified Leaflex device increased the mean valve area from 0.7±0.1 cm^2 to 1.2±0.3 cm^2. This treatment effect is much larger than that reported for BAV[3]. While BAV results in an overstretching of the valve apparatus, considerable recoil reduces the gain early after the procedure, limiting the clinical

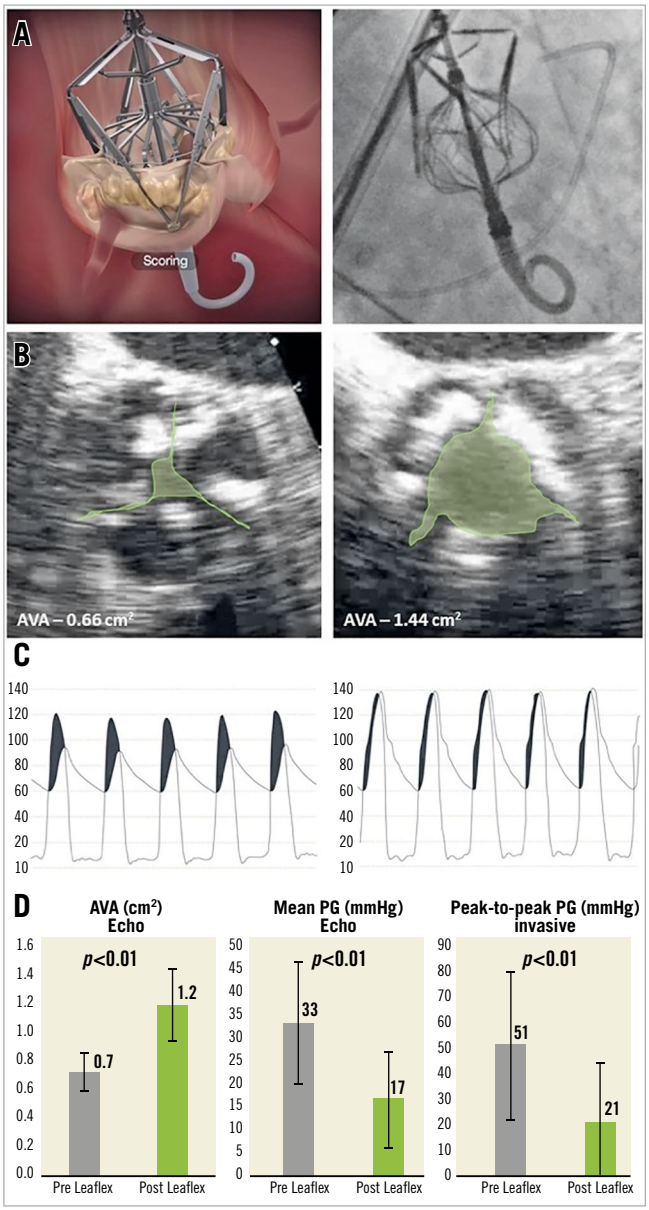

Figure 2. *Procedure and effects on valve area and haemodynamics. A) The Leaflex Performer during scoring - animation (left) and fluoroscopy (right). B) Example of aortic valve area pre (left) and post (right) treatment. C) Example of invasive pressure measurement pre (left) and post (right) treatment. D) Echocardiography and invasive measurement study results (n=11): aortic valve area (left), transvalvular mean pressure gradient (centre) and transvalvular peak-to-peak pressure measurement (right) pre and post treatment with the Leaflex Performer.*

benefit[4]. In contrast, the Leaflex approach leads to a more predictable and larger increase in the effective valve area, which has the potential to deliver a more significant and sustained clinical benefit. This feasibility study was designed in the context of a TAVI, and hence the direct clinical effect of the increased valve area could not be measured. However, the valve area achieved with the Leaflex would normally render patients free of exertional symptoms[5].

We did not observe any echocardiographic evidence of leaflet damage and, importantly, did not observe acute severe AR with haemodynamic effects. This is significant, as persisting severe AR following wire removal would limit a stand-alone approach in individual cases, similar to BAV. These data confirm bench tests on excised human stenotic aortic valves which documented a targeted interruption of the calcium deposits on the leaflets without tissue damage to the ventricular surface of the leaflets[1]. In two patients stroke occurred. These events were attributed to prolonged procedures with protracted periods of hypotension due to complications, rather than direct embolic events. The number of patients treated is small and does not allow an estimate of the true complication rate of the procedure.

In this very first transfemoral experience, several technical challenges that required device design iteration were encountered. With increasing experience and further device iteration, the procedure has the potential to become an important tool in the management of AS. Additional sizes will enable treatment of a wider range of annulus diameters, as well as more robust scoring leading to potentially higher, more consistent improvement in AVA. Potential future indications could include the treatment of patients with moderate AS to avoid or postpone the requirement for aortic valve replacement (AVR). Large prospective clinical trials evaluating the safety and efficacy of a stand-alone Leaflex procedure are clearly required and are in the development phase.

Limitations

Due to the small sample size we cannot draw definitive conclusions regarding the technology. The included patients were highly selected and the generalisability of the results is unclear. The procedure is presently limited by a single device size, which contributed to the prolonged recruitment. Echocardiographic assessment following the Leaflex procedure was limited by the presence of the guidewire.

Conclusion

The current study suggests that a non-implant repair of severely stenotic aortic valve leaflets with the Leaflex device is feasible and can improve valve haemodynamics. The initial experience was limited by technical problems. Further studies are needed and will aim to establish the clinical safety, efficacy, and durability of the results. This procedure has the potential to provide a treatment alternative for patients without current treatment options.

Impact on daily practice

An alternative approach to provide a reliable valve repair procedure that restores aortic valve mobility and renders patients asymptomatic would complement existing therapies.

Funding

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Conflict of interest statement

A. Baumbach reports personal fees from MicroPort, Sinomed, Abbott Vascular, and AstraZeneca, outside the submitted work. D. Mylotte reports grants and personal fees from Medtronic, personal fees from Boston Scientific and MicroPort, outside the submitted work. D. Hildick-Smith reports consultancy (stock options) from Pi-Cardia. M. Jonas reports personal fees from Pi-Cardia, outside the submitted work, and being a consultant to Pi-Cardia. R. Halevi, Y. Kislev, and L. Plotnikov are Pi-Cardia employees. The other authors have no conflicts of interest to declare.

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Supplementary data

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Supplementary Appendix 2. Inclusion and exclusion criteria, core labs.

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Moving image 1. The Leaflex Performer animation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00458

Supplementary data

Supplementary Appendix 1. List of participating centres

Site location	Institution	Investigator	Pts
Budapest, Hungary	Gottsegen Hungarian Institute of Cardiology	P. Andreka, G. Fontos	6
London, UK	Barts Heart Centre Queen Mary University of London	A. Baumbach, S. Kennon	3
Brighton, UK	Sussex Cardiac Centre Brighton and Sussex University Hospitals	D. Hildick-Smith, U. Trivedi, J. Cockburn	3
Krakow, Poland	John Paul II Hospital Jagiellonian University Medical College	K. Bartus, J. Trebacz	2
Galway, Ireland	University Hospital, SAOLTA Healthcare Group, and the National University of Ireland	D. Mylotte, A. Neylon	1
Rehovot, Israel	Kaplan Medical Centre	M. Jonas, G. Gandelman	1

Supplementary Appendix 2. Inclusion and exclusion criteria, core labs

Eligibility criteria included annulus dimensions of 23 to 26 mm, typical calcification of the aortic valve leaflets, and absence of extreme tortuosity of the descending aorta or iliofemoral arteries. Extremely bulky valve calcifications >8 mm were excluded **(Supplementary Figure 1)**. The full list of inclusion and exclusion criteria is provided below.

Anatomical eligibility was assessed by an independent CT core lab (A. Hamdan; Petah-Tiqva, Israel) and echocardiograms were analysed by an independent echocardiography core lab (B. Scott; Antwerp, Belgium).

Inclusion criteria

1. Male and female age >18 years.

2. Patient with a native aortic valve.

3. Patient with degenerative calcified aortic stenosis who requires treatment, according to the treating physician, and is planned to undergo a transfemoral TAVI procedure.

4. Patient understands the nature of the procedure and provides written informed consent.

5. Patient is willing and able to comply with the specified study requirements and follow-up evaluations.

Exclusion criteria

1. Severe aortic regurgitation.
2. History of a cerebral vascular accident (CVA) or transient ischaemic attack (TIA) in the past six months.
3. History of a myocardial infarction (MI) in the past three months.
4. Known severe carotid artery disease requiring intervention.
5. Cardiac arrhythmia, which is severe and difficult to control.
6. Left ventricular ejection fraction (LVEF) of <25%.
7. Known severely calcified aorta or significant atheroma on the aorta.
8. Percutaneous intervention or other invasive cardiac or peripheral procedure, that is not related to the index procedure, within one month prior to index procedure.
9. Planned PCI or peripheral angioplasty during current TAVI procedure.
10. Active or recent endocarditis.
11. Echocardiographic evidence of LV thrombus, aortic valve or adjacent vegetation or soft mobile structures.
12. Haemodynamic instability that requires inotropic support or mechanical heart assistance.
13. Acute fulminant pulmonary oedema.
14. Known hypersensitivity or contraindication to all intraprocedural anticoagulation or to antiplatelet medication.
15. Known allergy to contrast medium that cannot be adequately controlled with pre-medication.
16. Known allergy to nitinol alloys, stainless steel, ultra-high-molecular-weight polyethylene, polyamide 12, polyether block amide, Teflon, polyacetal, silicone, PVC (DEHP free), polycarbonate.
17. Renal insufficiency assessed by serum creatinine >2.5 mg/dl, and/or creatinine clearance <30 ml/min, and/or end-stage renal disease requiring chronic dialysis.
18. Ongoing severe infection or sepsis.
19. Blood dyscrasias as one of the following: leukopaenia (WBC <3,000 mm^3), acute anaemia (Hb <9 gr%), thrombocytopaenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
20. Known significant aortic disease, including: abdominal aortic aneurysm, thoracic aneurysm, significant narrowing of the abdominal or thoracic aorta.
21. Active peptic ulcer or acute gastrointestinal bleeding within the past 90 days prior to the index procedure.
22. An exception to structurally normal cardiovascular anatomy.
23. Congenitally unicuspid, bicuspid or quadricuspid native aortic valve as seen by echocardiography.
24. Femoral/iliac arteries with severe calcification or tortuosity or aorto-femoral bypass.

25. Significant hypertrophic cardiomyopathy.
26. Known pregnancy.
27. Patient is currently participating in another investigational drug or device study.
28. Patient is too frail to withstand the index procedure, as determined by the investigator.
29. Patient with malignancy or other major illness that might require surgery in the next 1 month.
30. Patient has other medical, social, or psychological conditions which, in the opinion of the investigator or any of his team, preclude the patient from study participation.
31. Patient held in an institution for governmental or judicial reasons.
32. Patient who is dependent on the sponsor, any of the CROs and core laboratories, the study centre, or the investigator.

Supplementary Appendix 3. Device description

The Leaflex™ Performer, developed by Pi-Cardia Ltd., Rehovot, Israel, is comprised of several key components **(Supplementary Figure 2)**: the handle, delivery system and distal unit. The handle has a lever which, when pressed, transmits mechanical force along the 14 Fr delivery system to the distal unit which performs leaflet scoring. The distal unit itself is composed of (i) an integrated distal tip pigtail catheter (0.035" guidewire compatible), (ii) an expander which pushes the native aortic leaflets towards the (iii) frame which has six scoring elements for the creation of scoring lines. The distal unit is delivered over a stiff guidewire to the aortic valve where the expander and frame are unsheathed and manipulated into position for leaflet scoring. A deflection knob facilitates steering around the aortic arch and a rotation knob allows precise positioning of the frame on the calcified aortic leaflets.

Supplementary Appendix 4. Endpoints and definitions

Safety endpoints were all-cause mortality and stroke at 30 days post index procedure and Leaflex procedural complications.

Performance endpoints were Leaflex procedure success, Leaflex acute effect and final valve implantation assessment.

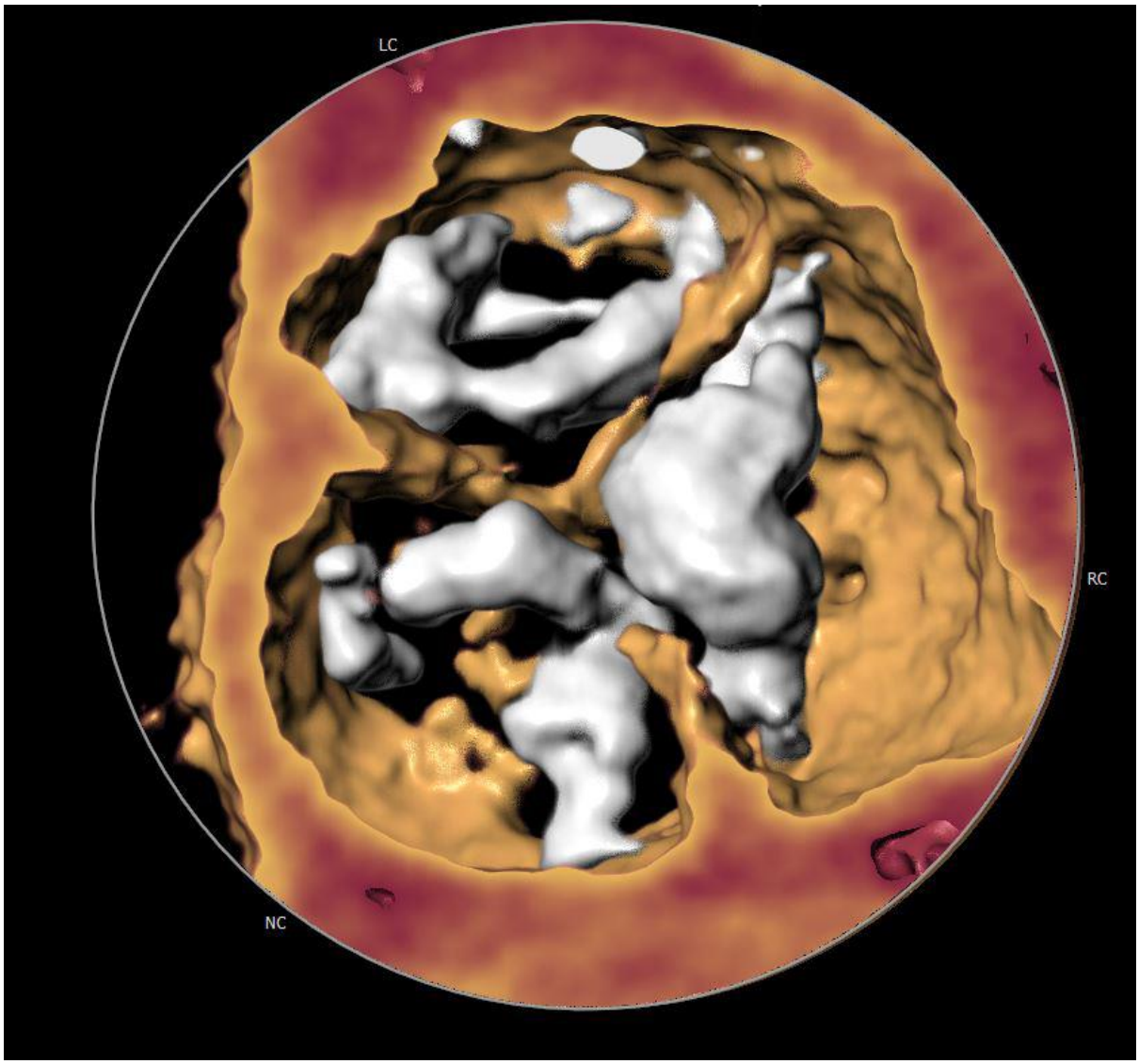
Stroke was defined according to the VARC-2 definition [2]. Leaflex procedural complications were assessed post-Leaflex procedure and pre-TAVR procedure and included: aortic regurgitation, conduction defects, and any structural injury such as aortic rupture, aortic valve leaflet injury, annular rupture, LV injury, and mitral valve injury.

Leaflex procedure success was defined as successful Leaflex device introduction, positioning, operating and withdrawal, assessed by fluoroscopy.

Leaflex acute effect was assessed pre and post Leaflex procedure, pre-TAVR procedure, and defined as improvement in pressure gradient assessed by invasive measurements and/or echocardiography, and/or aortic valve area post procedure assessed by echocardiography. Final valve implantation assessment was defined as the need for post-dilatation BAV, and PVL assessment by echocardiography.

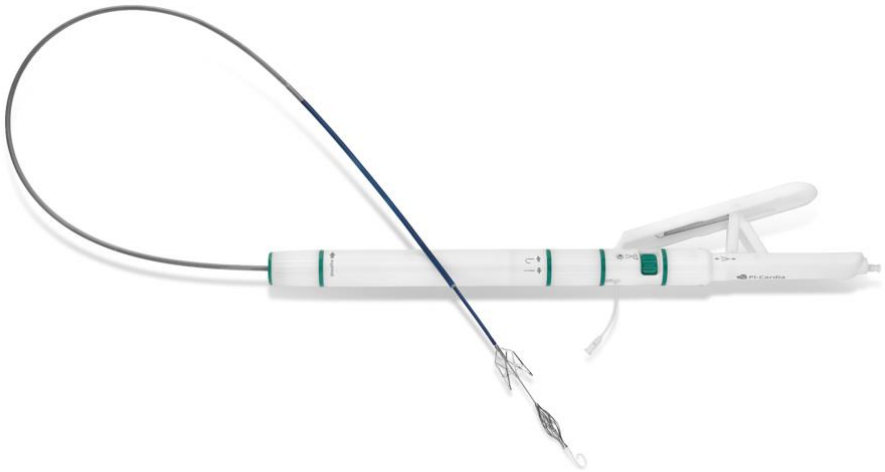
Supplementary Appendix 5. Statistical analysis

All continuous variables were presented as mean±standard deviation, whereas categorical values were presented as frequencies and percentages, when appropriate. Independence of observations was assumed, and the Kolmogorov-Smirnov test was used to validate normal distribution. Repeated measurement design with a two-tailed paired t-test was conducted to determine the statistical significance within treatment groups, with accordance to the study endpoints. All statistical analyses were two-tailed tests and significance was set at 5%. Results were analysed using SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA).



Supplementary Figure 1. Example of excluded aortic valve with bulky calcification pattern.

A.



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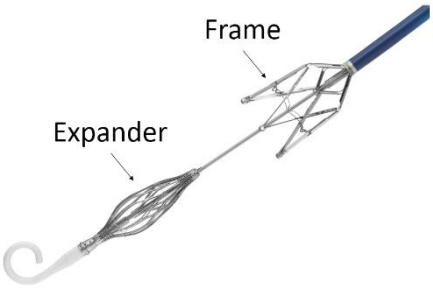

C.

Supplementary Figure 2. The Leaflex Performer system.

A) Handle, delivery system and distal unit.

B) Distal unit: frame and expander.

C) Handle.

Supplementary Table 1. Patient demographics and baseline echocardiographic findings.

Characteristics (N=16)		**N (%) or mean±SD**
Gender, male		11 (68.8)
Age, years		83.5±4.4
Logistic EuroSCORE I		15.7±6.6
EuroSCORE II		4.2±2.9
Hypertension		13 (81.3)
Hyperlipidaemia		12 (75.0)
Diabetes		6 (37.5)
Coronary artery disease		10 (62.5)
Congestive heart failure		3 (18.8)
Cerebrovascular disease		3 (18.8)
Previous BAV		3 (18.8)
Renal impairment	Moderate	7 (43.8)
	Severe	4 (25.0)
Chronic lung disease		2 (12.5)
Pulmonary hypertension	Moderate	5 (31.3)
	Severe	2 (12.5)
LVEF, %		58.3±7.3
AVA, cm^2		0.7±0.2
Mean pressure gradient, mmHg		40±11
Aortic regurgitation	Mild	8 (50.0)
	Moderate	2 (12.5)

Supplementary Table 2. Echocardiographic and haemodynamic assessments in the total patient cohort.

	Echo–AVA (cm^2)		Echo-mean PG (mmHg)		Invasive–peak-to-peak (mmHg)		Comment
Patient no.	Pre Leaflex	Post Leaflex	Pre Leaflex	Post Leaflex	Pre Leaflex	Post Leaflex	
1	0.86	1.1	30	19	19	6	No scoring
2	0.68	ND	39	ND	35	ND	No scoring
3	0.73	1	13	13	14	ND	No scoring, invasive measurement post ND
4	0.48	0.59	39	33	61	41	No scoring
5	0.69	0.87	52	34	41	35	
6	0.66	1.44	24	10	25	0	
7	0.58	ND	44	ND	79	27	Echo post ND
8	0.69	1.24	41	13	53	12	
9	0.82	1.07	55	33	123	68	
10	0.87	1.51	30	9	36	3	
11	0.73	1.20	26	9	32	4	
12	0.53	1.39	35	14	43	25	
13	0.95	1.19	16	8	30	3	
14	0.72	ND	21	ND	28	ND	No scoring
15	0.52	0.68	37	26	66	51	
16	0.76	1.24	18	10	31	0	

AVA: aortic valve area; PG: peak gradient

Supplementary Table 3. Echocardiographic core lab classification of aortic regurgitation pre and post Leaflex procedure.

Core lab	**Pre Leaflex** AR	**Post Leaflex** AR
Patient no.		
1	Mild	Mild
2	Mild	ND
3	Mild	Mild
4	Mild	Mild
5	None	None
6	Mild	Moderate
7	Mild	ND
8	None	Mild
9	Mild	Moderate
10	Mild	Moderate
11	None	Mild
12	None	Mild
13	None	None
14	Moderate	Mild
15	Moderate	Moderate
16	Mild	Severe