Structural Heart 9 (2025) 100391

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Original Research

First-In-Human Experience of the New Fully Repositionable IMPERIA Delivery System to Implant the ALLEGRA Transcatheter Heart Valve in Patients With Severe Calcific Aortic Stenosis or Degenerated Surgical Bioprosthesis: Thirty-Day Results of the EMPIRE I Study

José Antonio Baz, MD [a], Christof Burgdorf, MD [b], Christian Frerker, MD [c], Ignacio Cruz González, MD [d], Joan Antoni Gômez, MD [e], Joseph Graham, MD [f], José Maria Hernândez, MD [g], Pilar Jimenez, MD [h], Claire B. Ren, MD [i,j], Ernest Spitzer, MD [j], Pim Tonino, MD [k], Pieter Vriesendorp, MD [l], Nicolas van Mieghem, MD [i], Samuel Copt, PhD [m,*], Anders Jönsson, MD [m], Keith G. Oldroyd, MD [m], Nicolas Doll, MD [n]

[a] Servicio de Cardiología, Hospital Alvaro Cunqueiro, Vigo, Spain
[b] Herz- und Gefäßzentrum Bad Bevensen, Bad Bevensen, Germany
[c] Department of Cardiology, Universitätsklinik Schleswig-Holstein Campus Lübeck, Lübeck, Germany
[d] Servicio de Cardiología, Hospital Universitario de Salamanca, Salamanca, Spain
[e] Cardiology Department, Hospital Universitario de Bellvitge, Barcelona, Spain
[f] Royal Sussex Hospital, Brighton, UK
[g] Servicio de Cardiología, Hospital Universitario Virgen de la Victoria, Malaga, Spain
[h] Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain
[i] Department of Cardiology, Cardiovascular Institute, Erasmus Medical Center, Rotterdam, The Netherlands
[j] Cardialysis, Rotterdam, The Netherlands
[k] Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands
[l] Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands
[m] Biosensors Europe, Morges, Switzerland
[n] Department of Cardiac Surgery, Schüchtermann Klinik, Bad Rothenfelde, Germany

ARTICLE INFO

Article history:
Submitted 3 September 2024
Revised 11 November 2024
Accepted 21 November 2024
Available online 6 February 2025

Keywords:
Aortic valve stenosis
Self-expanding heart valve
Transcatheter aortic valve replacement

ABSTRACT

Background: The ALLEGRA (Biosensors International) transcatheter heart valve is a self-expanding supra-annular bovine pericardial aortic valve. A new delivery system (IMPERIA™, Biosensors International) has been designed which allows the valve to be fully resheathed and repositioned in situ. The aim of this premarket study was to assess the safety and efficacy of transcatheter aortic valve implantation using the combination of the CE (Conformite Europeenne) marked ALLEGRA valve and the new IMPERIA delivery system.

Methods: One hundred thirty-seven patients were enrolled in 11 centers from January to November 2023. There were 30 roll-in patients, 91 in the intention-to-treat (ITT) population and 16 with degenerated surgical aortic bioprostheses. The primary outcome was device success according to the Valve Academic Research Consortium-2 from discharge up to 7 days in the ITT cohort.

Results: Implantation of the ALLEGRA valve was successful in 136 patients (99.3%). There were no device embolizations and no patient required a second valve. Device success was achieved in 91.9% of the ITT cohort. At 30 days, all-cause mortality was 2.2% in the native aortic stenosis (AS) cohort and 0% in the valve-in-valve cohort. New pacemaker implantation was required in 12.4% (17/137). There was no patient prosthesis mismatch (PPM) in the 121 patients with native AS and moderate PPM in 2/16 valve-in-valve patients.

* Address correspondence to: Samuel Copt, PhD, Rue de lausanne 29, Morges 1110, Switzerland.
E-mail address: s.copt@biosensors.com (S. Copt).

https://doi.org/10.1016/j.shj.2024.100391

Conclusions: This study confirms the safety and efficacy of transcatheter aortic valve implantation using the IMPERIA delivery system to implant the CE marked ALLEGRA transcatheter heart valve in patients with severe calcific native AS or a degenerated surgical aortic bioprostheses.

ABBREVIATIONS

AS, aortic stenosis; CSC, Central Screening Committee; CT, computed tomography; EMPIRE I, invEstigation of the safety and perforMance of the NVT ALLEGRA THV System with a new delivery system in Patients with severe calcified aortIc stenosis or failed suRgical aortic bioprosthEsis I; EOA, effective orifice area; ITT, intention-to-treat; NYHA, New York Heart Association; PG, pressure gradient; PPM, patient prosthesis mismatch; PVL, paravalvular leak; TAVI, transcatheter aortic valve implantation; VARC-2, Valve Academic Research Consortium-2; ViV, valve-in-valve.

Introduction

Transcatheter aortic valve implantation (TAVI) has become the standard of care for patients suffering from severe symptomatic aortic valve stenosis (AS) with a high or prohibitive risk for surgical aortic valve replacement and is now a routine treatment alternative at heart centers globally. In parallel with increasing operator experience, preoperative computed tomography (CT) imaging and design improvements of existing TAVI systems have contributed to better clinical outcomes, but complications including paravalvular leakage (PVL), conduction system abnormalities, stroke, vascular injury, and residual high gradients after implantation resulting from patient prosthesis mismatch (PPM) still occur frequently.

The ALLEGRA TAVI System (NVT GmbH, Hechingen, Germany) was approved in Europe in 2017 for the treatment of patients with severe native aortic stenosis (AS) and in 2020 for the treatment of patients with degenerated surgical aortic bioprostheses (valve-in-valve [ViV]). The ALLEGRA transcatheter valve is a self-expanding supra-annular bovine pericardial aortic bioprosthesis with several unique features designed to provide patients with excellent hemodynamic performance and durability, including a short barrel shaped stent frame and a flexible outflow resulting in effective orifice areas (EOAs) which exceed the geometric orifice area. It also has a unique transfemoral delivery system which provides stable hemodynamics during implantation without an occlusive phase ("Permaflow"). Excellent short to medium term outcomes have been reported in patients treated for native AS and in the ViV setting. The current delivery system permits retrieval of the valve after the inflow has been opened and prior to final release but does not allow repositioning in situ. To provide operators with the ability to optimize implant depth and position, a new delivery system has been designed (IMPERIA) which allows the valve to be fully resheathed and repositioned in the aortic root. The invEstigation of the safety and perforMance of the NVT ALLEGRA THV System with a new delivery system in Patients with severe calcified aortIc stenosis or failed suRgical aortic bioprosthEsis (EMPIRE) I trial was designed to assess the safety and efficacy of TAVI performed using the combination of the current CE marked ALLEGRA valve and the new delivery system.

Methods

Study Design

EMPIRE I is a premarket, prospective, multicenter, single-arm study performed to obtain regulatory approval for the IMPERIA delivery system under the new European Union Medical Device Regulations.

Patient Screening and Selection

Patients with either symptomatic severe calcific AS defined according to Valve Academic Research Consortium-2 (VARC-2) or a degenerated surgical bioprosthesis were screened in 11 sites in Spain, Germany, and the Netherlands and, if eligible, were invited to participate. After providing written informed consent, the clinical and imaging data were presented to a Central Screening Committee (CSC) who had to confirm suitability. Clinical specialists analyzed all CT scans and provided at least 2 independent reports to the CSC. An independent Clinical Events Committee, Data Safety Monitoring Board, and Echocardiographic Core Laboratory (Cardialysis, Rotterdam, The Netherlands) assessed adverse events, patient safety, and echocardiograms, respectively. The primary endpoint was the rate of device success as defined by VARC-2 at discharge from index procedure or 7 days post implant, whichever came first.[1] We used VARC-2 as this was also employed in the study from which the performance goal was derived. The study is registered at ClinicalTrials.gov (NCT05478161), complies with the Declaration of Helsinki, and was approved by the relevant national and local ethics committees and competent authorities. Patients were informed about the study details and provided written informed consent prior to participation. The study was executed with the assistance of a contract research organization (Cardialysis, Rotterdam, The Netherlands).

As this was a first-in-human study, each site was required to treat 3 roll-in patients prior to entering subjects into the intention-to-treat (ITT) cohort. Roll-in patients underwent the same procedures as those in the ITT cohort (Figure 1). In parallel, sites could also enroll patients with degenerated surgical bioprostheses into a ViV substudy. Patients were considered enrolled after the informed consent was signed, all eligibility criteria were met and confirmed by the local heart team, participation has been approved by the CSC, and vascular access had been obtained.

Study Device and Valve Implantation

The intention in all patients was to implant the current commercially available ALLEGRA valve using the new IMPERIA delivery system (Figure 2). The valve has 3 pairs of radiopaque markers on the stent frame positioned at the level of the new valve plane on either side of the commissural fixation points and the delivery system also has a marker band. These markers can be used to guide and optimize valve implantation. It is available in 3 sizes (23, 27, and 31 mm) covering an annulus perimeter size range of 16.5 mm to 27.0 mm. The new IMPERIA delivery system has an integrated wire reinforced sheath with a hydrophilic coating and a winding mechanism to progressively open the valve from inflow to outflow and then close it if repositioning is required. The shaft of the delivery catheter is 15 Fr with an 18 Fr cartridge for all 3 valve sizes. Accordingly, the iliofemoral vascular anatomy had to allow the safe placement of an 18 Fr internal diameter sheath. There is an automatic safety lock mechanism to prevent accidental release. At the safety lock position, the valve is sufficiently functioning to provide approximately 80% of maximal flow and can be fully resheathed and repositioned up to 3 times if necessary. The instructions for use recommend predilatation in all native cases with optional postdilatation.

Study Endpoints and Assessments

Patients were assessed at baseline, during the procedure, discharge, 30 days, 6 and 12 months. The primary endpoint was device success rate

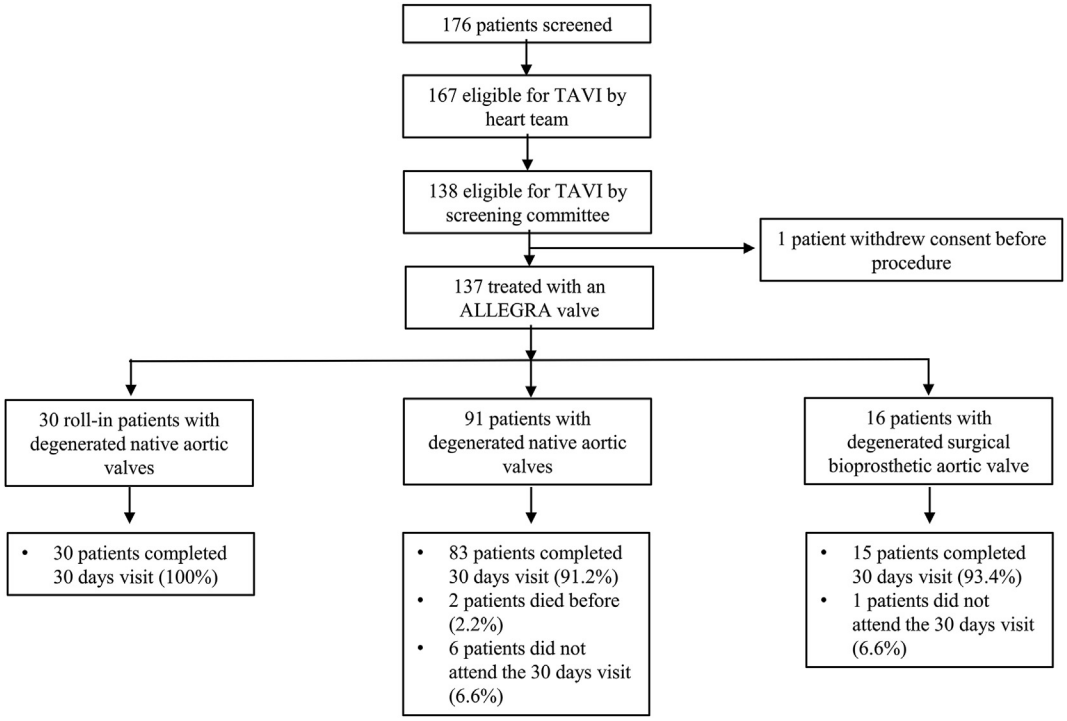

Figure 1. Study flow chart.
Abbreviation: TAVI, transcatheter aortic valve implantation.

as defined in VARC-2 at 7 days (discharge from index procedure or 7 days postimplant, whichever comes first) in the native ITT cohort.[1] Secondary endpoints include procedural success, assessment of the functional status and the need for new permanent pacemaker implantations. Additional endpoints including cardiovascular death, early safety and hemodynamic parameters were adjudicated according to the VARC-2.[1]

Statistical Analysis

The performance goal was derived from the CoreValve EvolutR CE Mark Clinical Study which used the same primary endpoint.[2] In that study, 22% of patients failed to meet the criteria for device success. We chose an upper boundary for device failure of 33% representing a relative increase of 1.5. This is in line with previous trials of cardiovascular devices including new TAVI systems. Based on this, a sample size of 88 evaluable patients was needed to provide 80% power with a one-sided type I error of 5%. Allowing for a drop-out rate of 5%, 92 patients with native AS needed to be enrolled. The main analysis group for this report are the patients with native AS who were enrolled into the ITT population. Study success will be declared if the null hypothesis of no difference between the performance goal and the observed device failure rate can be rejected. In addition, we separately report results for the 30 roll-in patients and the 16 ViV patients.

Baseline categorical variables are presented as percentages and continuous variables as mean ± SD or median and interquartile range. Event rates are reported as Kaplan-Meier estimates. An interim analysis was performed after all patients had completed 30 days follow-up. Since this interim analysis was to assess safety and did not influence the conduct of the study, no adjustment of *p* values is necessary. The analysis was prespecified in the clinical investigation plan and the statistical analysis plan. All statistical analyses were performed using Statistical Analysis Systems software version 9.4 (SAS Institute, Cary, North Carolina).

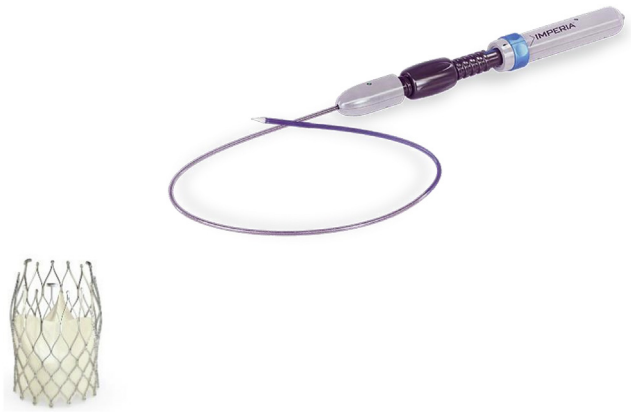

Figure 2. ALLEGRA Transcatheter Heart Valve and IMPERIA Delivery System.

Results

Study Population

One hundred seventy-six patients were screened between January and November 2023. Subsequently 30 patients with native AS underwent roll-in procedures and 91 patients with native AS were recruited into the ITT cohort. An additional 16 patients underwent ViV procedures. Patient demographics and baseline data are shown in Table 1. The average age of the roll-in and ITT cohorts was 82.7 ± 5.9 and 82.1 ± 4.7 years, 66.7 and 68.1% were female and 46.7 and 57.1% were in New York Heart Association (NYHA) class III or IV. In the roll-in and ITT populations, Society of Thoracic Surgeons risk scores were 4.0% ± 2.9% and 4.2% ± 2.8% and European System for Cardiac Operative Risk Evaluation II risk scores were 3.5% ± 2.1% and 3.8% ± 2.6% respectively. The ViV patients were aged 80.0 ± 5.3 years, 31.2% were female and 75% were in NYHA class III or IV. The Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation II risk scores in the ViV cohort were 11.1% ± 15.1% and 16.6% ± 19.7% respectively.

Table 1
Patient demographics

	Roll-in (native) (N = 30)	ITT (native) (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Age (y)	82.7 ± 5.9	82.1 ± 4.7	82.2 ± 5.0	80.0 ± 5.3	81.9 ± 5.1
Gender (male)	33.3% (10)	31.9% (29)	32.2% (39)	68.8% (11)	36.5% (50)
STS score (%)	4.0 ± 2.9	4.2 ± 2.8	4.1 ± 2.8	11.1 ± 15.1	4.9 ± 6.1
EuroSCORE (%)	3.5 ± 2.1	3.8 ± 2.6	3.7 ± 2.5	16.6 ± 19.7	5.2 ± 81
NYHA class III/IV	46.7% (14)	57.1% (52)	54.5% (66)	75.0% (12)	56.9% (78)
Coronary artery stenosis >50%	33.3% (10)	23.1% (10)	25.6% (31)	56.3% (9)	29.2% (40)
Angina (stable)	10% (3)	7.7% (7)	8.3% (10)	6.3% (1)	8.0% (11)
Previous myocardial infarction	13.3% (4)	12.1% (11)	12.4% (15)	18.8% (3)	13.1% (18)
Previous cardiac decompensation	6.7% (2)	11.0% (10)	9.9% (12)	37.5% (6)	13.1% (18)
Pulmonary hypertension	13.3% (4)	13.2% (12)	13.2% (16)	31.3% (5)	15.3% (21)
Previous endocarditis	0.0% (0)	0.0% (0)	0.0% (0)	6.3% (1)	0.7% (1)
Atrial fibrillation or flutter	20.0% (6)	30.8% (28)	28.1% (34)	25.0% (4)	27.7% (38)
LBBB/RBBB	3.3% (1)	8.8% (8)	7.4% (9)	37.5% (6)	10.9% (15)
Previous stroke	6.7% (2)	5.5% (5)	5.8% (7)	6.3% (1)	5.8% (8)
COPD	3.3% (1)	5.5% (5)	5.0% (6)	18.8% (3)	6.6% (9)
Chronic renal insufficiency	36.7% (11)	22.0% (20)	25.6% (31)	31.3% (5)	26.3% (36)
Diabetes type II	33.3% (10)	24.2% (22)	28.1% (34)	37.5% (6)	29.2% (40)
Permanent pacemaker	3.3% (1)	8.8% (8)	7.4% (9)	18.8% (3)	8.8% (12)
Cancer	10% (3)	9.9% (9)	9.9% (12)	0.0% (0)	8.8% (12)

Notes. Data shown as percentages (n) or mean ± SD.
Abbreviations: COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ITT, intention-to-treat; LBBB, left bundle branch block; NYHA, New York Heart Association; RBBB, right bundle branch block; STS, Society of Thoracic Surgeons; ViV, valve-in-valve.

Baseline CT Parameters

In the patients with native AS, the perimeter derived diameter ranged from 19.1 mm to 26.8 mm in keeping with the recommended sizing of the ALLEGRA valve (Table 2). Volumetric calcification measurements suggested that on average the patients with native AS had severe calcification. A list of the type and size of the treated surgical valves is included in Supplementary Table 1.

Procedural Results

In the roll-in and ITT cohorts combined (all native AS), 10.6% were treated with the 23 mm valve, 54.5% with the 27 mm valve, and 34.8% with the 31 mm (Table 3). In the ViV cohort, 82.4% were treated with the 23 mm valve, 11.8% with the 27 mm valve, and 5.9% with the 31 mm valve. In the roll-in patients, a single ALLEGRA valve was successfully implanted in 29/30 patients (96.7%) with one patient requiring conversion to a balloon expandable valve. In the ITT and ViV cohorts, a single ALLEGRA valve was implanted in all patients. Predilatation was mandated in the protocol for patients with native AS and was performed in all patients. Predilatation was also performed in 43.8% of the ViV patients. Postdilatation was performed in 56.7% of patients with native AS and 50% of ViV patients. Valve fracturing was not performed in any of the ViV cases. Resheathing and repositioning were performed in 56.7% of the roll-in patients, 47.3% in the ITT and 75% in the ViV cohorts, respectively. Fluoroscopy time was 17.7 ± 6.7 minutes for the roll-in patients, 14.7 ± 6.1 minutes for the ITT cohort, and 17.3 ± 6.3 minutes for the ViV cohort. Contrast usage was 182.3 ± 59.6 ml for the roll-in patients, 168 ± 65.2 ml for the ITT cohort, and 71.2 ± 28.3 ml for the ViV cohort.

Table 2
Baseline CT parameters

	Roll-in (native) (N = 30)	ITT (native) (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Aortic annulus					
Perimeter derived diameter (mm)	23.7 ± 1.7	23.6 ± 1.7	23.6 ± 1.7	20.9 ± 2.0	23.3 ± 1.9
Perimeter (mm)	74.1 ± 5.4	73.9 ± 5.4	74.0 ± 5.4	65.8 ± 6.4	73.0 ± 6.1
Area (mm^2)	425.7 ± 65.4	424.6 ± 61.4	424.9 ± 62.1	343.1 ± 67.5	415.6 ± 67.7
Left ventricular outflow tract					
Perimeter derived diameter (mm)	23.4 ± 2.2	23.2 ± 1.7	23.3 ± 2.0	25.6 ± 3.7	23.6 ± 2.4
Perimeter (mm)	72.9 ± 5.3	73.4 ± 6.8	73.3 ± 6.4	80.3 ± 11.6	74.1 ± 7.5
Area (mm^2)	397. 3 ± 65.7	405.5 ± 78.7	403.5 ± 75.5	501.4 ± 154.4	415.0 ± 93.2
Sinus of Valsalva width					
Left coronary (mm)	30.5 ± 2.6	30.7 ± 2.6	30.6 ± 2.6	30.5 ± 2.7	30.6 ± 2.6
Right coronary (mm)	28.9 ± 2.5	29.3 ± 2.5	29.2 ± 2.5	29.5 ± 3.3	29.2 ± 2.6
Noncoronary (mm)	30.2 ± 3.0	30.7 ± 2.8	30.5 ± 2.8	31.9 ± 4.7	30.7 ± 3.0
Sino-tubular junction diameter (mm)	27.5 ± 2.7	28.1 ± 2.6	26.8 ± 2.5	29.1 ± 3.6	26.9 ± 2.7
Membranous septum length (mm)	4.8 ± 2.3	5.1 ± 2.2	5.0 ± 2.2	5.6 ± 2.8	5.1 ± 2.3
Aorta to annulus angle (°)	47.4 ± 9.7	47.7 ± 10.2	47.6 ± 10.1	43.3 ± 9.8	47.1 ± 10.1
Calcification					
Total (mm^3)	803.4 ± 373.9	856.0 ± 505.1	842.9 ± 474.8	317.2 ± 226.7	795.1 ± 317.2
Noncoronary cusp (mm^3)	343.1 ± 160.2	365.3 ± 208.2	359.9 ± 197.1	138.8 ± 130.8	339.6 ± 202.1
Right coronary cusp (mm^3)	231.8 ± 121.9	260.0 ± 205.9	253.1 ± 188.8	91.0 ± 97.3	238.3 ± 188.0
Left coronary cusp (mm^3)	232.3 ± 170.0	232.0 ± 169.5	232.1 ± 168.9	108.8 ± 109.3	220.8 ± 167.9
Femoral access					
Common iliac mean diameter (mm)	9.4 ± 1.4	9.3 ± 1.5	9.3 ± 1.5	9.7 ± 1.7	9.3 ± 1.5
External iliac mean diameter (mm)	7.8 ± 1.3	7.5 ± 1.3	7.6 ± 1.3	8.2 ± 2.0	7.6 ± 1.4
Common femoral mean diameter (mm)	7.8 ± 1.2	7.6 ± 1.2	7.7 ± 1.2	7.8 ± 1.5	7.7 ± 1.2

Notes. Data shown as mean ± SD.
Abbreviations: CT, computed tomography; ITT, intention-to-treat; ViV, valve-in-valve.

Table 3
Procedural characteristics

	Roll-in (native) (N = 30)	ITT (native) (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Predilatation	100% (30)	100% (91)	100% (91)	43.8% (7)	94.9% (130)
Postdilatation	51.7% (15)	58.2% (53)	56.7% (68)	50% (8)	55.9% (76)
Time from insertion to deployment (min)	7.3 ± 6.8	6.2 ± 8.6	6.5 ± 8.2	5.9 ± 5.4	6.4 ± 7.9
Time from insertion to removal (min)	12.3 ± 6.8	10.3 ± 8.8	9.1 ± 4.5	9.1 ± 4.5	10.5 ± 8.0
Successful ALLEGRA implantation	96.7% (29)	100% (91)	99.2% (120)	100% (16)	99.3% (136)
Conversion to other TAVI-system	3.3% (1)	0% (0)	0.8% (1)	0% (0)	0.7% (1)
Need for resheathing/repositioning	56.7% (17)	47.3% (43)	49.6% (60)	75.0% (12)	52.6% (72)
Coronary occlusion	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Need for a second valve	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Contrast medium (ml)	182.3 ± 59.6	168.0 ± 65.2	171.36 ± 64.0	71.2 ± 28.3	159.4 ± 68.9
Fluoroscopy time (min)	17.7 ± 6.7	14.7 ± 6.1	15.4 ± 6.4	17.3 ± 6.3	15.6 ± 6.4
Valve size					
23	9.1%	11.1%	10.6%	82.4%	18.8%
27	69.7%	49.5%	54.4%	11.8%	49.7%
31	21.2%	39.4%	34.8%	5.9%	31.5%

Notes. Data shown as percentages (n) or mean ± SD.
Abbreviations: ITT, intention-to-treat; TAVI, transcatheter aortic valve implantation; ViV, valve-in-valve.

Primary Outcome

Device success rate at 7 days as defined by VARC-2 was achieved in 91.9% of the ITT cohort (95% CI 83.5%-100.0%; $p < 0.001$ vs. performance goal) (Table 4). Device success was 93.0% in all patients with native AS and 87.5% in the ViV patients. The respective causes of device failure were 2 procedural deaths (neither device related) and 5 patients with moderate PVL in the ITT cohort, 1 patient with moderate PVL in the roll-in group, and 2 patients with moderate PPM in the ViV cohort. None of the 121 patients with native AS had any PPM.

Safety Outcomes at 30 Days

One hundred thirteen patients with native AS, including all 30 roll-in patients and 15/16 ViV patients completed 30-day follow-up (Figure 1) (Table 5). The rate of VARC-2 defined early safety was 90.9% in the native AS cohort and 91.2% in the ViV cohort. As described above, 2 patients in the ITT cohort died during the index admission, one due to a late major hemorrhage secondary to arterial injury at site of jugular vein cannulation and the other due to a left main coronary dissection prior to implantation of the ALLEGRA valve. There were no additional deaths postdischarge resulting in an overall mortality rate at 30 days of 1.5%. The rates of disabling stroke were 2.5% (3) in the native AS cohort, 6.3% (1) in the ViV cohort, and 2.9% in the total study population. The rates of life-threatening bleeding were 3.4% in the native AS cohort (4 patients including 1 death outlined above), zero in the ViV cohort, and 3.0% in the total study population. None of the life-threatening bleeding events were related to femoral vascular access complications. The major vascular complication rate was 1.7% in the native AS cohort (one death outlined above and one femoral false aneurysm at the contralateral side not used for the valve insertion), zero in the ViV cohort, and 1.5% in the total study population. There were no cases of myocardial infarction, acute kidney injury stage 2 and 3, coronary artery obstruction, or valve related dysfunction requiring a repeat procedure. New pacemakers were implanted in 16.7% (5) and 13.2% (12) of the roll-in and native patient populations with no new pacemaker implantations in the ViV cohort. In the combined native AS population, the new pacemaker implantation rate was 14%.

Echocardiographic Findings

There was a consistent decrease of the mean pressure gradient (PG) across the aortic valve from baseline to 30 days in all 3 cohorts: roll-in patients from 48.43 ± 11.65 mmHg to 7.62 ± 2.15 mmHg, ITT patients from 43.63 ± 13.85 mmHg to 7.67 ± 3.15 mmHg, and ViV patients from 34.77 ± 18.13 mmHg to 13.19 ± 4.14 mmHg (all $p < 0.001$) (Table 6 and Figure 3). Similarly, the EOA increased in all 3 cohorts from baseline to 30 days: roll-in patients from 0.68 ± 0.15 cm^2 to 2.00 ± 0.26 cm^2, ITT patients from 0.63 ± 0.15 cm^2 to 2.06 ± 0.19 cm^2, and ViV patients from 0.78 ± 0.15 cm^2 to 1.73 ± 0.25 cm^2 (all $p < 0.001$). At 30 days, the mean indexed EOA was 1.14 ± 0.18 cm^2/m^2 and 1.17 ± 0.15 cm^2/m^2 in the roll-in and ITT cohorts and no patient had any degree of PPM. The mean indexed EOA in the ViV patients was 0.96 ± 0.18 cm^2/m^2 with 2/16 subjects having moderate PPM only. At 30 days, moderate PVL was reported in 5.6% (6/107) of patients with native AS consisting of 6.9% (2/29) of the roll-in and 5.1% (4/78) of the ITT patients. No patients had severe PVL in either group. There was no mild, moderate or severe PVL in the ViV cohort.

Functional Status

Implantation of the ALLEGRA valve was associated with an improvement in NYHA class after 30 days with 6.9% (2), 7.5% (6), and

Table 4
VARC-2 device success at 7 d

	Roll-in (native) (N = 30)	ITT (native)* (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Composite VARC-2 device success	96.6% (28/29)	91.9% (79/86)	93.0% (107/115)	87.5% (14/16)	92.4% (121/131)
Absence of procedural mortality	100% (30/30)	97.8% (89/91)	98.3% (119/121)	100% (16/16)	98.5% (135/137)
Correct positioning of single valve in proper anatomic location	100% (29/29)	100% (91/91)	100% (120/120)	100% (16/16)	100% (136/136)
Intended performance of the prosthetic heart valve	96.6% (28/29)	94.0% (79/84)	94.7% (107/113)	87.5% (14/16)	93.8% (121/129)
No patient prosthesis mismatch	100% (29/29)	100% (84/84)	100% (113/113)	87.5% (14/16)	98.4% (127/129)
MPG <20 mm Hg or peak velocity <3 m/s	100% (29/29)	100% (87/87)	100% (116/116)	100% (16/16)	100% (132/132)
No moderate or severe PVL	96.6% (28/29)	94.4% (84/89)	94.9% (112/118)	100% (16/16)	95.5% (128/134)

Notes. Data shown in percentages (n).
Abbreviations: ITT, intention-to-treat, MPG, mean pressure gradient; PVL, paravalvular leak; VARC-2, Valve Academic Research Consortium-2; ViV, valve-in-valve.
* Primary endpoint.

Table 5
VARC-2 safety outcomes at 30 d and pacemaker rates

	Roll-in (native) (N = 30)	ITT (native) (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Composite early safety outcome	100%	87.9%	90.9%	93.7%	91.2%
All-cause mortality	0.0% (0)	2.2% (2)	1.7% (2)	0.0% (0)	1.5% (2)
Cardiovascular mortality	0.0% (0)	2.2% (2)	1.7% (2)	0.0% (0)	1.5% (2)
Disabling stroke	0.0% (0)	3.3% (3)	2,5% (3)	6.3% (1)	2.9% (4)
Nondisabling stroke	0.0% (0)	2.2% (2)	1.7% (2)	0.0% (0)	1.5% (2)
Myocardial infarction	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Life-threatening bleeding	0.0% (0)	4.5% (4)	3.4% (4)	0.0% (0)	3.0% (4)
Acute kidney injury: stage 2 or 3	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Coronary artery obstruction	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Major vascular complications	0.0% (0)	2.2% (2)	1.7% (2)	0.0% (0)	1.5% (2)
Minor vascular complications	3.3% (1)	7.7% (7)	6.6% (8)	0.0% (0)	5.9% (8)
Valve related dysfunction requiring repeat procedure	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
New pacemaker implantation	16.7% (5)	13.7% (12)	14.5% (17)	0.0% (0)	12.7% (17)

Notes. Data shown as Kaplan-Meier estimates (n).
Abbreviations: ITT, intention-to-treat; VARC-2, Valve Academic Research Consortium-2; ViV, valve-in-valve.

7.1% (1) of the roll-in, ITT, and ViV patients being in NYHA class III and IV compared to 46.7% (14), 57.1% (52), and 75% (12) at baseline (Figure 4).

Discussion

This study confirms the safety and efficacy of the new IMPERIA delivery system when used to implant the existing commercially available ALLEGRA transcatheter aortic valve. The new delivery system permits the valve to be fully resheathed and repositioned in the aortic root for up to 3 implantation attempts, allowing the operator to optimize implant depth and position if required. Despite the operators having no prior experience of using the delivery system, only around half of the procedures required the valve to be repositioned. Moreover, there was no incidence of valve embolization and only 1 patient required conversion to an alternative (balloon expandable) device because of multiple failed attempts to obtain secure fixation of the valve. This patient had an unusual pattern of asymmetric calcification which may have contributed to the difficulty and ultimately, despite multiple resheathings, the procedure was completed without any complications. As this was a first-in-human study, operators were required to include 3 roll-in patients before recruiting into the ITT cohort. However, the procedural outcomes were very similar in the roll-in and ITT groups with only a slight increase in fluoroscopy times in the roll-in patients, suggesting that the IMPERIA delivery system is associated with a short learning curve. Importantly, despite the use of an 18 Fr femoral sheath in all cases, this did not result in any major vascular access site complications perhaps related to a combination of prescreening of the vascular anatomy and single vessel entry. Finally, as this was a first-in-human study with a new delivery system, we did not attempt to implement any specific implantation technique to facilitate commissural alignment. However, the commercially available version of the system will have a modification of the loading anchor which has been shown in preclinical testing to facilitate commissural alignment.

This study is also the first to confirm the excellent hemodynamic results achievable with the ALLEGRA valve in patients with native AS

Table 6
Echocardiographic findings at baseline and 7 and 30 d postprocedure

	Roll-in (native) (N = 30)	ITT (native) (N = 91)	Total native (N = 121)	ViV (N = 16)	Total (N = 137)
Baseline					
Mean pressure gradient, mmHg	48.4 ± 11.7 (30)	43.6 ± 13.9 (89)	44.8 ± 13.4 (119)	34.8 ± 18.1 (16)	43.6 ± 14.4 (135)
Maximum aortic velocity, m/s	4.4 ± 0.5 (30)	4.2 ± 0.7 (89)	4,2 ± 0.6 (119)	3.7 ± 0.9 (16)	4,2 ± 0.7 (135)
Effective orifice area, cm^2	0.7 ± 0.2 (29)	0.6 ± 0.2 (82)	0.6 ± 0.2 (111)	0.8 ± 0.2 (12)	0.7 ± 0.2 (123)
Effective orifice area index cm^2/m^2	0.4 ± 0.1 (29)	0.4 ± 0.1 (82)	0.4 ± 0.1 (111)	0.4 ± 0.1 (12)	0.4 ± 0.1 (123)
7 d					
Mean pressure gradient, mmHg	9.0 ± 2.8 (28)	7.4 ± 2.9 (83)	7.8 ± 2.9 (111)	12.5 ± 3.4 (16)	8.4 ± 3.4 (127)
Maximum aortic velocity, m/s	2.0 ± 0.3 (28)	1.8 ± 0.4 (83)	1.9 ± 0.4 (111)	2.4 ± 0.3 (16)	2.0 ± 0.2 (127)
Effective orifice area, cm^2	1.9 ± 0.3 (24)	2.1 ± 0.2 (76)	2,0 ± 0.2 (100)	1.8 ± 0.3 (14)	2.0 ± 0.2 (114)
Effective orifice area index cm^2/m^2	1.1 ± 0.2 (24)	1.2 ± 0.2 (76)	1.2 ± 0.2 (100)	1.0 ± 0.1 (14)	1.1 ± 0.2 (114)
Paravalvular leak	n = 29	n = 86	n = 115	n = 16	n = 131
None or trace	27.6% (8)	45.3% (39)	40.9% (47)	56.3% (9)	42.7% (56)
Mild	69.0% (20)	48.8% (42)	53.9% (62)	43.7% (7)	52.7% (69)
Moderate	3.4% (1)	5.8% (5)	5.2% (6)	0.0% (0)	4.6% (6)
Severe	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
30 d					
Mean pressure gradient, mmHg	7.7 ± 3.2 (29)	7.6 ± 2.2 (72)	7.7 ± 2.9 (101)	13.2 ± 4.1 (14)	8.3 ± 3.5 (115)
Maximum aortic velocity, m/s	1.9 ± 0.3 (29)	1.9 ± 0.4 (72)	1.9 ± 0.3 (101)	2.4 ± 0.4 (14)	1.9 ± 0.4 (115)
Effective orifice area, cm^2	2.0 ± 0.3 (28)	2.1 ± 0.2 (66)	2.0 ± 0.2 (94)	1.7 ± 0.3 (14)	2.0 ± 0.2 (108)
Effective orifice area index cm^2/m^2	1.1 ± 0.2 (28)	1.2 ± 0.2 (66)	1.2 ± 0.2 (94)	1.0 ± 0.2 (14)	1.1 ± 0.2 (108)
Paravalvular leak	n = 29	n = 78	n = 107	n = 14	n = 121
None or trace	24.1% (7)	33.4% (26)	30.8% (33)	64.3% (9)	34.4% (42)
Mild	69.0% (20)	61.5% (48)	63.6% (68)	35.7% (5)	59.8% (73)
Moderate	6.9% (2)	5.1% (4)	5.6% (6)	0.0% (0)	4.9% (6)
Severe	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Patient prosthesis mismatch per VARC-2	0.0% (0)	0.0% (0)	0.0% (0)	14.6% (2)	1.6% (2)

Notes. Data shown as percentages (n) or mean ± SD (n).
Abbreviation: VARC-2, Valve Academic Research Consortium-2.

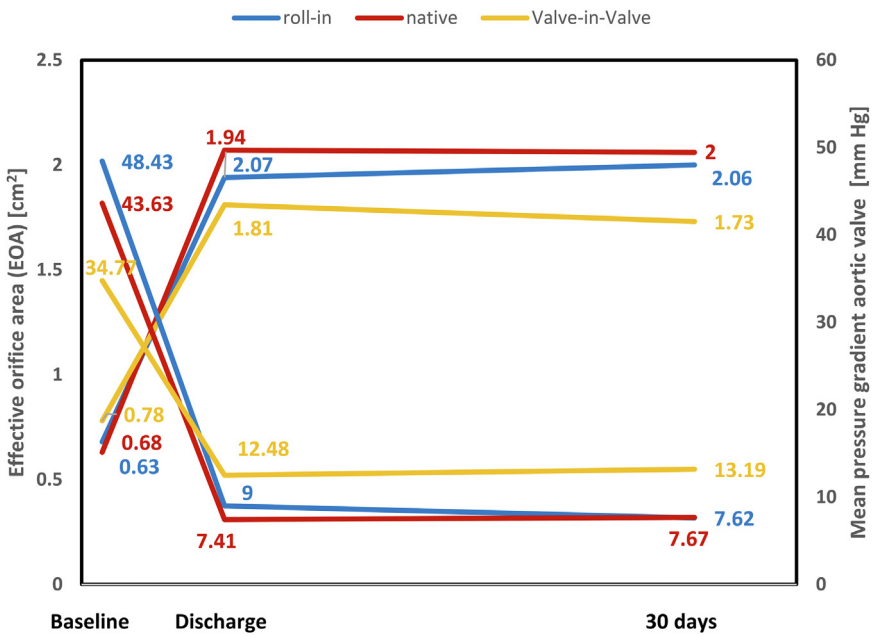

Figure 3. Mean pressure gradient and effective orifice area up to 30 days.

using an independent echocardiographic core laboratory. In a prior postmarket registry study utilizing self-reported data, Wolfrum et al. reported a mean EOA of 2.2 ± 0.5 cm^2 and a mean PG of 6.9 ± 3.8 mmHg in 255 patients treated in 4 European centers.[3] In the current study, a mean EOA of 2.1 ± 0.2 cm^2 and a mean PG of 7.6 ± 2.2 mmHg were reported. Overall, the ALLEGRA valve provides excellent hemodynamic performance in terms of both EOA and mean PG, comparable to published data for the Evolut/CoreValve device and superior to balloon expandable transcatheter heart valve.[4] Perhaps the clearest evidence of the hemodynamic benefits of the ALLEGRA valve is the complete absence of PPM in the native AS cohort and even in the ViV cohort, only 2/16 patients had moderate PPM with no patients having severe PPM.

Comparison With Other Studies

We derived our performance goal from the Evolut R CE Mark study which was an analogous premarket study of a new repositionable delivery system for a self-expanding transcatheter aortic valve conducted in Europe.[2] In that study, moderate or severe PPM was present in 16.4% of patients, despite using only the 26 and 29 mm sizes of the device. In the parallel Evolut R U.S study, moderate and severe PPM at 30 days was present in 26.8% of patients despite the 23 mm valve being used in only 1.3% of the population.[5] In the Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation 2 trial, moderate and severe PPM at 30 days was present in 29% of patients randomized to receive the Evolut device, similar to the incidence of 35% in patients

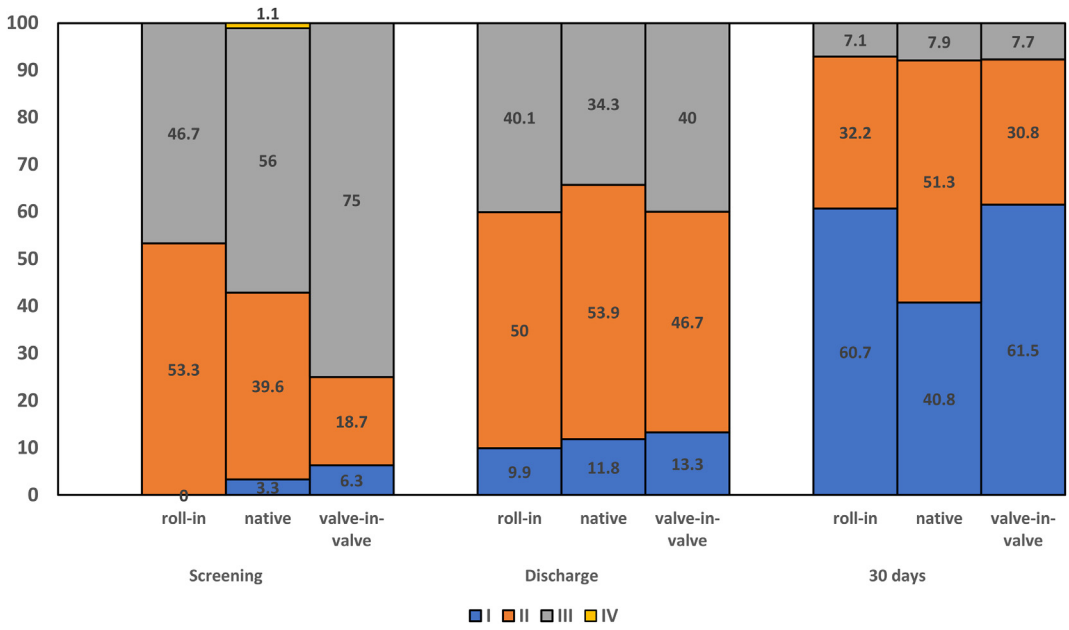

Figure 4. NYHA change over time.
Abbreviation: NYHA, New York Heart Association.

randomized to receive the ACURATE Neo device.[6] In the recent Small Annuli Randomized to Evolut or SAPIEN Trial with an upper annulus area inclusion limit of 430 mm^2, moderate and severe PPM at 30 days was present in 10.3% of patients randomized to receive the Evolut™ device.[7]

Wolfrum et al. reported moderate PVL at 30 days in 3.3% of patients with native AS treated with the ALLEGRA valve using the Permaflow delivery system compared to 5.6% in this study.[3] Similarly, moderate PVL at 30 days was reported in 3.4% of patients in the Evolut R CE Mark study and in 5.3% of patients in the Evolut R U.S study, in line with the rates in our study.[2,5] Although moderate to severe PVL contributes to the VARC-2 composite endpoint of device failure, this was more than offset in EMPIRE I by the absence of PPM resulting in an overall device success rate which exceeded the performance goal. The clinical implications of PPM such as mortality, heart failure related hospitalization, and structural valve deterioration are subject to debate and conflicting reports have been published in the literature. Evaluating the influence of PPM requires consideration of multiple parameters including follow-up time, quantification method and grading of PPM severity. However, 3 recent studies, including very large patient cohorts undergoing surgical aortic valve replacement or TAVI, found a strong association between all-cause mortality and PPM.[8–10] Finally, the new pacemaker rate in the Evolut R CE Mark study[2] was 11.7% and in the Evolut R U.S study[5] 16.4%, in line with the figure of 12.4% in this study with the ALLEGRA valve.

Limitations

This was a relatively small study albeit with twice the sample size of the study from which the performance goal was derived. It is single-arm and a formal comparison with any other TAVI device will require a randomized trial.

Conclusions

EMPIRE I confirms the safety and efficacy of TAVI using the next generation fully repositionable IMPERIA delivery system to implant the CE marked ALLEGRA transcatheter heart valve in patients with severe calcific native AS or a degenerated surgical aortic bioprosthesis.

ORCIDs

Joseph Graham https://orcid.org/0009-0002-7541-4892
Claire B. Ren https://orcid.org/0000-0002-8227-8094
Ernest Spitzer https://orcid.org/0000-0003-2371-5431
Nicolas van Mieghem https://orcid.org/0000-0002-2732-1205
Anders Jönsson https://orcid.org/0009-0005-7921-2624
Keith G. Oldroyd https://orcid.org/0000-0002-7842-3463

Ethics Statement

The study was performed according to the Declaration of Helsinki and ISO14155:2020. It was approved by the ethics committees of participating centers and all patients provided written informed consent before enrolling into the study.

Funding

This study was fully funded and sponsored by Biosensors Europe SA.

Disclosure Statement

Christian Frerker received speaking and lecture fees and travel reimbursement from Biosensors and Bluesails. Ignacio Cruz Gonzalez is a proctor and consultant for Boston, Medtronic, Biosensors, and Sahajanand Medical Technologies Pvt Ltd. Pilar Jimenez is a proctor and consultant for Abbott and Edwards Lifesciences. Claire B. Ren reports institutional contracts for echocardiography core laboratory analyses with Boston Scientific, Edwards Lifesciences, NVT GmBH/Biosensors, and Shenqi Medical, for which she has received no personal compensation and has received honoraria from Abbott. Ernest Spitzer declares institutional contracts/grants for which he receives no direct compensation from Abbott, Biosensors Europe SA, Boston Scientific, Edwards Lifesciences, Medtronic, Mixin Medtech (Suzhou) Co, Ltd, Shanghai Microport Medical Co, Ltd, NVT GmbH, Philips Healthcare, Pie Medical Imaging, Shanghai Shenqi Medical Technologies Co, Ltd, and Siemens Healthcare GmbH; declares being board member of Cardialysis, European Cardiovascular Research Institute, EU-MDR Cardiovascular Collaboratory, and Academic Research Consortium. Pim Tonino declares research grants form Opsens and Biosensors and speaking and lecture fees from Medtronic. Pieter Vriesendorp reports consultancy fees from Abbott, Biosensors, and Boehringer Ingelheim all paid to the institution. Nicolas Doll reports speaking and lecture fees and travel reimbursement by Biosensors. Samuel Copt, Anders Jönsson, and Keith G. Oldroyd are employees of Biosensors.

The other authors had no conflicts to declare.

Supplementary Data

Supplemental data for this article can be accessed on the publisher's website.

References

1 Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *Eur Heart J*. 2012;33(19):2403-2418. https://doi.org/10.1093/eurheartj/ehs255
2 Manoharan G, Walton AS, Brecker SJ, et al. Treatment of symptomatic severe aortic stenosis with a novel resheathable supra-annular self-expanding transcatheter aortic valve system. *JACC Cardiovasc Interv*. 2015;8(10):1359-1367. https://doi.org/10.1016/j.jcin.2015.05.015
3 Wolfrum M, Moccetti F, Piuhola J, et al. The ALLEGRA transcatheter heart valve: short term results from a multicenter registry. *Catheter Cardiovasc Interv*. 2021;98(6):1204-1209.
4 Hahn RT, Leipsic J, Douglas PS, et al. Comprehensive echocardiographic assessment of normal transcatheter valve function. *JACC Cardiovasc Imaging*. 2019;12(1):25-34. https://doi.org/10.1016/j.jcmg.2018.04.010
5 Popma JJ, Reardon MJ, Khabbaz K, et al. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery: results of the evolut R U.S. study. *JACC Cardiovasc Interv*. 2017;10(3):268-275. https://doi.org/10.1016/j.jcin.2016.08.050
6 Tamburino C, Bleiziffer S, Thiele H, et al. Comparison of self-expanding bioprostheses for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: SCOPE 2 randomized clinical trial. *Circulation*. 2020;142(25):2431-2442. https://doi.org/10.1161/CIRCULATIONAHA.120.051547
7 Herrmann HC, Mehran R, Blackman DJ, et al. Self-expanding or balloon-expandable TAVR in patients with a small aortic annulus. *N Engl J Med*. 2024;390(21):1959-1971. https://doi.org/10.1056/NEJMoa2312573
8 Dayan V, Vignolo G, Soca G, Paganini JJ, Brusich D, Pibarot P. Predictors and outcomes of prosthesis-patient mismatch after aortic valve replacement. *JACC Cardiovasc Imaging*. 2016;9(8):924-933. https://doi.org/10.1016/j.jcmg.2015.10.026
9 Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. *J Am Coll Cardiol*. 2018;72(22):2701-2711. https://doi.org/10.1016/j.jacc.2018.09.001
10 Sá MP, Jacquemyn X, Van den Eynde J, et al. Impact of prosthesis-patient mismatch after surgical aortic valve replacement: systematic review and meta-analysis of reconstructed time-to-event data of 122 989 patients with 592 952 patient-years. *J Am Heart Assoc*. 2024;13(7):e033176. https://doi.org/10.1161/JAHA.123.033176