CLINICAL COMPENDIUM

TRIFECTA™ VALVE
TEN-YEAR DATA

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TRIFECTA™ VALVE POST-MARKET PROSPECTIVE, MULTICENTER STUDY

The Trifecta™ valve is a tri-leaflet stented pericardial valve designed for supra-annular placement in the aortic position. The valve is fabricated using a polyester-covered titanium stent. The stent, excluding the sewing cuff, is then covered with porcine pericardial tissue. This covering is designed to provide protection from mechanical wear by allowing only tissue-to-tissue contact during valve function. A silicone insert in the polyester sewing cuff is slightly contoured to conform to the shape of the native annulus. The valve leaflets are fabricated from bovine pericardium. The porcine and bovine pericardium are preserved and cross-linked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process. Additionally, the Trifecta valve is processed with Linx™ anticalcification treatment, an anticalcification treatment that in animal studies has demonstrated resistance to calcification in four (4) ways.[1-6*]

STUDY DESIGN

The Trifecta Long Term Follow-Up (LTFU) study is a multicenter, prospective, nonrandomized, post-market study conducted in the United States and Canada to collect LTFU for safety and effectiveness data through ten (10) years post-implant on the Trifecta valve. This study was designed as a follow-up study to the Trifecta investigational device exemption (IDE) study (NCT00475709). A total of 11 investigational sites in the United States (n = 9) and Canada (n = 2) participated in the Trifecta LTFU study.

A total of 710 subjects from these 11 participating sites underwent valve implants between 2007 and 2009 as part of the Trifecta IDE study. Following the IDE study, subjects from six (6) sites were invited to participate in an FDA-mandated five-year (5-year) post-approval study (PAS; NCT01514162), and subjects from the remaining five (5) sites were invited to participate in a ten-year (10-year) post-market LTFU study (NCT01593917). A total of 245 subjects consented to participate in the PAS. Once the PAS study was completed, the remaining subjects were invited to participate in the LTFU study. All together, a total of 329 subjects consented to participate in the LTFU study (140 from the Trifecta PAS and 189 directly from the Trifecta IDE study). For properly characterizing clinical outcomes, a total of 710 subjects (444 subjects from the Trifecta PAS at six (6) IDE sites and 266 from the Trifecta IDE study at five (5) sites) contributed to the results presented in this clinical compendium for the Trifecta LTFU study.

Subjects were followed on an annual basis with either an in-clinic visit or a telephone follow-up. Each in-clinic visit consisted of a transthoracic echocardiogram and assessments for New York Heart Association (NYHA) functional classification, serious adverse events and general clinical status. The seven-year (7-year) and ten-year (10-year) follow-ups consisted of an in-clinic visit, while the eight-year (8-year) and nine-year (9-year) follow-ups were performed using a telephone.

Table 1: Study Centers

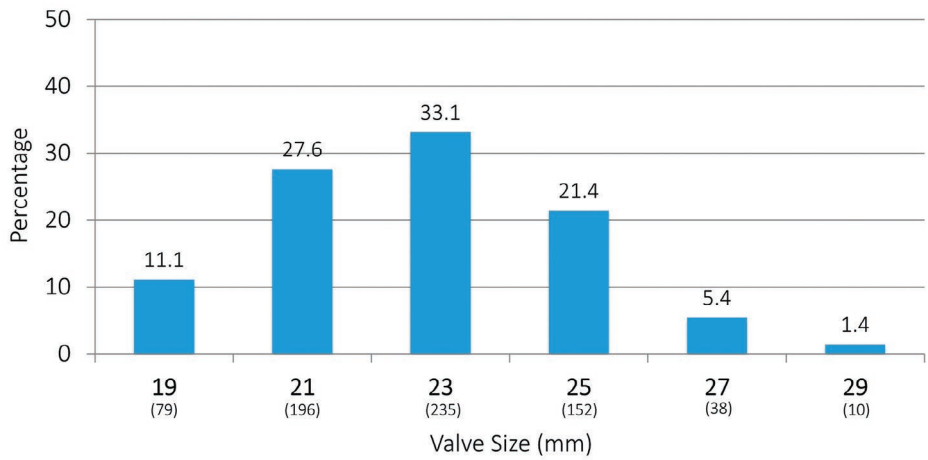
STUDY CENTERS	LOCATION
Mayo Clinic	Rochester, MN, USA
Hospital of the University of Pennsylvania	Philadelphia, PA, USA
Abbott Northwestern Hospital	Minneapolis, MN, USA
Mission Health and Hospitals	Asheville, NC, USA
Vanderbilt University Medical Center	Nashville, TN, USA
Intermountain Medical Center	Salt Lake City, UT, USA
Cleveland Clinic Foundation	Cleveland, OH, USA
Lankenau Medical Center	Wynnewood, PA, USA
University of Southern California	Los Angeles, CA, USA
St. Paul's Hospital — University of British Columbia	Vancouver, BC, Canada
Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval	Quebec City, Quebec, Canada

SUMMARY OF SUBJECT DEMOGRAPHICS[7]

The subject population in this study had the following characteristics:

- 471 subjects (66%) were male and 239 subjects (34%) were female
- Mean age was 72.4 years (± 9.3); age range was 32–95 years
- Prior to implantation, 5.4% were NYHA Functional Class I, 43.8% Class II, 46.8% Class III and 4.1% Class IV

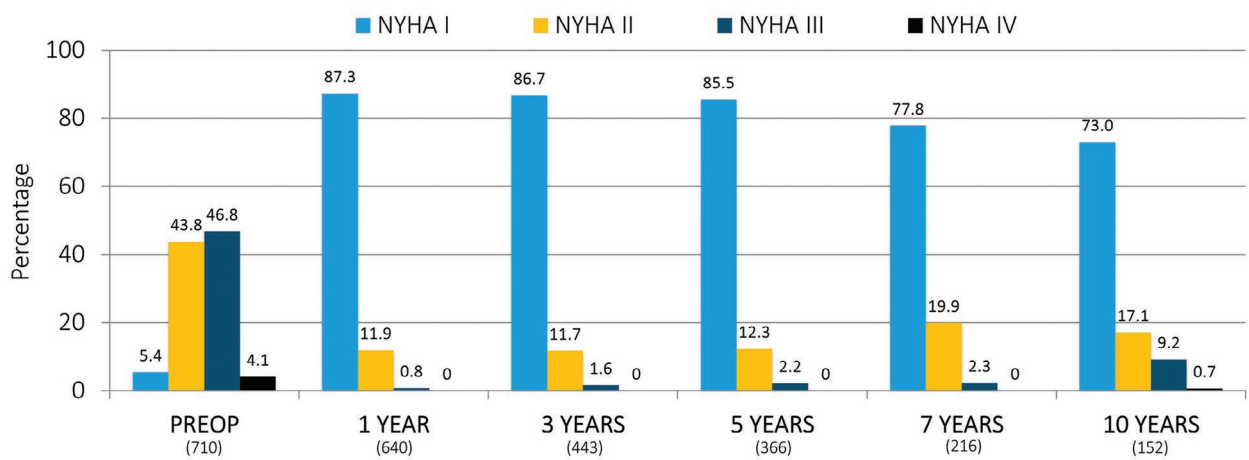
Figure 1: Distribution of Valve Sizes



- The most common size implanted was 23 mm (33.1%)

FOLLOW-UP DATA AND CLINICAL RESULTS

Figure 2: NYHA Functional Classification Over Time

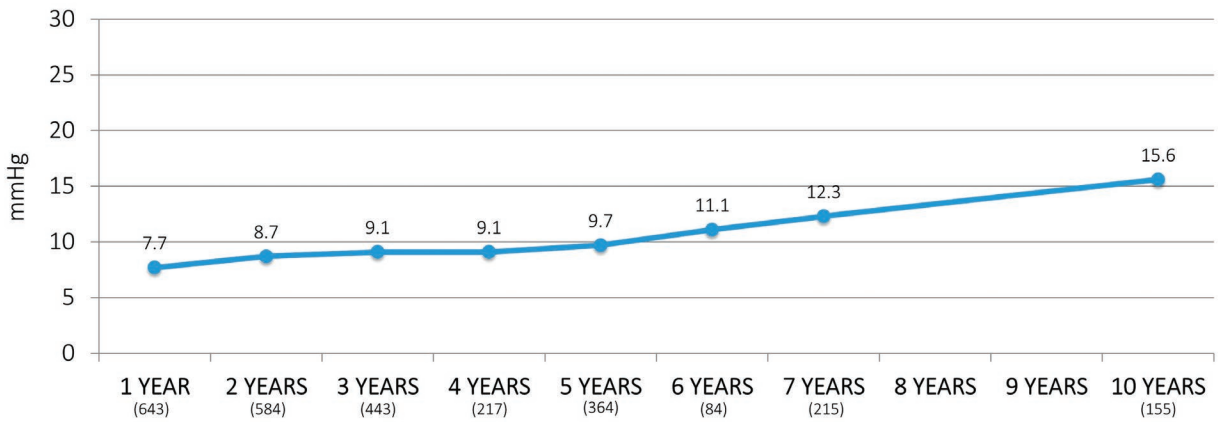


- Preoperatively, 50.9% of subjects were NYHA Class III or IV. At one (1) year postoperatively, 99.2% were NYHA Class I or II. At ten (10) years postoperatively, 90.1% were NYHA Class I or II

HEMODYNAMIC DATA

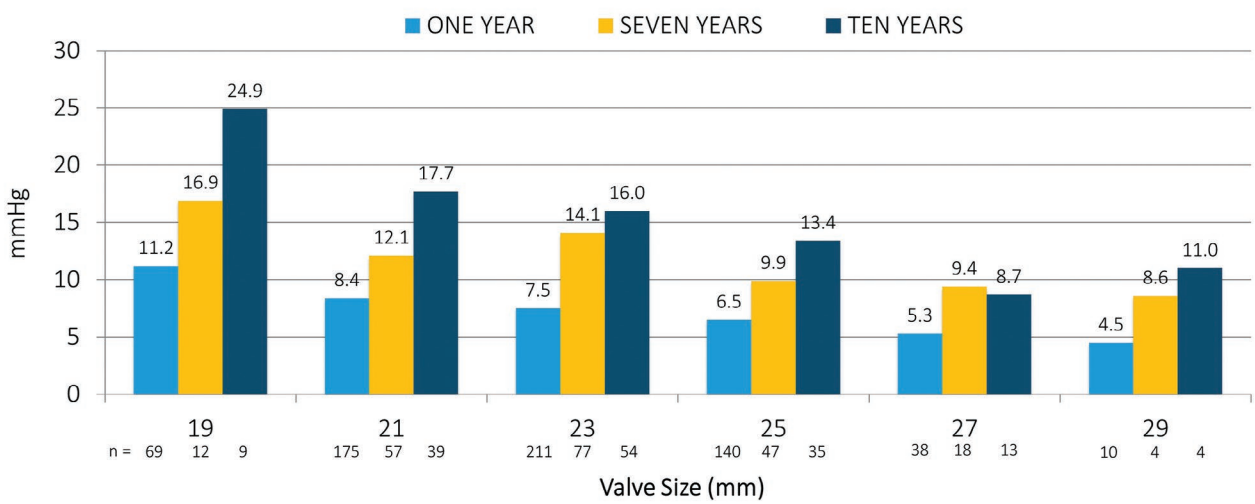
The following average hemodynamic parameters were evaluated by valve size, mean gradient, effective orifice area (EOA) and effective orifice area index (EOAI) (Figures 3–6). Average mean gradient and aortic regurgitation for all valve sizes over time are shown in Figures 3 and 7, respectively. All echocardiograms were evaluated at an independent core laboratory to minimize interobserver variability and ensure a standard of quality interpretation.

Figure 3: Average Mean Gradient Over Time



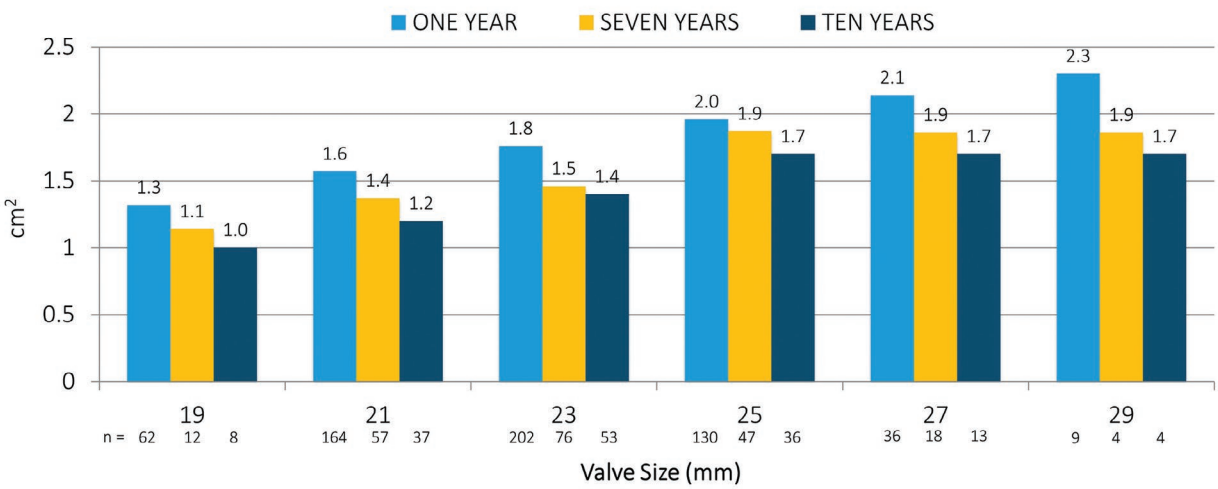
- Average mean gradient across all valve sizes was 15.6 mmHg at ten (10) years postoperatively which corresponds to an average increase of less than 1.0 mmHg per year

Figure 4: Average Mean Gradient by Valve Size



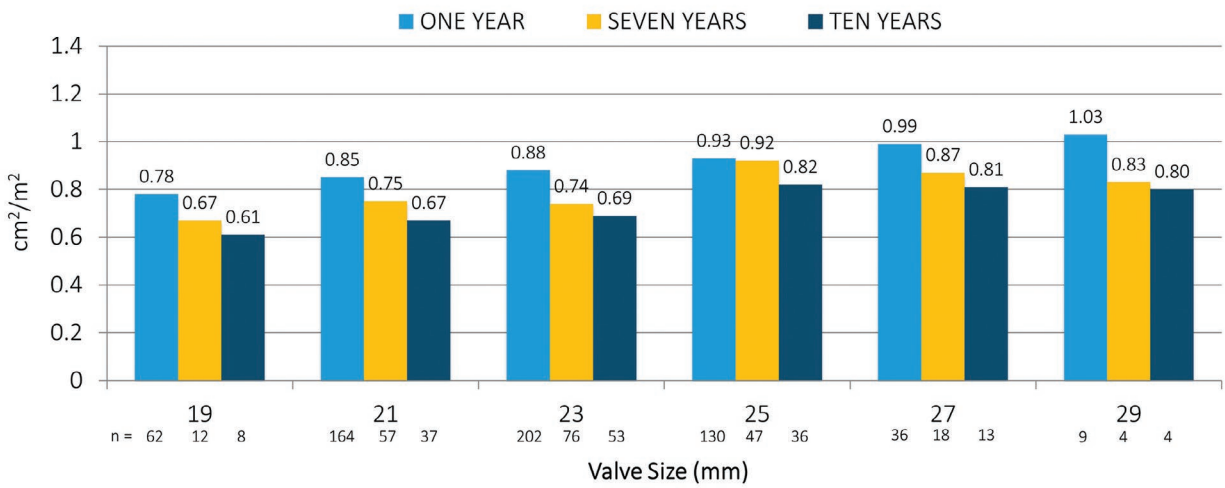
- Average mean gradient for 19 mm valve size was 24.9 mmHg at ten (10) years postoperatively

Figure 5: Average Effective Orifice Area by Valve Size



- Large EOAs across all valve sizes reduce the risk of prosthesis-patient mismatch

Figure 6: Average Effective Orifice Area Index by Valve Size

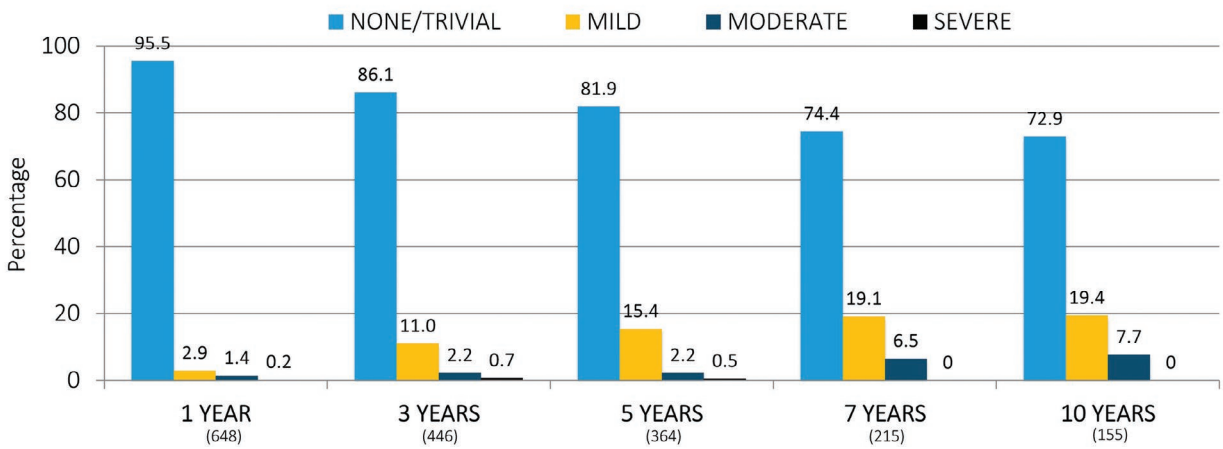


- Average EOAI across all valve sizes at one (1) year = 0.88 cm^2/m^2 and at ten (10) years = 0.73 cm^2/m^2

AORTIC REGURGITATION

The following figure presents the total aortic valve regurgitation over time for all valve sizes.

Figure 7: Aortic Regurgitation Over Time



- 92.3% of subjects were without moderate-to-severe valvular regurgitation at ten (10) years

KAPLAN-MEIER ANALYSES

Figures 8–12 present the Kaplan-Meier analyses for structural valve deterioration (SVD) and mortality. The 95% confidence interval is indicated by the dashed lines, and the number of subjects at risk for each interval is shown at the bottom. Cumulative percentage freedom from the event at five (5) years, eight (8) years and ten (10) years post-implant are indicated on each figure.

Figure 8: Surgical Explant Due to Structural Valve Deterioration

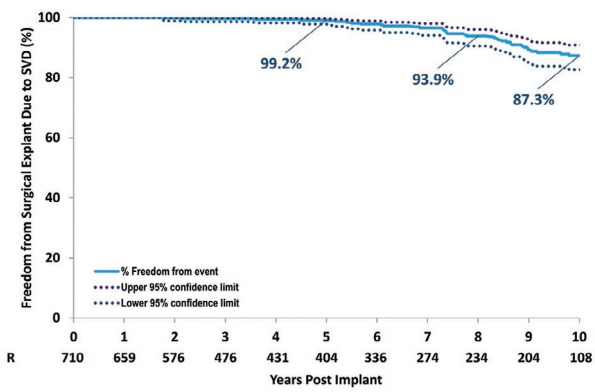


Figure 9: Reintervention Due to Structural Valve Deterioration (Surgical Explant or Transcatheter Valve-in-Valve Intervention)

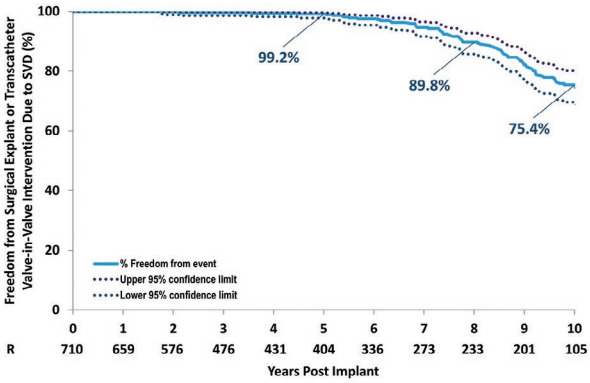


Figure 10: Valve-related Mortality

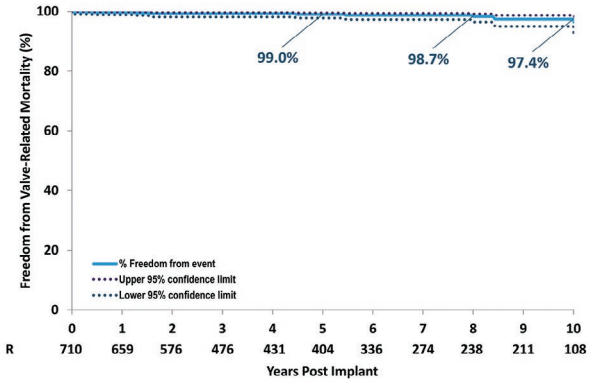


Figure 11: All-cause Mortality

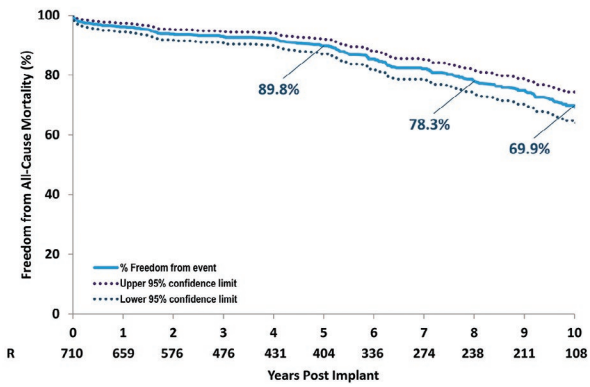
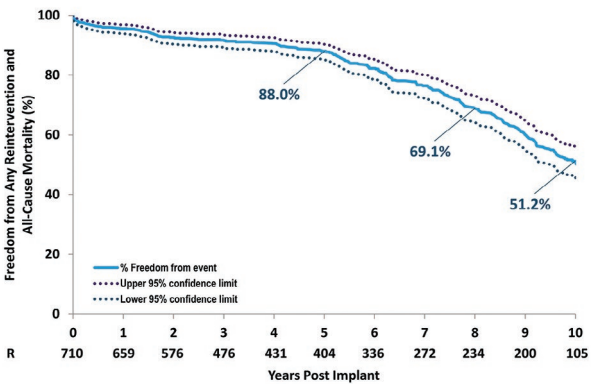


Figure 12: All-cause Mortality and Any Reintervention



SUMMARY OF ADVERSE EVENTS

Early and late rates for serious adverse events are presented in Table 2. Early rates are presented as simple percentages, and late rates as the percentage per late patient-years (%/Lt Pt-yr) of follow-up. No unanticipated device effects were reported.

Table 2: Early and Late Adverse Event Rates

	EARLY RATE (≤ 30 days)		LATE RATE (≥ 31 days) (%/Lt Pt-yr = 3944.6)	
	EVENTS	%**	EVENTS	%/Lt Pt-yr
Embolism	20	2.8	30	0.76
Neurologic	18	2.5	27	0.68
TIA	2	0.3	15	0.38
RIND	10	1.4	3	0.08
Stroke	6	0.8	9	0.23
Systemic	2	0.3	1	0.03
Thrombosis	0	0.0	1	0.03
Major Bleed	52	7.3	64	1.62
Endocarditis	0	0.0	10	0.25
Structural Deterioration	0	0.0	91	2.31
Nonstructural Dysfunction	1	0.1	7	0.18
Paravalvular Leak	1	0.1	5	0.13
Reintervention	1	0.1	79	2.00
Explant due to SVD	0	0.0	35	0.89
ViV due to SVD	0	0.0	34	0.86
Mortality	11	1.5	118	2.99
Valve-related	1	0.1	10	0.25

RIND: reversible ischemic neurological deficit; TIA: transient ischemic attack; ViV: valve-in-valve

SUMMARY

Outcomes from the Trifecta™ valve post-market prospective, multicenter study (n = 710) demonstrate that the Trifecta valve has potential hemodynamic and survival benefits that may be balanced against an increased rate of SVD seen beyond 8 years post-implant. Among patients who experienced SVD in this study, there were 34 patients who underwent a transcatheter valve-in-valve (ViV) intervention which is a less invasive approach for treating SVD.

Key clinical outcomes from the study include:

- Average mean gradient across all valve sizes was 15.6 mmHg at 10 years post-implant which corresponds to an average increase of less than 1.0 mmHg per year
- 97.4% freedom from valve-related mortality at 10 years post-implant
- 69.9% freedom from all-cause mortality at 10 years post-implant
- 87.3% freedom from surgical explant due to SVD at 10 years post-implant
- 75.4% freedom from surgical explant or transcatheter ViV intervention due to SVD at 10 years post-implant
- 51.2% freedom from any reintervention and all-cause mortality at 10 years post-implant

*There are no clinical data currently available that evaluate the long-term impact of anticalcification tissue treatment in humans.
**The early adverse rate (%) is calculated as the number of early events divided by the total number of subjects, times 100.

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