



Four-Year Pooled Results of the ALTERRA Trials: Transcatheter Pulmonary Valve Replacement with the Alterra Adaptive Prestent and SAPIEN 3 Transcatheter Heart Valve

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on behalf of the ALTERRA Trial Investigators

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As a faculty member for this program, I disclose the following relationships with industry:

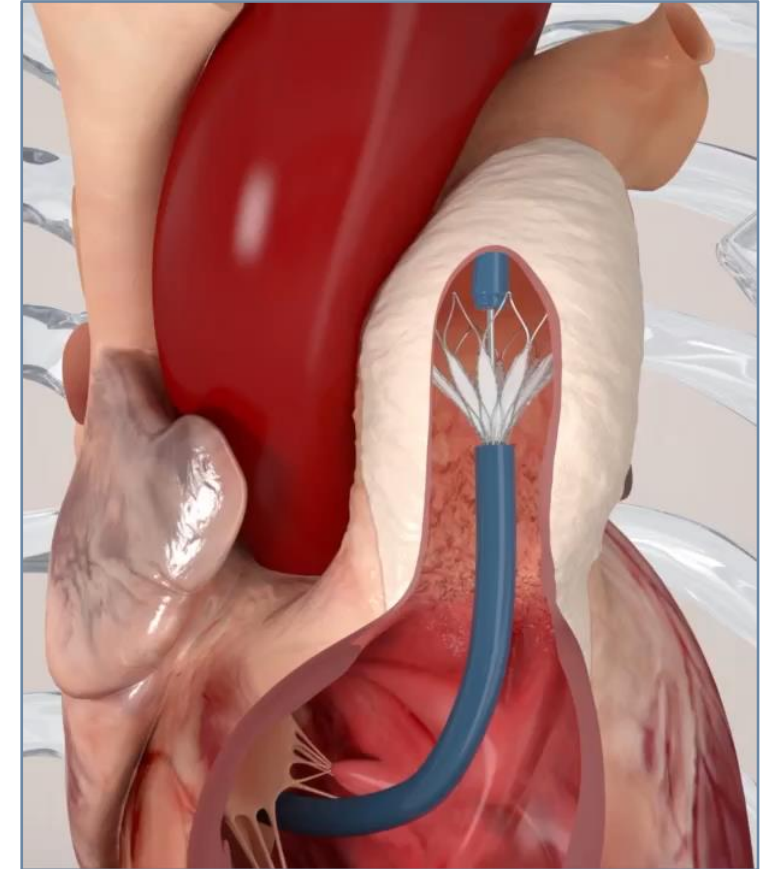
- Investigator & Proctor: Edwards Lifesciences
- Investigator & Proctor: Medtronic Inc

Background and Study Objective

The Alterra Adaptive Presept:

1. Internally reduces and reconfigures dysfunctional, native RVOT in patients with $\geq$ moderate PR
 - Suitable Anatomy
 - ≥ 27 mm **landing zone diameter** ≤ 38 mm
 - ≥ 35 mm **landing zone length**
2. Creates a **landing zone** for a **29mm SAPIEN 3 THV**
3. Has an extensive patient screening process

Following enrollment completion in the Main Cohort, the **Pulmonic Delivery System (PDS)**, a covered delivery system for the SAPIEN 3 THV, was introduced. The PDS was employed for patients in the PDS Registry and Continued Access Protocol (CAP)



Objective: Demonstrate safety and effectiveness of the Alterra Adaptive Presept with the SAPIEN 3 THV in subjects with a dysfunctional right ventricular outflow tract/pulmonary valve (RVOT/PV) for treatment of pulmonary regurgitation (PR)

Primary Endpoint in the Main Cohort (N=61)



THV Dysfunction at 6 months*

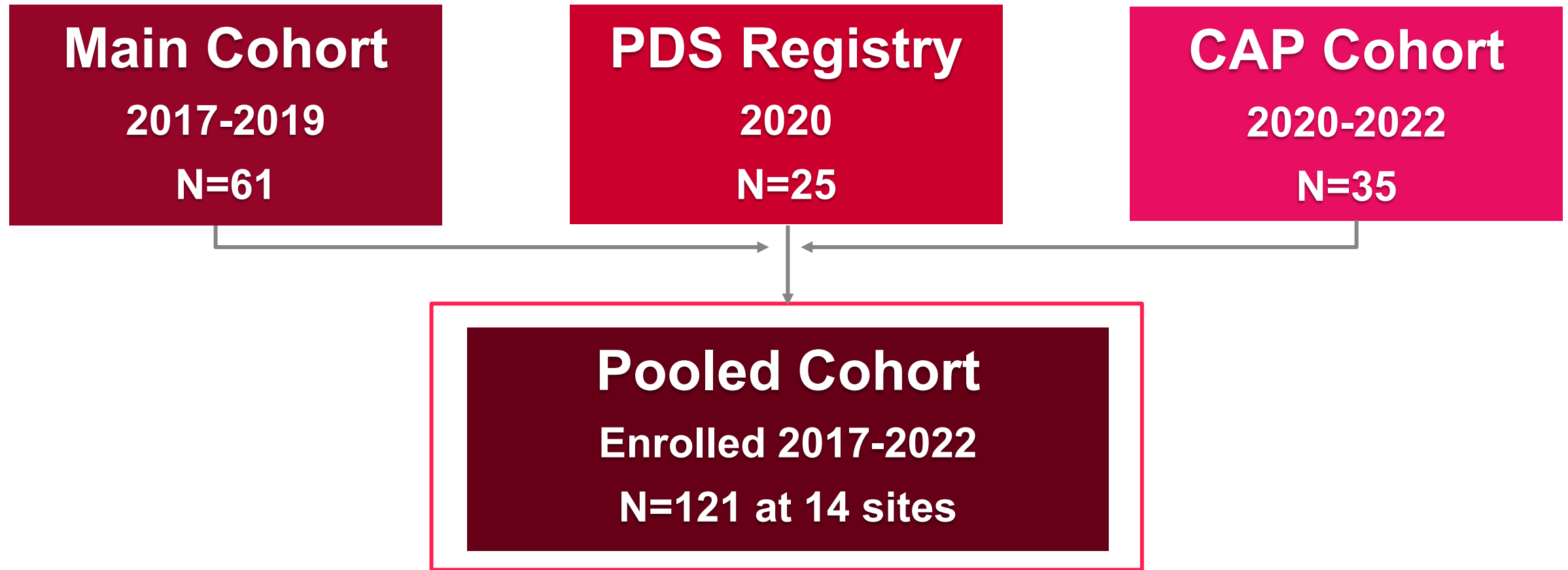
Non-hierarchical composite of:

- RVOT/PV reintervention
- Moderate or greater total PR (Core Lab TTE)
- Mean RVOT/PV gradient ≥ 35 mmHg (Core Lab TTE)

→ 0%

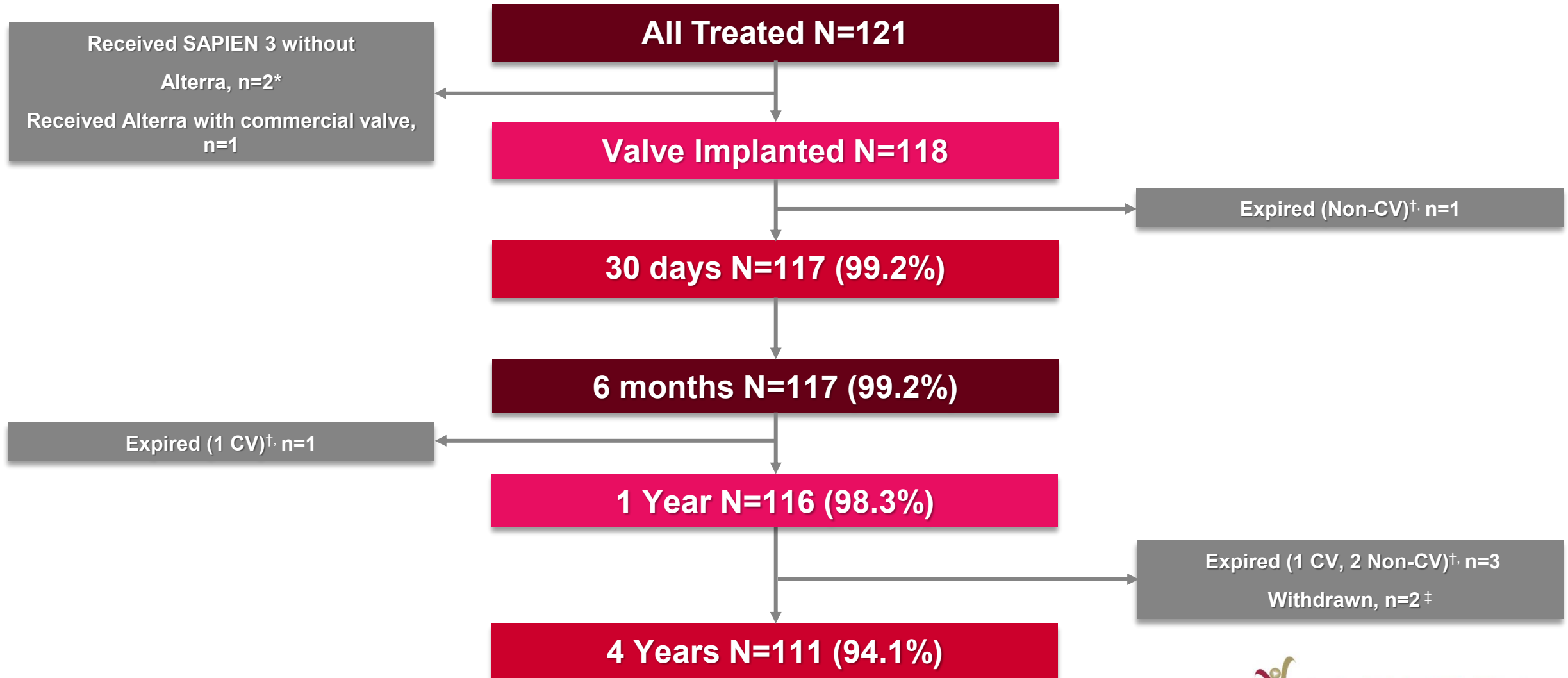
Here, we report **4-year pooled clinical and echocardiographic outcomes** from the Main Cohort, PDS Registry and CAP

ALTERRA Trial: Study Design



Follow-up: 30 days, 6 months, and **annually through 10 years**

Subject Accountability: Pooled Cohort



*Unsuitable/borderline anatomy. †All deaths adjudicated by the CEC. ‡Patient no longer wanted to participate (n=1) Patient relocated (n=1)

Baseline Characteristics: Pooled Cohort



Variable	Summary Statistics (N=121)
Age (years)	28.6 ± 15.9
>21 years (%)	51.2%
Weight (kg)	72.5 ± 21.7
Primary CHD Diagnosis*	
Tetralogy of Fallot	66.1 % (80/121)
Pulmonary valve stenosis	27.3 % (33/121)
Pulmonary atresia	3.3% (4/121)
Other†	3.3% (4/121)

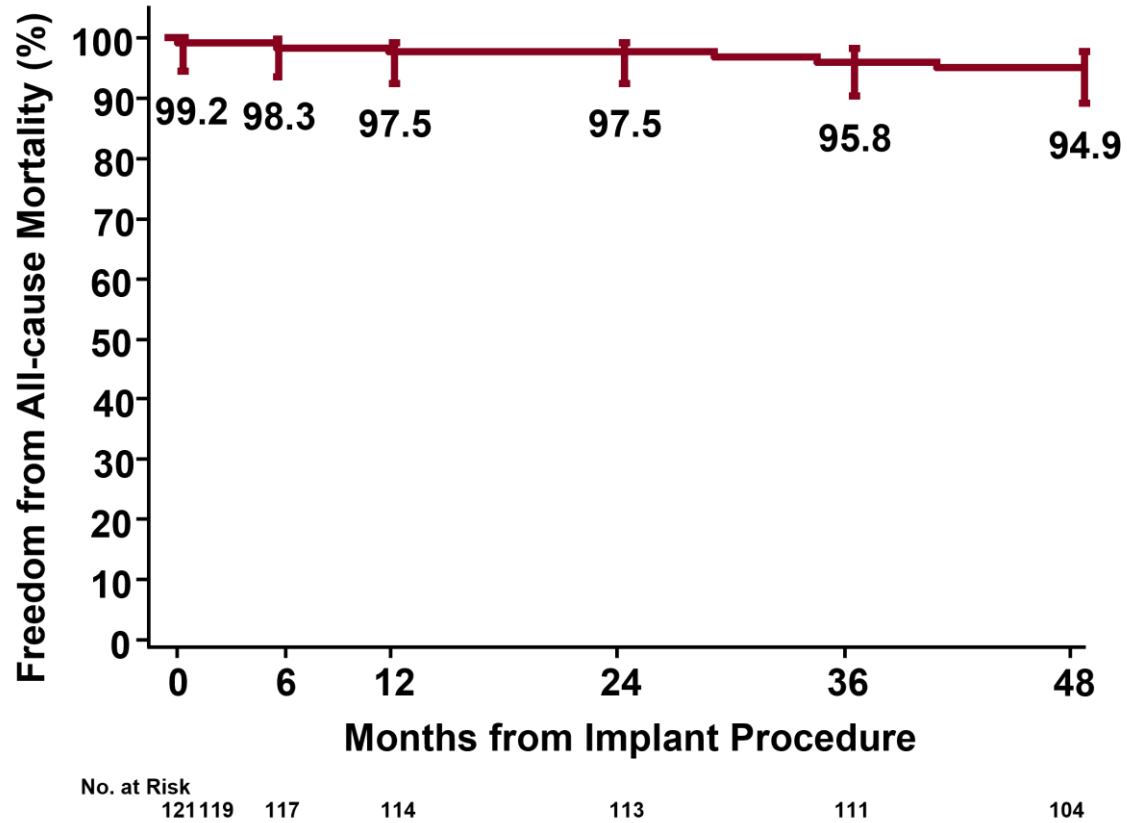
Categorical measures – %; Continuous measures - mean ± SD

*Site-reported †Moderate-severe PR (n=1), pulmonary valve prolapse (n=1), multivalvular heart disease (n=1), pulmonary atresia with intact ventricular septum (n=1)

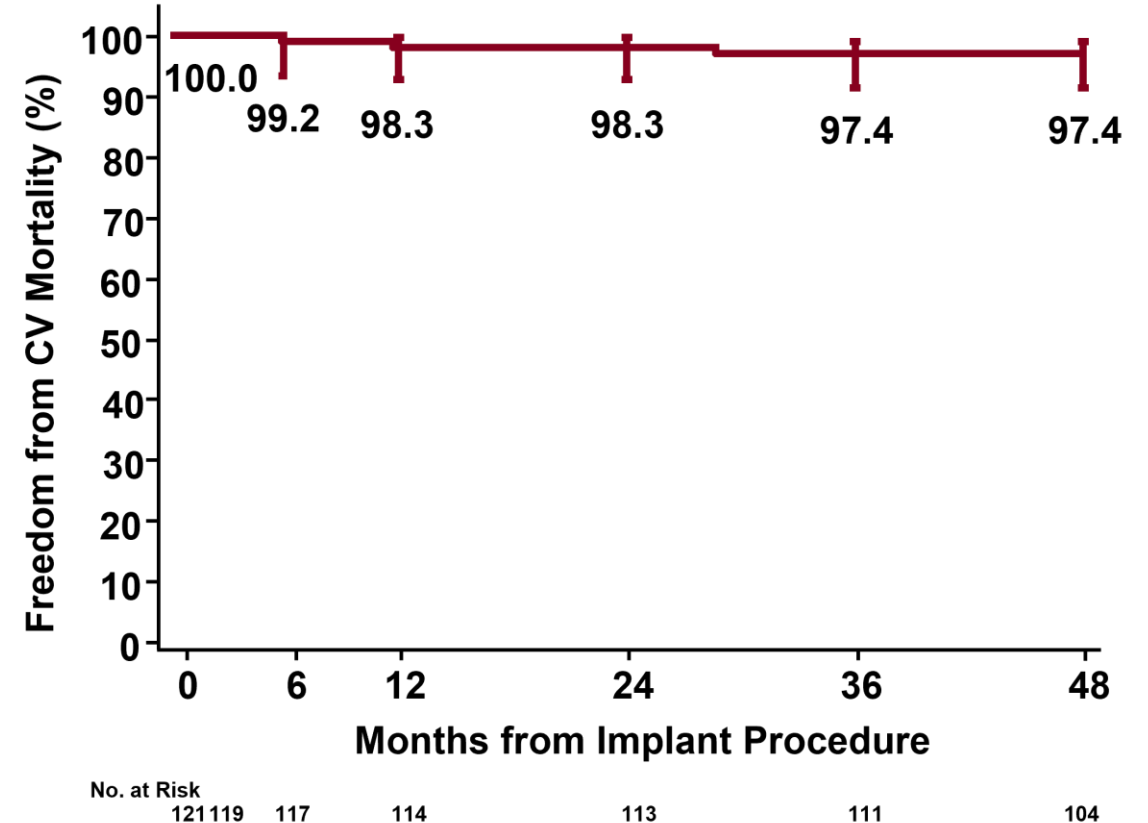
Freedom from Mortality



All-cause Mortality



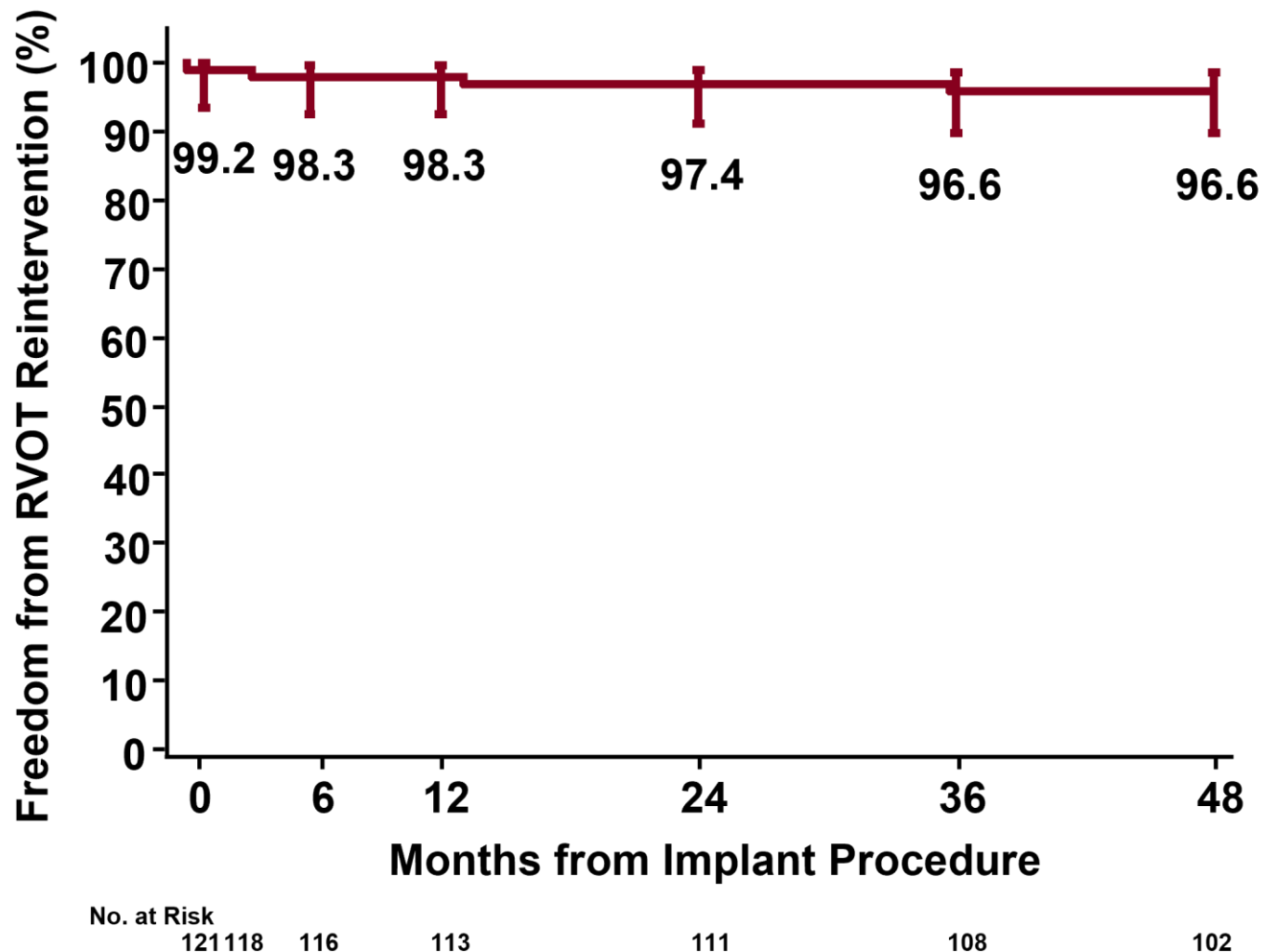
Cardiovascular Mortality



CEC adjudicated

All Treated population (N=121): 1 CV death was a patient who received a commercial valve and exited the study approx. 6 months prior to expiring, and not included in the VI population

Freedom from Reintervention



CEC adjudicated

All Treated population (N=121): 1 reintervention was a patient who received a commercial valve and exited the study approx. 6 months prior, and not included in the VI population

Other Clinical Outcomes



Incidence Rate, % (n events)	0 – 4 Years (N=121)
Device-Related Endocarditis [*]	0%
Pulmonary Embolism	0%
Stroke/TIA	0%
Coronary Artery Compression [†]	0%
Acute Kidney Injury [†]	0%

CEC adjudicated

**1 case of aortic valve endocarditis was reported, adjudicated as not related to the procedure, or study devices. †CEC adjudicated out to 30 days, site-reported thereafter.*

CEC Adjudicated Arrhythmias

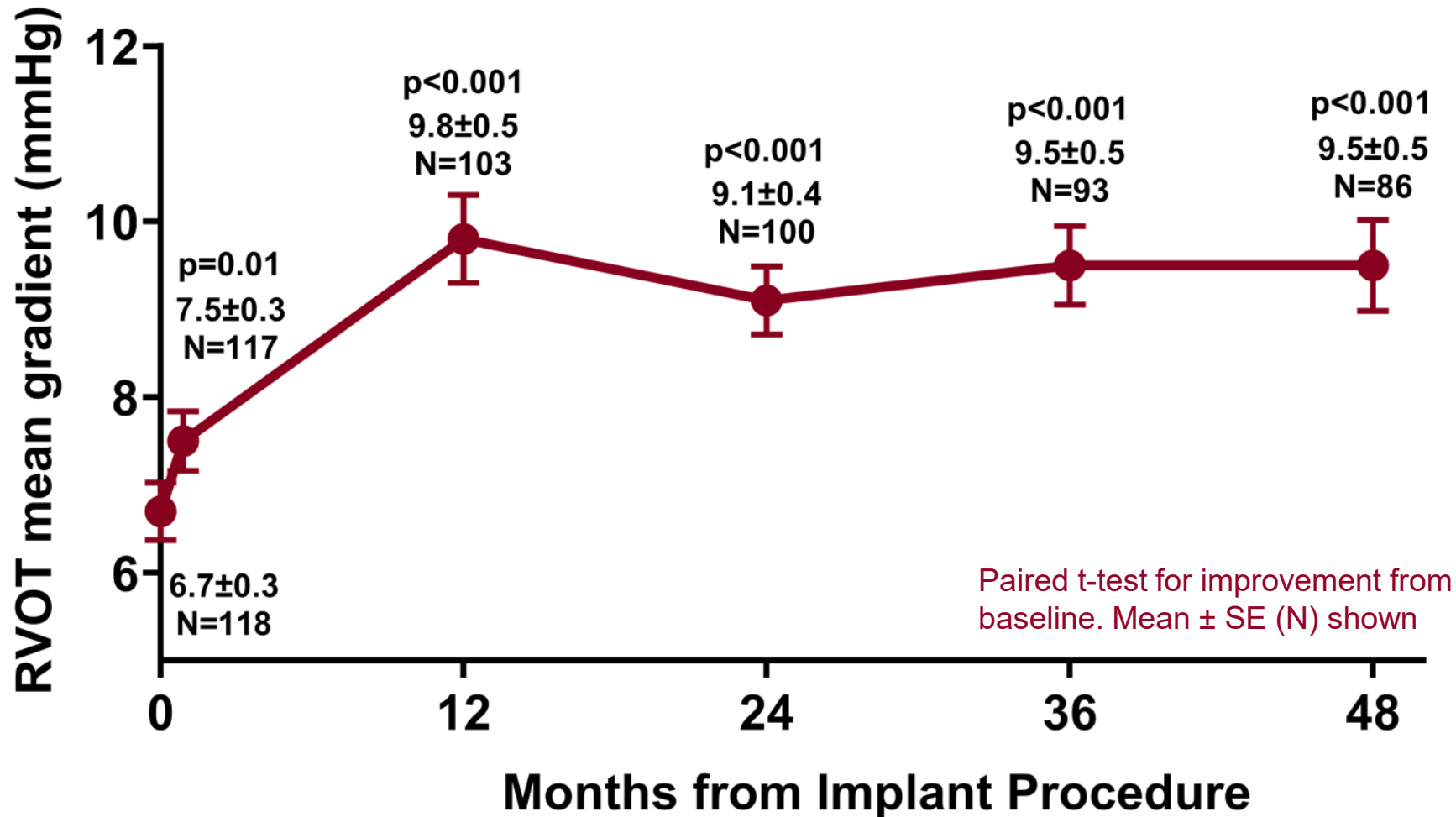


Incidence Rate, % (n events) N=121	0 - 30 Days	31 Days – 3 Years	3 - 4 Years
Arrhythmias	38.0% (52)*	2.5% (3)	0.9% (1)
Ventricular tachycardia	22	0	0
NSVT	21	0	0
PVCs	21	1	0
Atrial fibrillation/flutter	2	0	1 [†]
Ventricular fibrillation	0	2	0
Other [§]	7	0	0

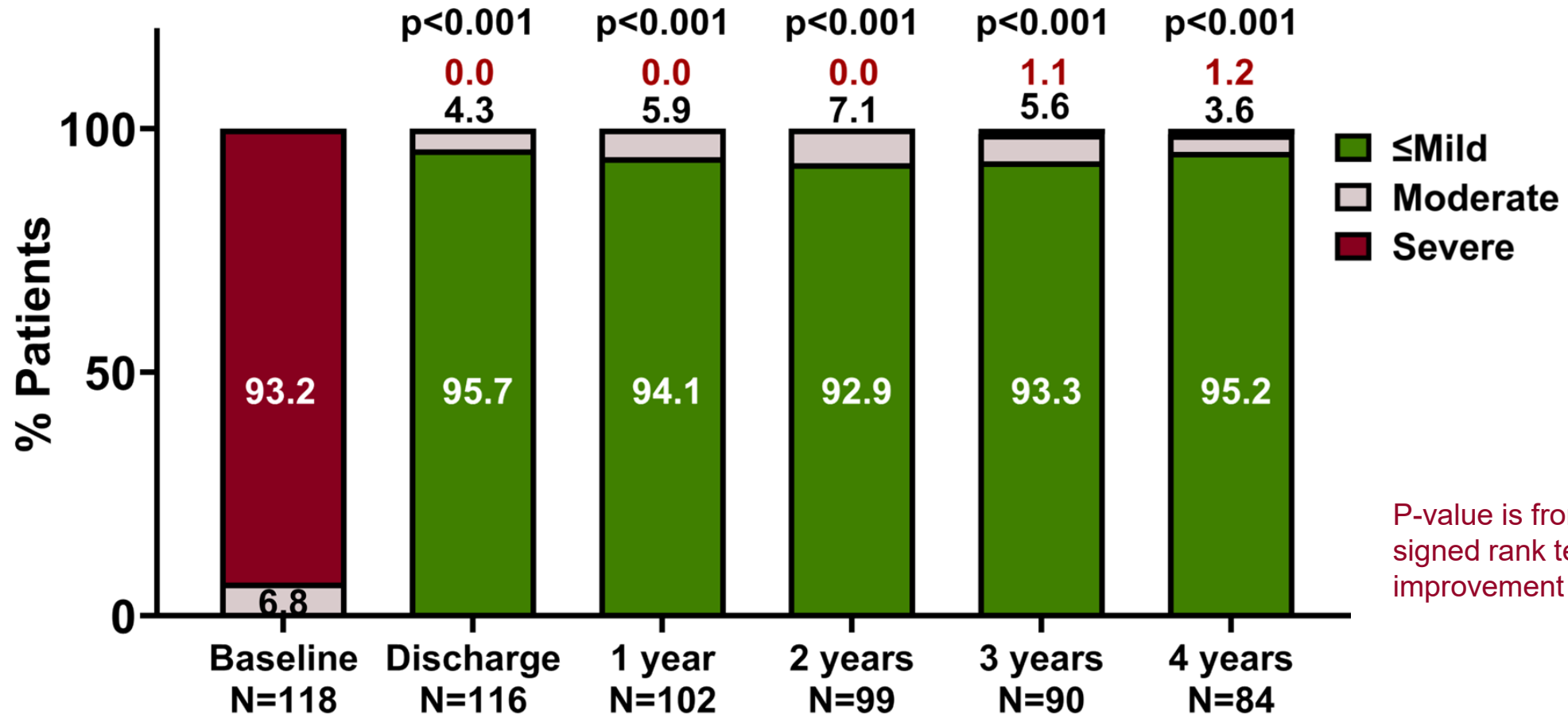
*52 CEC adjudicated arrhythmia events in 46 patients.

[†]Patient had documented history of paroxysmal atrial fibrillation; event described as worsening of a pre-existing condition. Medical treatment initiated on POD 1187 for paroxysmal atrial flutter.

Mean RVOT Gradient



Total Pulmonic Regurgitation



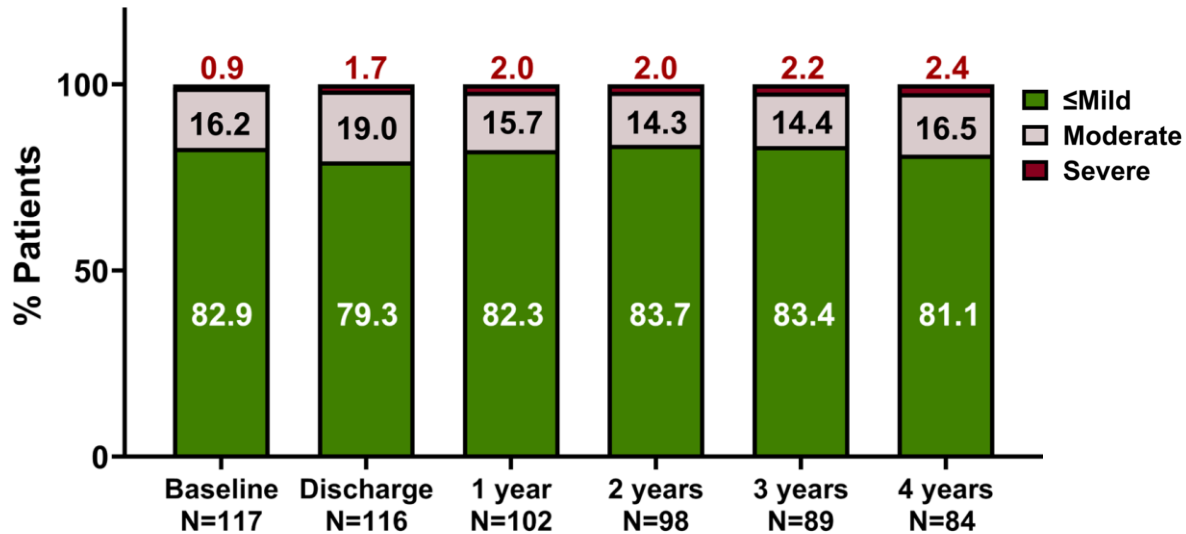
P-value is from a Wilcoxon signed rank test for improvement from baseline

All patients had ≤Mild paravalvular regurgitation post-procedure through 4-year

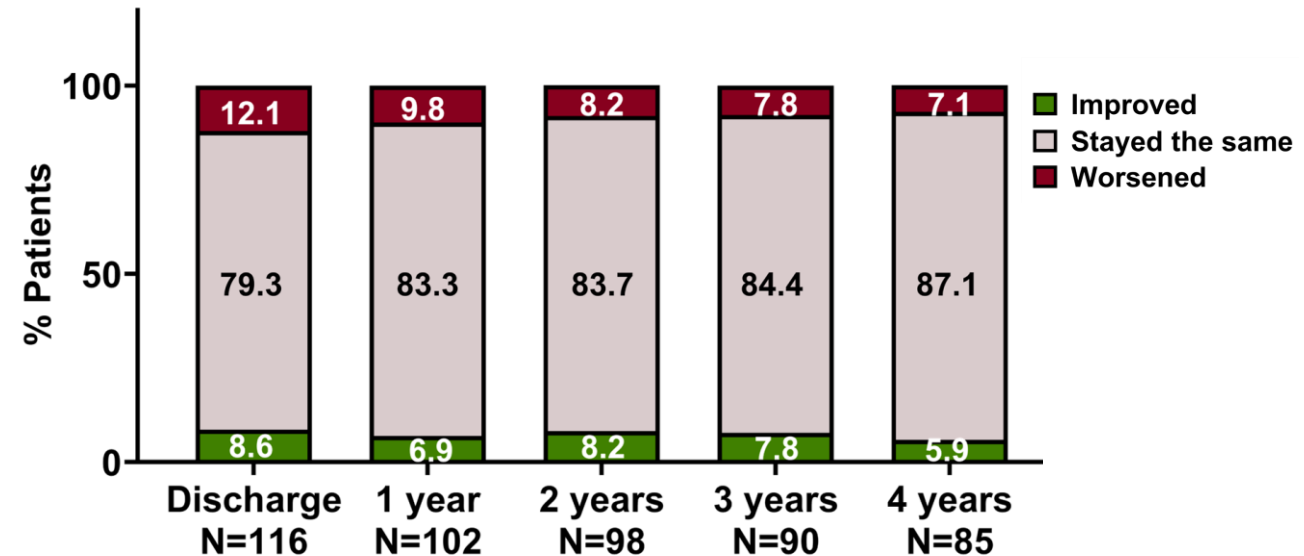
Tricuspid Regurgitation



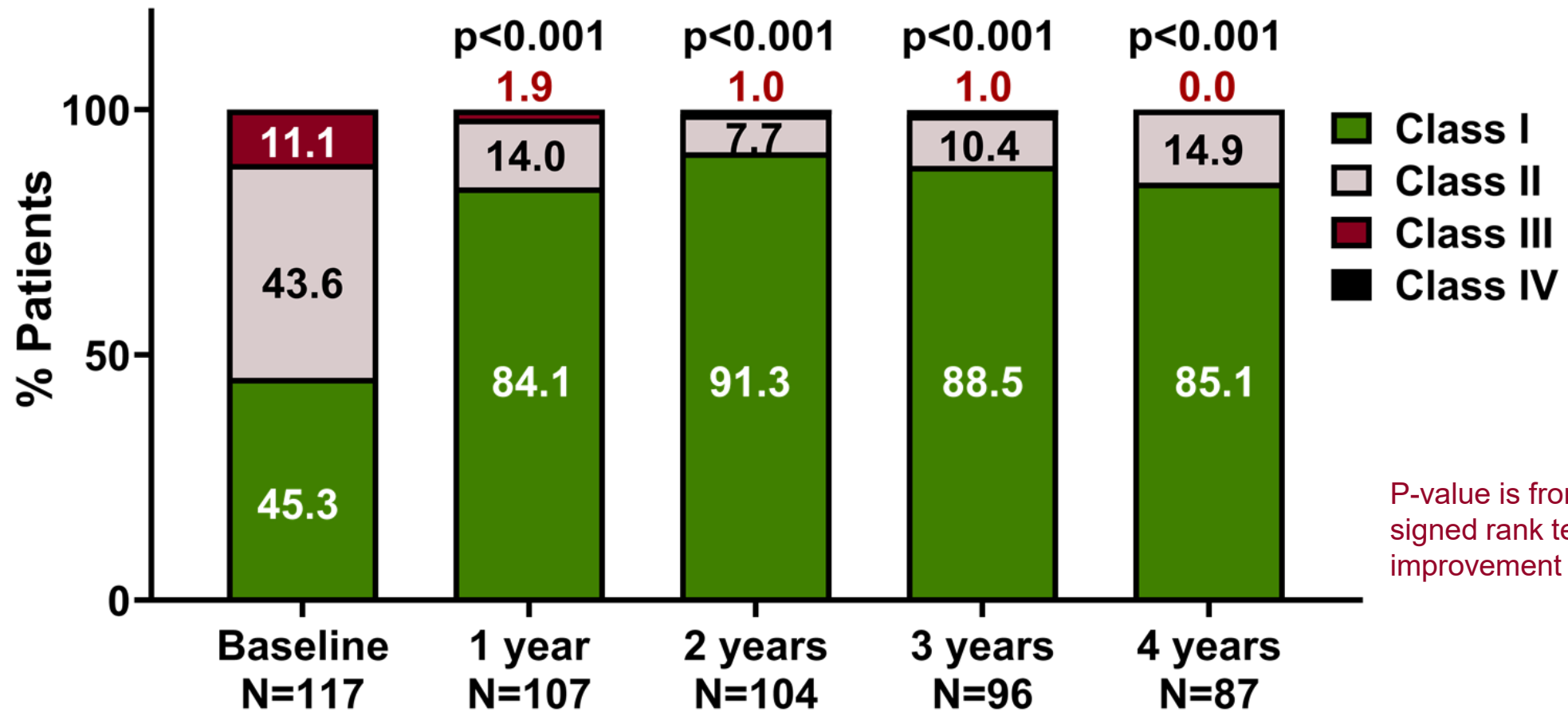
Tricuspid Regurgitation



Change in TR from Baseline



NYHA Functional Class



Conclusions

The Alterra Adaptive Prestent/SAPIEN 3 THV system demonstrated safety and effectiveness through 4-year follow-up:

- Excellent valve performance
 - 98.8% patients had improved PR from baseline at 4 yrs (95.2% with $\leq$ Mild PR)
 - Mean gradients remained low and stable
- Low rate of reintervention (3.3%)
 - Two patients underwent successful transcatheter reinterventions with a 29 mm S3 THV, achieving excellent procedural outcomes
- No cases of coronary artery compression
- Ventricular arrhythmias were predominantly periprocedural and resolved

Future Perspectives



In the ALTERRA trials

- Patient follow-up is scheduled annually through 10 years, including:
 - Key clinical outcomes, including reintervention and arrhythmias
 - Echocardiographic outcomes at 5-, 7-, and 10-year follow-up
- CT imaging will be performed at 5 years and 10 years, with CT Core Lab assessment of Alterra Prestent appearance
 - There are no acute perforations or chronic erosions at 4 years
- These long-term data will contribute to the body of clinical evidence on lifetime management post-TPVR

Thanks and Recognition



Participating Sites

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Clinical Events Committee

Cardiovascular Research Foundation, New York, NY

CT Core Laboratory

St. Paul's Hospital, Vancouver, Canada

Directors: Jonathon Leipsic, Philipp Blanke

Echocardiographic Core Laboratory

Children's Mercy, Kansas City, MO

Directors: Girish Shirali, Anitha Parthiban

Sponsor

Edwards Lifesciences, Irvine, CA

Dr. Shahanavaz is now with Cincinnati Children's Hospital, OH
Dr. Dimas and Dr. Stapleton are now with Medical City Children's Hospital Heart Center, TX
Dr. Lim is now at the University of British Columbia, Vancouver, Canada
Dr. Armstrong is now at Johns Hopkins University School of Medicine
Dr. Parthiban is now with Texas Children's Hospital, Baylor College of Medicine, TX



Important Safety Information

Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent

Indications: The Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation as measured by echocardiography who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for pulmonary valve replacement.

Contraindications: The Edwards SAPIEN 3 Transcatheter Pulmonary Valve System with Alterra Adaptive Prestent is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

Warnings: The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing. The physician must verify correct orientation of the valve prior to its implantation; the inflow (outer skirt end) of the valve should be oriented towards the proximal end (handle) of the delivery system to prevent the risk of severe patient harm. Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve. Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed. Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g., kinked or stretched), or the expiration date has elapsed. Do not add or apply antibiotics to the storage solution, rinse solutions or to the valve.

Precautions: Long-term durability has not been established for the device. Regular medical follow-up is advised to evaluate device performance. Patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials may have an allergic reaction to these materials. Accelerated deterioration of the valve may occur in patients with an altered calcium metabolism. Assessment for coronary compression risk prior to implantation is recommended. Patient venous anatomy should be evaluated to prevent the risk of access that would preclude the delivery and deployment of the device. Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored. Fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. Patient radiation dose should be monitored during the procedure. Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences. Patient should be heparinized to maintain the ACT at ≥ 250 sec prior to introduction of the delivery system in order to prevent thrombosis. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Device recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without antiplatelet therapy. It is recommended that all device recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection. Correct sizing of the prestent into the RVOT is essential to minimize risks such as paravalvular leak, migration, embolization, and/or RVOT rupture. If a prestent fracture is detected with significant loss in valve functionality, reintervention should be considered. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: blood dyscrasias defined as: leukopenia, acute anemia, thrombocytopenia, or history of bleeding diathesis or coagulopathy; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid™), or clopidogrel (Plavix™), or sensitivity to contrast media, which cannot be adequately premedicated; positive urine or serum pregnancy test in female patients of childbearing potential.

Potential Adverse Events: Potential risks associated with the anesthesia, interventional procedure, and imaging include but are not limited to death; stroke/transient ischemic attack; respiratory insufficiency or respiratory failure; cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium, or valvular structures, including rupture of the RVOT that may require intervention; pericardial effusion/cardiac tamponade; cardiac failure; embolic event: air, calcific material, thrombus, device fragments; infection, including incisional site infection, septicemia, and endocarditis; myocardial infarction; renal insufficiency or renal failure; conduction system injury; arrhythmia; deep vein thrombosis; arteriovenous (AV) fistula; systemic or peripheral nerve injury; systemic or peripheral ischemia; pulmonary edema; pneumothorax; pleural effusion; dyspnea; atelectasis; dislodgement of previously implanted devices (i.e. pacing lead); blood loss requiring transfusion; anemia; radiation injury; electrolyte imbalance; hypertension or hypotension; allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials; hematoma or ecchymosis; syncope; pain; exercise intolerance or weakness; inflammation; angina; fever. Potential risks, that may or may not require intervention, associated with the valve, prestent, delivery system, and/or accessories include, but may not be limited to, the following: cardiac arrest; cardiogenic shock; coronary flow obstruction/transvalvular flow disturbance; device thrombosis; injury to tricuspid valve; device fracture; device embolization; device acute migration or malposition; endocarditis; chest pain/discomfort; hemolysis/ hemolytic anemia; device penetration/perforation into surrounding vasculature; device dysfunction (regurgitation and/or stenosis); aortic root distortion; embolic events: device fragments; mechanical failure of delivery system, and/or accessories.

Important Safety Information (continued)

Edwards Crimper

Indications: The Edwards crimper is indicated for use in preparing the Edwards SAPIEN 3 transcatheter heart valve for implantation.

Contraindications: There are no known contraindications.

Warnings: The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing. Do not mishandle the device. Do not use the device if the packaging or any components are not sterile, have been opened or are damaged, or the expiration date has elapsed.

Precautions: For special considerations associated with the use of the Edwards crimper prior to THV implantation, refer to the THV Instructions for Use.

Potential Adverse Events: There are no known potential adverse events associated with the Edwards crimper.

CAUTION: Federal (United States) law restricts these devices to sale by or on the order of a physician.

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