

Transcatheter vs. Surgical Aortic Valve Replacement in Women: A Pooled Analysis of the RHEIA and PARTNER 3 Trials

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Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had the following relevant financial relationships:

Nature of Financial Relationship

Consultant Fees/Honoraria

Company

Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, Venus MedTech; minor shares from Pi-Cardia, T-Heart and Rampart IC and Electroducer

All relevant financial relationships have been mitigated.

Faculty disclosure information can be found on the app

Background

- Limited data indicate **outcome differences** following **transcatheter aortic valve replacement (TAVR)** compared to **surgery** in **women** with **severe aortic stenosis (AS)**.
- In this **pooled analysis**, we examined **1-year outcomes in women** from the Randomized research in womEn all comers with Aortic stenosis (**RHEIA**) and Placement of Aortic Transcatheter Valves (**PARTNER 3**) randomized controlled trials who underwent **TAVR** or **surgery**.
 - PARTNER 3 and RHEIA trials examined the **same** primary endpoint (all-cause death, stroke or rehospitalization) as well as other clinical outcomes and shared a **common echo core lab**.

1 Year Primary Endpoint for RHEIA and PARTNER 3

PARTNER 3 Low-risk 2019	TAVR (N=496)	Surgery (N=454)	RHEIA All-comers 2024	TAVR (N=215)	Surgery (N=205)
Age (years, mean ± SD)	73.3 ± 5.8	73.6 ± 6.1	Age (years, mean ± SD)	73.1 ± 4.5	73.3 ± 5.2
Sex, % Female	32.5%	28.9%	Sex, % Female	100%	100%
STS Score	1.9 ± 0.7	1.9 ± 0.6	STS Score	2.1 ± 1.1	2.2 ± 1.3
STS Score <4, %	100%	100%	STS Score <4, %	92.5%	92.0%
Primary Endpoint (KM Rates %)	8.5%	15.1%*	Primary Endpoint (KM Rates %)	8.9%	15.6%*
All-cause Death	1.0%	2.5%	All-cause Death	0.9%	2.0%
All Stroke	1.2%	3.1%*	All Stroke	3.3%	3.0%
Rehospitalization†	7.3%	11.0%*	Rehospitalization†	4.8%	11.4%*

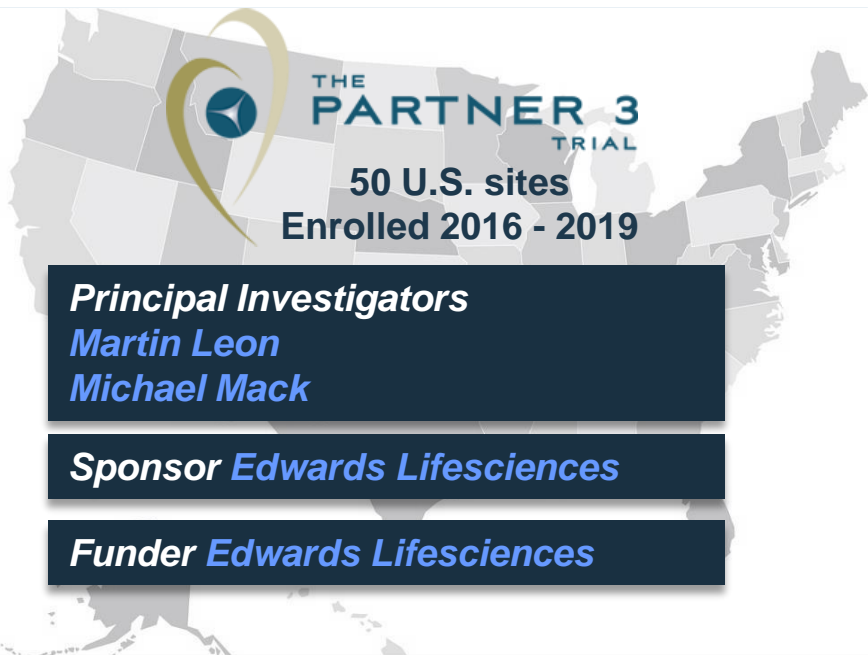
PARTNER 3: ACC 2019 and Mack *et al.*, *NEJM* 2019

RHEIA: ESC 2024, manuscript under review

†related to the procedure, the valve, or heart failure

*p-value <0.05 for TAVR vs. Surgery

Trial Leadership



Principal Investigators

Martin Leon
Michael Mack

Sponsor *Edwards Lifesciences*

Funder *Edwards Lifesciences*



Principal Investigators

Hélène Eltchaninoff
Didier Tchétché

Sponsor *Independent CRO*

Funder *Edwards Lifesciences*

Echo Core Lab
Philippe Pibarot

Objectives

- **Examine 30-day and 1-year clinical and echocardiographic outcomes** following **TAVR** with a balloon-expandable valve vs. **surgery** in **women** with **symptomatic, severe AS**.
 - Compare outcomes post-TAVR or surgery according to **age** or **CT annular size**
- **Pooling patient-level data** from **RHEIA** and **PARTNER 3** (women only) will increase power to assess outcomes in **women** and **guide clinical decision-making**.

Study Design

Women with symptomatic, severe AS in the PARTNER 3 Low Risk and RHEIA RCT

Randomization
N=712

TAVR N=376
SAPIEN 3 / SAPIEN 3 Ultra
Balloon-expandable valve

Surgery N=336
Any commercially available
surgical valve

Follow-up: 30 days and 1 year

PRIMARY ENDPOINT at 1 Year
Composite of all-cause DEATH, STROKE and REHOSPITALIZATION*

**related to the procedure, the valve, or heart failure.*

Clinical Endpoints

Primary Endpoint

- Composite of all-cause death, all stroke and rehospitalization

Secondary Endpoints

- Composite of all-cause death and all stroke
- All-cause death
- All stroke
- Rehospitalization related to the valve, procedure or congestive heart failure

Additional Outcomes

- Hemodynamics assessed by transthoracic echocardiography (TTE), patient-prosthesis mismatch (PPM), functional and quality of life outcomes, safety outcomes

Baseline Characteristics

Demographics & Vascular Disease (As-Treated Population*)	TAVR (N=376)	Surgery (N=336)	Other Comorbidities (As-Treated Population)	TAVR (N=376)	Surgery (N=336)
Age (years)	73.4 ± 4.78	73.3 ± 5.18	Peripheral Vascular Disease	4.0%	4.8%
BMI (kg/m ²)	29.9 ± 5.95	30.2 ± 5.95	Diabetes	25.5%	26.6%
STS Score	2.1 ± 0.95	2.1 ± 1.06	COPD (any)	3.2%	4.8%
EuroSCORE II (%)	1.7 ± 1.18	1.7 ± 1.03	Pulmonary Hypertension	3.2%	5.1%
NYHA Class III or IV	36.2%	34.2%	Prior Stroke or TIA	4.3%	4.8%
CT annular area (mm ²)	406.7 ± 67.69	408.7 ± 63.27	Atrial Fibrillation	6.1%	7.8%
Coronary Artery Disease	14.9%	17.9%	Permanent Pacemaker (%)	1.6%	3.6%

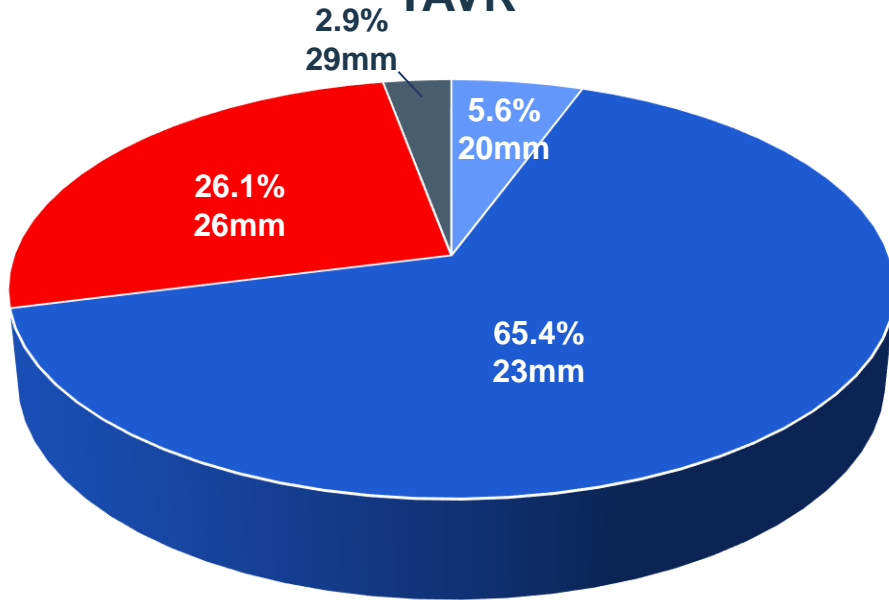
% or mean ± SD

All p-values are non-significant ($p > 0.05$).

*Denominators may vary for each parameter according to data availability.

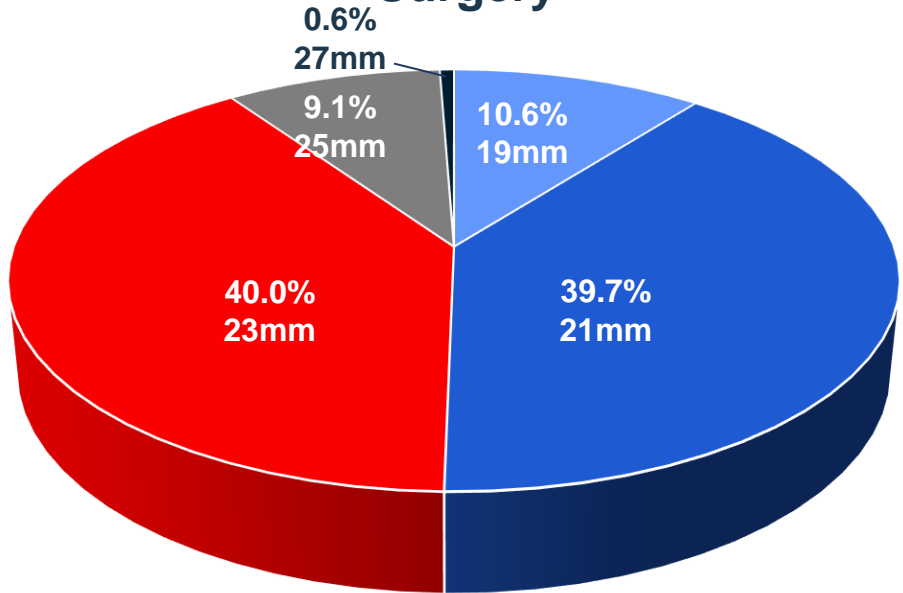
Valves Sizes

TAVR



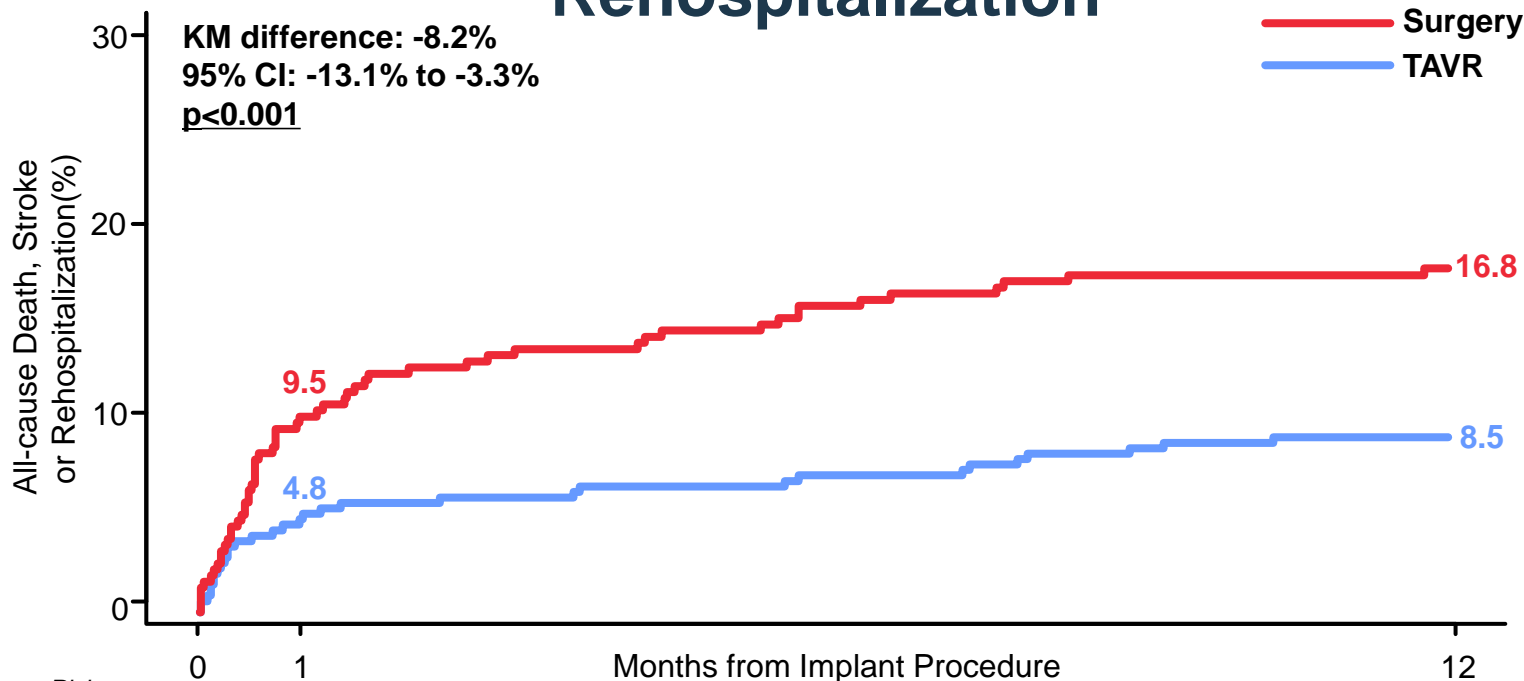
■ 20mm ■ 23mm ■ 26mm ■ 29mm

Surgery



■ 19mm ■ 21mm ■ 23mm ■ 25mm ■ 27mm

Primary Endpoint: All-cause Death, Stroke or Rehospitalization

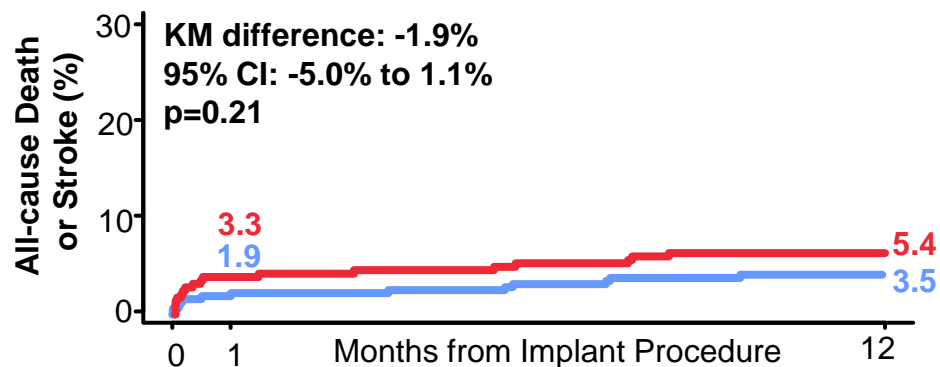
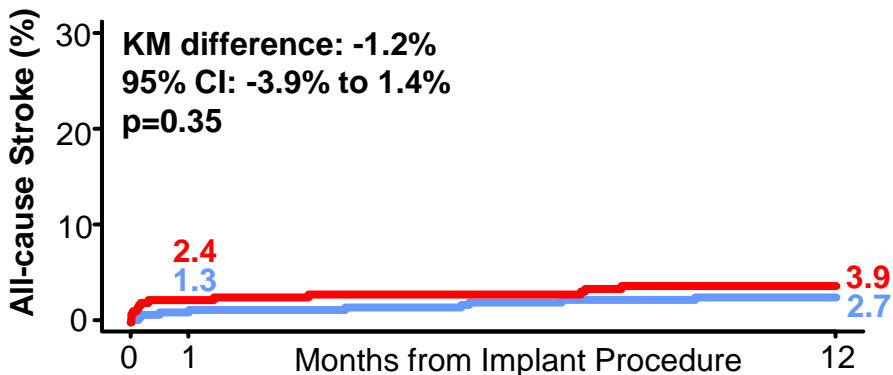
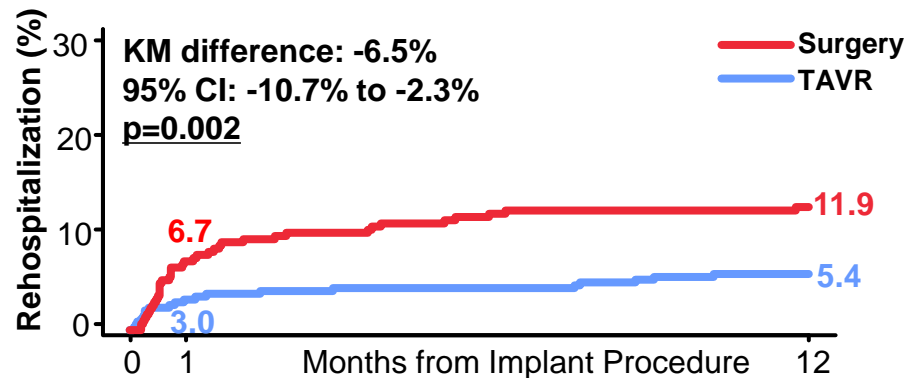
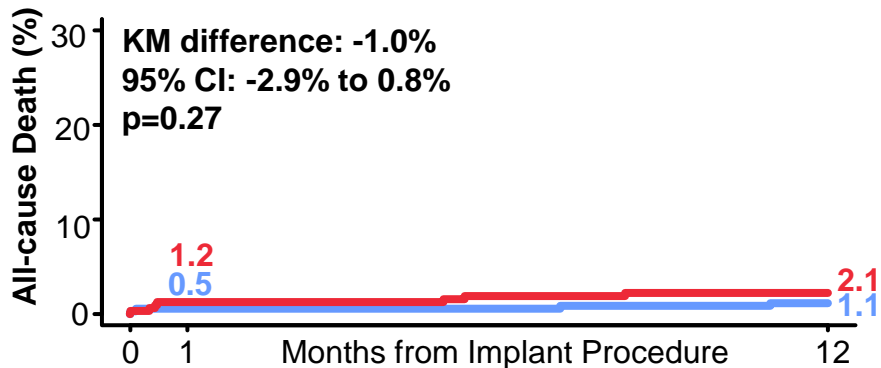


No. at Risk
 TAVR
 Surgery

	0	1	12
TAVR	376	358	277
Surgery	336	302	220

As Treated

Secondary Endpoints



Primary Endpoint: by Age or Annular Size

Subgroups:

Subgroups:	TAVR KM (%)	Surg. KM (%)	Hazard Ratio (95% CI)	Interaction P value*
Age				0.60
≤ 75 years (472)	8.2	17.6	0.47 [0.28 - 0.77]	
> 75 years (240)	9.2	15.2	0.60 [0.30 - 1.22]	
Systolic Annular Area [†]				0.71
≤ 430mm ² (466)	8.8	15.4	0.57 [0.34 - 0.95]	
> 430mm ² (228)	8.6	18.1	0.48 [0.23 - 0.97]	

0.016 0.062 0.250 1.00 4.00 16.000

<---Favors TAVR--- & ---Favors Surgery---

*Cox model interaction p value of the treatment and respective subgroups is calculated using Wald's test.

[†]Systolic annular area subgroup analysis is based on the VI population.

Additional Outcomes

Event n (KM Rates %) As-Treated Population†	30 Days		1 Year	
	TAVR (N=376)	Surgery (N=336)	TAVR (N=376)	Surgery (N=336)
Aortic Valve Reintervention	2 (0.5%)	0 (0.0%)	2 (0.5%)	1 (0.3%)
Endocarditis	0 (0.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Valve Thrombosis‡	3 (0.8%)	0 (0.0%)	5 (1.3%)	1 (0.3%)
Myocardial Infarction	1 (0.3%)	5 (1.5%)	1 (0.3%)	6 (1.8%)
New Onset Atrial Fibrillation§	9 (2.6%)	72 (23.3%)*	14 (4.0%)	73 (23.6%)*
New Permanent Pacemaker§	23 (6.2%)	14 (4.3%)	25 (6.8%)	16 (5.0%)
Bleeding (Life-threatening or major)	9 (2.4%)	53 (15.8%)*	13 (3.5%)	56 (16.7%)*

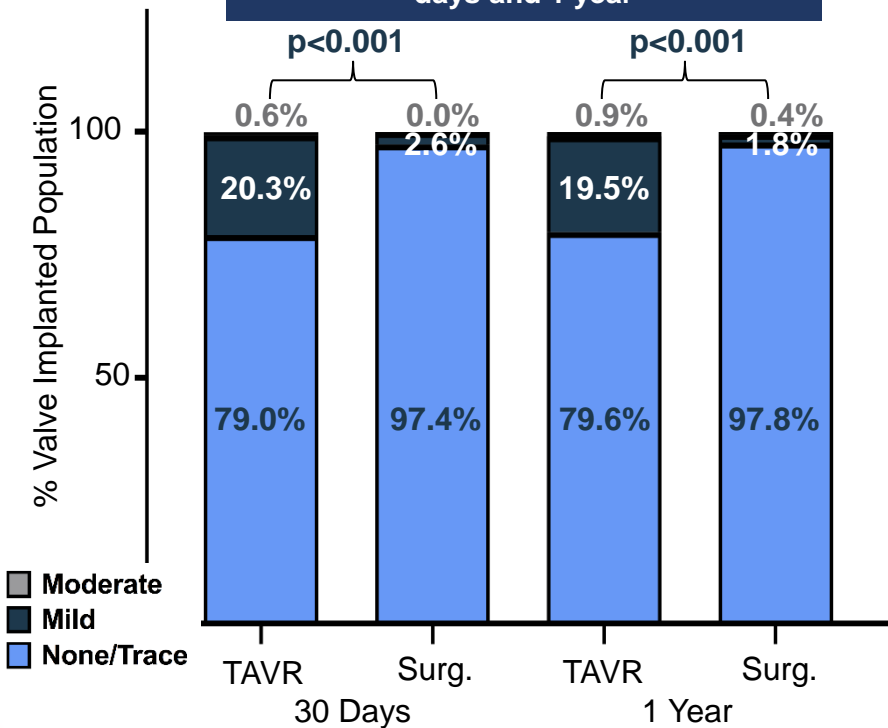
*p-value <0.05 for TAVR vs. Surgery

†Denominators may vary for each parameter according to data availability

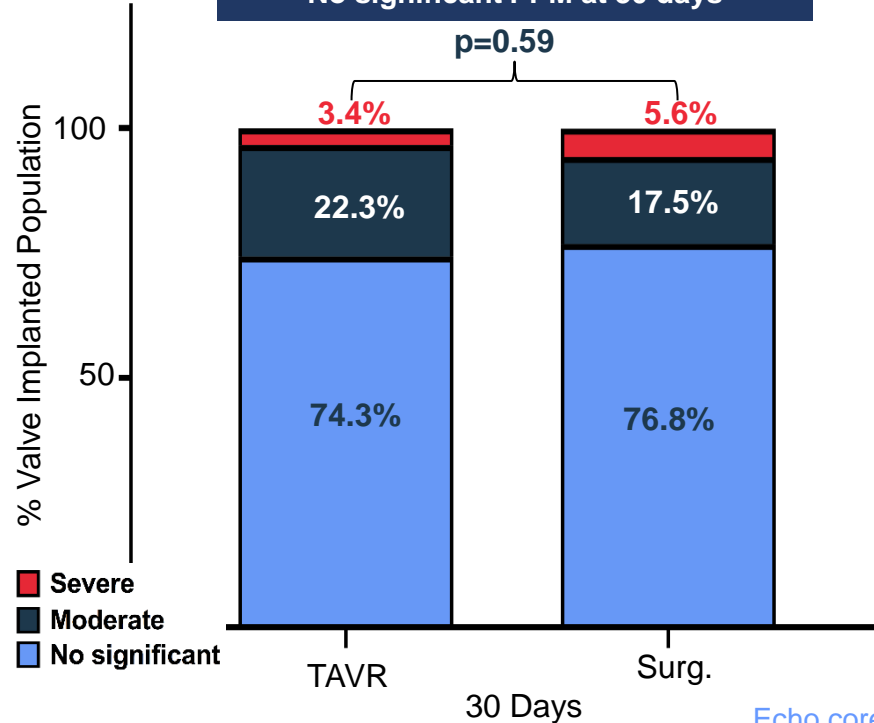
‡VARC-2 criteria §KM rates excludes patients with Afib or permanent pacemaker at baseline.

Paravalvular AR and 30-day PPM

>99% patients had ≤ Mild PV AR at 30 days and 1 year

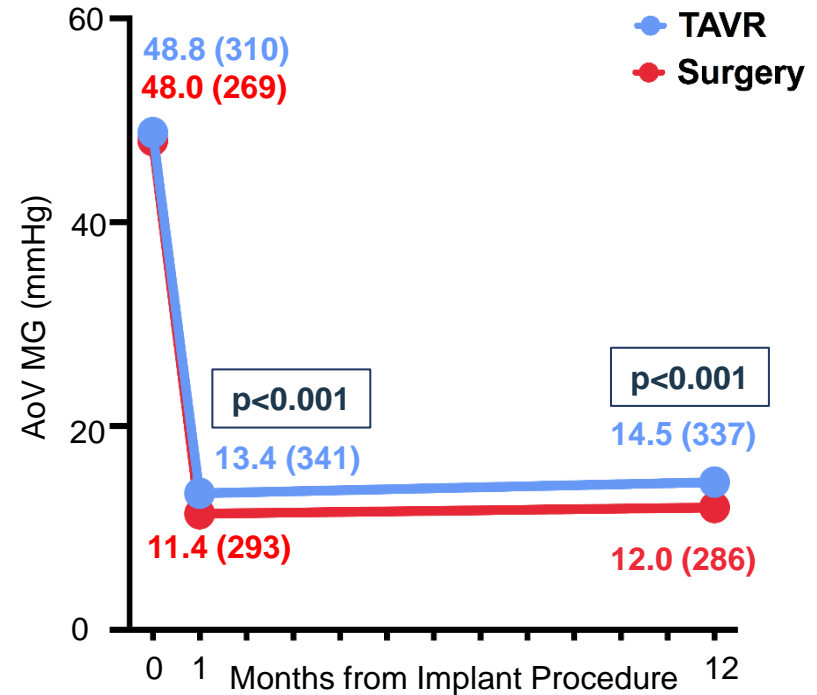
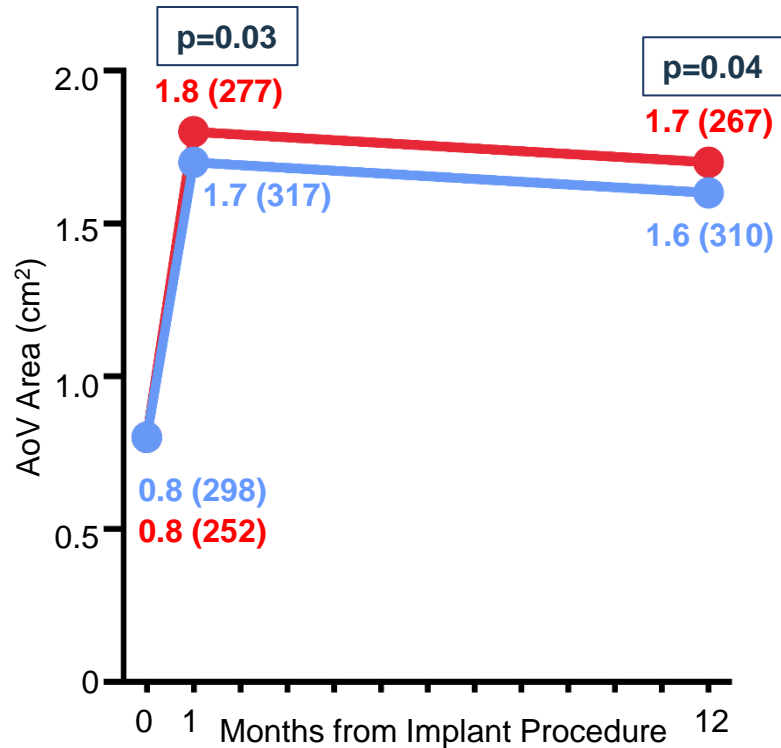


>74% patients had No significant PPM at 30 days



Echo core lab

Echocardiographic Assessment: AV Area and Gradient

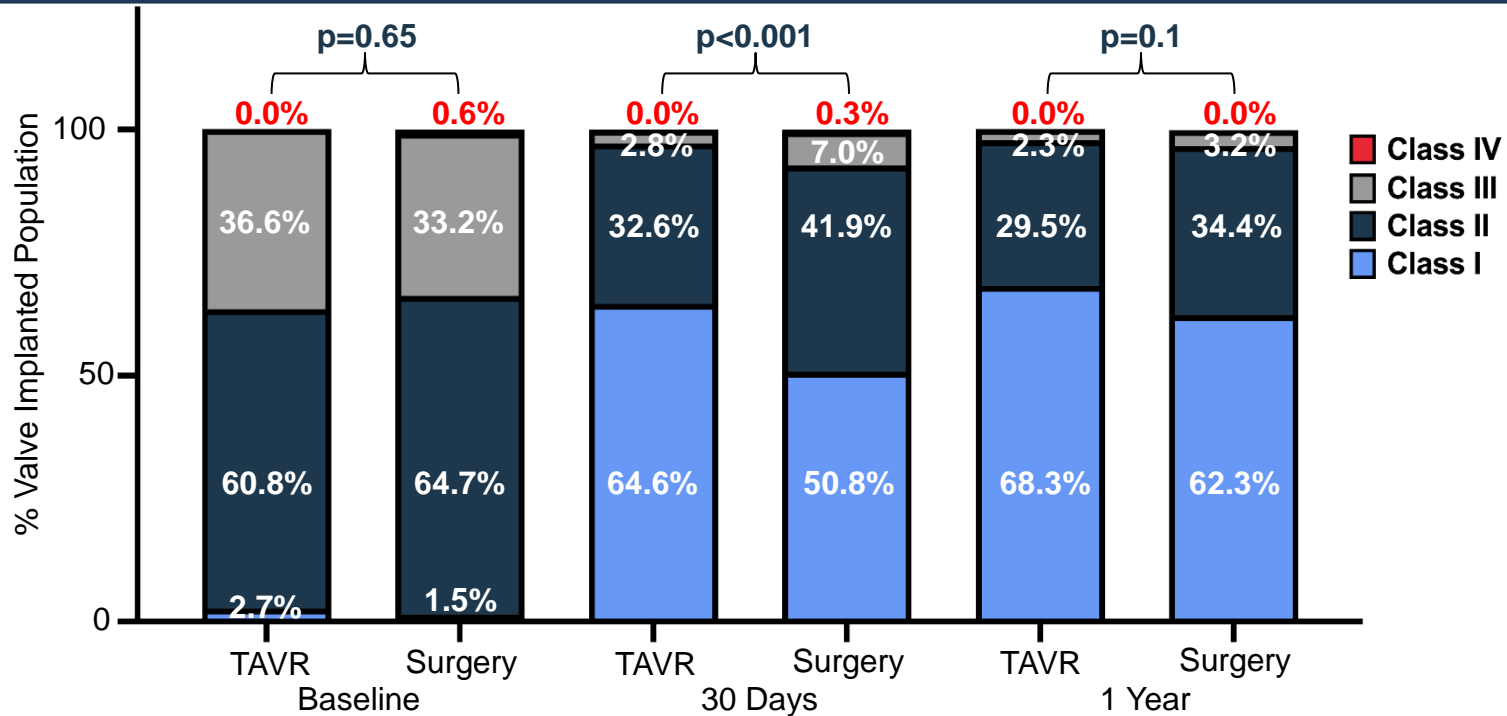


Mean (n). P values for TAVR vs. Surgery

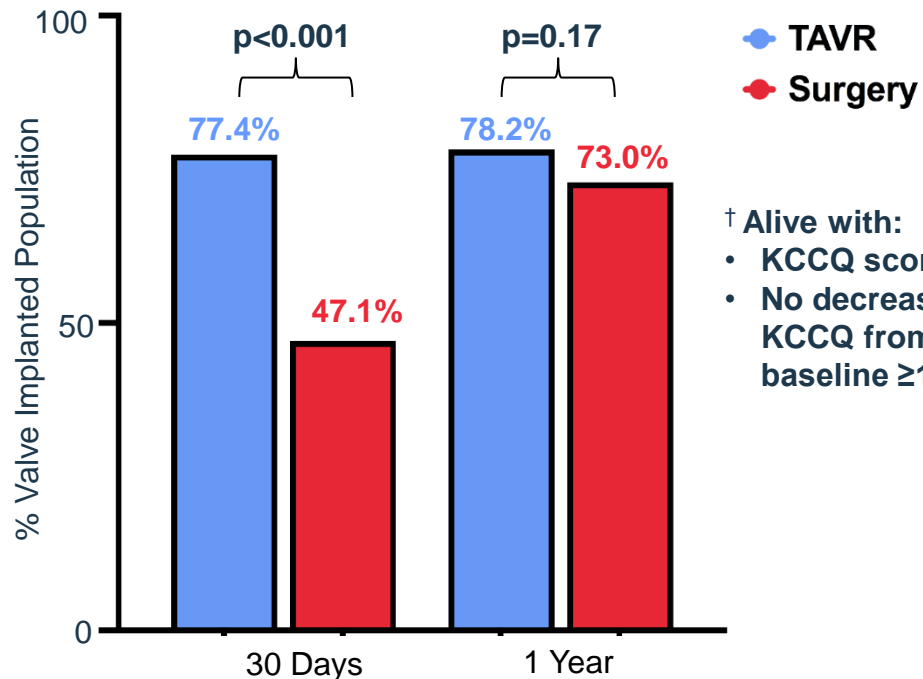
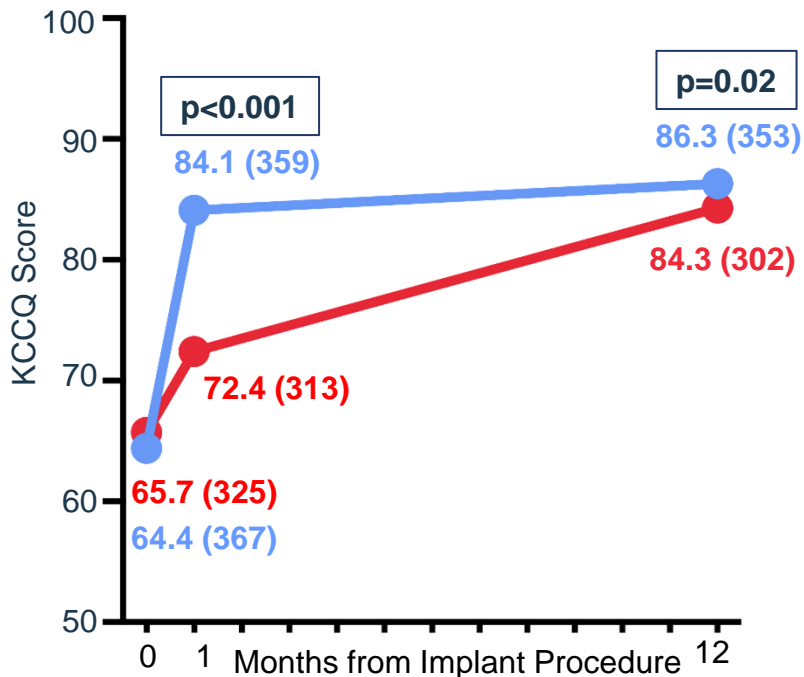
Echo core lab

Symptoms: NYHA Functional Classifications

97.7% TAVR and 96.8% surgery patients were Class I/II at 1 year



Quality of Life: KCCQ and Alive and Well†



† Alive with:

- KCCQ score ≥ 75
- No decrease in KCCQ from baseline ≥ 10

Mean (n). P value for TAVR vs .Surgery

Summary

- ***In women with symptomatic, severe AS receiving TAVR with the balloon-expandable SAPIEN 3 or SAPIEN 3 Ultra system or surgical aortic valve replacement, at 1 year follow-up:***
 - The **primary composite endpoint of death, stroke and rehospitalization** was **superior for TAVR** compared to surgery, due to lower rehospitalization rates for TAVR
 - Similarly low rates of **reintervention, endocarditis and thrombosis** were observed in **both treatment groups**
 - Interaction analysis did *not* reveal a different effect of treatment type on outcomes according to annular size (small vs. large) or age (≤ 75 vs. > 75 years).
- ***Excellent hemodynamics and echocardiographic assessments were observed out to 1 year with both procedures:***
 - **> 99%** patients had **none/trace or mild paravalvular AR** at 30 days and 1 year
 - 30-day **mean gradients** were **low and sustained** out to 1 year

Translational Outlook

- We report the **largest all-female analysis** in **symptomatic, severe AS patients** exploring the relative treatment effects of **TAVR vs. surgery** during the first year after therapy.
- In **women with symptomatic, severe AS**, **TAVR** using balloon-expandable devices may be the **preferred therapeutic option** over surgery.

Important Safety Information

Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, and Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve System

Indications: The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical or transcatheter bioprosthetic aortic valve, or a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality \geq 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator).

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical bioprosthetic mitral valve who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality \geq 4% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

Contraindications: The valves and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections, or who have significant annuloplasty ring dehiscence.

Warnings: Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation. There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients. 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. Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch), and/or annular rupture. Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism. 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. Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease. Patients with pre-existing prostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment. Do not use the valve if the tamper-evident seal is broken or the storage solution does not completely cover the valve (SAPIEN 3 and SAPIEN 3 Ultra only), 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 if the expiration date has elapsed. 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. Patient injury could occur if the delivery system is not un-flexed prior to removal. Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials. The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting. Valve 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 anticoagulation. Do not add or apply antibiotics to the storage solution (SAPIEN 3 and SAPIEN 3 Ultra only), rinse solution, or to the valve. Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets. Do not perform stand-alone balloon aortic valvuloplasty procedures in the INSPIRIS RESILIA aortic valve for the sizes 19-25 mm. This may expand the valve causing aortic incompetence, coronary embolism or annular rupture. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial annuloplasty ring dehiscence due to high risk of PVL. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial (incomplete) annuloplasty rings in the absence of annular calcium due to increased risk of valve embolization. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of rigid annuloplasty rings due to increased risk of PVL or THV deformation.

Important Safety Information (continued)

Precautions: Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established. 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 Safety Data Sheet available from Edwards Lifesciences. If a significant increase in resistance occurs when advancing the catheter through the vasculature, stop advancement and investigate the cause of resistance before proceeding. Do not force passage, as this could increase the risk of vascular complications. As compared to SAPIEN 3, system advancement force may be higher with the use of SAPIEN 3 Ultra/SAPIEN 3 Ultra RESILIA THV in tortuous/challenging vessel anatomies. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis. Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, the presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; and the presence of an Atrial Septal Occluder Device or calcium preventing safe transseptal access. Special care must be exercised in mitral valve replacement to avoid entrapment of the subvalvular apparatus. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: non-calcified aortic annulus; severe ventricular dysfunction with ejection fraction < 20%; congenital unicuspid aortic valve; pre-existing prosthetic ring in the tricuspid position; severe mitral annular calcification (MAC); severe (> 3+) mitral insufficiency, or Gorlin syndrome; blood dyscrasias defined as leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy; hypertrophic cardiomyopathy with or without obstruction (HOCM); echocardiographic evidence of intracardiac mass, thrombus, or vegetation; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated; significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater, marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta; access characteristics that would preclude safe placement of the Edwards sheath, such as severe obstructive calcification or severe tortuosity; bulky calcified aortic valve leaflets in close proximity to coronary ostia; a concomitant paravalvular leak where the failing prosthesis is not securely fixed in the native annulus or is not structurally intact (e.g., wireframe frame fracture, annuloplasty ring dehiscence); or a partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium. For Left axillary approach, a left subclavian takeoff angle $\approx 90^\circ$ from the aortic arch causes sharp angles, which may be responsible for potential sheath kinking, subclavian/axillary dissection and aortic arch damage. For left/right axillary approach, ensure there is flow in Left Internal Mammary Artery (LIMA)/Right Internal Mammary Artery (RIMA) during procedure and monitor pressure in homolateral radial artery. Residual mean gradient may be higher in a "THV-in-failing prosthesis" configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting prosthesis be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

Potential Adverse Events: Potential risks associated with the overall procedure, including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography: death; stroke/transient ischemic attack, clusters, or neurological deficit; paralysis; permanent disability; respiratory insufficiency or respiratory failure; hemorrhage requiring transfusion or intervention; cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, septum, myocardium, or valvular structures that may require intervention; pericardial effusion or cardiac tamponade; thoracic bleeding; embolization including air, calcific valve material, or thrombus; infection including septicemia and endocarditis; heart failure; myocardial infarction; renal insufficiency or renal failure; conduction system defect which may require a permanent pacemaker; arrhythmia; retroperitoneal bleed; arteriovenous (AV) fistula or pseudoaneurysm; reoperation; ischemia or nerve injury or brachial plexus injury; restenosis; pulmonary edema; pleural effusion; bleeding; anemia; abnormal lab values (including electrolyte imbalance); hypertension or hypotension; allergic reaction to anesthesia, contrast media, or device materials; hematoma; syncope; pain or changes (e.g., wound infection, hematoma, and other wound care complications) at the access site; exercise intolerance or

Important Safety Information (continued)

weakness; inflammation; angina; heart murmur; and fever. Additional potential risks associated with the use of the valve, delivery system, and/or accessories include: cardiac arrest; cardiogenic shock; emergency cardiac surgery; cardiac failure or low cardiac output; coronary flow obstruction/transvalvular flow disturbance; device thrombosis requiring intervention; valve thrombosis; device embolization; device migration or malposition requiring intervention; left ventricular outflow tract obstruction; valve deployment in unintended location; valve stenosis; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis); device degeneration; paravalvular or transvalvular leak; valve regurgitation; hemolysis; device explants; nonstructural dysfunction; mechanical failure of delivery system and/or accessories; and non-emergent reoperation.

Edwards Crimper

Indications: The Edwards crimper is indicated for use in preparing the Edwards SAPIEN 3 transcatheter heart valve, Edwards SAPIEN 3 Ultra transcatheter heart valve, and the Edwards SAPIEN 3 Ultra RESILIA 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.

Edwards, Edwards Lifesciences, Edwards SAPIEN, Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, INSPIRIS, INSPIRIS RESILIA, PARTNER, PARTNER 3, the PARTNER design logo, RESILIA, SAPIEN, SAPIEN 3, and SAPIEN 3 Ultra are trademarks or service marks of Edwards Lifesciences Corporation or its affiliates. All other trademarks are the property of their respective owners.

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