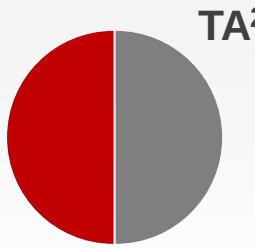
Transcatheter Aortic Valve Replacement

Larry L. Wood
Corporate Vice President
Transcatheter Aortic Valve Replacement

Edwards

Over a decade ago, we set out to establish new frontiers in heart valve therapy

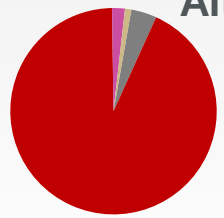
Original SAPIEN System used in PARTNER Study



TA[2], 50%

TF[1], 50%

SAPIEN 3 Ultra System



Alt[3], 7%

TF, 93%

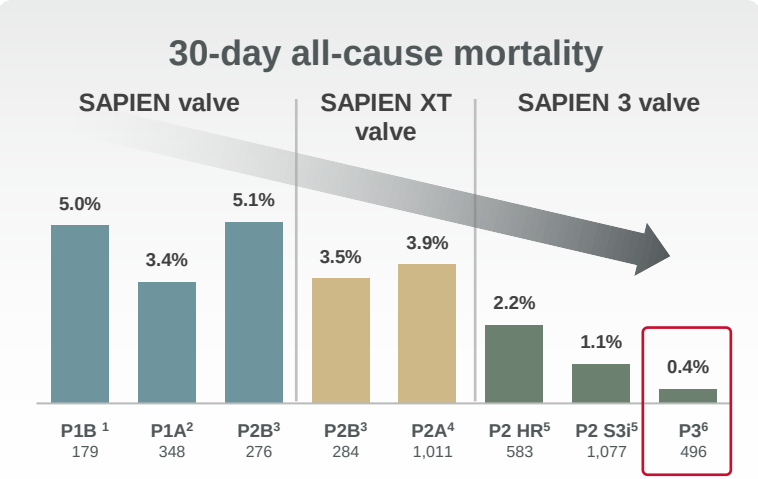
Over 600,000 patients treated with SAPIEN platform

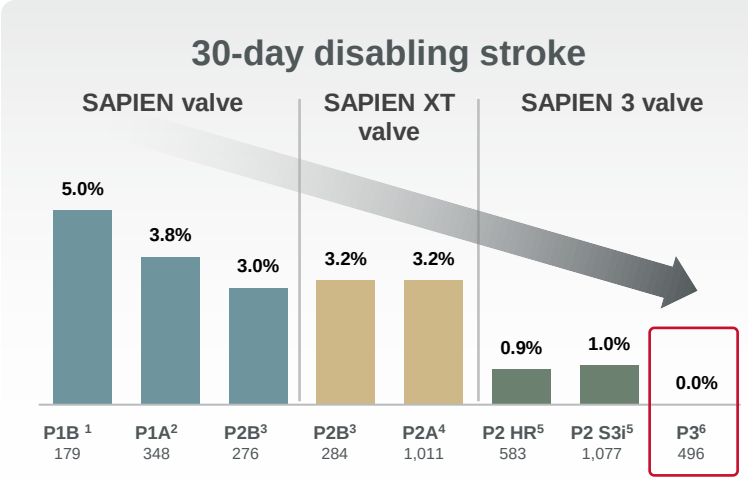
1. TF = Transfemoral; 2. TA = Transapical; 3. Alt = Alternative Access

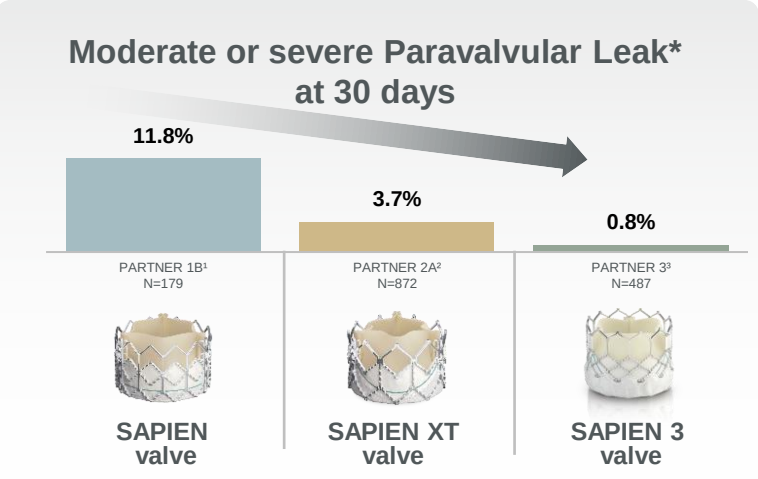
Where we are today

	THE PARTNER TRIAL 2011	THE PARTNER 3 TRIAL 2019
All-cause Death	3.4%	1%
All-Stroke	5.5%	1.2%
Major Vascular Complications	11%	2%
Index Hospitalization	8 days	3 days
	At 30-days	At 1-year

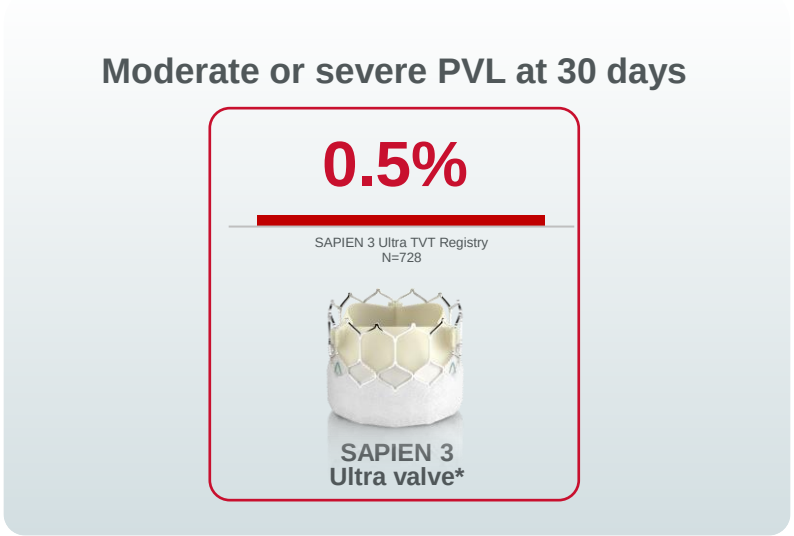
We have made significant progress







SAPIEN 3 Ultra has further elevated the benchmark of SAPIEN Platform

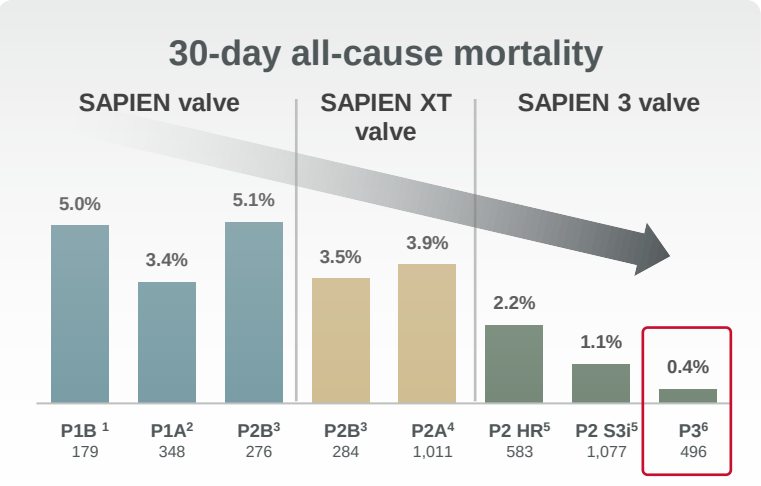


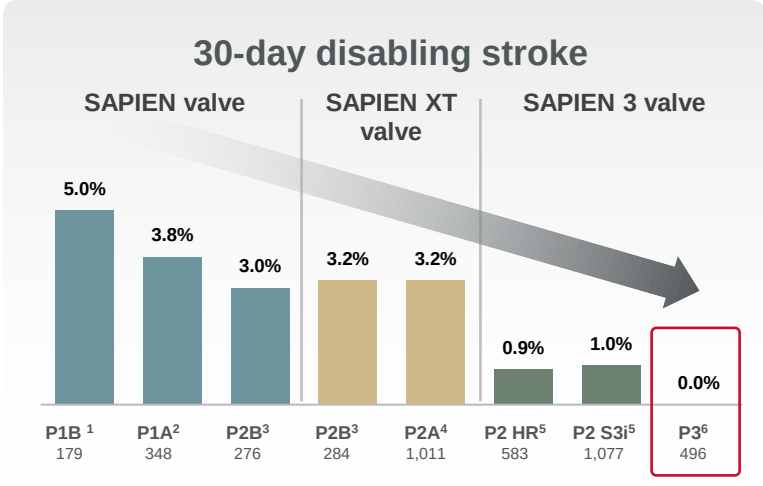
SAPIEN 3 Ultra now accounts for **92%** of global sales

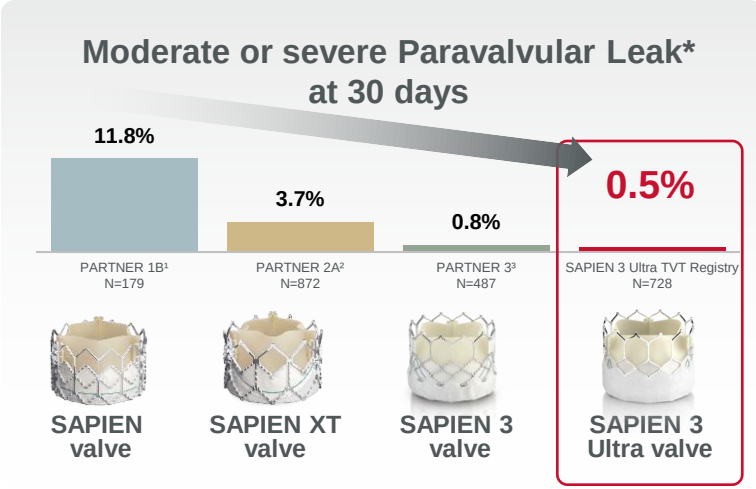
For references 1 through 6, see supplemental slides

** Nazif T, Daniels D, McCabe J, Chehab B, et al. Real-world experience with the SAPIEN 3 Ultra TAVI: A propensity matched analysis from the United States. Presented virtually at TVT Connect 2020.*

We have made significant progress







45 minutes — Median procedure time[7]

80% — Next day discharge rate[7]

96% — Discharged home[8]

For references 1 through 6, see supplemental slides

7. Wood, D.A.; Lauck, S.B.; Cairns, J.A. et al. The Vancouver 3M (Multidisciplinary, Multimodality, But Minimalist) Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low-, Medium-, and High-volume Transfemoral Transcatheter Aortic Valve Replacement Centers: The 3M TAVI Study. J Am Coll Cardiol Intv. 2019.
8. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019.

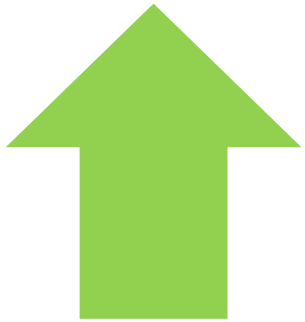
Improvement reflects a disciplined approach of advancing the technology, procedural techniques and partnership with regulators

TAVR has transformed patient care for the Severe Symptomatic AS patient

Median Survival Years for All SAS Patients

Pre-TAVR era

Before 2008



Overall survival for SAS patients ***doubled*** *from 6.8 years to >11.5 years*

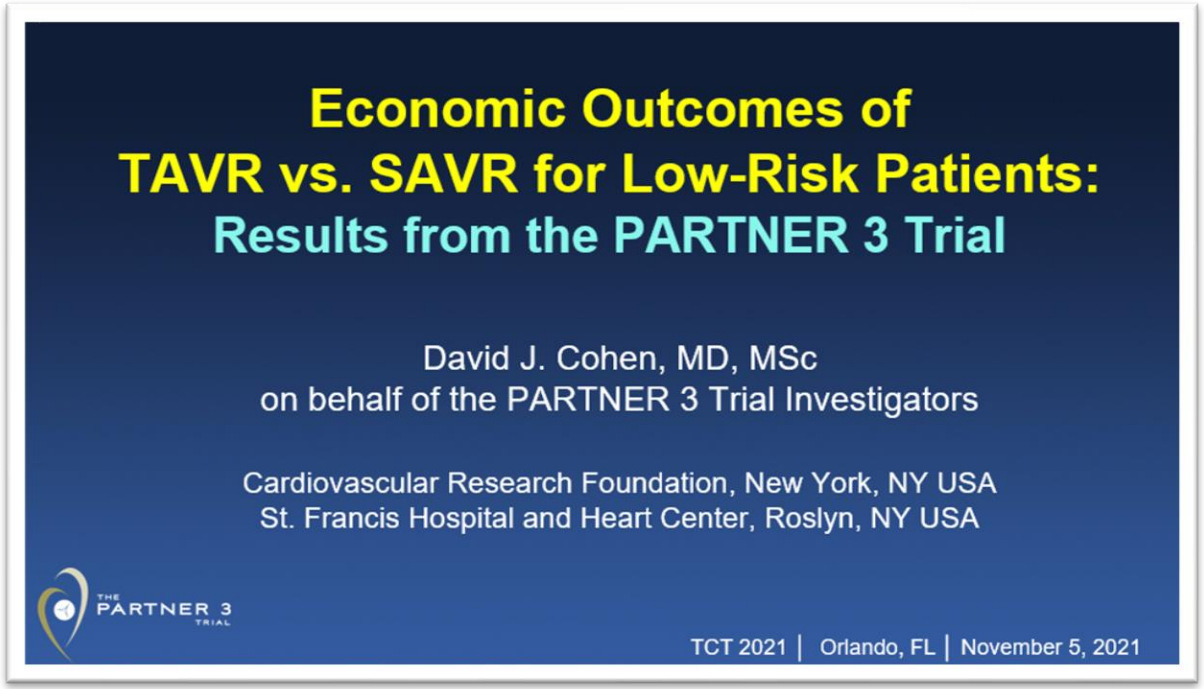
Post-TAVR era

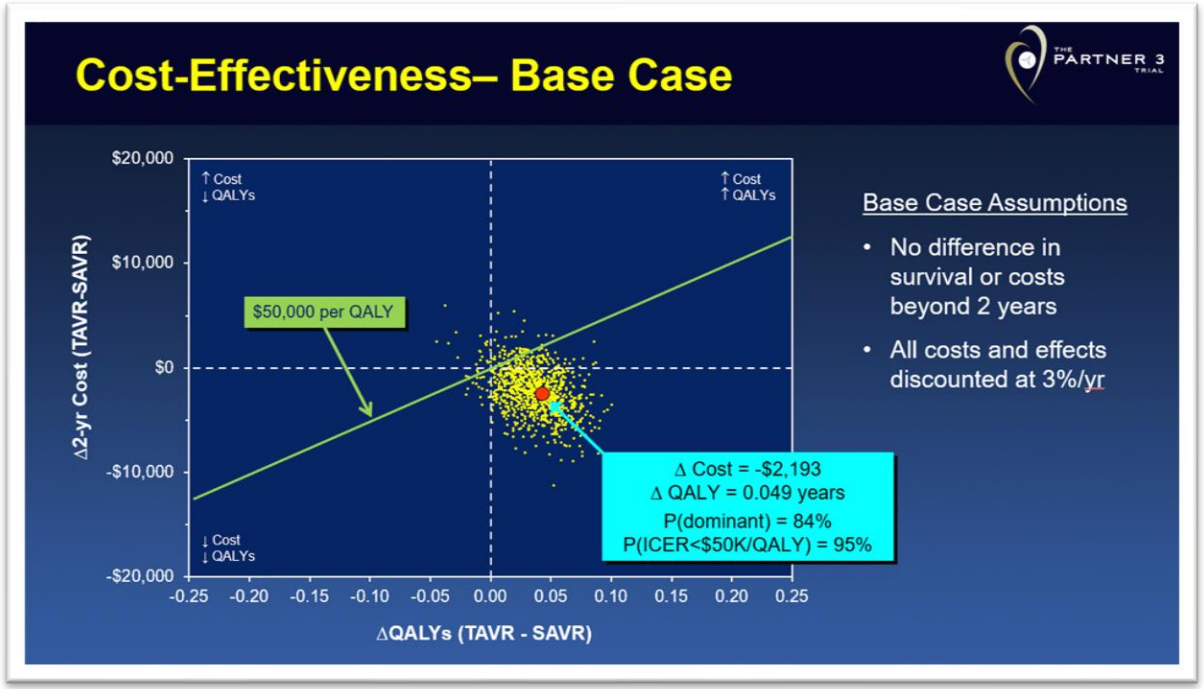
After 2008

Demonstrates Our Commitment to Our Innovation Strategy

Create Meaningful Value by **Transforming** Patient Care

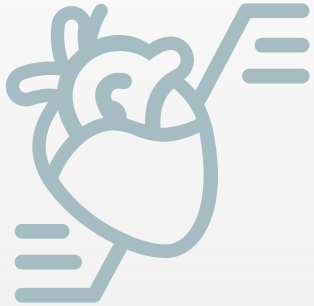
SAPIEN 3 economically dominant compared to SAVR in low-risk patients





- SAPIEN 3 resulted in **cost savings of >$2,000 per patient** through the 2-year study period
- Driven by **reductions in LOS and substantially lower follow-up costs**
- **SAPIEN 3 had small but significant improvement in quality-adjusted life expectancy,** driven by improved early quality of life and survival

Next generation valve platforms are focused on future needs of AS patients



Optimizing valve sizing in complex anatomy

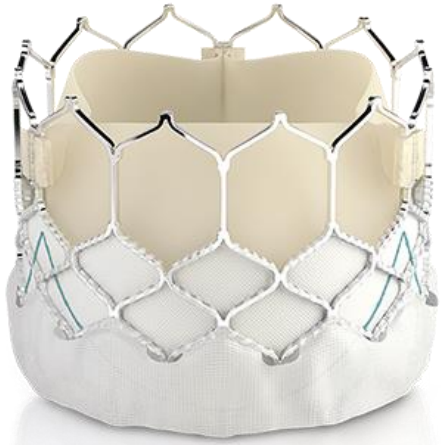
Enhanced durability for patients with longer life expectancy

Continue to raise benchmark and eliminate mild PV leak

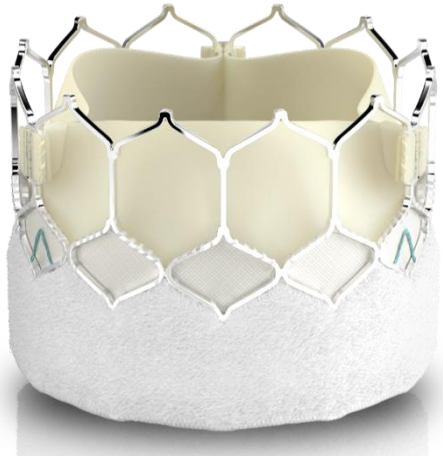
Further enhance future Coronary access

We are just getting started…

We will continue to advance our portfolio



SAPIEN 3



SAPIEN 3 Ultra

US and EU launches
Evolutionary advancements

SAPIEN X4

ALLIANCE U.S. IDE approval expected by end of 2021

Future Platform

The treatment of other progressive diseases focuses on early detection and intervention – cancer is an example

Progression of Cancer

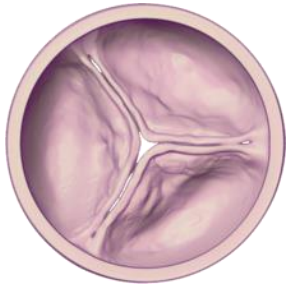
Stage 0	Stage I	Stage II	Stage III	Stage IV
Carcinoma in situ – early form	Localized	Early Locally Advanced	Late Locally Advanced	Metastasized

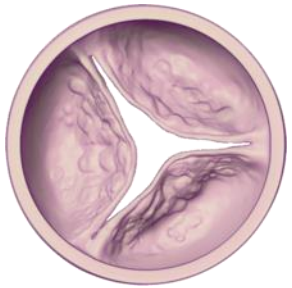
Early intervention prevents the disease from progressing further and causing additional damage to the body

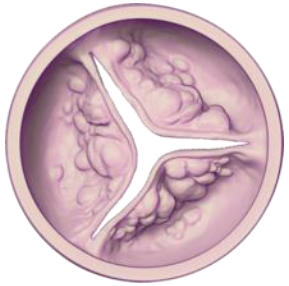
Aortic stenosis is a progressive disease but the treatment paradigm is to wait until symptoms

Progression of Aortic Stenosis

Mild → **Moderate** → **Severe Asymptomatic** → **Severe Symptomatic**





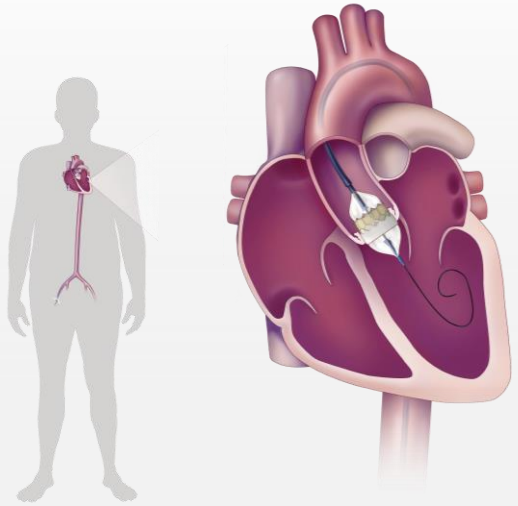


For 20 Years, We Have Been Focused on This

THE PARTNER TRIALS

- **PARTNER 1:** Inoperable/ High-risk
- **PARTNER 2:** Intermediate risk
- **PARTNER 3:** Low risk

With TAVR as a treatment option to treat progressive AS disease, we believe the current paradigm needs a deeper look



TAVR - Minimally Invasive Therapy

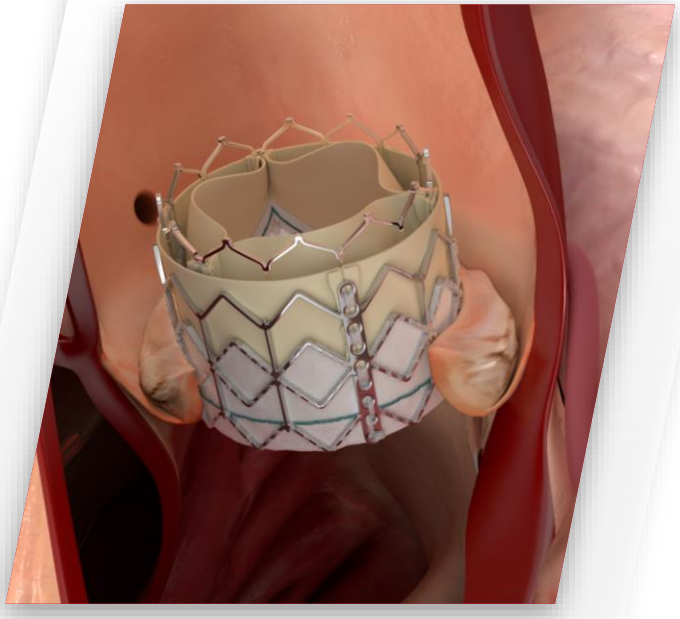
99% Freedom from death[1]

99% Freedom from disabling stroke[1]

80% Next day Discharge[2]

96% Discharged home[1]

Superior Patient Outcomes and Benefits



TAVR-in-TAVR Indication

1. Mack M, Leon M, Thourani R, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695-705.
2. Wood, D.A.; Lauck, S.B.; Cairns, J.A. et al. The Vancouver 3M (Multidisciplinary, Multimodality, But Minimalist) Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low-, Medium-, and High-volume Transfemoral Transcatheter Aortic Valve Replacement Centers: The 3M TAVI Study. J Am Coll Cardiol Intv. 2019

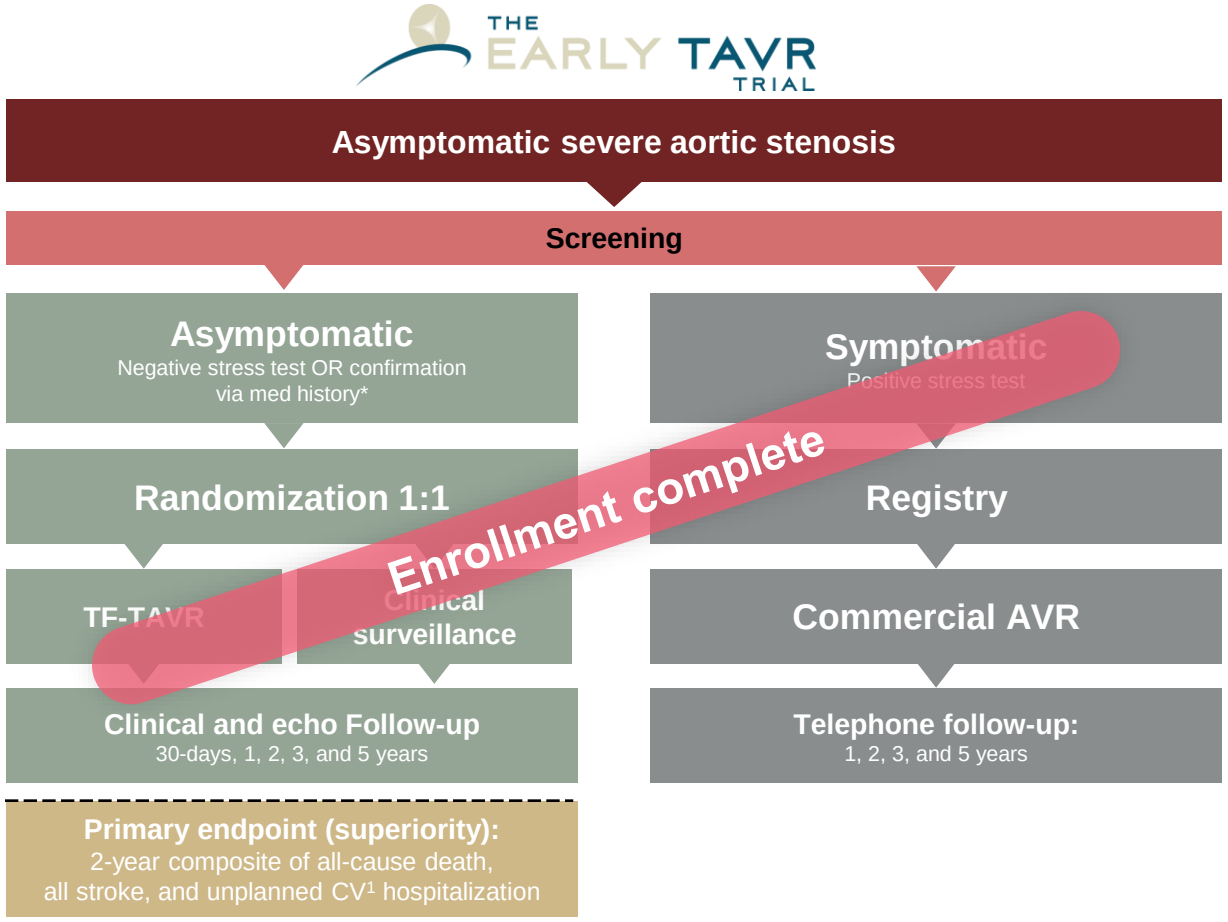
The first step is understanding if intervention should occur before symptoms develop

Key questions

What percentage of patients are truly asymptomatic?

How fast do asymptomatic patients progress to symptomatic?

Does treating patients earlier prevent damage to the heart?



(1) CV = Cardiovascular

* In patients who cannot perform stress test

With EARLY TAVR, we are still only addressing Severe AS patients

For 20 Years, We Have Only Been Focused on This

Progression of Aortic Stenosis

Mild → **Moderate** → **Severe Asymptomatic** → **Severe Symptomatic**

THE EARLY TAVR TRIAL

- **Asymptomatic** patients who still have **severe AS**
- Currently **enrolling**

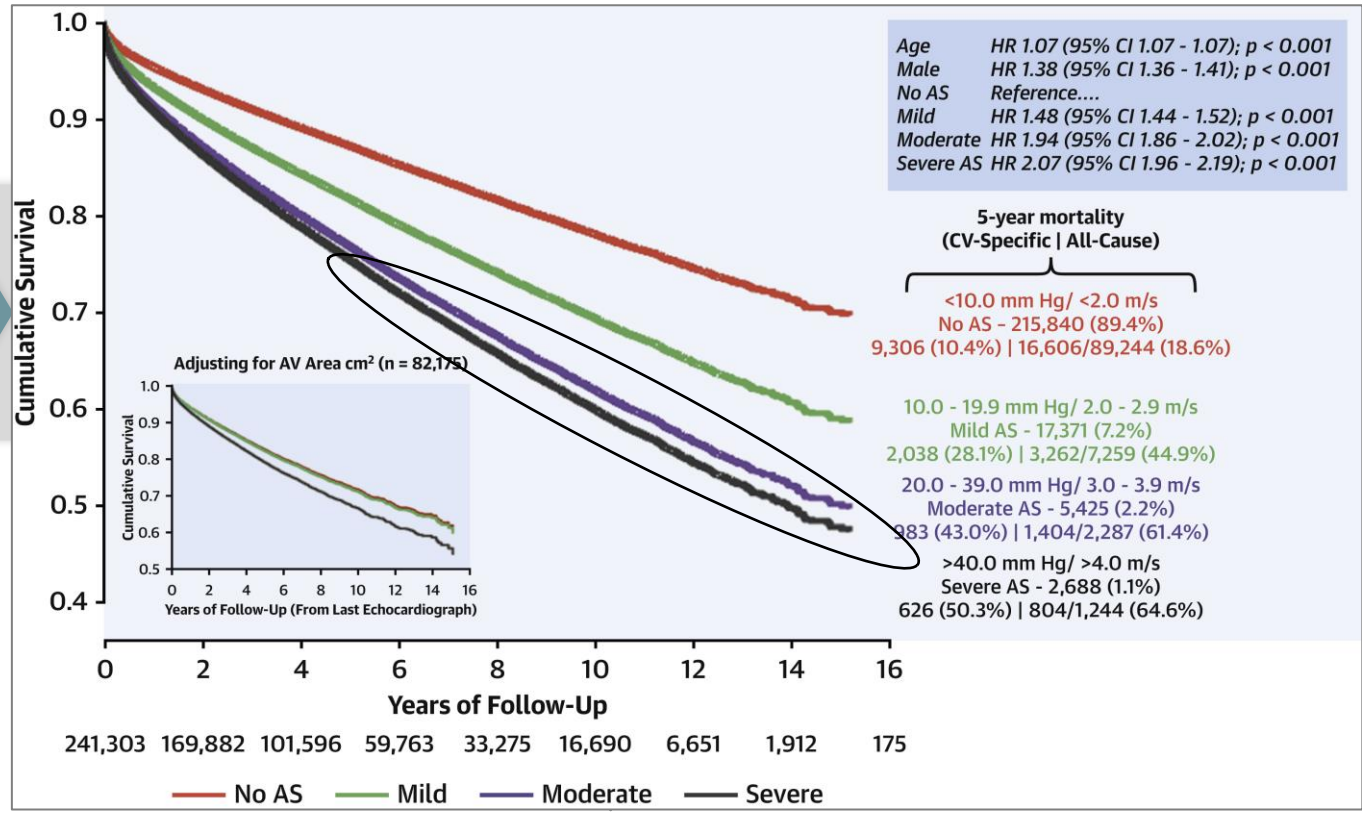
THE PARTNER TRIALS

- **PARTNER 1:** Inoperable/ High-risk
- **PARTNER 2:** Intermediate risk
- **PARTNER 3:** Low risk

Studies have suggested that Moderate AS disease may have a similarly poor prognosis

Progression of Aortic Stenosis

Mild → **Moderate**



Geoff Strange et al. J Am Coll Cardiol 2019; 74:1851-1863.

We believe that Moderate AS patients may benefit from early intervention

We are also embarking on understanding the true impact of Moderate AS

Key questions

How fast do people progress from moderate to severe AS?

Do all patients progress at the same rate?

THE PROGRESS TRIAL

Moderate, calcific AS and appropriate anatomy for transfemoral TAVR

1:1 Randomization (n = 750)

TAVR
(SAPIEN 3/ SAPIEN 3 Ultra)

Clinical surveillance

Potential delayed-AVR[1]

Enrollment has begun

Primary endpoint
Death, stroke and unplanned CV2 rehospitalization at 2 years

Follow-up
Annually through 10 years

(1) AVR = Aortic Valve Replacement (2) CV = Cardiovascular

We have an opportunity to increase our understanding of AS disease progression and timing of intervention with the PROGRESS Trial

For 20 Years, We Have Only Been Focused on This

Progression of Aortic Stenosis

Mild → **Moderate** → **Severe Asymptomatic** → **Severe Symptomatic**

THE PROGRESS TRIAL

- Patients with moderate AS who have **not yet progressed to severe**
- Enrollment has begun

THE EARLY TAVR TRIAL

- **Asymptomatic** patients who still have **severe AS**
- Currently **enrolling**

THE PARTNER TRIALS

- **PARTNER 1:** Inoperable/ High-risk
- **PARTNER 2:** Intermediate risk
- **PARTNER 3:** Low risk

Early intervention may prevent the disease from progressing further and causing additional damage to the heart

We believe the moderate AS patient cohort is significantly larger than the severe AS cohort

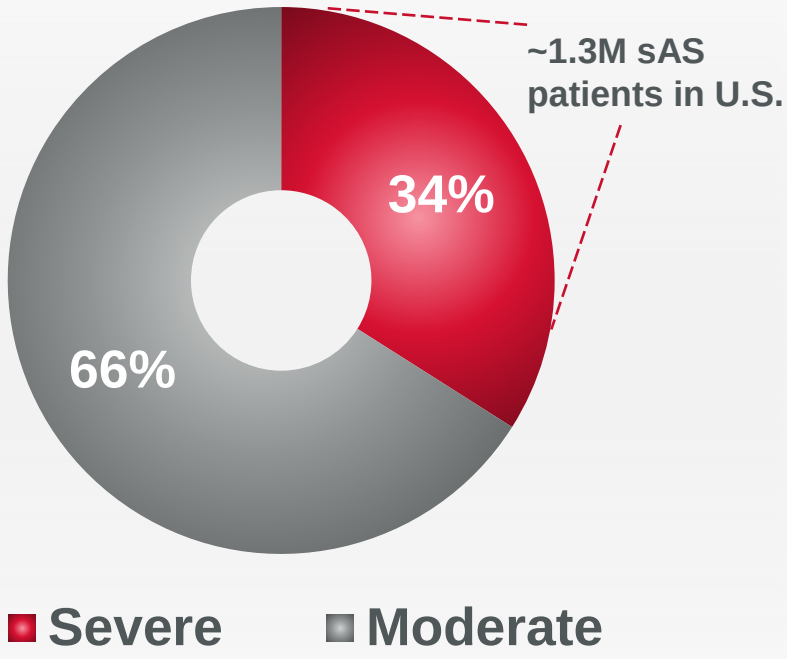
In 2021, I-ENHANCED-AS1, **retrospective study, examined 240K+ patients Echo database**

Over 210K echos from Australia[2] and over 30K echos from U.S.[3] met study inclusion criteria (≥65 years age with native aortic valve on the last echo)

Moderate : Severe AS patients identified 11,987:5658

Ratio mAS:sAS ≈ 2:1

Ratio of moderate to severe AS patients



1. The International ENHancing the ANalysis of Clinical Events & Death in Aortic Stenosis (I-ENHANCED-AS) study, presented by Dr. Jordan Strom, MD MSc, Harvard Medical School, 2021 European Society of Cardiology Congress, August 27-30, 2021
2. NEDA database Australia
3. Beth Israel Deaconess Medical Center + Harvard Medical School database; Largest single-center Echo dataset linked to complete Medicare Claims

Despite continued COVID challenges, we delivered on the key milestones we set out in the last year

Low-risk Approval in Japan

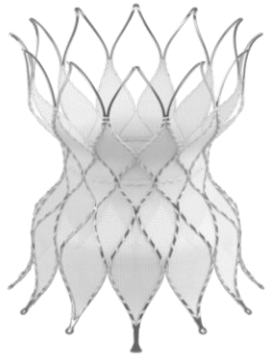
THE EARLY TAVR TRIAL

EARLY TAVR Enrollment Complete

THE PROGRESS TRIAL

Moderate AS Trial FDA Approved

Expecting Approval of SAPIEN X4 IDE by Year End



ALTERRA Adaptive Pre-stent FDA Approval On Track for Year End

Bringing patients off the sidelines was challenging even before COVID

- **Despite progressive nature and poor prognosis of AS, the rate of people "knowing and being concerned" about AS is still very low[1]**

- **2019 Survey of ~13,000 people aged ≥60 years old across 11 European Countries showed:**
  - 34% of people were "most concerned" with cancer vs **only 5%** for Heart Valve Disease (HVD)
  - **Only 6%** were able to correctly describe Aortic stenosis

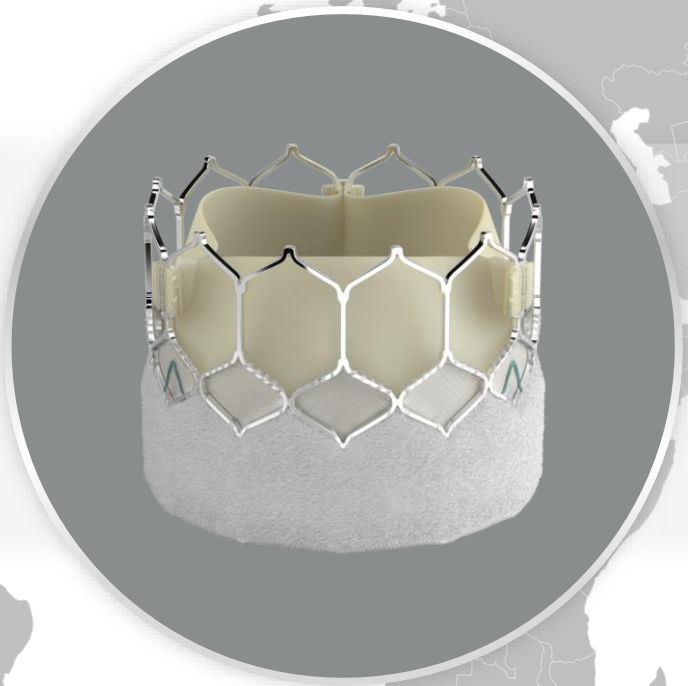
COVID has exacerbated the challenges of getting patients off the sidelines

[1] *Gaede, L, Sitges, M, Neil, J, et al. European heart health survey 2019. Clin Cardiol. 2020; 43: 1539– 1546 https://doi.org/10.1002/clc.23478*

We have launched a nationwide TV ad campaign to drive awareness of patients to TAVR therapy

The fundamentals of TAVR remain strong and the opportunity ahead is significant

We expect the global TAVR market to double and reach **$10B by 2028**



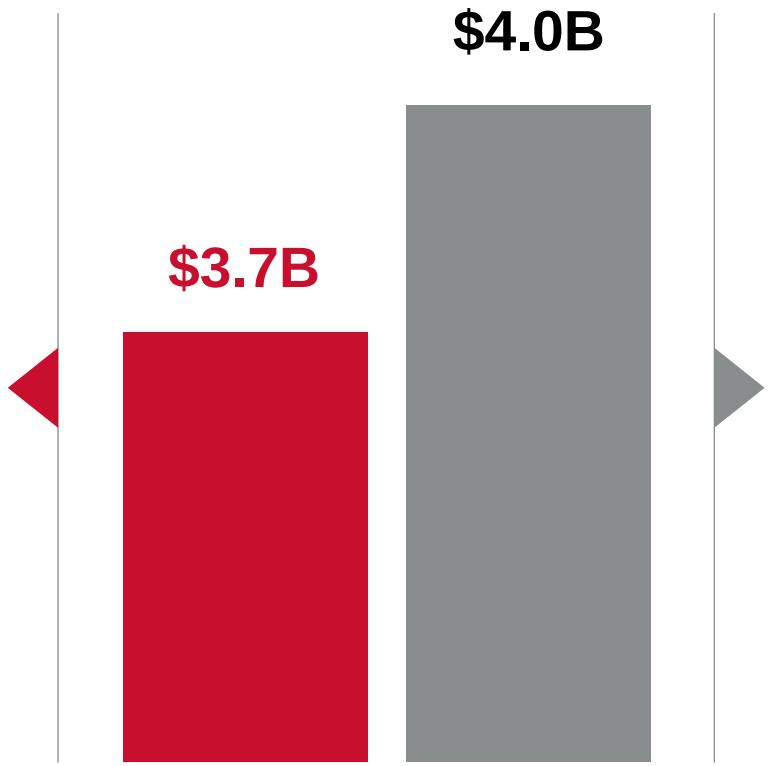
Growth drivers beyond the plan horizon remain strong

2022 Underlying Global Sales Growth Outlook

Headwinds

Overall healthcare spending pressures

COVID recovery



Tailwinds

Benefits of TAVR therapy and strong patient preference

Low risk expansion in key regions

2022E

Underlying **Global TAVR** Estimated Sales Growth
12-15%

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

Indications: The Edwards SAPIEN 3 and SAPIEN 3 Ultra 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 and SAPIEN 3 Ultra Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve, a surgical bioprosthetic mitral 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 ≥ 8% 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, 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 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, 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.

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 is 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. 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 in the atrial septum 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; 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., wireform 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 ~ ≥ 90° 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 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 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 SAPIEN 3 and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System

INVESTIGATIONAL DEVICES. CAUTION: The Edwards SAPIEN 3 transcatheter heart valve is an investigational device when used in asymptomatic patients. Limited by Federal (USA) law to investigational use only. These devices are not available for marketing or commercial sale in the United States for asymptomatic patients. See Instructions for Use for full information, including indications, contraindications, warnings, precautions, and adverse events.

SAPIEN M3 Transcatheter Heart Valve System

INVESTIGATIONAL DEVICES. CAUTION: The SAPIEN M3 System consists of investigational devices, limited by Federal (United States) law to investigational use. These devices are not available for marketing or commercial sale. See instructions for use for full information, including indications, contraindications, warnings, precautions, and adverse events**.**

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Helping Patients is Our Life's Work, and *life is now*