Seven-year Outcomes of the PARTNER 3 Low-risk Trial

Michael J. Mack, MD &
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on behalf of the PARTNER 3 Trial Investigators

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TRANSCATHETER CARDIOVASCULAR THERAPEUTICS®

Disclosures: Michael J. Mack, MD

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Within the past 36 months, I or my spouse/partner has had a financial interest/arrangement or affiliation with the organization(s) listed below.

Financial Relationship	Company
• Institutional Research Support	NA
• Consulting Fees	NA
• Trial Co-PI	Abbott, Edwards Lifesciences
• Trial Study Chair	Medtronic

Background

- The PARTNER 3 low-risk randomized trial showed superior outcomes for TAVR vs Surgery at 1 year, but between-group differences attenuated through 5-year follow-up.
- Favorable surgical bioprosthetic valve durability has been reported for 10 or more years, but early valve failure can occur as soon as 5 to 7 years.
- As TAVR is increasingly performed in younger patients with longer life expectancy, understanding long-term transcatheter and surgical valve durability is essential to inform patient-centered decision making.

THE PARTNER 3 TRIAL

Purpose

To report the clinical, echocardiographic, and valve durability outcomes of the PARTNER 3 Trial at ***7 years*** for low-risk patients with symptomatic severe AS treated with balloon-expandable, SAPIEN 3 TAVR vs. Surgery

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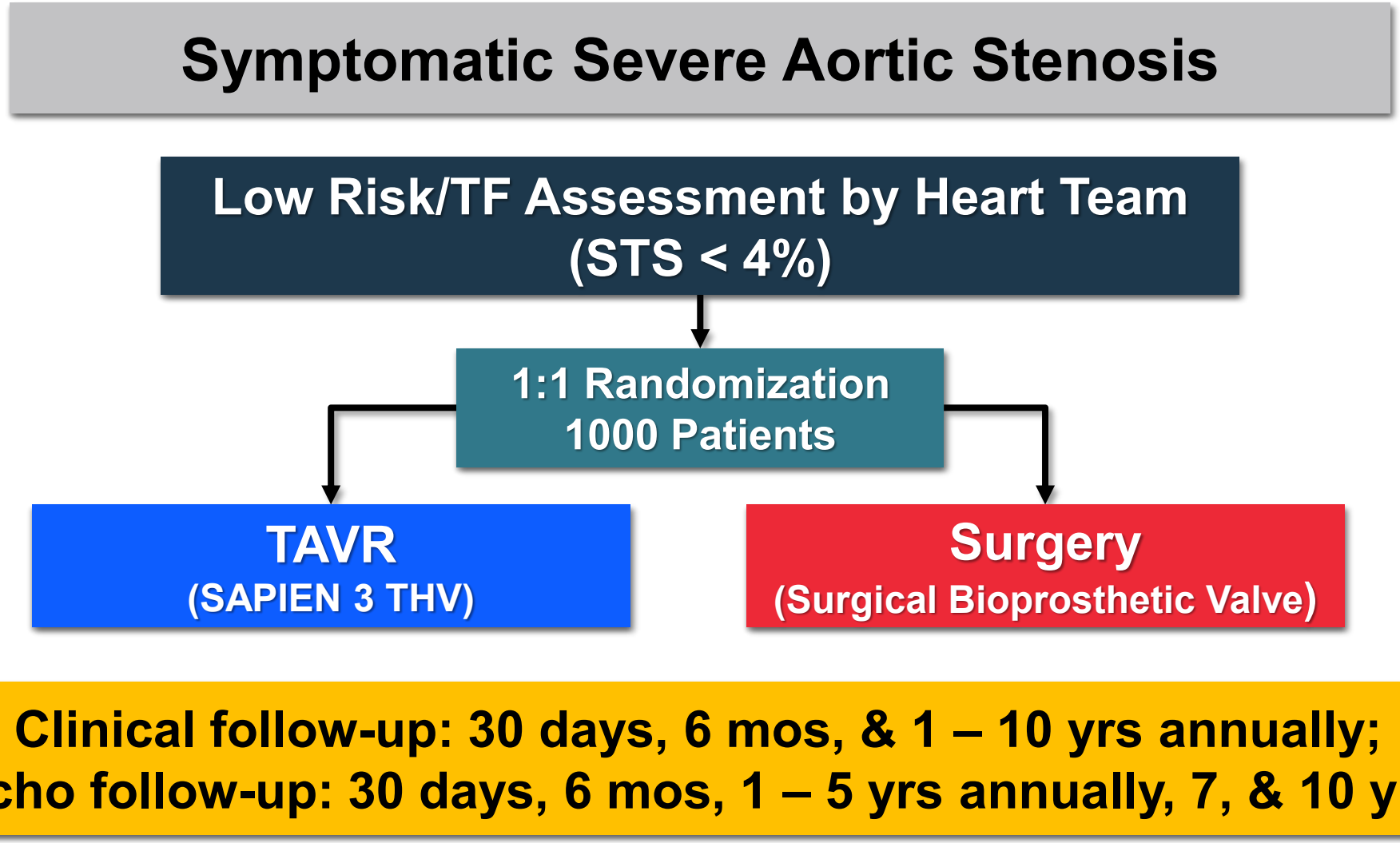
PARTNER 3 Study Design



Clinical follow-up: 30 days, 6 mos, & 1 – 10 yrs annually;
Echo follow-up: 30 days, 6 mos, 1 – 5 yrs annually, 7, & 10 yrs

Methodology Considerations
For Long-term Follow-up

- One-year endpoints and definitions were supplemented with outcomes more relevant to long-term follow-up, especially valve durability and late clinical events.
- Challenges of long-term follow-up include data missingness, withdrawal/lost to follow-up, and the competing risk of death as patients age.
- To improve completeness of follow-up, FDA-mandated annual **vital status sweeps (VSS)** were performed by sites using patient/family phone calls, medical records, and/or publicly-available data.

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Primary Endpoints

Primary Endpoint 1

- **Non-hierarchical composite** of all-cause death, all stroke, or rehospitalization* (time to first event)
- Assessed as the KM rate difference at 7 years
- Also depicted as a hazard ratio (HR)

Primary Endpoint 2

- **Hierarchical composite** of all-cause death, disabling stroke, non-disabling stroke, and rehospitalization* days
- Assessed using the ***win ratio*** method

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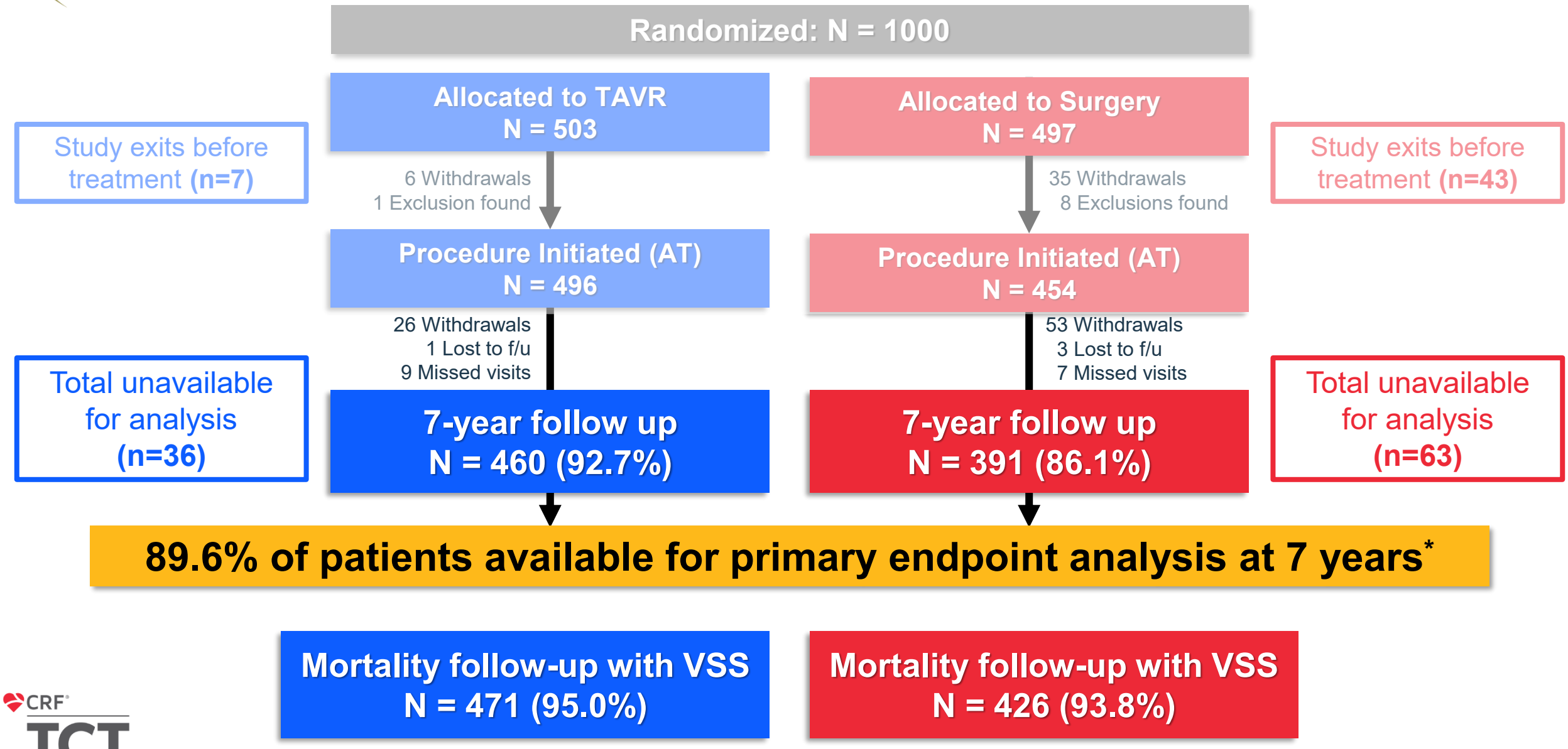
*Rehosp related to the valve, procedure, or heart failure

Patient Disposition



*Includes patients evaluable for the primary composite endpoint; does not include VSS data

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Baseline Characteristics

% or mean ± SD

Demographics & Vascular Disease	TAVR (N=496)	Surgery (N=454)	Other Comorbidities	TAVR (N=496)	Surgery (N=454)
Age (years)	**73.3 ± 5.8**	**73.6 ± 6.1**	Diabetes	31.3%	30.2%
Male	67.5%	71.1%	COPD (any)	5.1%	6.2%
BMI (kg/m^2)	30.7 ± 5.5	30.3 ± 5.1	Pulmonary Hypertension	4.6%	5.3%
STS Score	**1.9 ± 0.7**	**1.9 ± 0.6**	Creatinine > 2mg/dL	0.2%	0.2%
NYHA Class III or IV*	31.3%	23.8%	Frailty (overall; > 2/4+)	0	0
Coronary Disease	**27.7%**	**28.0%**	**Atrial Fibrillation (h/o)**	**15.7%**	**18.8%**
Prior CVA	3.4%	5.1%	**Permanent Pacemaker**	**2.4%**	**2.9%**
Peripheral Vascular Disease	6.9%	7.3%	Left Bundle Branch Block	3.0%	3.3%

*$P = 0.01$

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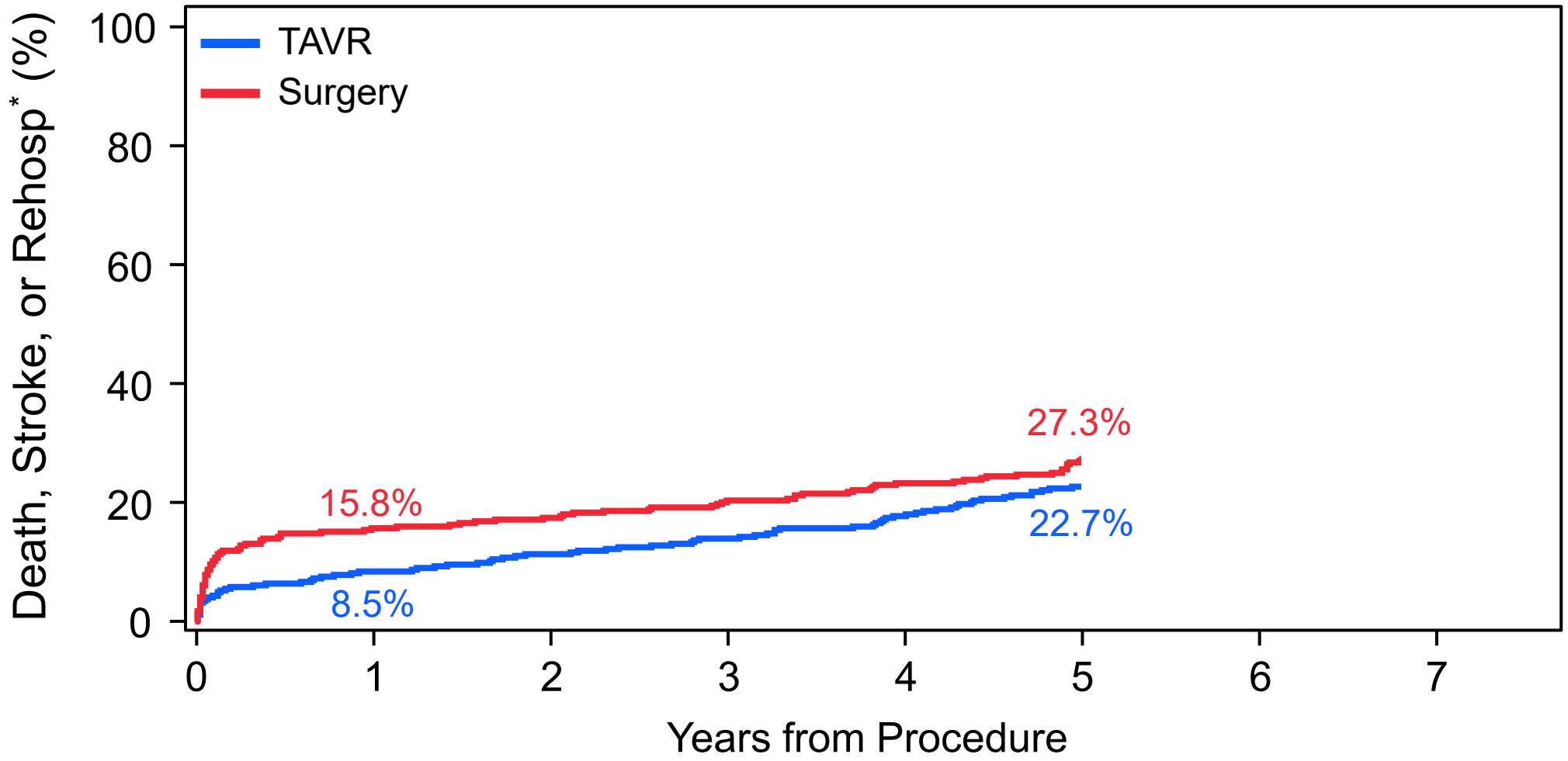
Primary Endpoint 1



Number at risk:

TAVR	496	453	435	418	394	366	333	288
Surgery	454	371	349	328	310	288	265	229

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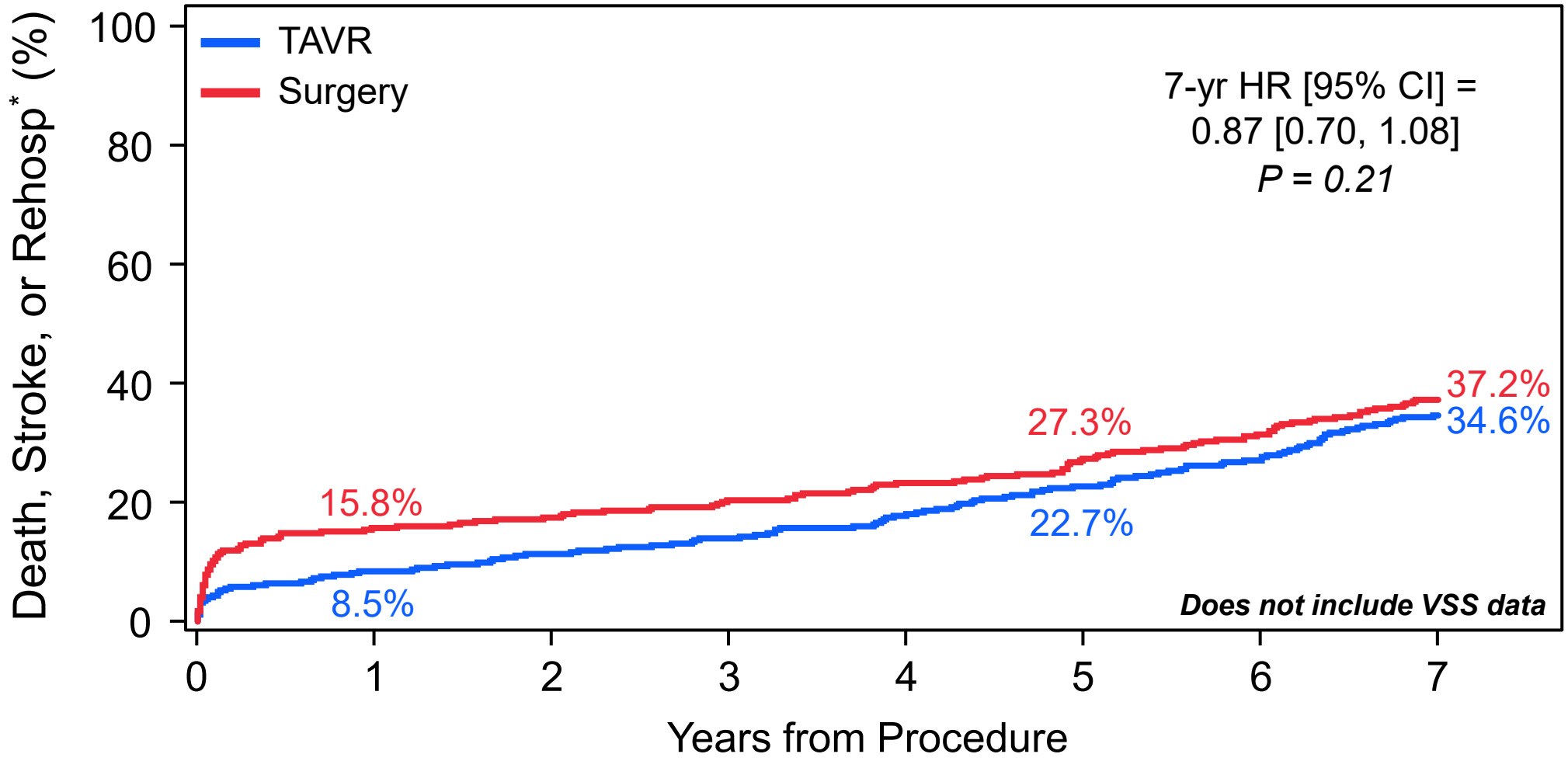
*Rehosp related to the valve, procedure, or heart failure

Primary Endpoint 1



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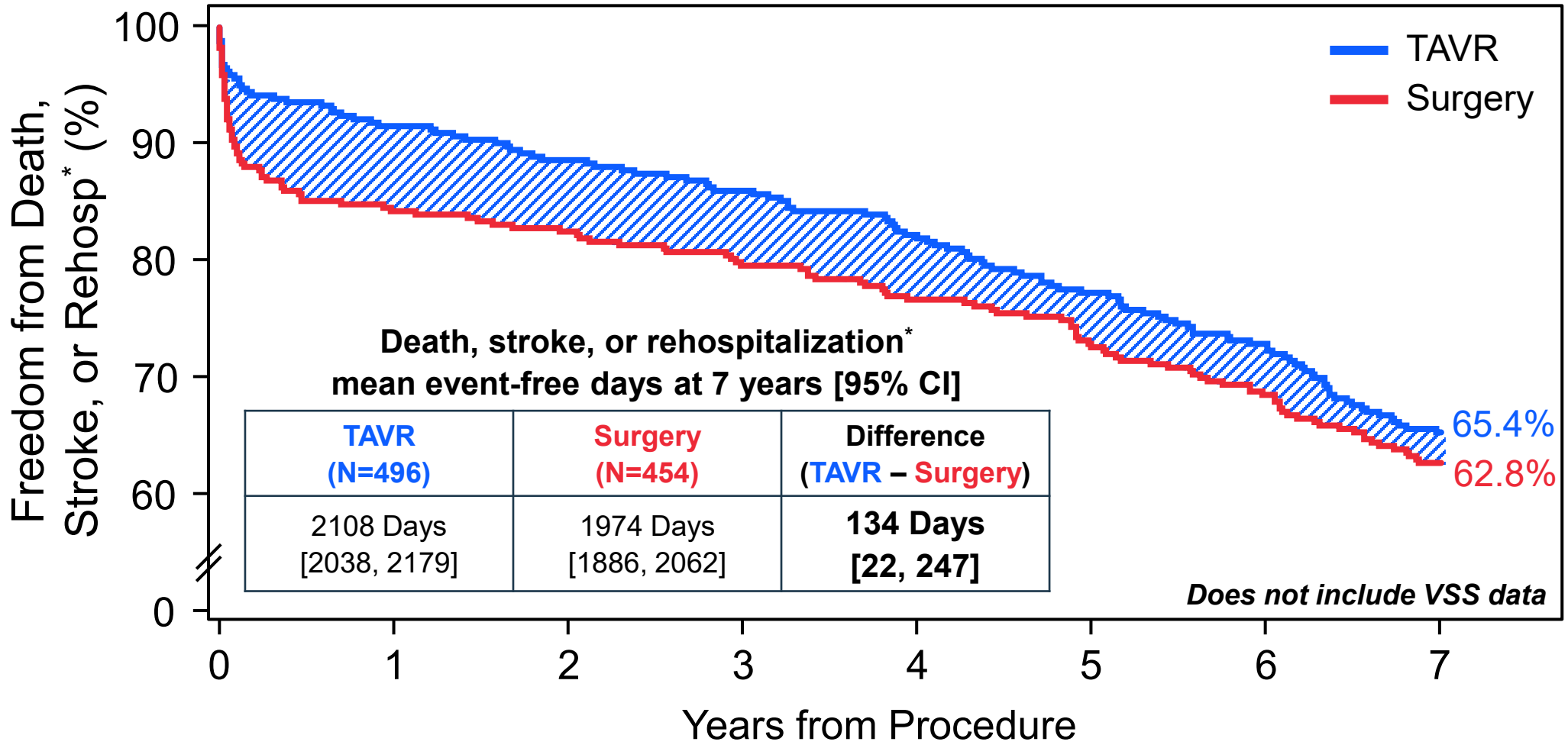
Restricted Mean Event-free Time



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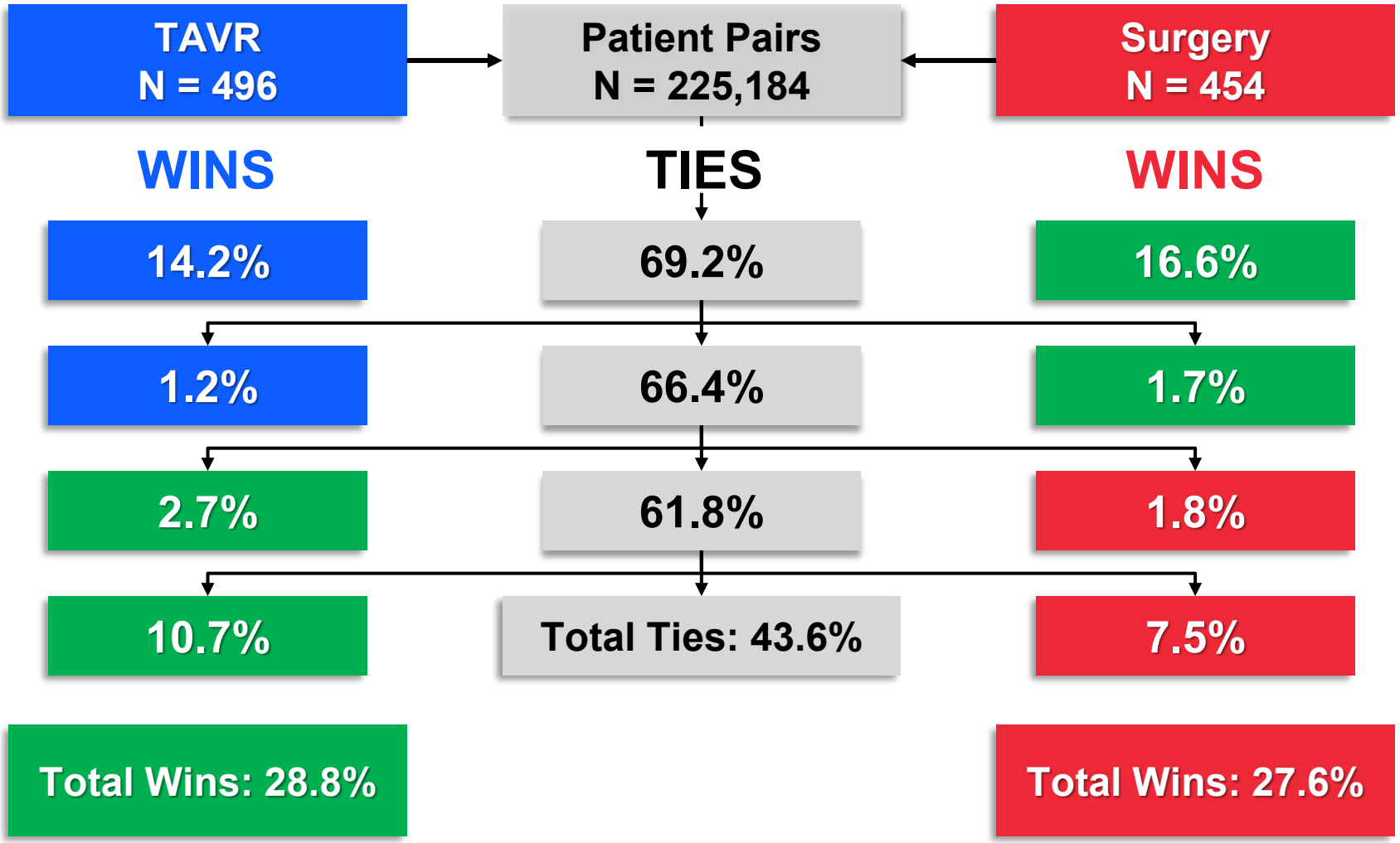
Primary Endpoint 2



Hierarchical Components:

1. All-cause Death (with VSS)
2. Disabling Stroke
3. Non-disabling Stroke
4. Rehospitalization Days
   (valve-, procedure-, or HF-related)

Win Ratio [95%CI] = $\frac{28.8}{27.6}$ = 1.04 [0.84, 1.30]; P = 0.70

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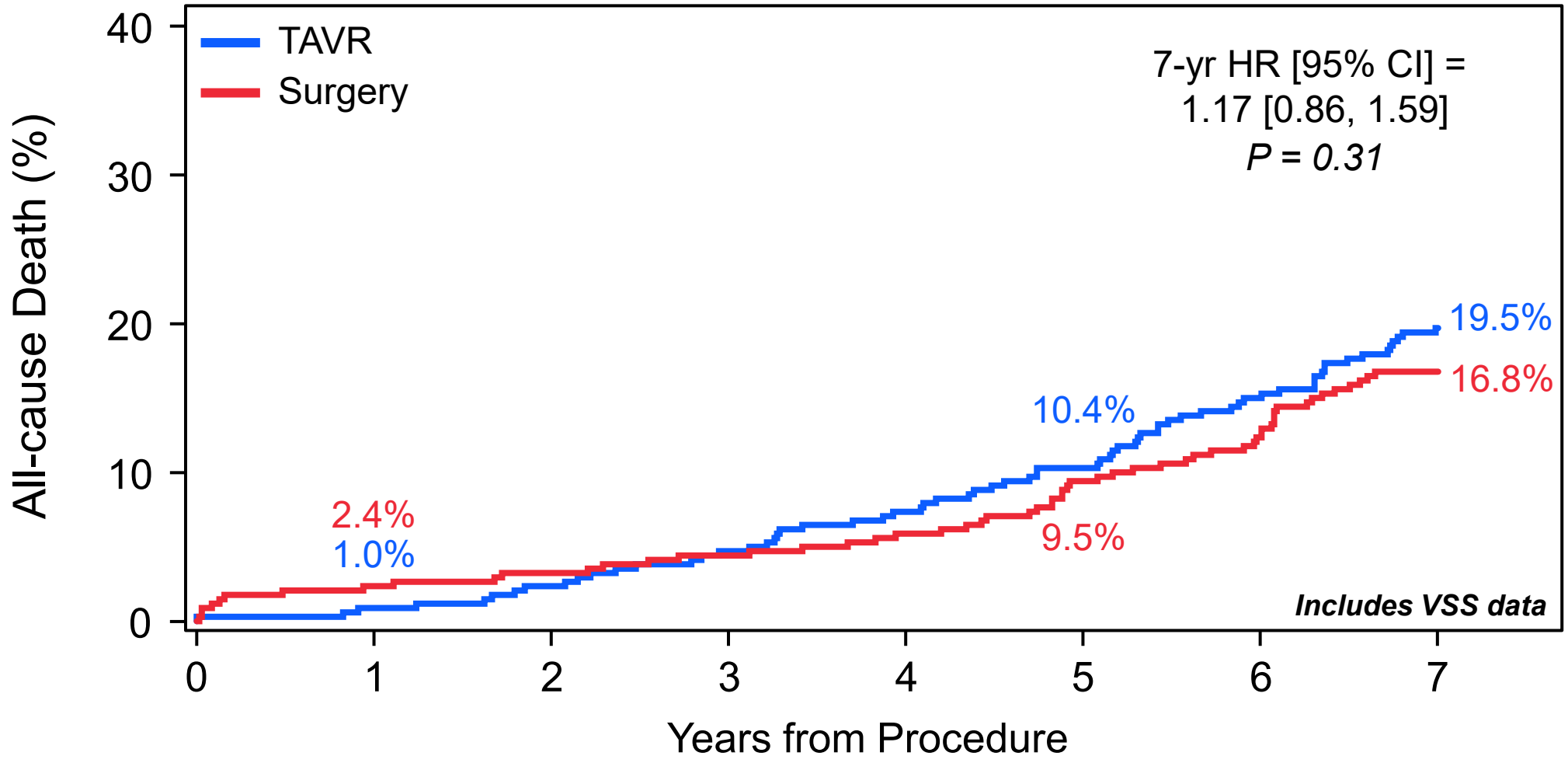
All-cause Death



Number at risk:

TAVR	496	490	481	468	449	433	405	377
Surgery	454	441	430	418	407	390	375	353

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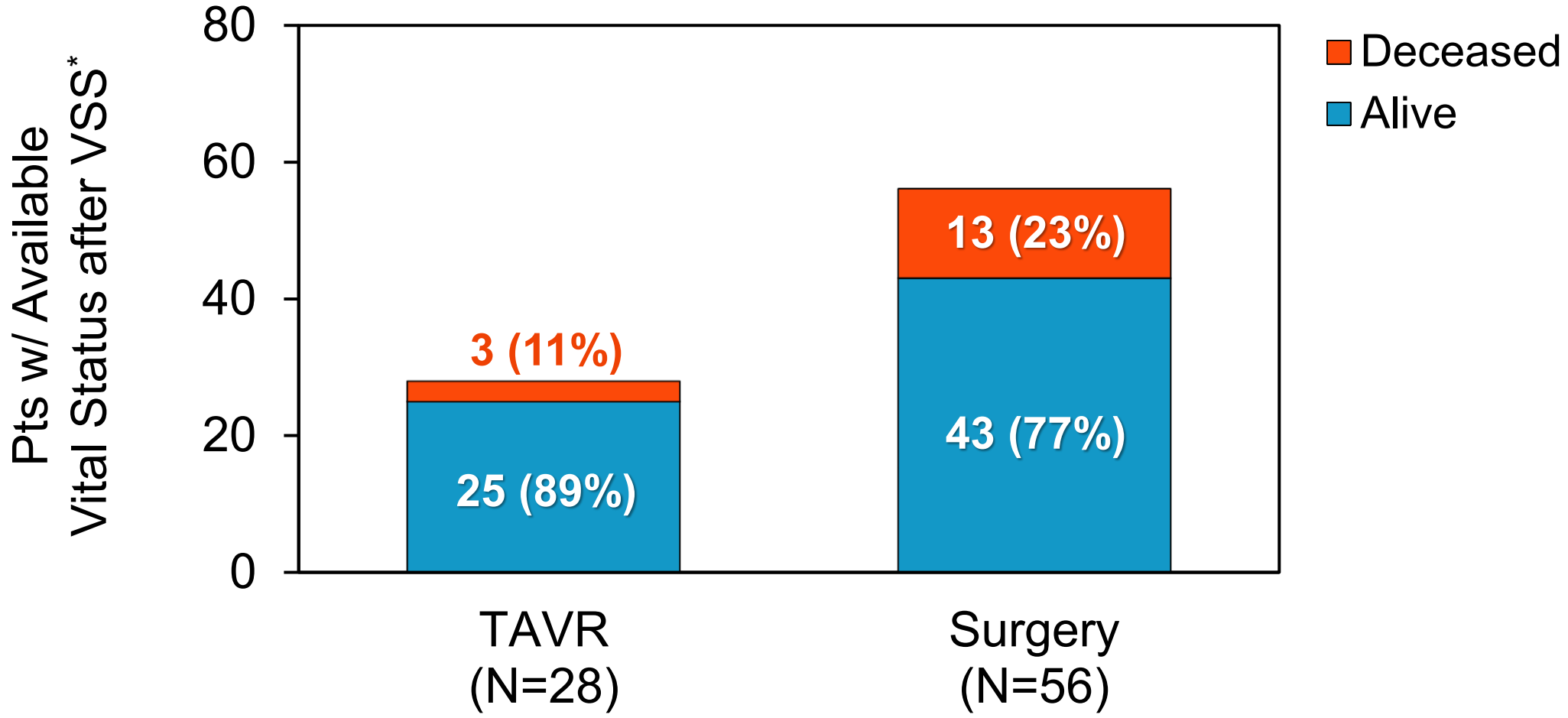
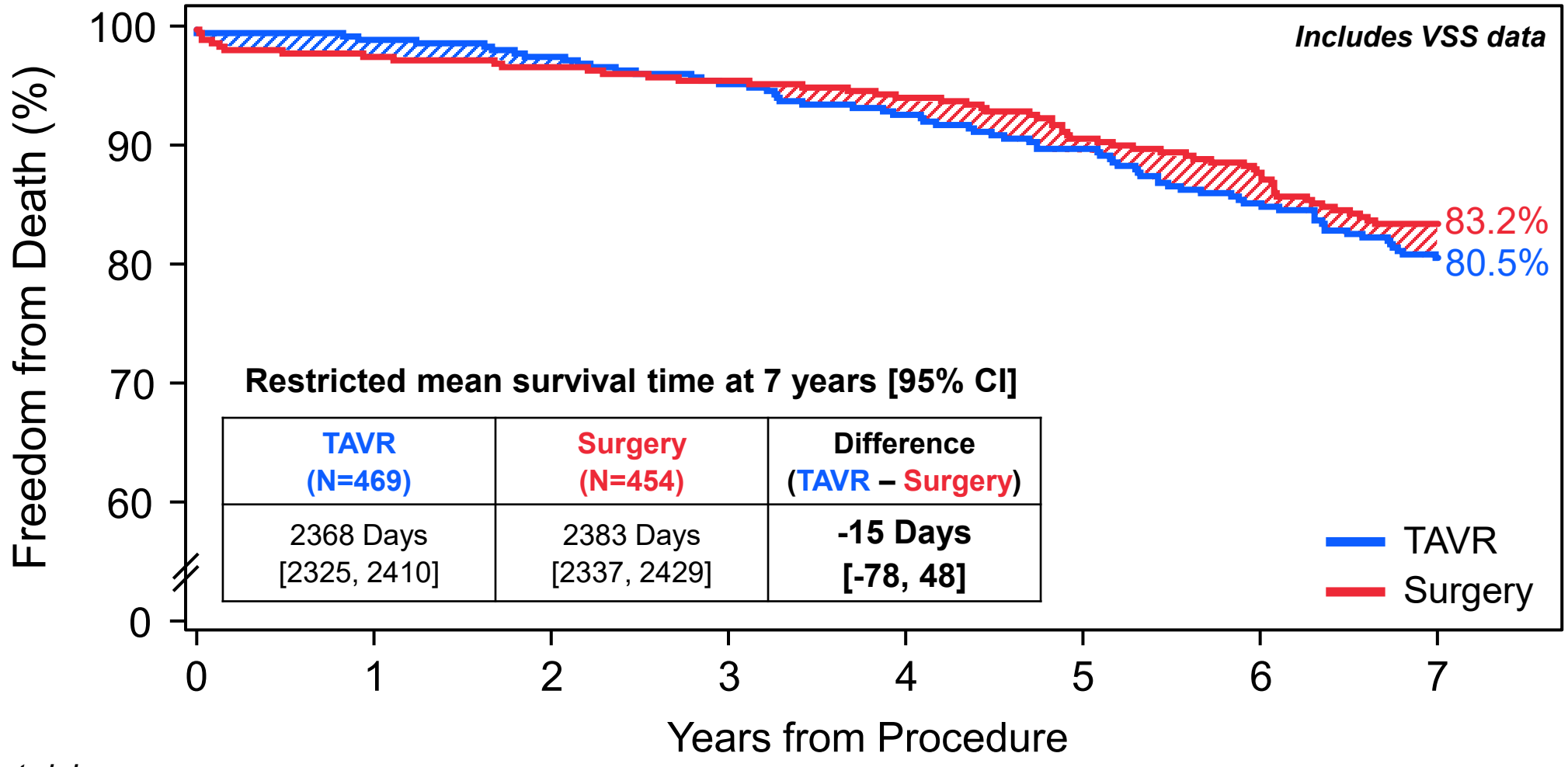
Vital Status Sweep (VSS)



VSS showed higher mortality in the Surgery arm among study exits

*VSS was performed by sites on patients who withdrew, were lost to follow-up, or missed a visit

Restricted Mean Survival Time



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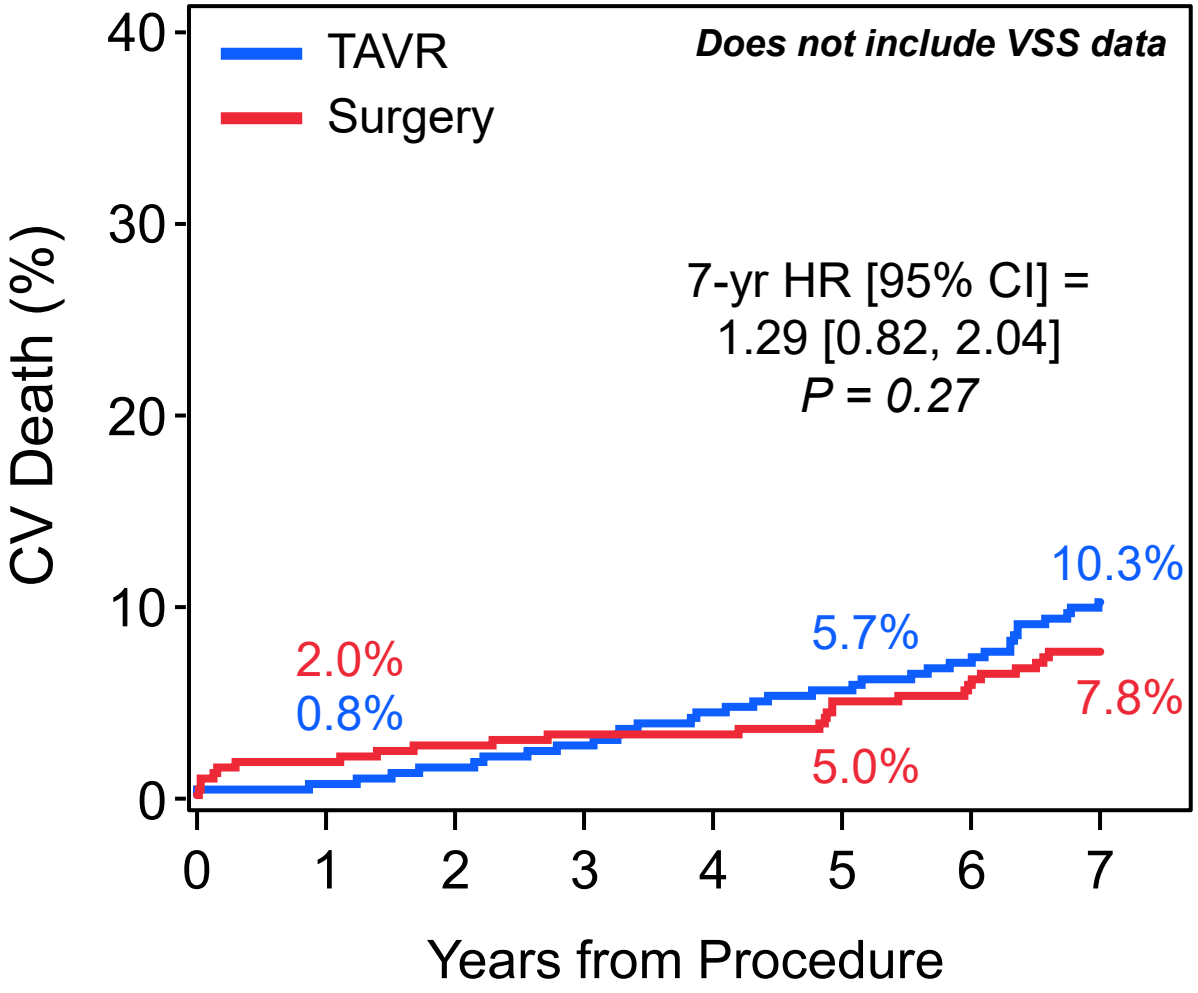
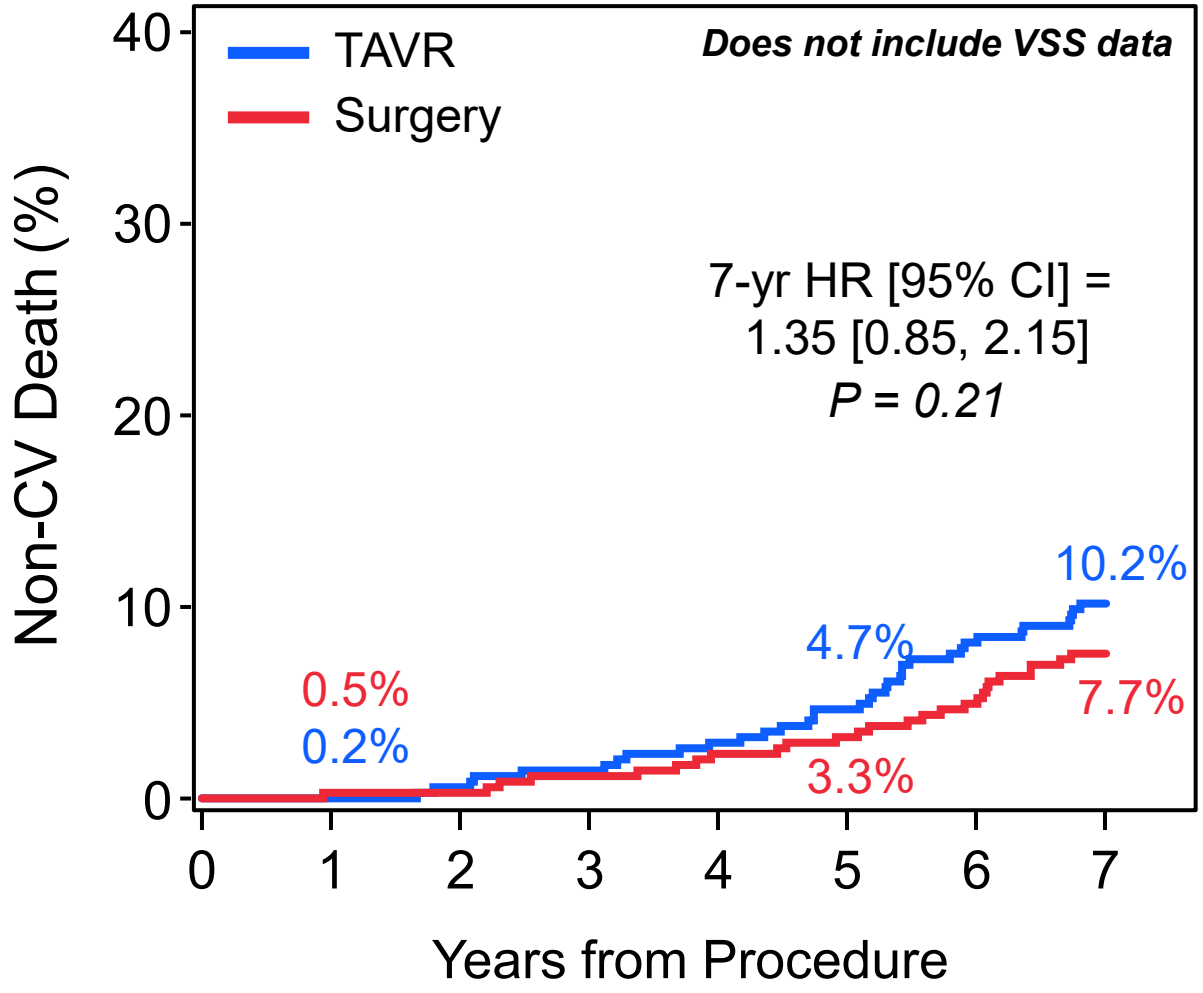
CV and Non-CV Death



No. at risk:

TAVR	496	490	480	465	443	422	388	352
Surgery	454	427	410	395	381	361	343	310



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Causes of Death 0 – 7 Years

CV Causes

Cause, No. of pts	TAVR	Surgery
Totals	**N=46**	**N=31**
Cardiac Cause	**18 (39.1%)**	**12 (38.7%)**
Acute MI	0	2
Cardiac Arrest	3	1
Cardiogenic Shock	1	1
CHF	7	6
Endocarditis	3	1
Sudden Cardiac Death	4	1
Non-coronary Vascular Conditions	**14 (30.4%)**	**6 (19.4%)**
Procedure-related	2	2
Stroke	6	4
Traumatic Head Injury from Fall	6	0
Unknown	**14 (30.4%)**	**13 (41.9%)**

Non-CV Causes

Cause, No. of pts	TAVR	Surgery
Totals	**N=45**	**N=29**
Cancer	18	11
Respiratory Failure*	12	10
Sepsis	8	3
Neurodegenerative Disease	1	2
Cirrhosis	1	1
MVA	1	1
GI Bleed	0	1
Homicide	1	0
Acute Renal Failure	1	0
Suicide	1	0
Toxic Metabolic Encephalopathy	1	0

*Due to COVID-19, chronic respiratory disease, or pneumonia

Vital-status Sweep

No. of VSS deaths	TAVR	Surgery
VSS (cause not determinable)	**3**	**13**

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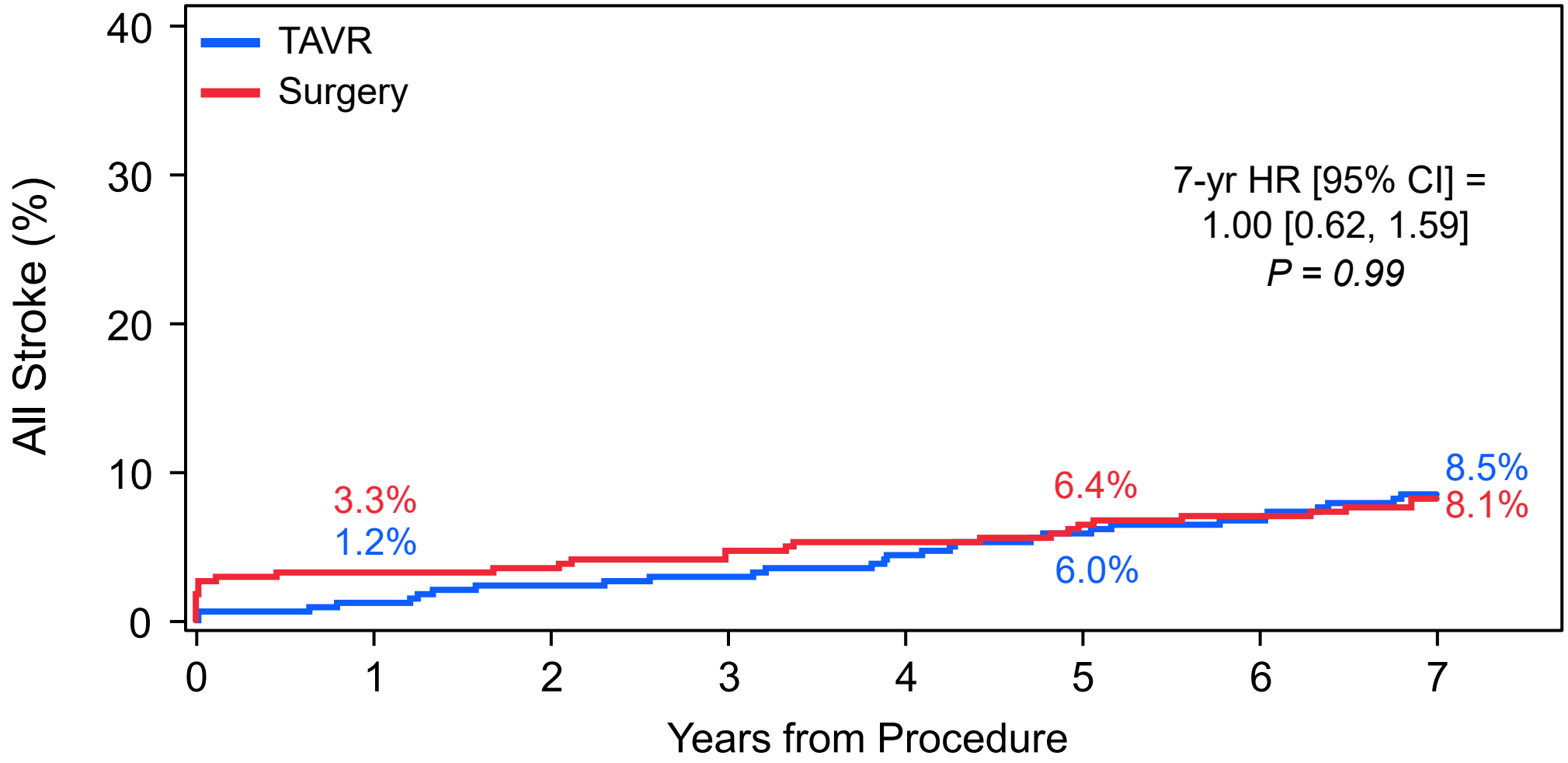
All Stroke



Number at risk:

TAVR	496	486	470	454	432	407	372	333
Surgery	454	416	398	379	363	344	326	291

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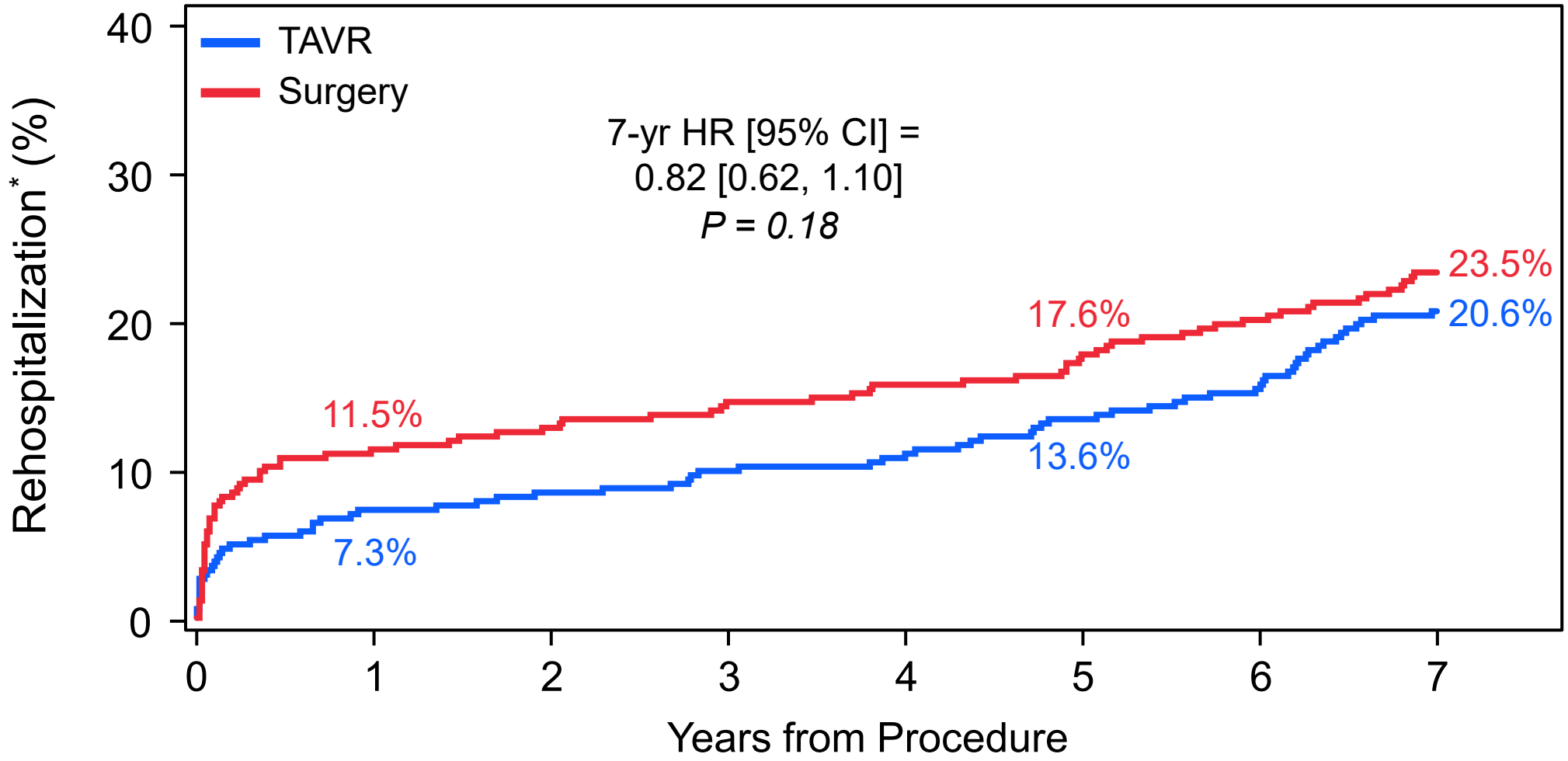
Rehospitalization



Number at risk:

TAVR	496	455	440	422	399	375	342	298
Surgery	454	380	359	339	322	301	277	240

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*Related to the valve, procedure, or heart failure

Additional Clinical Endpoints

KM% (No. of patients)

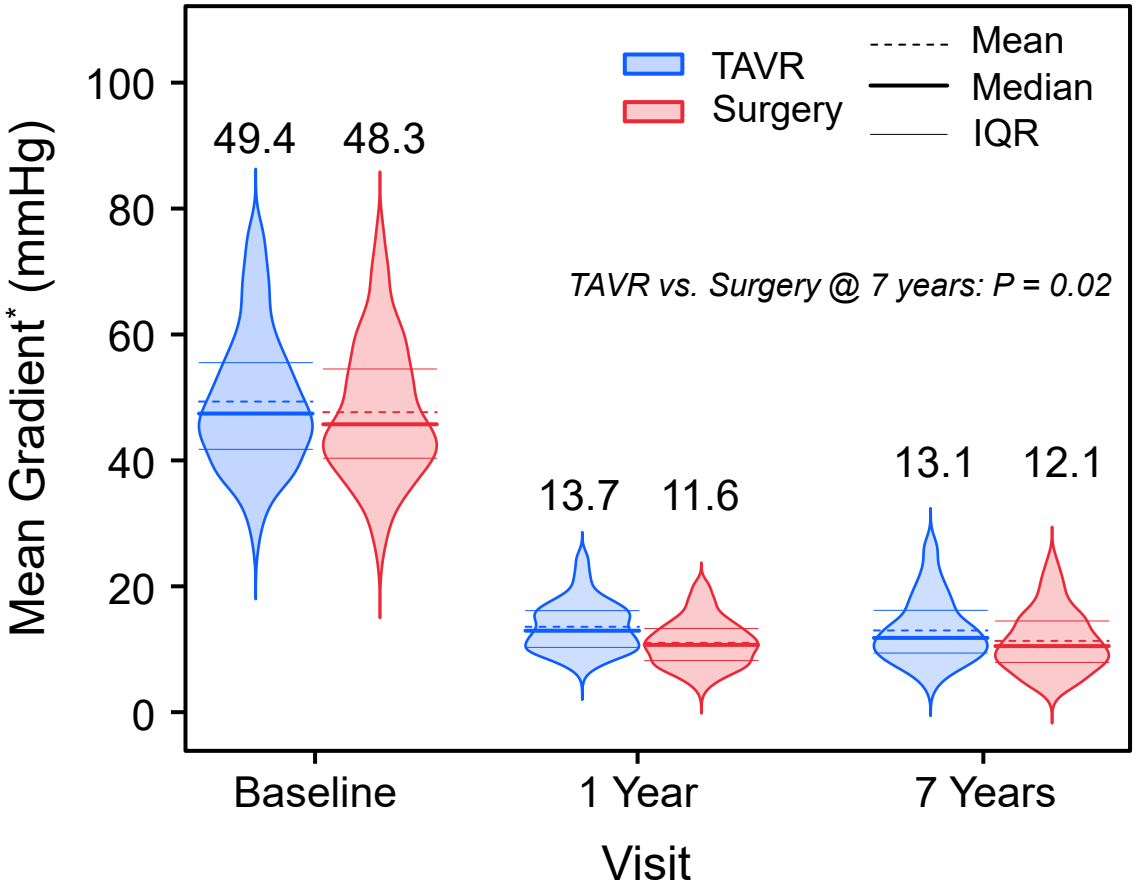
Endpoints	0 – 7 Years			
	TAVR (N=496)	Surgery (N=454)	HR [95% CI]	*P-value*
Death or disabling stroke*	21.7% (102)	16.8% (68)	1.31 [0.96, 1.78]	0.08
Aortic valve reintervention	6.7% (28)	6.0% (22)	1.11 [0.63, 1.94]	0.72
Endocarditis	2.9% (12)	2.8% (11)	0.94 [0.42, 2.14]	0.89
Clinical valve thrombosis†	**2.8% (13)**	**0.5% (2)**	**5.70 [1.29, 25.25]**	**< 0.01**
New-onset atrial fibrillation	**17.7% (69)**	**43.5% (158)**	**0.30 [0.23, 0.41]**	**< 0.0001**
New pacemaker	17.3% (78)	12.8% (51)	1.38 [0.97, 1.97]	0.07
Serious bleeding	15.6% (71)	18.5% (77)	0.79 [0.57, 1.09]	0.14
MI	6.0% (25)	5.6% (22)	0.99 [0.56, 1.75]	0.96
Revascularization	7.3% (31)	7.7% (31)	0.86 [0.53, 1.42]	0.57
PCI	6.6% (28)	6.6% (26)	0.94 [0.55, 1.60]	0.81
CABG	1.0% (4)	1.4% (6)	0.59 [0.17, 2.10]	0.41

*Does not include VSS data

†Per VARC-3; there was 1 new event in each arm from 5-7 years

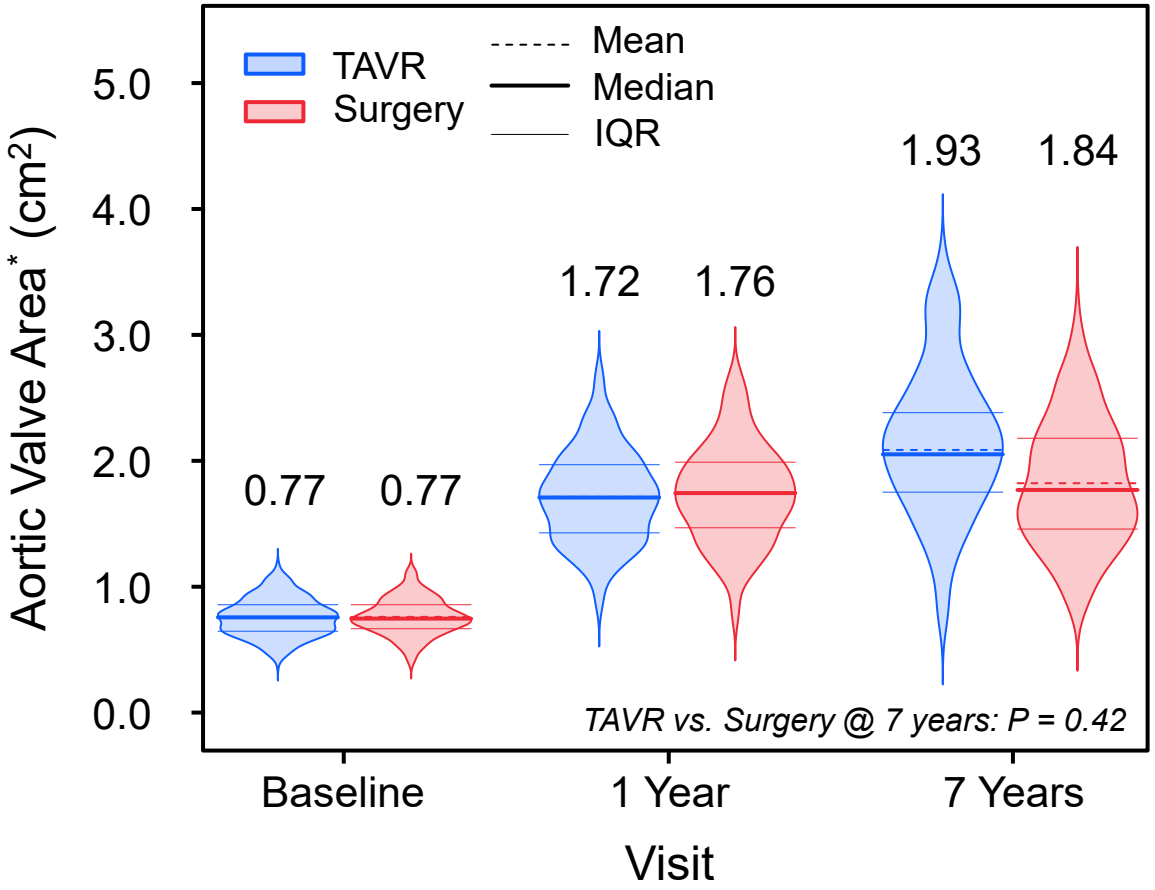
Valve Hemodynamics

Mean Gradient



No. of Echos			
TAVR	483	473	287
Surgery	442	391	246

Aortic Valve Area

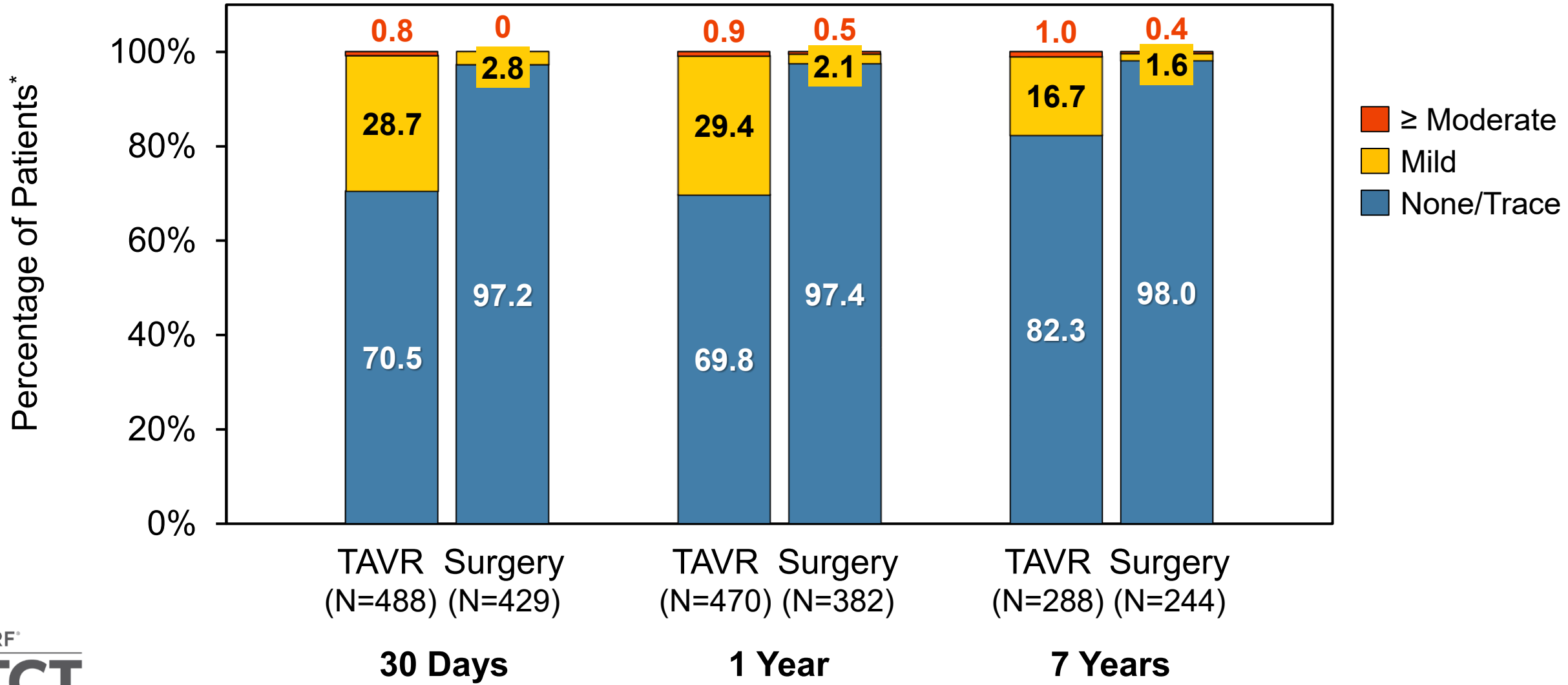


No. of Echos			
TAVR	458	449	283
Surgery	424	371	241

**Mean values are shown; Pts w/ explants/ViVs were censored post-reintervention*

Paravalvular Regurgitation

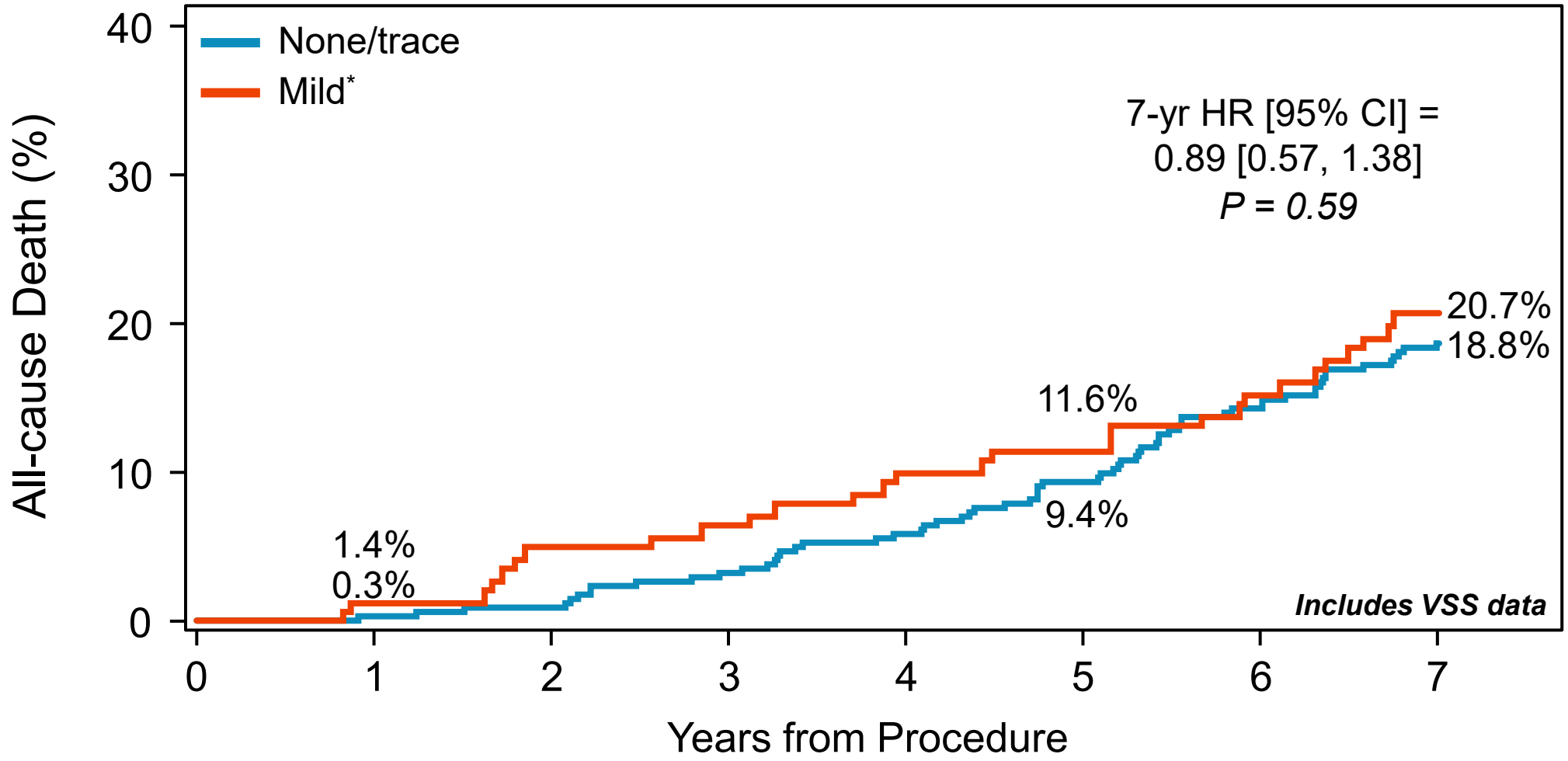
≥ mild P < 0.0001 at all time points



*Pts w/ explants/ViVs were censored post-reintervention

All-cause Death

By 30-day PVR – TAVR Only

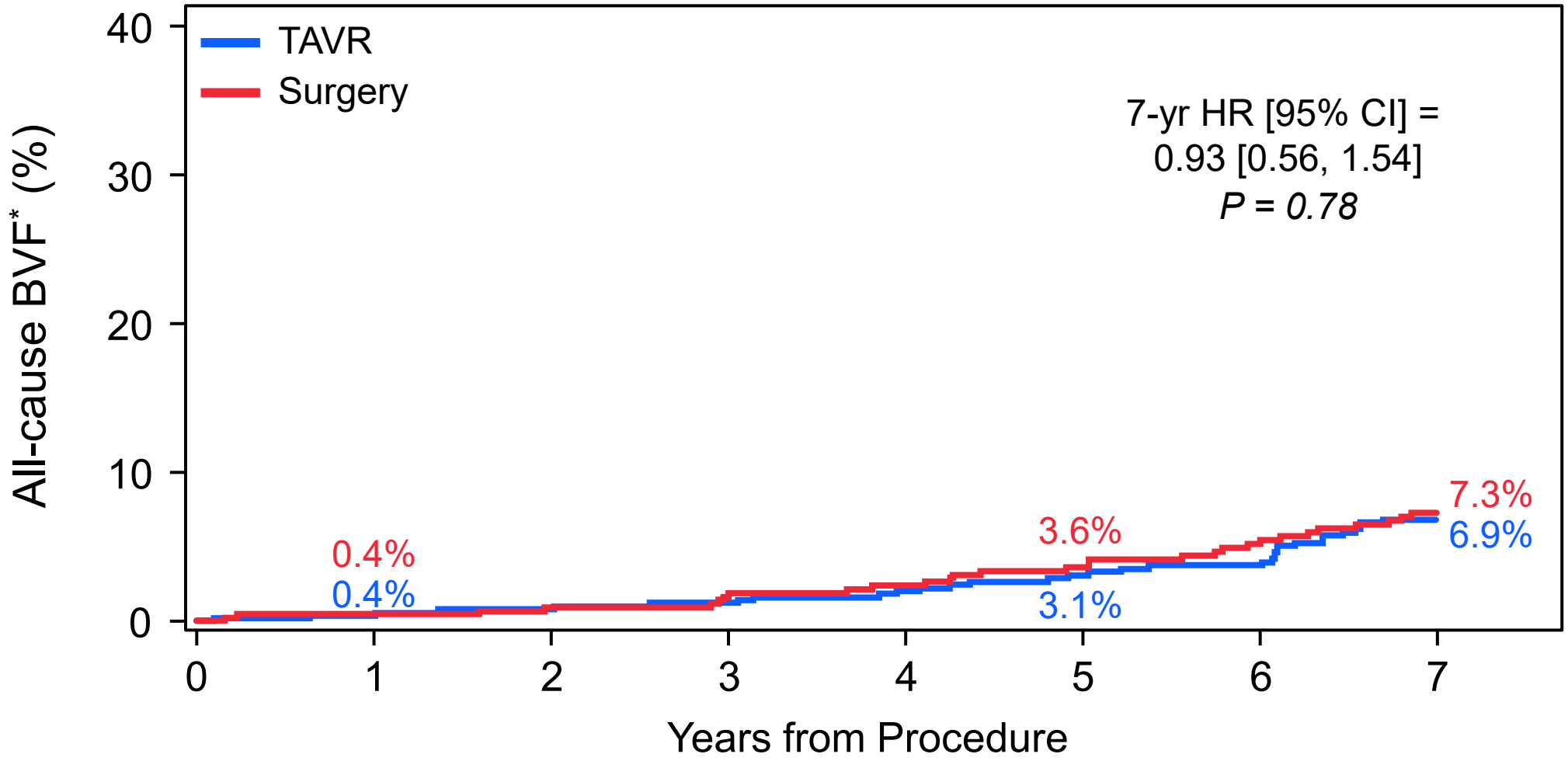


Number at risk:

None/trace	344	342	339	330	317	304	284	266
Mild*	140	138	132	129	123	120	112	102

**Only 4 patients had moderate PVR at 30 days and none of them died*

All-cause BVF (VARC-3)

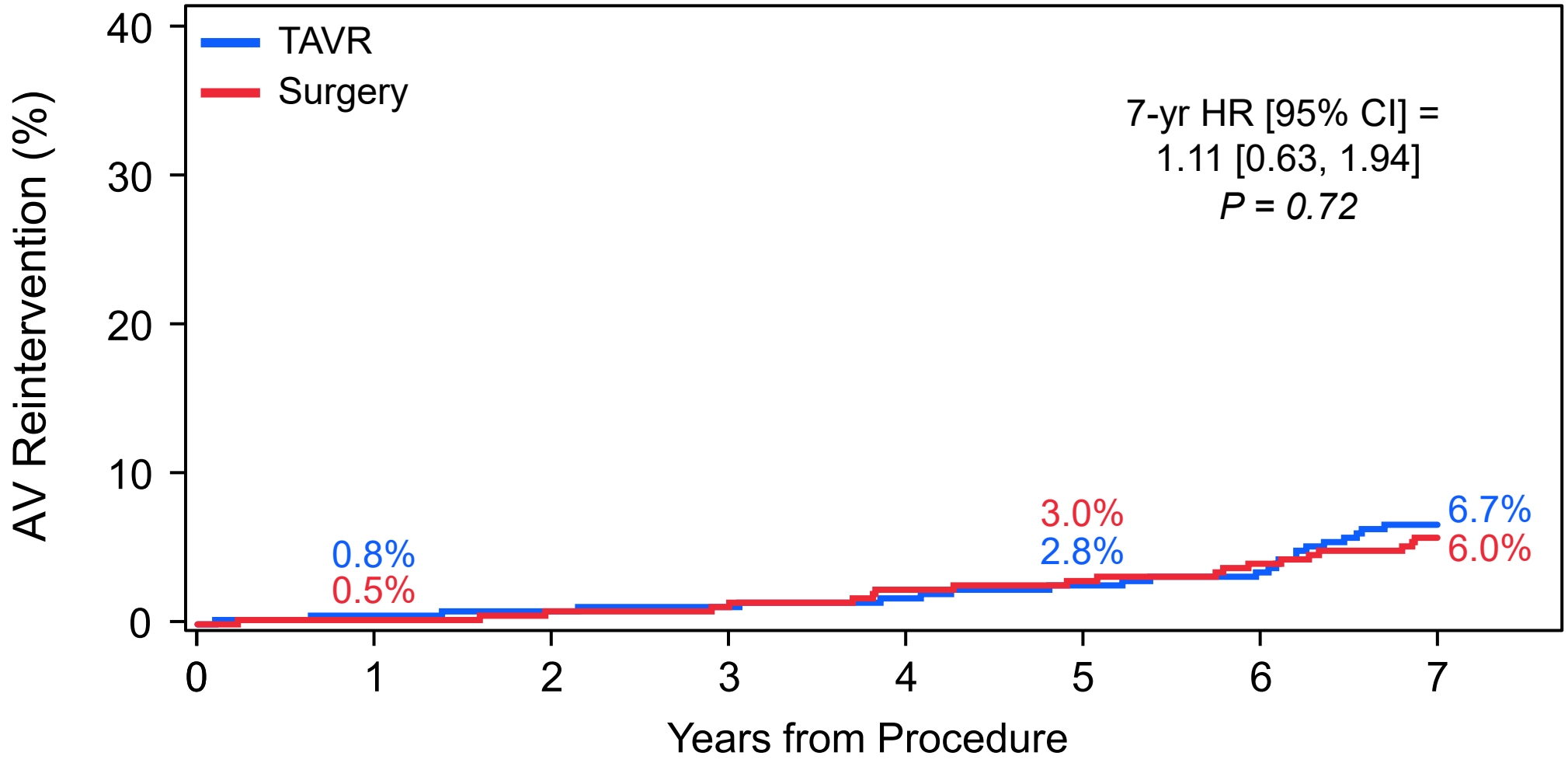


Number at risk:

TAVR	496	488	476	459	433	408	374	330
Surgery	454	426	407	390	372	348	327	288

*Cumulative incidence with death as a competing risk; HR estimated using the Fine and Gray method

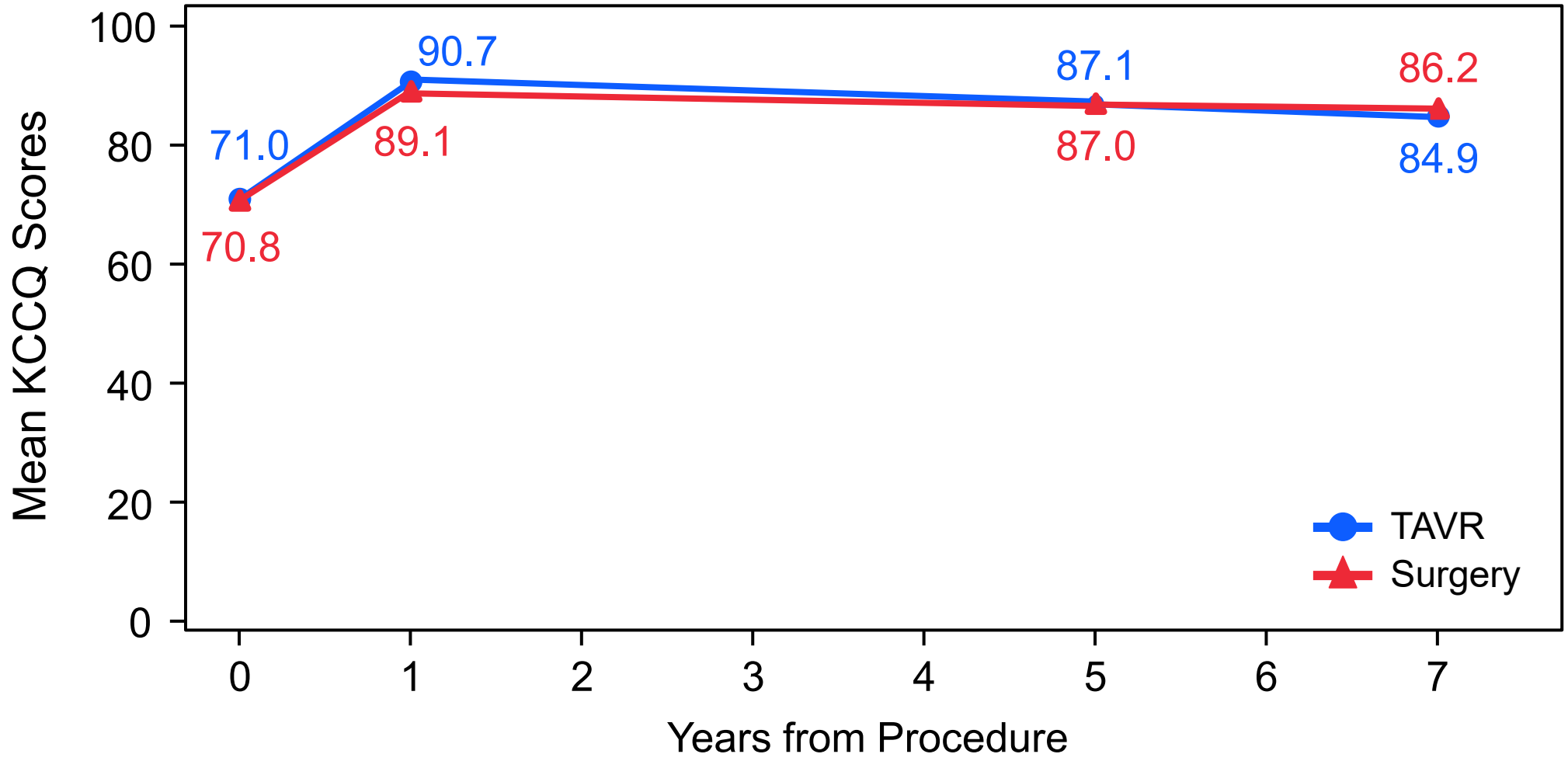
Aortic Valve Reintervention



Number at risk:

TAVR	496	488	477	461	437	413	378	333
Surgery	454	426	407	391	373	352	332	294

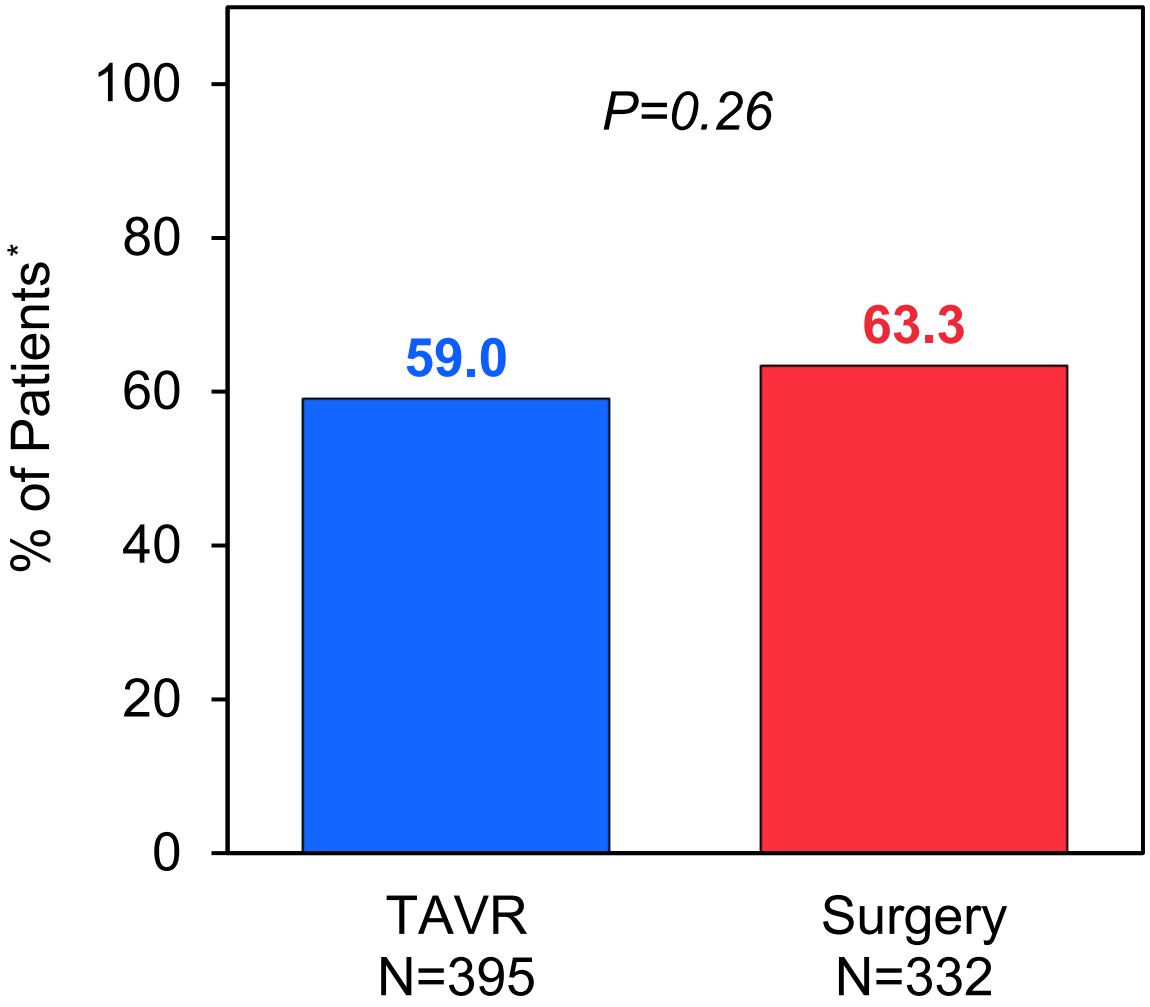
Mean KCCQ Overall Summary Scores



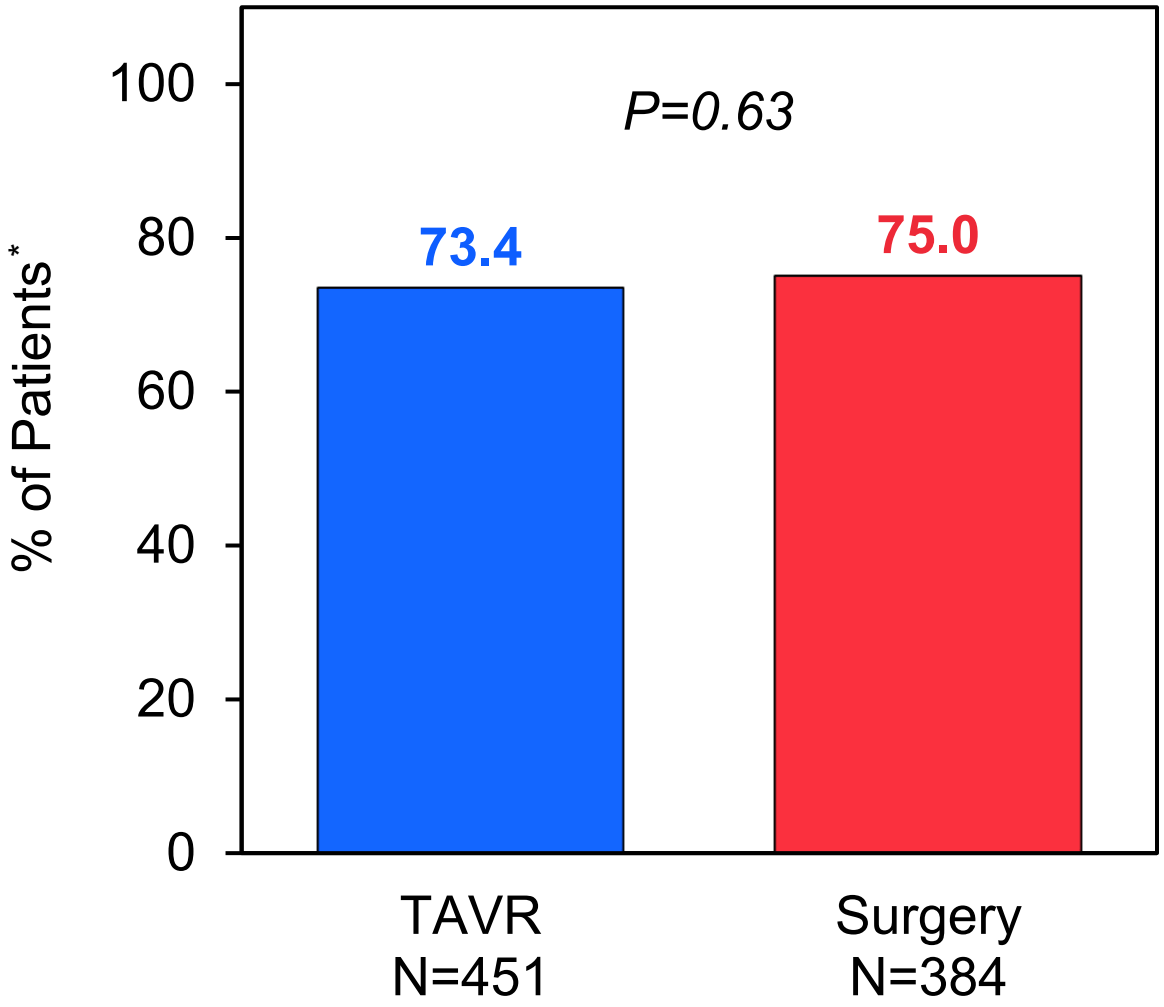
Number at risk:

TAVR	493	481	354	304
Surgery	448	403	301	262

QOL and Valve Durability at 7 Years



Alive with a KCCQ Score > 75



Alive with a Durable Valve (no BVF)

**Pts known to be deceased per VSS were included in the denominator*

Limitations and Context

- Results only apply to the enrolled population (bicuspid aortic valves, unsuitable TF access, and complex CAD excluded).
- Disproportionate withdrawal in the surgical arm could bias findings.
- Vital status sweeps, while essential for capturing complete mortality data, cannot be incorporated into composite outcomes or correct for possible biases in under-reporting of important nonfatal events.
- Long-term follow-up assessments in older patients can be confounded by competing non-valve-related events.
- Results are reported through 7 years; 10-year follow-up is planned.

Conclusions

Among patients with symptomatic severe AS at low surgical risk treated with SAPIEN 3 TAVR or Surgery, over 7 years of follow-up:

- **BOTH** TAVR and Surgery were associated with similar clinical event rates, with no significant differences in the 2 primary endpoints.
- The attenuation in primary endpoint differences observed at 5 years continued through 7 years.
- Marked 1-year improvements in hemodynamics and patient-reported outcomes were maintained and similar for both therapies.
- Valve function and durability were excellent and similar in both groups.

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Just Published in NEJM!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter or Surgical Aortic-Valve Replacement in Low-Risk Patients at 7 Years

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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 to reduce the risks associated with progression from asymptomatic to symptomatic severe native calcific aortic stenosis in patients who are judged by a heart team to be appropriate for transcatheter heart valve replacement therapy.

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 ≥ 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).

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 ≥ 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

Important Safety Information (continued)

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. Data on TAVR in patients with asymptomatic severe aortic stenosis are based on study of predominantly low surgical risk patients. Limited clinical data to inform benefit-risk considerations are available for TAVR in patients with asymptomatic severe aortic stenosis who are deemed to be at intermediate or greater surgical risk. 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., 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.

Important Safety Information (continued)

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, 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.

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