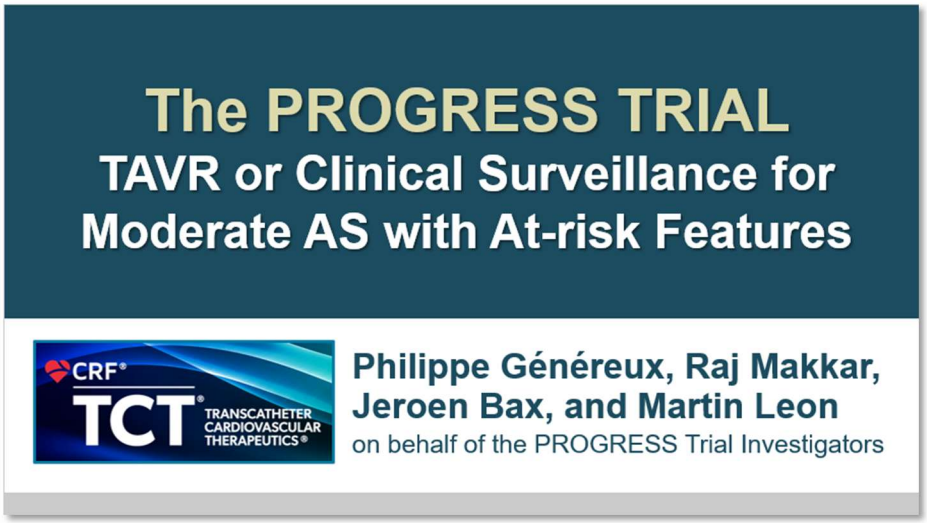
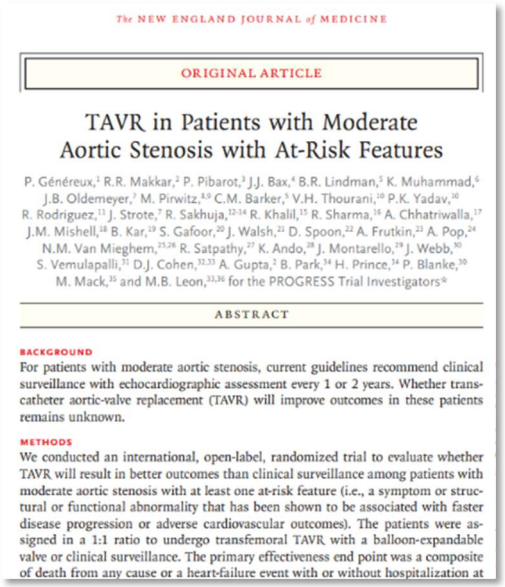
The PROGRESS Trial Results





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TAVR in Patients with Moderate Aortic Stenosis with At-Risk Features

P. Généreux,[1] R.R. Makkar,[2] P. Pibarot,[3] J.J. Bax,[4] B.R. Lindman,[5] K. Muhammad,[6] J.B. Oldemeyer,[7] M. Pirwitz,[8,9] C.M. Barker,[5] V.H. Thourani,[10] P.K. Yadav,[10] R. Rodriguez,[11] J. Strote,[7] R. Sakhuja,[12-14] R. Khalil,[15] R. Sharma,[16] A. Chhatriwalla,[17] J.M. Mishell,[18] B. Kar,[19] S. Gafoor,[20] J. Walsh,[21] D. Spoon,[22] A. Frutkin,[23] A. Pop,[24] N.M. Van Mieghem,[25,26] R. Satpathy,[27] K. Ando,[28] J. Montarello,[29] J. Webb,[30] S. Vemulapalli,[31] D.J. Cohen,[32,33] A. Gupta,[3] B. Park,[34] H. Prince,[34] P. Blanke,[30] M. Mack,[35] and M.B. Leon,[33,36] for the PROGRESS Trial Investigators*

ABSTRACT

BACKGROUND

For patients with moderate aortic stenosis, current guidelines recommend clinical surveillance with echocardiographic assessment every 1 or 2 years. Whether transcatheter aortic-valve replacement (TAVR) will improve outcomes in these patients remains unknown.

METHODS

We conducted an international, open-label, randomized trial to evaluate whether TAVR will result in better outcomes than clinical surveillance among patients with moderate aortic stenosis with at least one at-risk feature (i.e., a symptom or structural or functional abnormality that has been shown to be associated with faster disease progression or adverse cardiovascular outcomes). The patients were assigned in a 1:1 ratio to undergo transfemoral TAVR with a balloon-expandable valve or clinical surveillance. The primary effectiveness end point was a composite of death from any cause or a heart-failure event with or without hospitalization at

SAPIEN 3 TAVR platforms have not been approved by FDA for use in moderate aortic stenosis patients, and the safety and effectiveness of SAPIEN 3 TAVR platforms for moderate aortic stenosis patients have not been established.

CAUTION: Investigational device. Limited by Federal (United States) law to investigational use when used in patients with moderate AS.

For Important Safety Information for approved uses of SAPIEN 3 TAVR platforms see the end of the presentation.

This information is for educational purposes only and does not constitute a recommendation for off-label use.

The PROGRESS TRIAL

TAVR or Clinical Surveillance for Moderate AS with At-risk Features



Philippe Généreux, Raj Makkar, Jeroen Bax, and Martin Leon

on behalf of the PROGRESS Trial Investigators

Disclosures for Philippe Généreux, MD

Atlantic Health, Morristown Medical Center

THE PROGRESS TRIAL

TCT 2026 • San Diego, CA • Oct 31st – Nov 3rd

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

Financial Relationship	Company
• **Consulting Fees**	Abbott Vascular, Cardiawave, Egnite, EchoIQ, Edwards Lifesciences, Haemonetics, Medtronic, Pi-Cardia, Puzzle Medical Inc., Spiralis Medical, 4C Medical, Shockwave Medical, Antegrade Medical
• **Principal Investigator**	EARLY TAVR trial, PROGRESS trial, ECLIPSE trial, 4C Feasibility trial, ACTIVATE AS
• **Equity**	Puzzle Medical Inc., Pi-Cardia, Antegrade Medical, Spiralis Medical, Echo IQ, Cardiawave, Sparrow Bioacoustics

Background

THE PROGRESS TRIAL

- For patients with moderate AS, current guidelines recommend clinical surveillance (CS) with **echocardiography every 1 to 2 years**[1-2]
- **Moderate AS comprises a heterogenous patient population** with unpredictable disease progression, and echocardiographic severity may not reflect patient's clinical status
- Observational studies have shown that adverse outcomes among patients with **moderate AS and at-risk features** (e.g., symptoms or cardiac abnormalities) may be **similar to those seen with severe AS**[3-6]

To date, no randomized trials have explored whether TAVR will improve outcomes in these patients

[1]Otto et al. Circulation 2020; [2]Praz et al. EHJ 2025; [3]Strange et al. JACC 2019; [4]Genereux et al. JACC 2023; [5]Khan et al. JACC 2023; [6]van Gils et al. JACC 2017

Purpose of the PROGRESS Trial

THE PROGRESS TRIAL

To determine whether TAVR is superior to clinical surveillance for patients with moderate AS and at least 1 at-risk feature

Study Design

THE PROGRESS TRIAL

Prospective, global, multicenter randomized trial evaluating patients aged ≥ 65 years with moderate AS per echo core lab

At least 1 at-risk feature

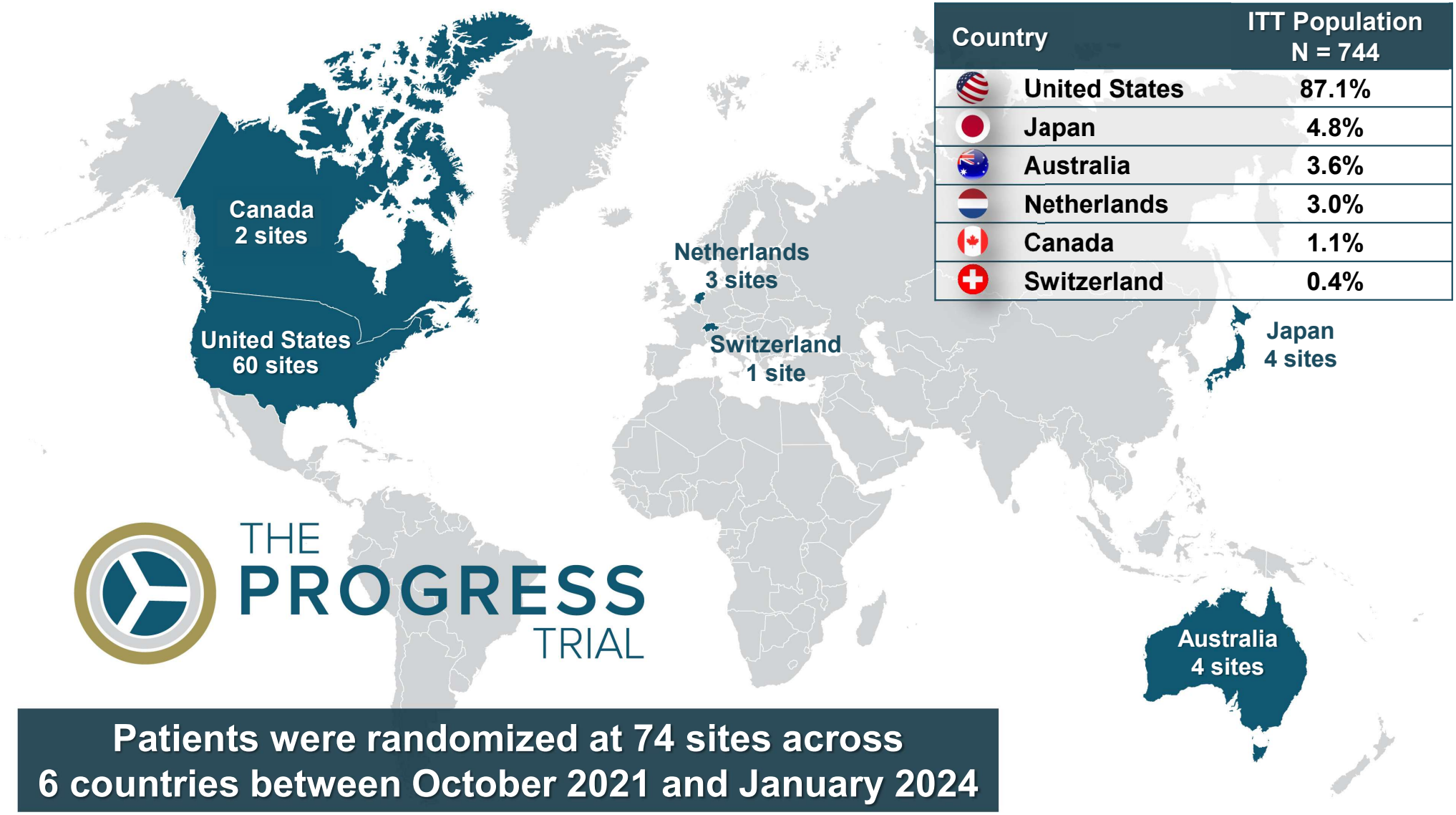
Randomized 1:1 (~750 pts)

Transfemoral TAVR
Balloon-expandable S3 platform

Clinical Surveillance
Annually per guidelines

Clinical and echo follow-up is performed through 10 years

Schematic adapted from *Genereux et al. Am Heart J 2026*



Country	ITT Population N = 744
United States	87.1%
Japan	4.8%
Australia	3.6%
Netherlands	3.0%
Canada	1.1%
Switzerland	0.4%

THE PROGRESS TRIAL

Patients were randomized at 74 sites across 6 countries between October 2021 and January 2024

Study Leadership

Steering Committee, Case Review Board, and Core Labs

THE PROGRESS TRIAL



Martin B Leon, MD
Steering Committee
Executive Chair



Philippe Généreux, MD
Global NPI
Steering Committee
Case Review Board



Raj Makkar, MD
NPI
Steering Committee



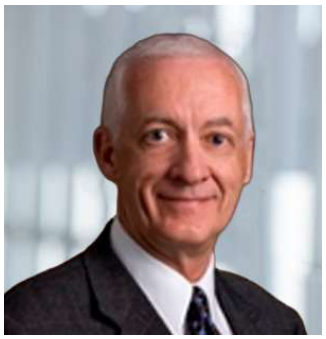
Jeroen J Bax, MD, PhD
NPI
Steering Committee



Philippe Pibarot, DVM, PhD
Echo Core Lab
Steering Committee



Brian Lindman, MD, MSc
Biomarker Core Lab



Michael Mack, MD
Steering Committee



J. Bradley Oldemeyer, MD
Steering Committee
Case Review Board



Mark Russo, MD
Case Review Board



Suzanne J Baron, MD, MSc
Steering Committee



John K Forrest, MD
Steering Committee



Philipp Blanke, MD,
CT Core Lab

Inclusion and Exclusion Criteria

THE PROGRESS TRIAL

Key Inclusion Criteria:

- Aged ≥ 65 years
- **Moderate AS** per echo core lab
  - **≥ 1 of the following at-risk features*:**
  - Valve-related symptoms (NYHA Class ≥ II)
  - Elevated NT-ProBNP > 3x normal
  - Reduced LVEF < 60%
  - Diastolic dysfunction ≥ Grade 2†
  - Reduced SVi < 35 ml/m^2
  - Presence of AF within the last 6 months
  - Elevated AV Ca^{++} score per CT core lab (> 1200 AU for females, > 2000 AU for males)

Key Exclusion Criteria:

- Unsuitable anatomy for transfemoral TAVR (e.g. severe PVD, significant LVOT Ca^{++})
- Significant clinical comorbidities (e.g. CKD, severe COPD, CAD requiring revasc.)
- LVEF < 20%
- Bicuspid AV with an ascending aorta > 4.5 cm or severe raphe/leaflet Ca^{++}
- Pre-existing AVR or valvuloplasty
- Severe aortic regurgitation

*These features were selected because of their known association with poor outcomes among patients with moderate AS; †Per ASE guidelines (*Nagueh et al. JASE 2016*)

Moderate AS Severity
Defined Per ACC/AHA Guidelines

THE PROGRESS TRIAL

Resting echo measurements from screening TTE per core lab:

CONCORDANT Moderate AS

Defined as **BOTH** criteria (AVA / AVAi and V_{peak} / MG criteria) in the moderate AS range

Moderate AVA / AVAi

AVA 1.0 – 1.5 cm^2 OR

AVAi > 0.6* or 0.5† cm^2/m^2 if AVA < 1.0 cm^2
AVAi < 0.9* or 0.8† cm^2/m^2 if AVA > 1.5 cm^2

Moderate V_{peak} / MG

V_{peak} 3.0 m/s – < 4.0 m/s
OR
MG 20 mmHg – < 40 mmHg

Concordant moderate AS criteria met on resting echo

91% of enrolled patients had concordant moderate AS

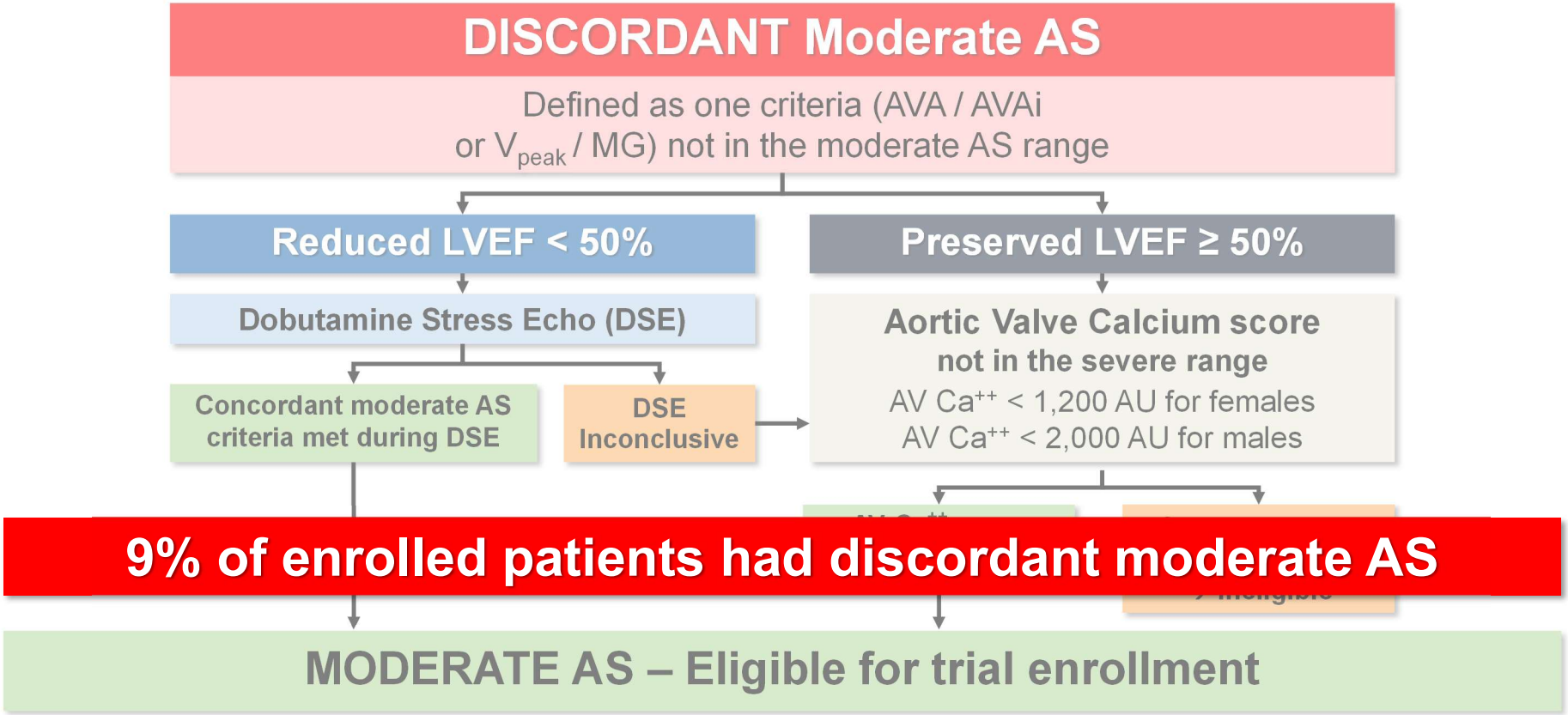
MODERATE AS – Eligible for trial enrollment

*If BMI is < 30 kg/m^2; †If BMI is ≥ 30 kg/m^2

Moderate AS Severity
Defined Per ACC/AHA Guidelines

THE PROGRESS TRIAL

Resting echo measurements from screening TTE per core lab:



Primary Endpoints

THE PROGRESS TRIAL

Safety Endpoint Assessed at 30 Days

- Non-hierarchical composite of death, stroke, life threatening or fatal bleeding, stage 4 AKI, hospitalization due to a device- or procedure-related complication, or valve dysfunction requiring reintervention
- Compared to a **performance goal of 13.7%** in the **TAVR AT population** at 30 days post-procedure*

Effectiveness Endpoint Assessed at 2 Years

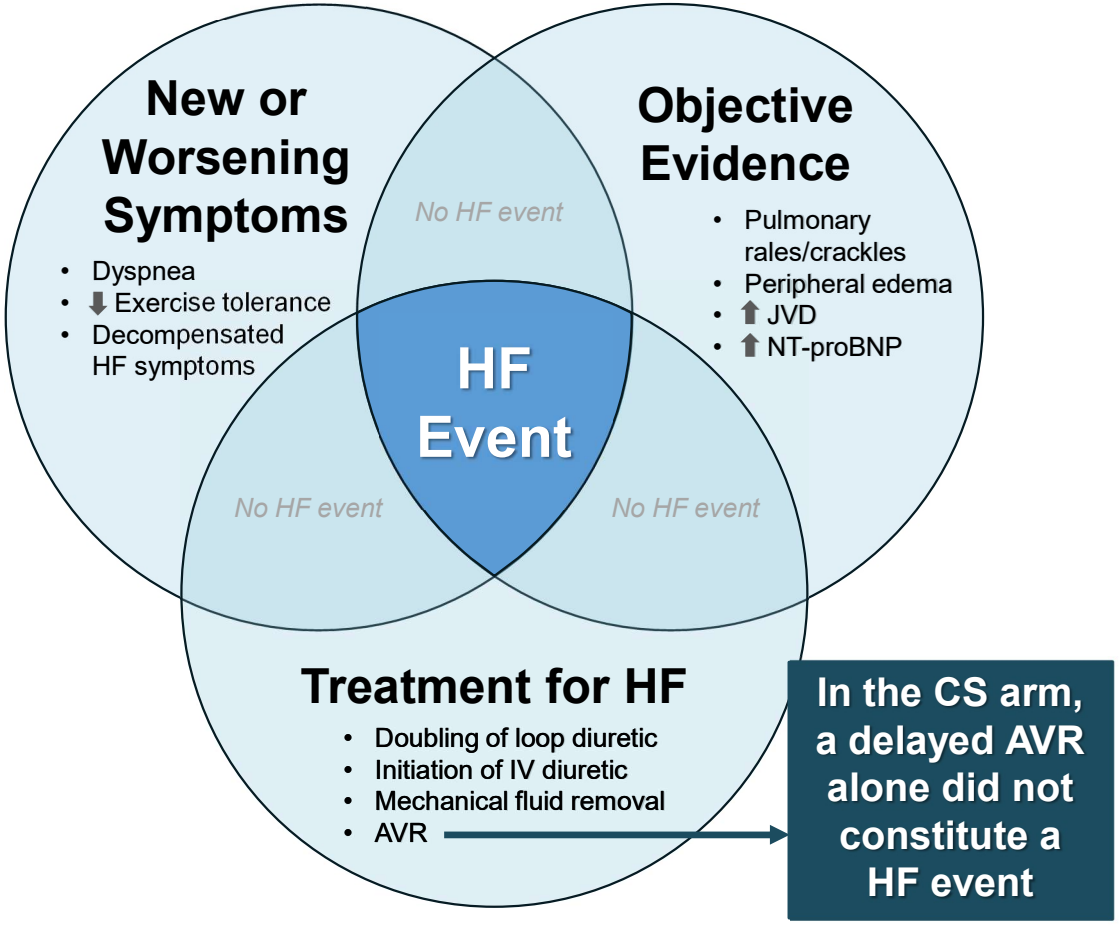
- Non-hierarchical composite of **death or HF event** w/ or w/out hospitalization
- Tested for **superiority** in the **ITT population** at 2 years post-randomization

*Performance goal as described in *Genereux et al. Am Heart J 2026*

Rigorous Definition of HF Event and HF Hospitalization

THE PROGRESS TRIAL

- To be considered a HF event, **ALL 3 criteria** had to be present*:
  1. **New or worsening HF symptoms**
  2. **At least 2 objective criteria** of new or worsening HF (physical, laboratory, imaging, and/or invasive findings)
  3. **Escalation** of HF treatment
- **HF hospitalization** was defined as any hospital admission **≥ 24 hours** or overnight stay **due to a HF event**



*Adapted from HFC-ARC criteria (*Abraham et al. JACC Heart Failure 2020*)

Secondary Endpoints

THE PROGRESS TRIAL

Secondary endpoints were assessed at **2 years post-randomization** in the **ITT population** and tested in a **pre-specified hierarchy** using a gatekeeping method adjusted for multiplicity:

1. Death, stroke, or heart failure hospitalization
2. Alive with a KCCQ score improvement ≥ 10 points from baseline at 1 and 2 years
3. Heart failure hospitalization
4. Left ventricular mass index per echo core lab
5. Diastolic dysfunction ≥ Grade 2* per echo core lab

*Per ASE guidelines (*Nagueh et al. JASE 2016*)

Patient Flow

THE PROGRESS TRIAL

N = 1,294 Patients consented for screening with presumed moderate AS and at-risk features

Excluded from randomization*: N = 550 (42.5%)

- **Did not have moderate AS (n=214)**
- **Anatomical exclusions (n=139)**
- Medical exclusions (n=78)
- Did not have an at-risk feature (n=16)
- Withdrew consent (n=70)
- Other exclusions (n=60)

N = 744 Patients Randomized 1:1

Transfemoral TAVR N = 373

Clinical Surveillance N = 371

*Pts could have ≥ 1 reason for screen failure

Patient Follow-up

THE PROGRESS TRIAL



93.7% of patients in the ITT population were available for primary effectiveness endpoint analysis at 2 years

*1 valve embolized into the LVOT on POD 1 requiring SAVR; 1 valve was explanted in the setting of urgent CABG on POD 189; both patients were alive at 2 years

Baseline Characteristics

THE PROGRESS TRIAL

Characteristics	TAVR N = 373	CS N = 371
Age, y	78.5 ± 6.5	78.3 ± 6.1
Female Sex	38.1%	40.2%
STS Score, %	3.1 ± 2.6	3.0 ± 2.6
Low-risk (heart team)	44.0%	47.2%
NYHA class III/IV	34.6%	36.4%
BMI, kg/m^2	29.5 ± 5.7	29.7 ± 5.9
Hypertension	90.3%	86.0%
Diabetes	36.2%	36.9%
PVD	11.0%	11.3%
Creatinine > 2 mg/dL	0.3%	1.1%
eGFR < 45 mL/min/1.73m^2	9.7%	12.5%

Characteristics	TAVR N = 373	CS N = 371
COPD	9.7%	11.6%
Prior MI	14.5%	14.3%
Prior PCI	30.6%	30.7%
Prior CABG	16.9%	11.6%
Prior Stroke	9.7%	7.8%
History of AFib	34.0%	32.1%
Prior PPM or ICD	12.3%	10.5%
LBBB	6.7%	7.5%
RBBB	16.6%	17.5%
KCCQ score	64.5 ± 23.8	63.9 ± 24.1
KCCQ < 60	42.8%	39.5%

Values presented as mean ± SD or % of pts

Baseline Characteristics

THE PROGRESS TRIAL

Characteristics	TAVR N = 373	CS N = 371
Age, y	78.5 ± 6.5	78.3 ± 6.1
Female Sex	38.1%	40.2%
STS Score, %	3.1 ± 2.6	3.0 ± 2.6
Low-risk (heart team)	44.0%	47.2%
NYHA class III/IV	34.6%	36.4%
BMI, kg/m^2	29.5 ± 5.7	29.7 ± 5.9
Hypertension	90.3%	86.0%
Diabetes	36.2%	36.9%
PVD	11.0%	11.3%
Creatinine > 2 mg/dL	0.3%	1.1%
eGFR < 45 mL/min/1.73m^2	9.7%	12.5%

Characteristics	TAVR N = 373	CS N = 371
COPD	9.7%	11.6%
Prior MI	14.5%	14.3%
Prior PCI	30.6%	30.7%
Prior CABG	16.9%	11.6%
Prior Stroke	9.7%	7.8%
History of AFib	34.0%	32.1%
Prior PPM or ICD	12.3%	10.5%
LBBB	6.7%	7.5%
RBBB	16.6%	17.5%
KCCQ score	64.5 ± 23.8	63.9 ± 24.1
KCCQ < 60	42.8%	39.5%

Values presented as mean ± SD or % of pts

Baseline Characteristics

THE PROGRESS TRIAL

Characteristics	TAVR N = 373	CS N = 371
Age, y	78.5 ± 6.5	78.3 ± 6.1
Female Sex	38.1%	40.2%
STS Score, %	3.1 ± 2.6	3.0 ± 2.6
Low-risk (heart team)	44.0%	47.2%
NYHA class III/IV	34.6%	36.4%
BMI, kg/m^2	29.5 ± 5.7	29.7 ± 5.9
Hypertension	90.3%	86.0%
Diabetes	36.2%	36.9%
PVD	11.0%	11.3%
Creatinine > 2 mg/dL	0.3%	1.1%
eGFR < 45 mL/min/1.73m^2	9.7%	12.5%

Characteristics	TAVR N = 373	CS N = 371
COPD	9.7%	11.6%
Prior MI	14.5%	14.3%
Prior PCI	30.6%	30.7%
Prior CABG	16.9%	11.6%
Prior Stroke	9.7%	7.8%
History of AFib	34.0%	32.1%
Prior PPM or ICD	12.3%	10.5%
LBBB	6.7%	7.5%
RBBB	16.6%	17.5%
KCCQ score	64.5 ± 23.8	63.9 ± 24.1
KCCQ < 60	42.8%	39.5%

Values presented as mean ± SD or % of pts

Baseline Characteristics

THE PROGRESS TRIAL

Characteristics	TAVR N = 373	CS N = 371
Age, y	78.5 ± 6.5	78.3 ± 6.1
Female Sex	38.1%	40.2%
STS Score, %	3.1 ± 2.6	3.0 ± 2.6
Low-risk (heart team)	44.0%	47.2%
NYHA class III/IV	34.6%	36.4%
BMI, kg/m^2	29.5 ± 5.7	29.7 ± 5.9
Hypertension	90.3%	86.0%
Diabetes	36.2%	36.9%
PVD	11.0%	11.3%
Creatinine > 2 mg/dL	0.3%	1.1%
eGFR < 45 mL/min/1.73m^2	9.7%	12.5%

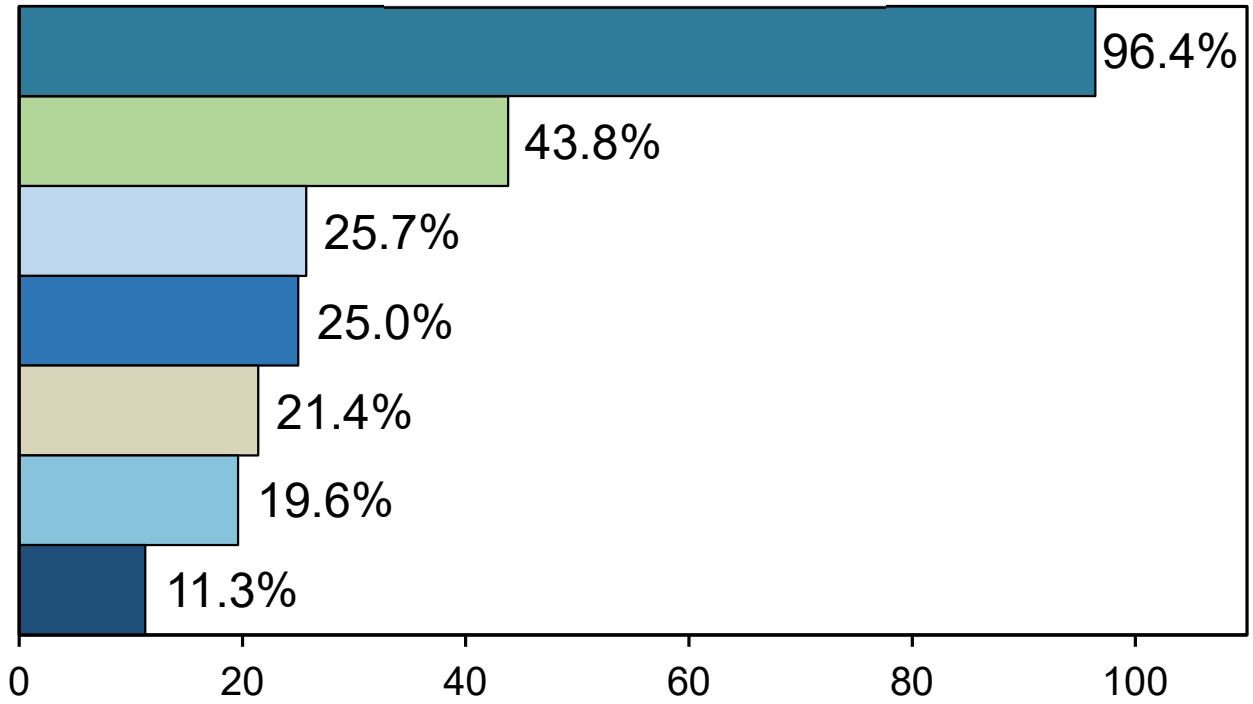
Characteristics	TAVR N = 373	CS N = 371
COPD	9.7%	11.6%
Prior MI	14.5%	14.3%
Prior PCI	30.6%	30.7%
Prior CABG	16.9%	11.6%
Prior Stroke	9.7%	7.8%
History of AFib	34.0%	32.1%
Prior PPM or ICD	12.3%	10.5%
LBBB	6.7%	7.5%
RBBB	16.6%	17.5%
KCCQ score	64.5 ± 23.8	63.9 ± 24.1
KCCQ < 60	42.8%	39.5%

Values presented as mean ± SD or % of pts

At-risk Features

THE PROGRESS TRIAL

7 At-risk Features	Distribution (%)
Symptoms (NYHA ≥ Class II)	96.4%
Diastolic Dysfunction (≥ Grade 2*)	43.8%
⬆ AV Calcium score†	25.7%
⬇ LVEF < 60%	25.0%
⬆ NT-Pro BNP > 3x Normal	21.4%
Persistent or Paroxysmal AF‡	19.6%
⬇ SVi < 35 mL/m²	11.3%



72% of patients had ≥ 2 at-risk features; 40% had ≥ 3

*Per ASE guidelines (*Nagueh et al. JASE 2016*); †Elevated defined as > 1200 AU for females and > 2000 AU for males per CT core lab; ‡Within 6 months prior to randomization

Echo & CT Characteristics

THE PROGRESS TRIAL

Characteristics*	TAVR N = 373	CS N = 371
AVA, cm^2	1.2 ± 0.2	1.2 ± 0.2
Mean gradient, mmHg	25.1 ± 5.1	25.4 ± 5.1
Peak velocity, m/s	3.3 ± 0.3	3.3 ± 0.3
Concordant mod. AS	90.3%	92.9%
LVEF, %	63.2 ± 9.8	63.6 ± 9.0
≥ 60%	75.3%	74.7%
50% to < 60%	15.5%	17.5%
> 40% to < 50%	5.1%	5.9%
≤ 40%	4.0%	1.9%
Bicuspid aortic valve	8.0%	6.7%

Characteristics*	TAVR N = 373	CS N = 371
SVi, mL/m^2	47.1 ± 10.7	47.5 ± 10.1
SVi < 35 $mL/m^{2\dagger}$	14.2%	8.4%
LAVi, mL/m^2	41.4 ± 16.4	40.5 ± 15.4
LAVi > 34 mL/m^2	63.9%	64.1%
LV mass index, g/m^2	97.2 ± 28.5	96.8 ± 27.1
LVH‡	31.5%	31.7%
LV GLS, %	18.3 ± 2.5	18.1 ± 2.7
LV GLS < 15%	8.0%	7.6%
AV Ca^{++} score, AU	1383 ± 785	1366 ± 736
Elevated Ca^{++} score§	28.2%	23.2%

*Echo and CT characteristics were not available for all pts; †P < 0.05; ‡LVH defined as > 95 mL/m^2 for females or > 115 mL/m^2 for males; §Elevated AV calcium score defined as > 1200 AU for females or > 2000 AU for males

Values presented as mean ± SD or % of pts

Echo & CT Characteristics

THE PROGRESS TRIAL

Characteristics*	TAVR N = 373	CS N = 371
AVA, cm^2	1.2 ± 0.2	1.2 ± 0.2
Mean gradient, mmHg	25.1 ± 5.1	25.4 ± 5.1
Peak velocity, m/s	3.3 ± 0.3	3.3 ± 0.3
Concordant mod. AS	90.3%	92.9%
LVEF, %	63.2 ± 9.8	63.6 ± 9.0
≥ 60%	75.3%	74.7%
50% to < 60%	15.5%	17.5%
> 40% to < 50%	5.1%	5.9%
≤ 40%	4.0%	1.9%
Bicuspid aortic valve	8.0%	6.7%

Characteristics*	TAVR N = 373	CS N = 371
SVi, mL/m^2	47.1 ± 10.7	47.5 ± 10.1
SVi < 35 $mL/m^{2\dagger}$	14.2%	8.4%
LAVi, mL/m^2	41.4 ± 16.4	40.5 ± 15.4
LAVi > 34 mL/m^2	63.9%	64.1%
LV mass index, g/m^2	97.2 ± 28.5	96.8 ± 27.1
LVH‡	31.5%	31.7%
LV GLS, %	18.3 ± 2.5	18.1 ± 2.7
LV GLS < 15%	8.0%	7.6%
AV Ca^{++} score, AU	1383 ± 785	1366 ± 736
Elevated Ca^{++} score§	28.2%	23.2%

*Echo and CT characteristics were not available for all pts; †P < 0.05; ‡LVH defined as > 95 mL/m^2 for females or > 115 mL/m^2 for males; §Elevated AV calcium score defined as > 1200 AU for females or > 2000 AU for males

Values presented as mean ± SD or % of pts

Echo & CT Characteristics

THE PROGRESS TRIAL

Characteristics*	TAVR N = 373	CS N = 371
AVA, cm^2	1.2 ± 0.2	1.2 ± 0.2
Mean gradient, mmHg	25.1 ± 5.1	25.4 ± 5.1
Peak velocity, m/s	3.3 ± 0.3	3.3 ± 0.3
Concordant mod. AS	90.3%	92.9%
LVEF, %	63.2 ± 9.8	63.6 ± 9.0
≥ 60%	75.3%	74.7%
50% to < 60%	15.5%	17.5%
> 40% to < 50%	5.1%	5.9%
≤ 40%	4.0%	1.9%
Bicuspid aortic valve	8.0%	6.7%

Characteristics*	TAVR N = 373	CS N = 371
SVi, mL/m^2	47.1 ± 10.7	47.5 ± 10.1
SVi < 35 $mL/m^{2\dagger}$	14.2%	8.4%
LAVi, mL/m^2	41.4 ± 16.4	40.5 ± 15.4
LAVi > 34 mL/m^2	63.9%	64.1%
LV mass index, g/m^2	97.2 ± 28.5	96.8 ± 27.1
LVH‡	31.5%	31.7%
LV GLS, %	18.3 ± 2.5	18.1 ± 2.7
LV GLS < 15%	8.0%	7.6%
AV Ca^{++} score, AU	1383 ± 785	1366 ± 736
Elevated Ca^{++} score§	28.2%	23.2%

*Echo and CT characteristics were not available for all pts; †P < 0.05; ‡LVH defined as > 95 mL/m^2 for females or > 115 mL/m^2 for males; §Elevated AV calcium score defined as > 1200 AU for females or > 2000 AU for males

Values presented as mean ± SD or % of pts

Echo & CT Characteristics

THE PROGRESS TRIAL

Characteristics*	TAVR N = 373	CS N = 371
AVA, cm^2	1.2 ± 0.2	1.2 ± 0.2
Mean gradient, mmHg	25.1 ± 5.1	25.4 ± 5.1
Peak velocity, m/s	3.3 ± 0.3	3.3 ± 0.3
Concordant mod. AS	90.3%	92.9%
LVEF, %	63.2 ± 9.8	63.6 ± 9.0
≥ 60%	75.3%	74.7%
50% to < 60%	15.5%	17.5%
> 40% to < 50%	5.1%	5.9%
≤ 40%	4.0%	1.9%
Bicuspid aortic valve	8.0%	6.7%

Characteristics*	TAVR N = 373	CS N = 371
SVi, mL/m^2	47.1 ± 10.7	47.5 ± 10.1
SVi < 35 mL/m^2†	14.2%	8.4%
LAVi, mL/m^2	41.4 ± 16.4	40.5 ± 15.4
LAVi > 34 mL/m^2	63.9%	64.1%
LV mass index, g/m^2	97.2 ± 28.5	96.8 ± 27.1
LVH‡	31.5%	31.7%
LV GLS, %	18.3 ± 2.5	18.1 ± 2.7
LV GLS < 15%	8.0%	7.6%
AV Ca^{++} score, AU	1383 ± 785	1366 ± 736
Elevated Ca^{++} score§	28.2%	23.2%

*Echo and CT characteristics were not available for all pts; †P < 0.05; ‡LVH defined as > 95 mL/m^2 for females or > 115 mL/m^2 for males; §Elevated AV calcium score defined as > 1200 AU for females or > 2000 AU for males

Values presented as mean ± SD or % of pts

Primary Safety Endpoint – 30 Days

Moderate AS with At-Risk Features

THE PROGRESS TRIAL

Composite Endpoint & Components	TAVR AT Population N = 358	P-value
Safety Endpoint Composite	**5.9%** *Upper 97.5% CL: 8.8%*	**< 0.001** *Tested vs 13.7% PG**
Death	0%	
Stroke *(all were non-disabling)*	0.8%	
Life-threatening bleeding *(none were fatal)*	0.6%	
Stage 4 AKI	0%	
Hosp. for device- or procedure-related complication†	5.6%	
Valve dysfunction requiring reintervention‡	0.3%	

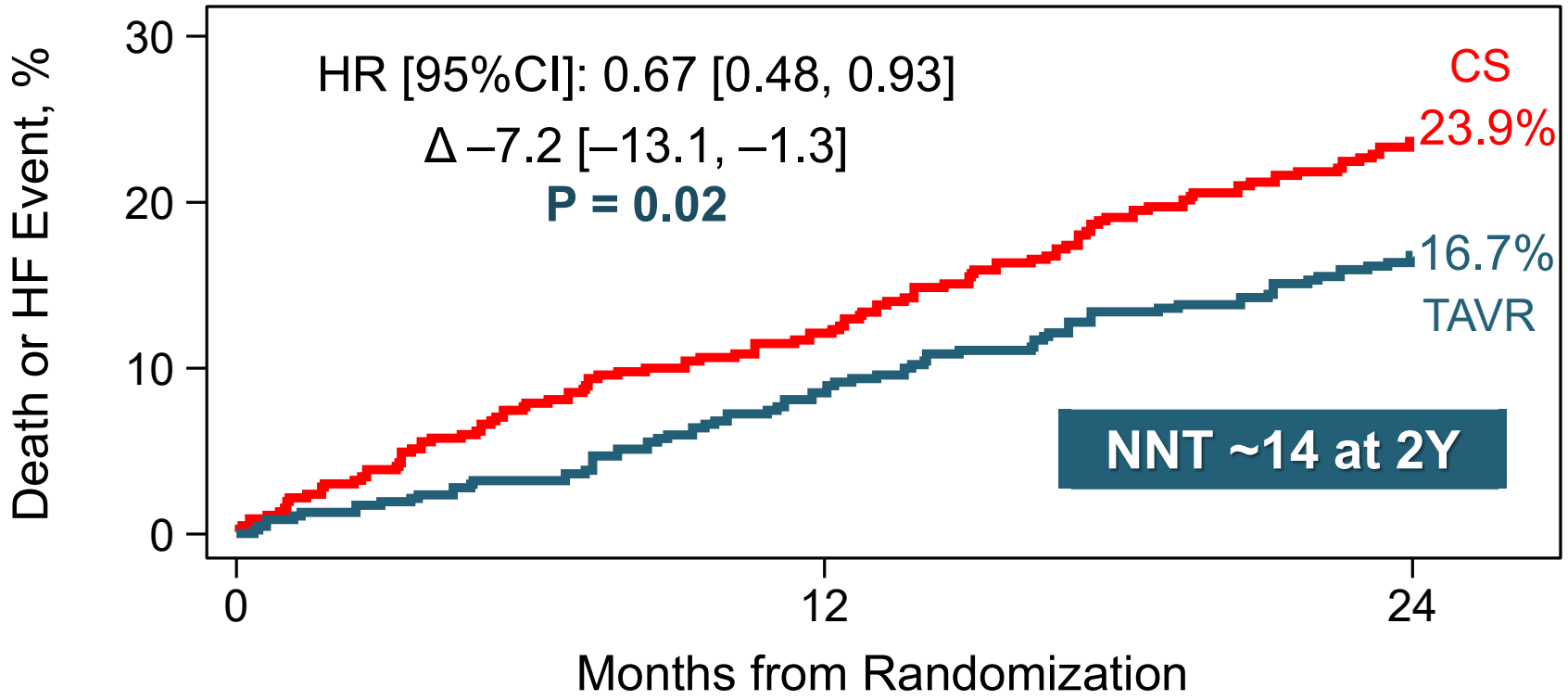
*Performance goal as described in *Genereux et al. Am Heart J 2026;* †Majority were for new pacemaker implantation/conduction system disturbances;
‡1 valve embolized into the LVOT on POD 1 requiring SAVR

Values presented as % of pts

Primary Effectiveness Endpoint – 2 Years

Moderate AS with At-Risk Features

THE PROGRESS TRIAL



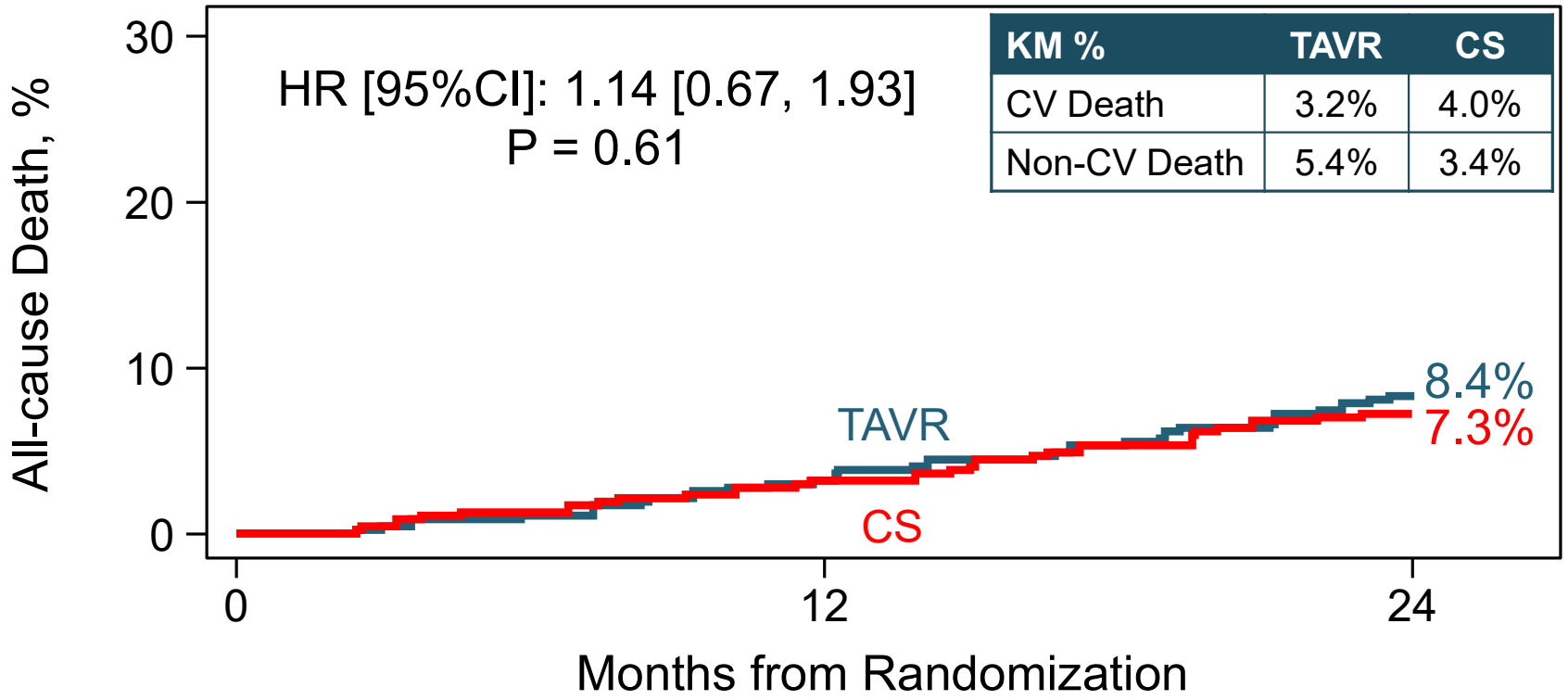
No. at risk:			
TAVR	373	329	296
CS	371	318	256

HF event = with or without hospitalization

All-cause Death

Moderate AS with At-Risk Features

THE PROGRESS TRIAL



KM %	TAVR	CS
CV Death	3.2%	4.0%
Non-CV Death	5.4%	3.4%

No. at risk:

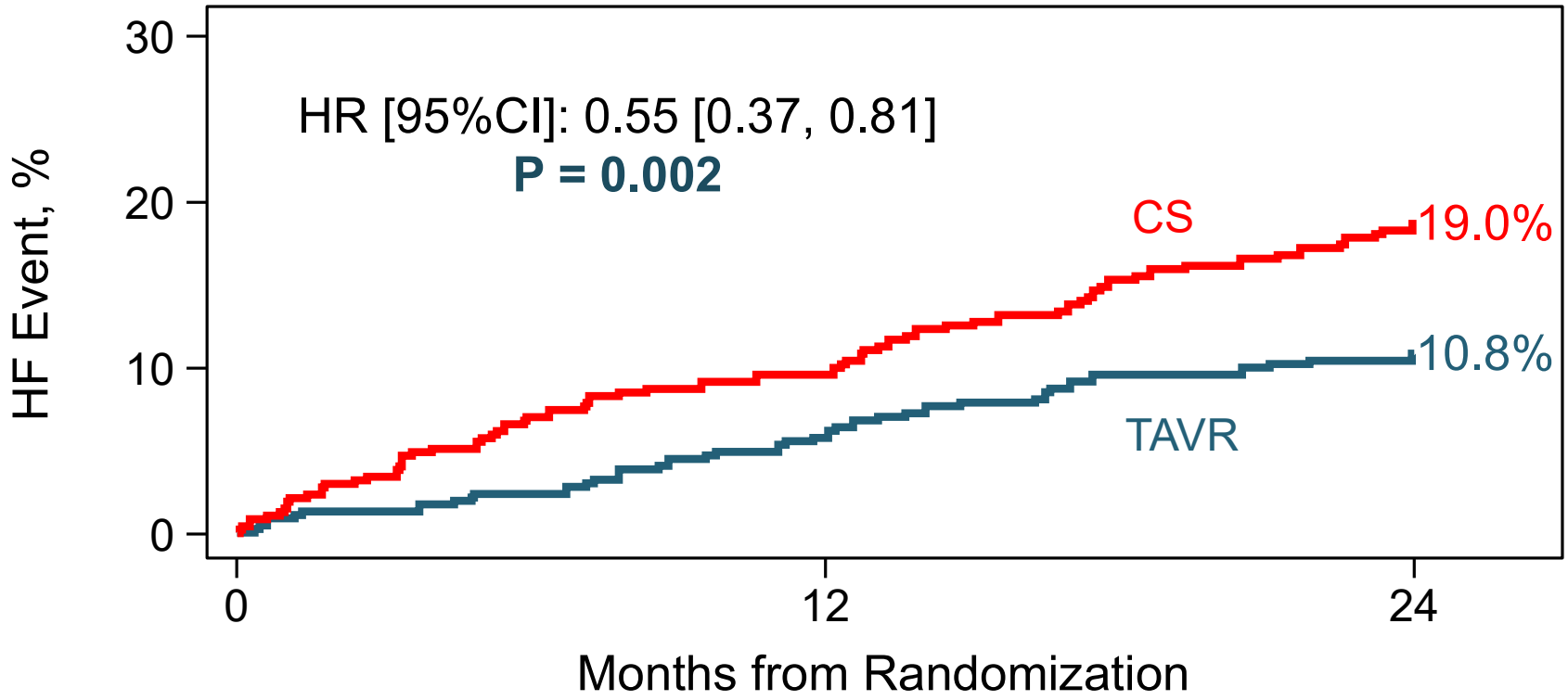
TAVR	373	348	326
CS	371	350	315

Exploratory P value based on the rate difference

Heart Failure Event

Moderate AS with At-Risk Features

THE PROGRESS TRIAL



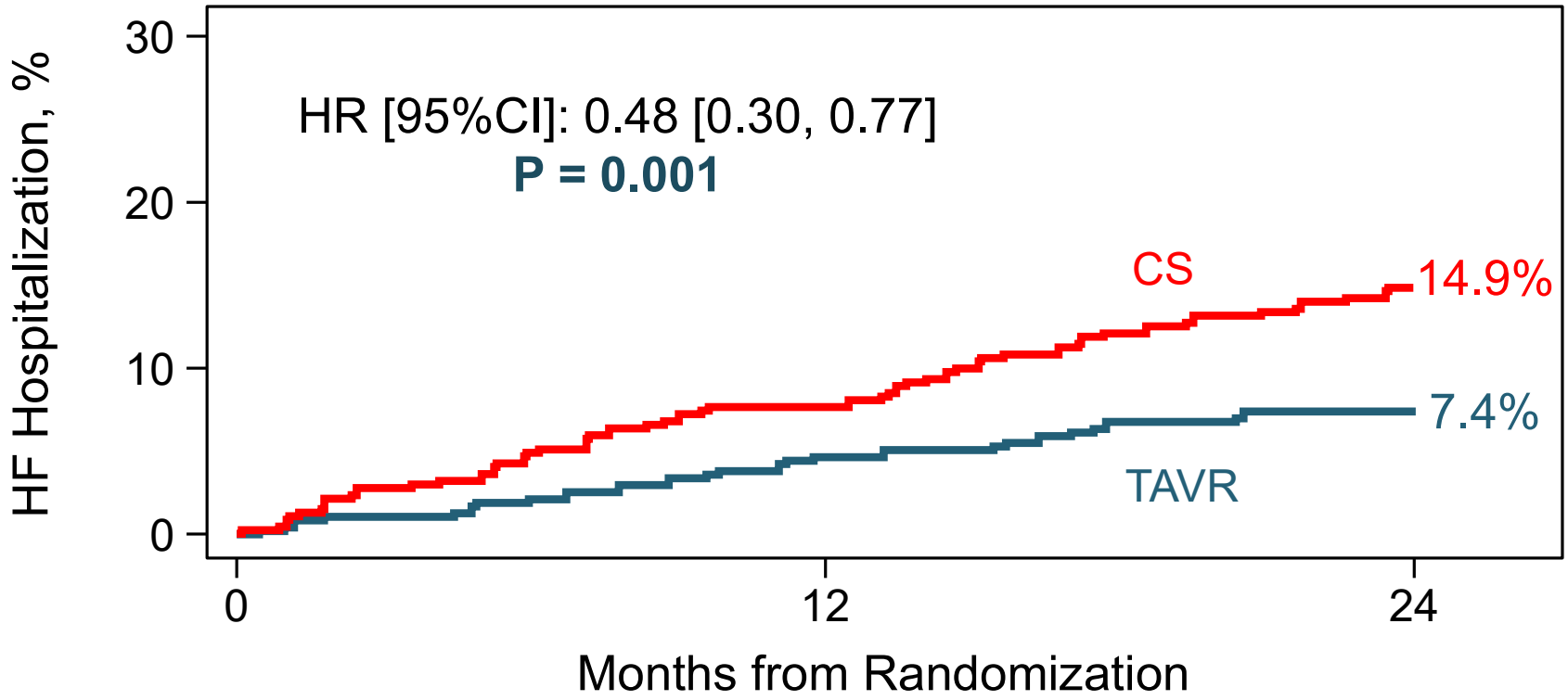
No. at risk:			
TAVR	373	329	296
CS	371	318	256

HF event = with or without hospitalization; exploratory P value based on the rate difference

Heart Failure Hospitalization

Moderate AS with At-Risk Features

THE PROGRESS TRIAL



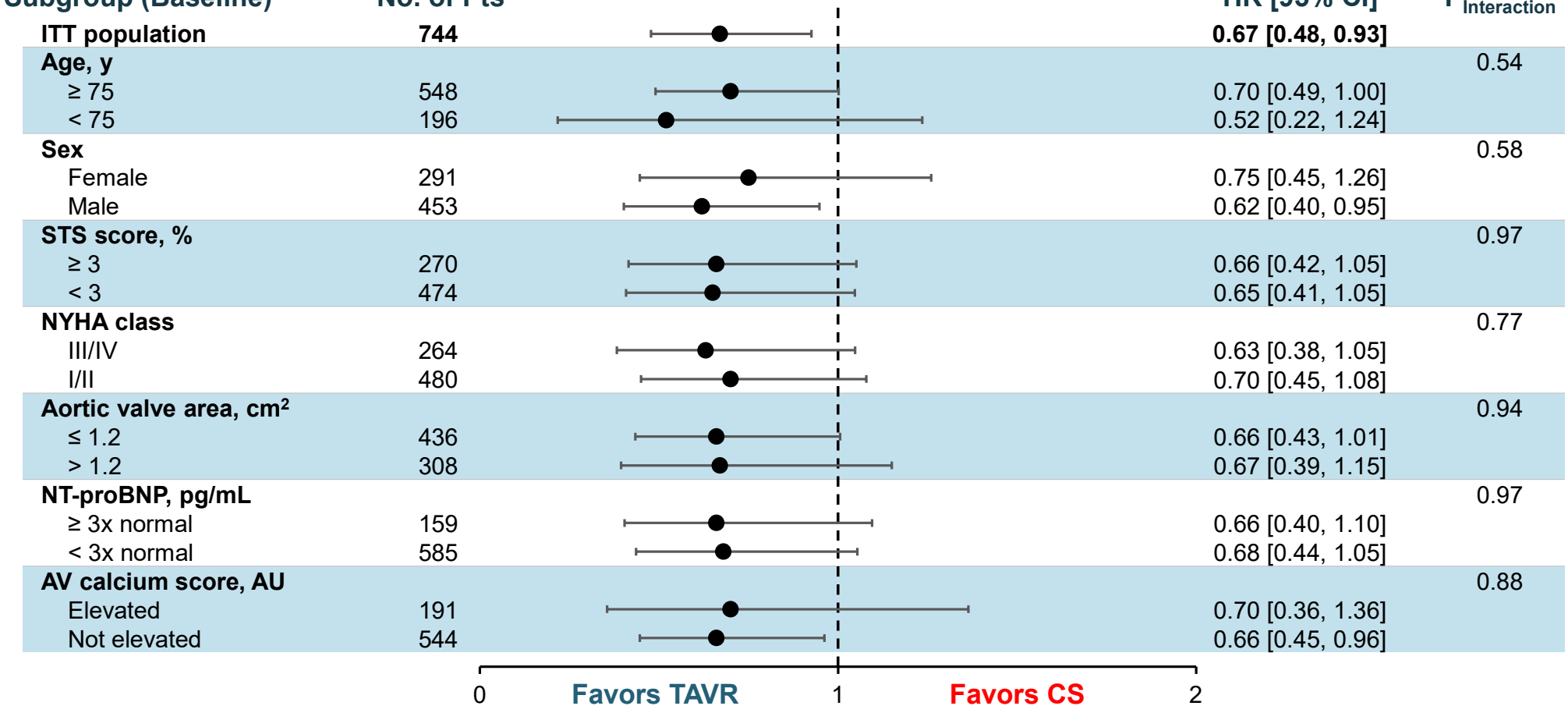
No. at risk:			
TAVR	373	333	308
CS	371	325	270

Nominal P value based on the rate difference for informative purposes

Primary Effectiveness Endpoint

The benefit of TAVR was consistent across all subgroups

THE PROGRESS TRIAL



Results were similar across additional baseline subgroups, including peak velocity ≥ 3 m/s, hx of AF, LVEF < 50%, cardiac damage stage 0-1,SVi < 35 mL/m², etc.

Pre-specified Secondary Endpoints

THE PROGRESS TRIAL

Hierarchical Endpoints at 2 Years		TAVR (N = 373)	CS (N = 371)	Rate Difference [95% CI]	P-value*
1	Death, stroke, or HF hospitalization	17.7%	23.3%	–5.6 [–11.5, 0.3]	0.07
2	Alive with a ≥ 10-point improvement in KCCQ score†	39.0%	23.2%	15.7 [8.8, 22.6]	-
3	HF hospitalization	7.4%	14.9%	–7.5 [–12.2, –2.9]	-
4	LV mass index (g/m^2)	97.1 ± 28.3	101.1 ± 30.1	–3.7 [–7.8, 0.5]	-
5	Diastolic dysfunction ≥ Grade 2‡	38.9%	36.5%	2.4 [–5.7, 10.6]	-

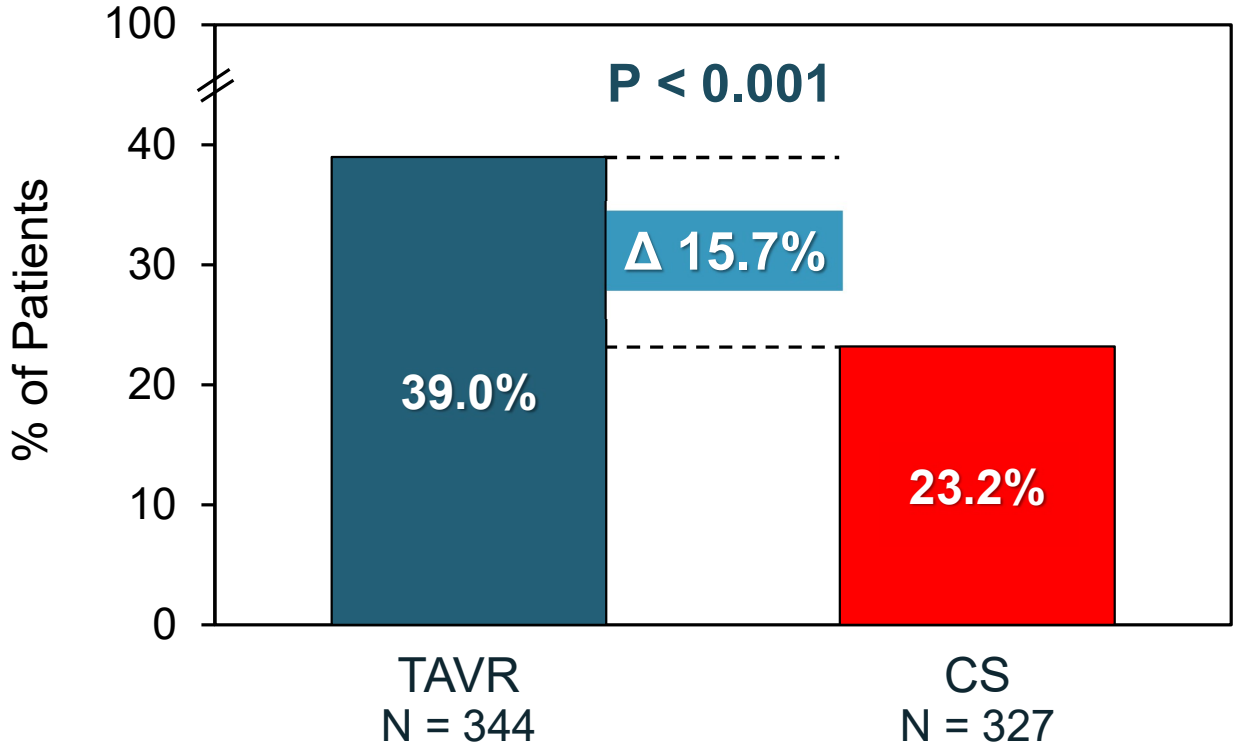
*P-values are two-sided, tested at an alpha level of 0.05; †Improvement from baseline at 1 and 2 years; ‡Per ASE guidelines (*Nagueh et al. JASE 2016)*

Values presented as KM% (endpoints 1 & 3), % of pts (endpoints 2 & 5), or mean ± SD (endpoint 4)

Quality of Life and Health Status

THE PROGRESS TRIAL

Proportion of patients alive with an improvement of ≥ 10 points in KCCQ score at 1 and 2 years

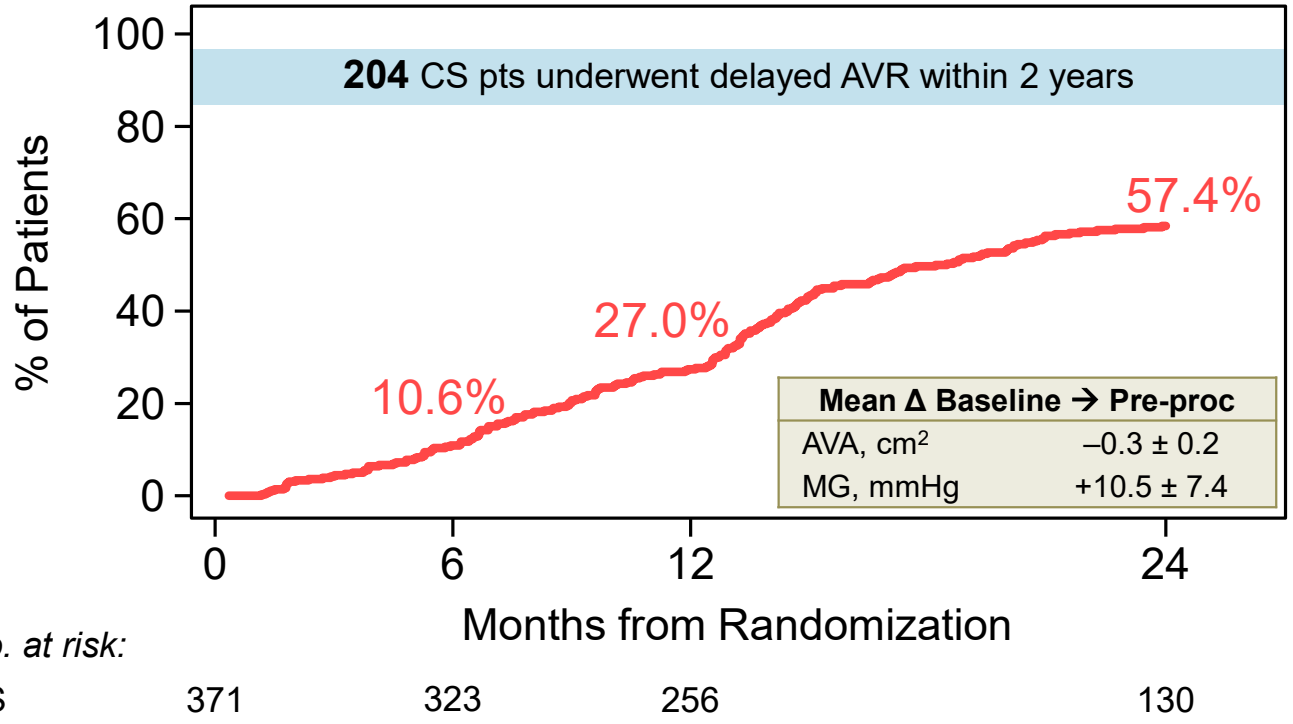


Nominal P value for informative purposes

Clinical Surveillance with Delayed AVR

THE PROGRESS TRIAL

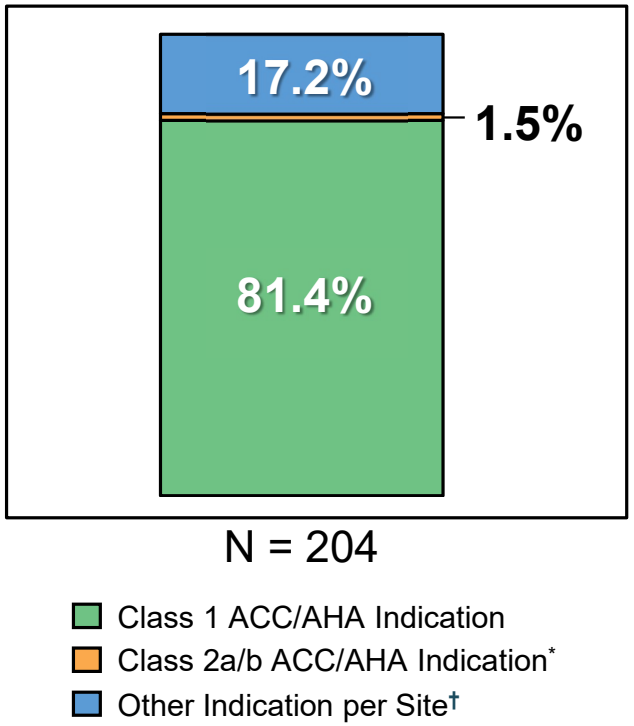
Timing of Delayed AVR



No. at risk:

CS	371	323	256	130

Indication for Delayed AVR



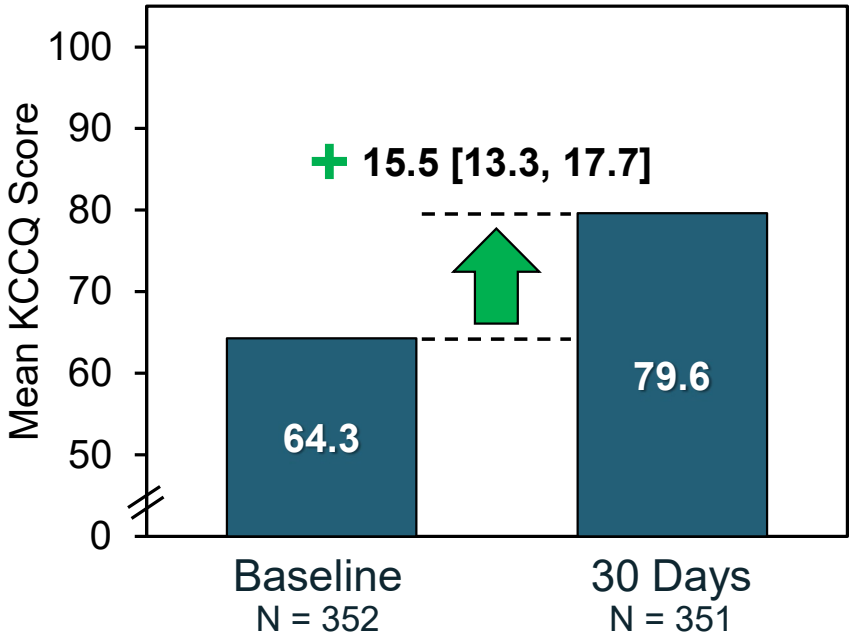
Among patients who underwent delayed AVR, > 80% progressed to severe AS

*No patients had a Class 2a indication through 2 years. †Other reasons included HF, symptom, and/or AS progression, increased NT-proBNP, elevated Ca+ score, etc.

KCCQ Improvement 30 Days Post-AVR

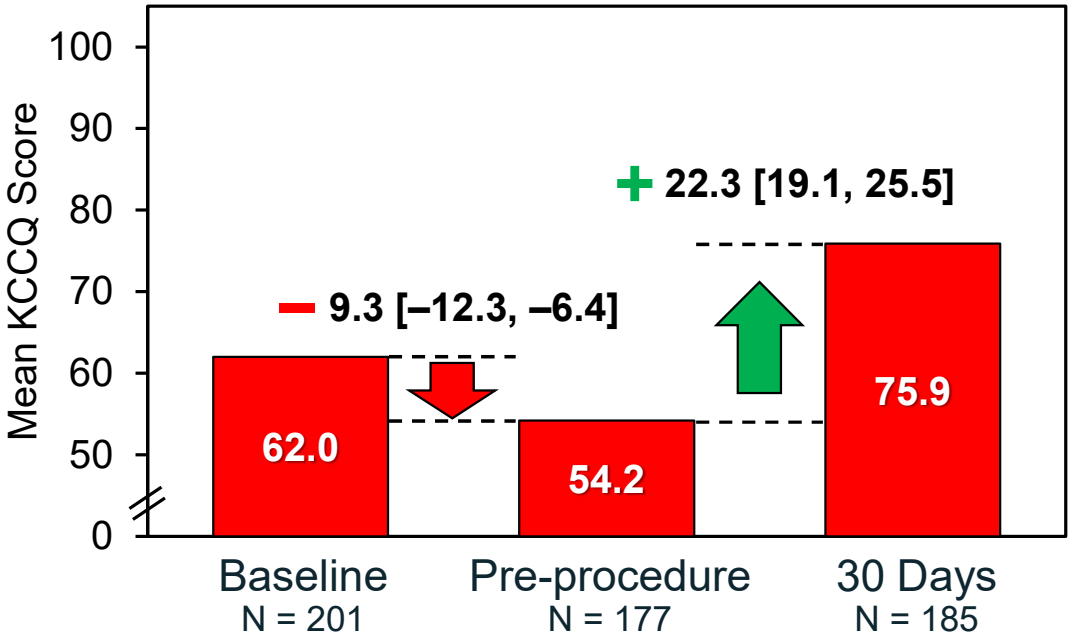
THE PROGRESS TRIAL

Randomized to TAVR*



Immediate and clinically-significant improvement in KCCQ score 30 days post-TAVR

Randomized to CS with Delayed AVR†



Decline in KCCQ score followed by a significant improvement 30 days post-AVR

*Randomized to TAVR and received the study valve; †Within 2 years

30-Day Outcomes in Patients with AVR

THE PROGRESS TRIAL

Clinical Outcomes	TAVR AT Population N = 358	CS with Delayed AVR* N = 204
Death	0%	0.5%
Cardiovascular	0%	0%
Non-cardiovascular	0%	0.5%
Stroke	0.8%	2.5%
Disabling stroke	0%	1.5%
Non-disabling stroke	0.8%	1.0%
Life-threatening or fatal bleeding	0.6%	2.5%
Major vascular complications	0.6%	1.5%
New onset atrial fibrillation†	4.6%	6.1%
New permanent pacemaker†	13.0%	10.4%
Stage 4 AKI	0%	0.5%

*Within 2 years of randomization; †Estimated in patients without a history of the outcome at baseline. For CS patients who underwent delayed AVR within 2 years, "baseline" refers to the pre-procedure visit.

Values presented as KM% (no. of pts)

Limitations

THE PROGRESS TRIAL

- Findings apply to the study population
  - *≥ 65 years, ≥ 1 at-risk feature, and suitable for TF-TAVR with the study valve*
- The rigorous clinical surveillance in PROGRESS may have facilitated earlier identification of disease progression than in real-world practice
- Heart failure GDMT optimization was not mandated in PROGRESS, mainly due to the limited evidence and lack of guideline recommendations for patients with AS
- Outcomes are limited to 2-year follow-up; longer follow-up may provide additional insights into the risks and benefits of earlier intervention

Conclusions

THE PROGRESS TRIAL

Among patients with moderate AS and at-risk features, a strategy of TAVR compared to rigorous clinical surveillance:

- Demonstrated excellent safety, with **0% mortality** and **0% disabling strokes at 30 days**
- Was **superior for the primary endpoint** of death or HF event at 2 years
- **Reduced HF hospitalizations by 52%** at 2 years
- **Improved quality of life** and prevented a meaningful decline in health status

Clinical Implications

THE PROGRESS TRIAL

- **Moderate AS is not benign,** and these patients would benefit from earlier referral to a valve clinic for comprehensive evaluation to establish the optimal management strategy
- Rather than waiting for progression to severe AS, **PROGRESS supports TAVR** for patients with moderate AS and at-risk features

THANK YOU!

To all the patients, sites, and investigators who participated in the PROGRESS trial

Just Published in NEJM

THE PROGRESS TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TAVR in Patients with Moderate Aortic Stenosis with At-Risk Features

P. Généreux,[1] R.R. Makkar,[2] P. Pibarot,[3] J.J. Bax,[4] B.R. Lindman,[5] K. Muhammad,[6] J.B. Oldemeyer,[7] M. Pirwitz,[8,9] C.M. Barker,[5] V.H. Thourani,[10] P.K. Yadav,[10] R. Rodriguez,[11] J. Strote,[7] R. Sakhuja,[12-14] R. Khalil,[15] R. Sharma,[16] A. Chhatriwalla,[17] J.M. Mishell,[18] B. Kar,[19] S. Gafoor,[20] J. Walsh,[21] D. Spoon,[22] A. Frutkin,[23] A. Pop,[24] N.M. Van Mieghem,[25,26] R. Satpathy,[27] K. Ando,[28] J. Montarello,[29] J. Webb,[30] S. Vemulapalli,[31] D.J. Cohen,[32,33] A. Gupta,[2] B. Park,[34] H. Prince,[34] P. Blanke,[30] M. Mack,[35] and M.B. Leon,[33,36] for the PROGRESS Trial Investigators*

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,

Important Safety Information (continued)

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.

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

Important Safety Information (continued)

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.

Important Safety Information (continued)

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, the stylized E logo, Edwards SAPIEN, Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, PROGRESS, The PROGRESS Trial logo, 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.

© 2026 Edwards Lifesciences Corporation. All rights reserved. PP--US-13375 v1.0

Edwards Lifesciences • One Edwards Way, Irvine CA 92614 USA • edwards.com

Edwards