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

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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

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- 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

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

Study Design

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

At least 1 at-risk feature

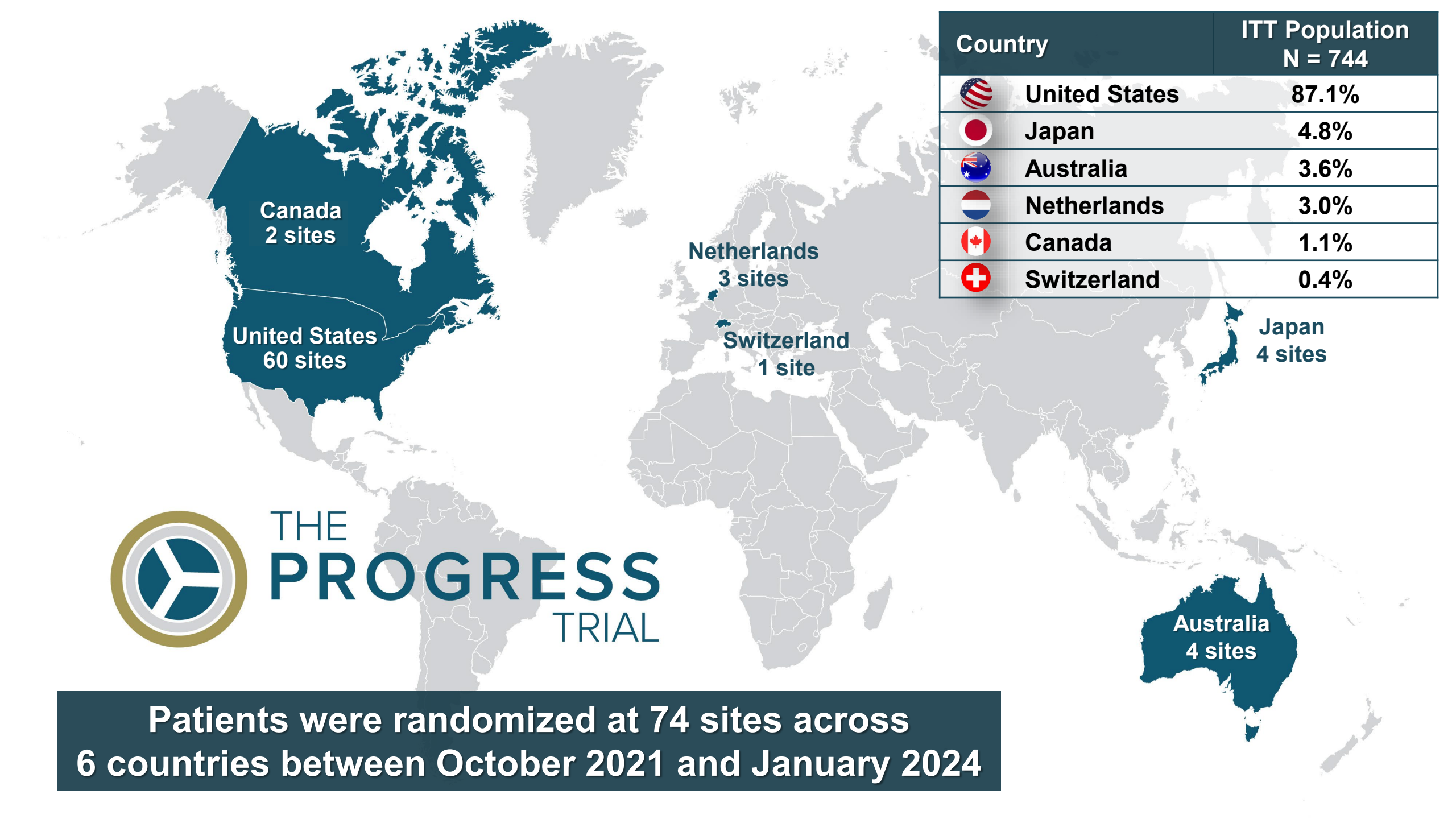
Randomized 1:1 (~750 pts)

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%

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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



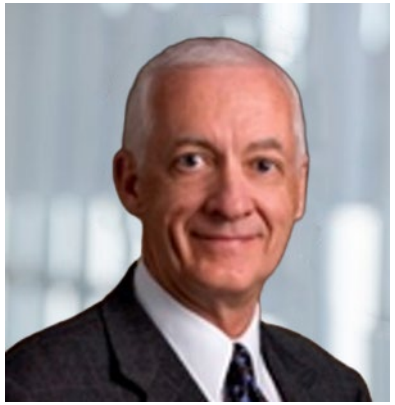
Jeroen J Bax, MD, PhD
NPI
Steering Committee



Philippe Pibarot, DVM, PhD
Echo Core Lab
Steering Committee



Brian Lindman, MD, MSc
Biomarker Core Lab



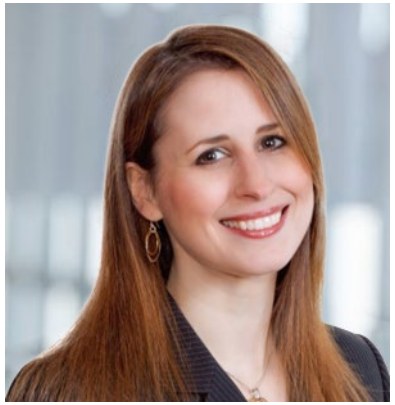
Michael Mack, MD
Steering Committee



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

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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

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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:

DISCORDANT Moderate AS

Defined as one criteria (AVA / AVAi or V_{peak} / MG) not in the moderate AS range

Reduced LVEF < 50%

Dobutamine Stress Echo (DSE)

Concordant moderate AS criteria met during DSE

DSE Inconclusive

Preserved LVEF ≥ 50%

Aortic Valve Calcium score not in the severe range

AV Ca^{++} < 1,200 AU for females

AV Ca^{++} < 2,000 AU for males

9% of enrolled patients had discordant moderate AS

MODERATE AS – Eligible for trial enrollment

Primary Endpoints

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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

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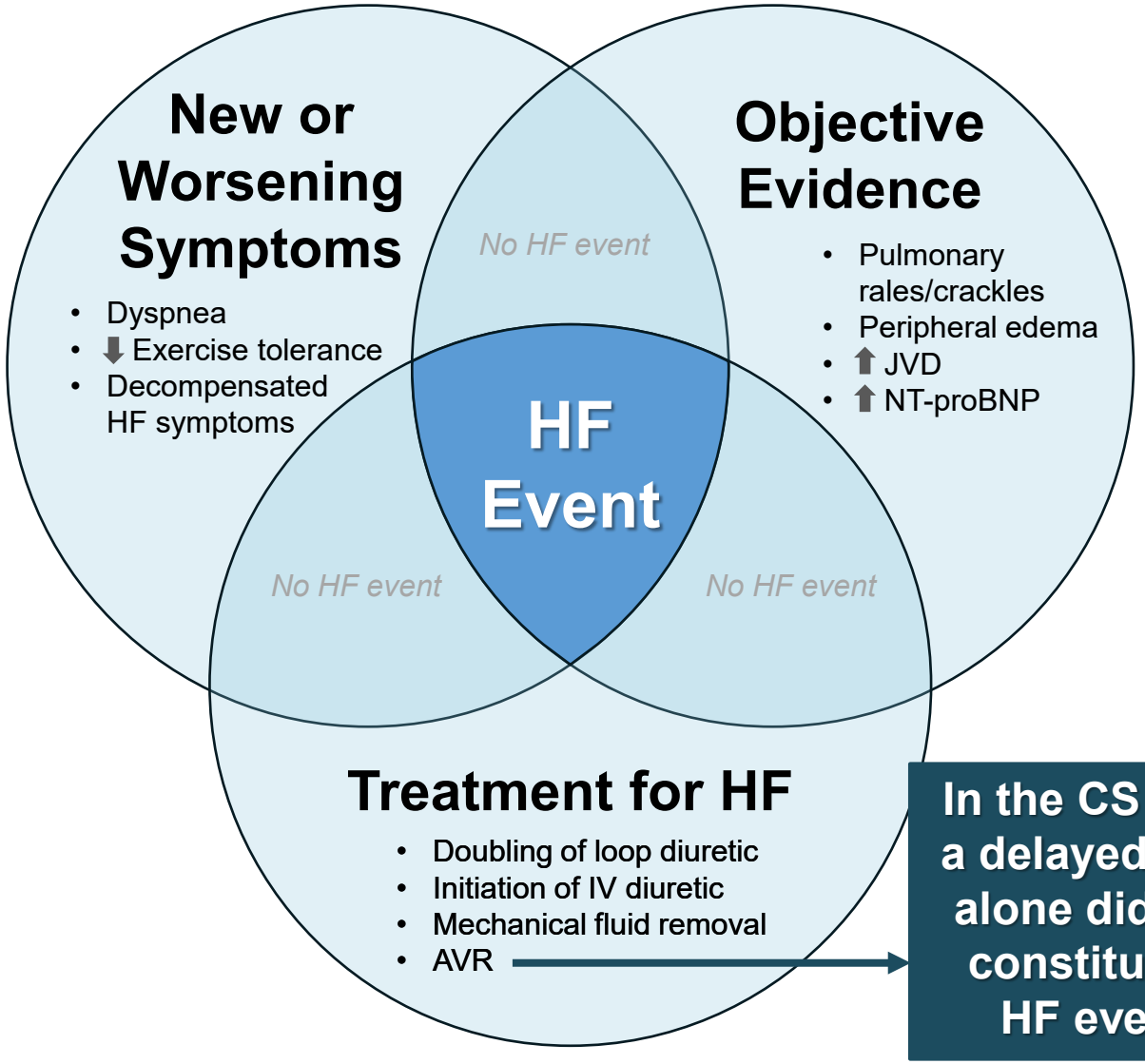
- To be considered a HF event, **ALL 3 criteria** had to be present*:
  1. **New or worsening HF symptoms**
  2. **At least 2 objective criteria** of new or worsening HF (physical, laboratory, imaging, and/or invasive findings)
  3. **Escalation** of HF treatment
- **HF hospitalization** was defined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

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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

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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

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Randomized to TAVR N = 373	Randomized to CS N = 371
11 Withdrew **2** Study THV explants*	**10** Withdrew
1-year Follow-up **N = 360 (96.5%)**	**1-year Follow-up** **N = 361 (97.3%)**
2 Withdrew **2** Missed visits	**18** Withdrew **2** Missed visits
2-year Follow-up **N = 356 (95.4%)**	**2-year Follow-up** **N = 341 (91.9%)**

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

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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

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At-risk Features

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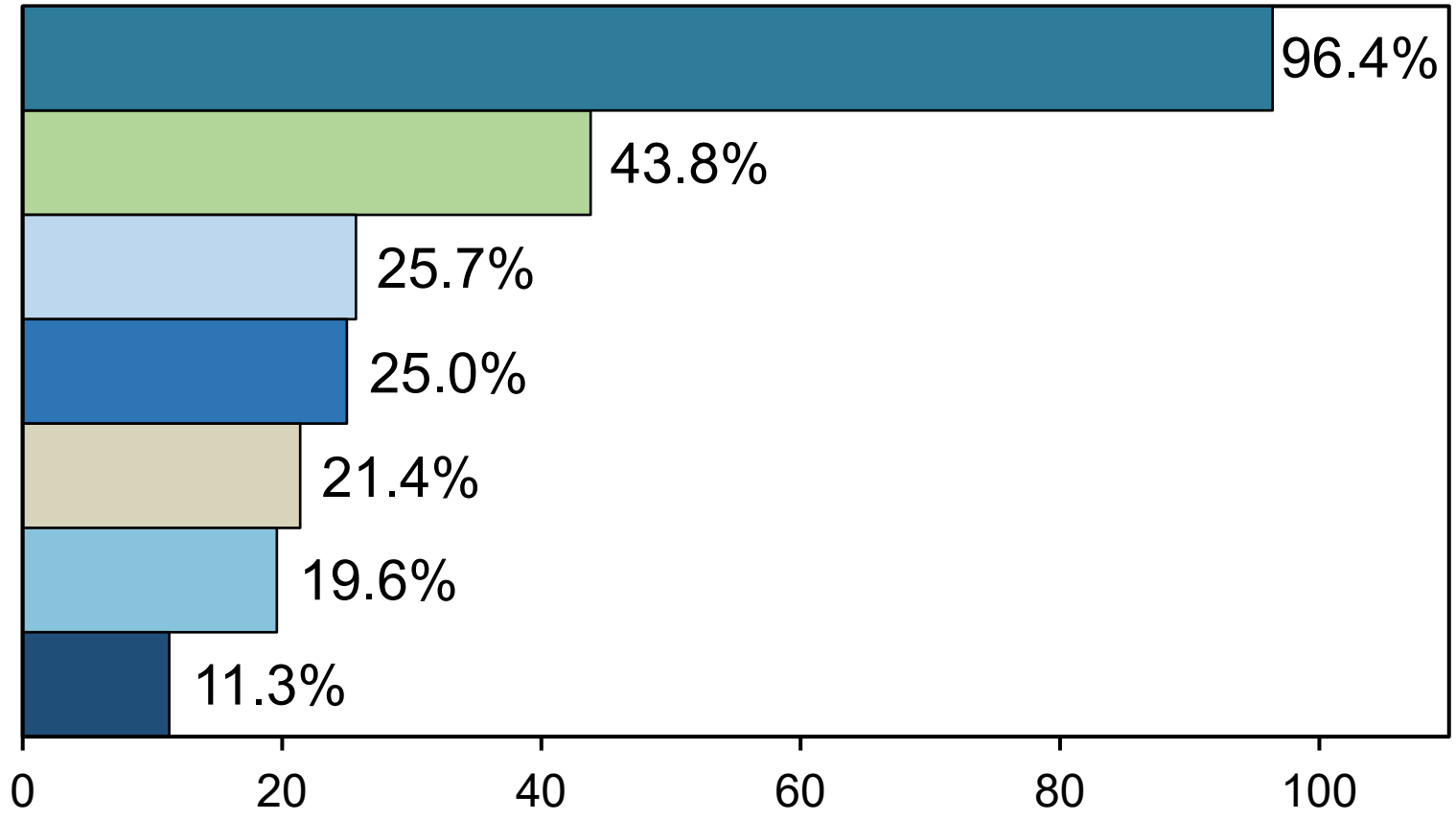
7 At-risk Features	Distribution (%)
Symptoms (NYHA ≥ Class II)	96.4%
Diastolic Dysfunction (≥ Grade 2*)	43.8%
⬆ AV Calcium score†	25.7%
⬇ LVEF < 60%	25.0%
⬆ NT-Pro BNP > 3x Normal	21.4%
Persistent or Paroxysmal AF‡	19.6%
⬇ SVi < 35 mL/m²	11.3%



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

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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

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Primary Safety Endpoint – 30 Days

Moderate AS with At-Risk Features

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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

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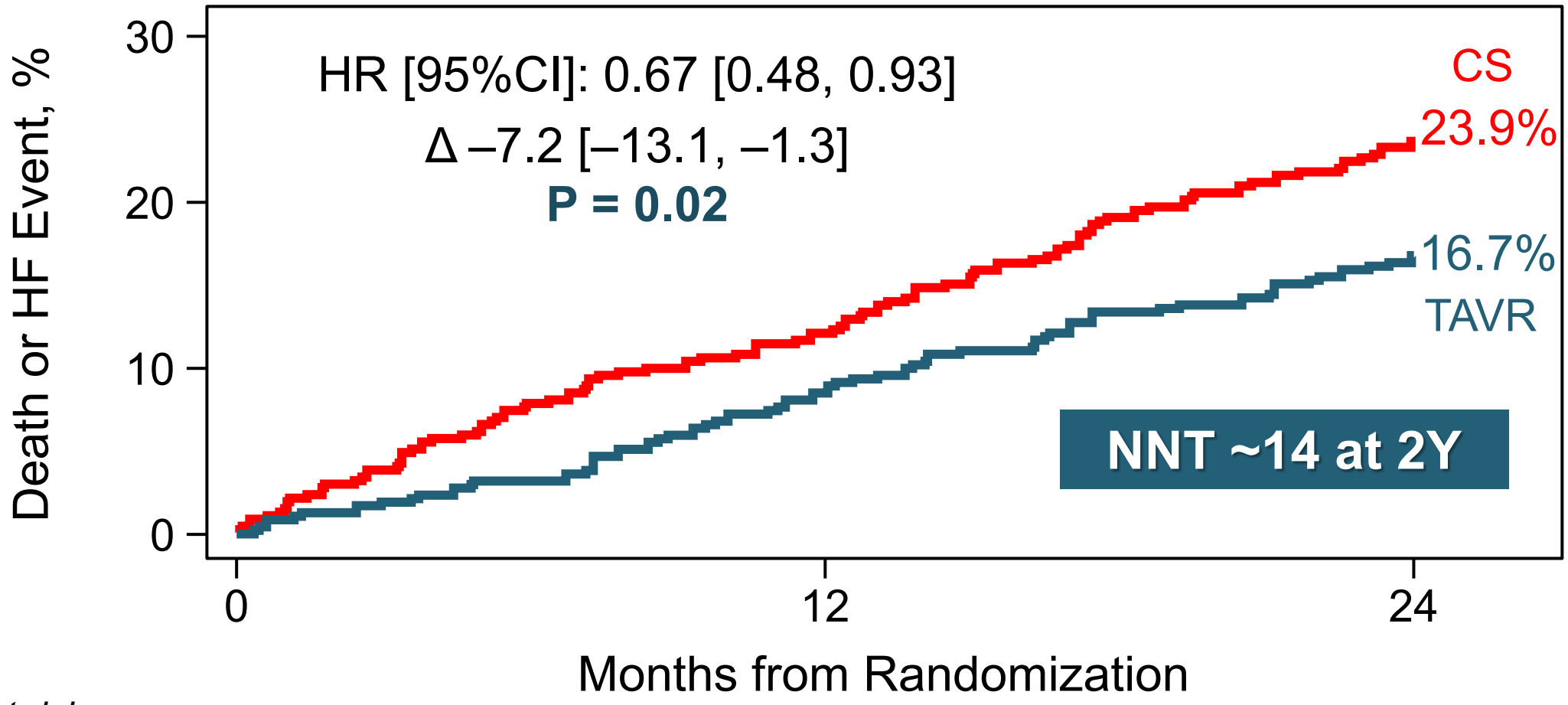

No. at risk:			
TAVR	373	329	296
CS	371	318	256

HF event = with or without hospitalization

All-cause Death

Moderate AS with At-Risk Features

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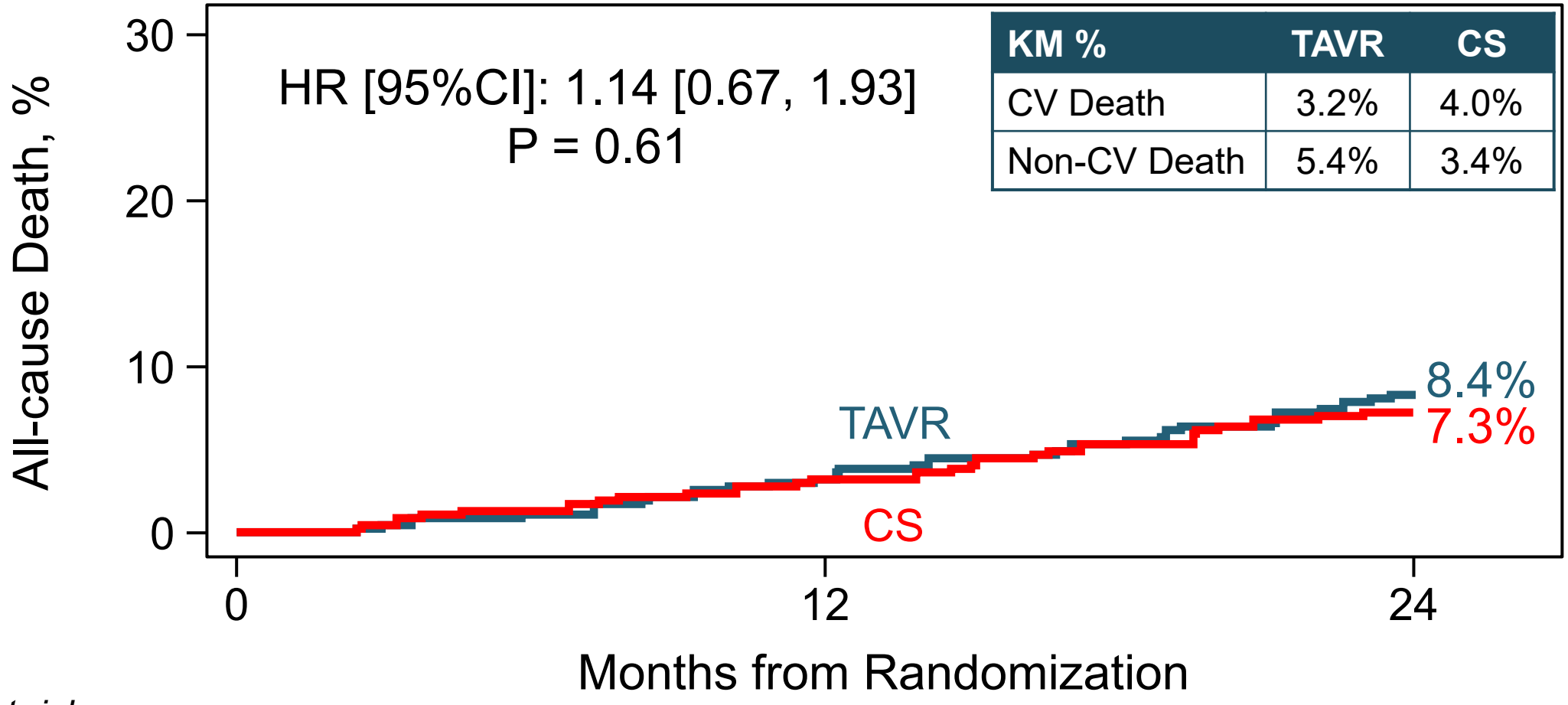

KM %	TAVR	CS
CV Death	3.2%	4.0%
Non-CV Death	5.4%	3.4%

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

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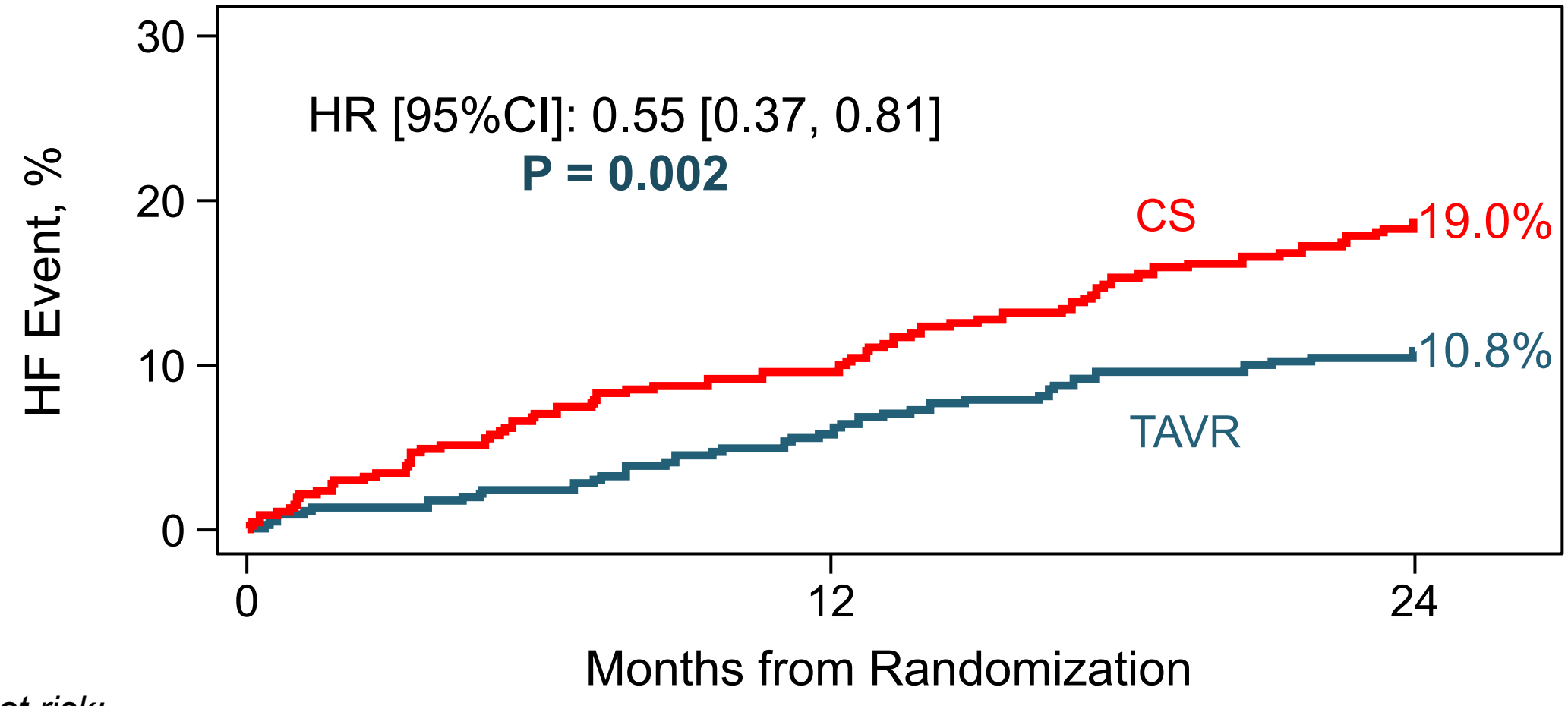

No. at risk:			
TAVR	373	329	296
CS	371	318	256

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

Heart Failure Hospitalization

Moderate AS with At-Risk Features

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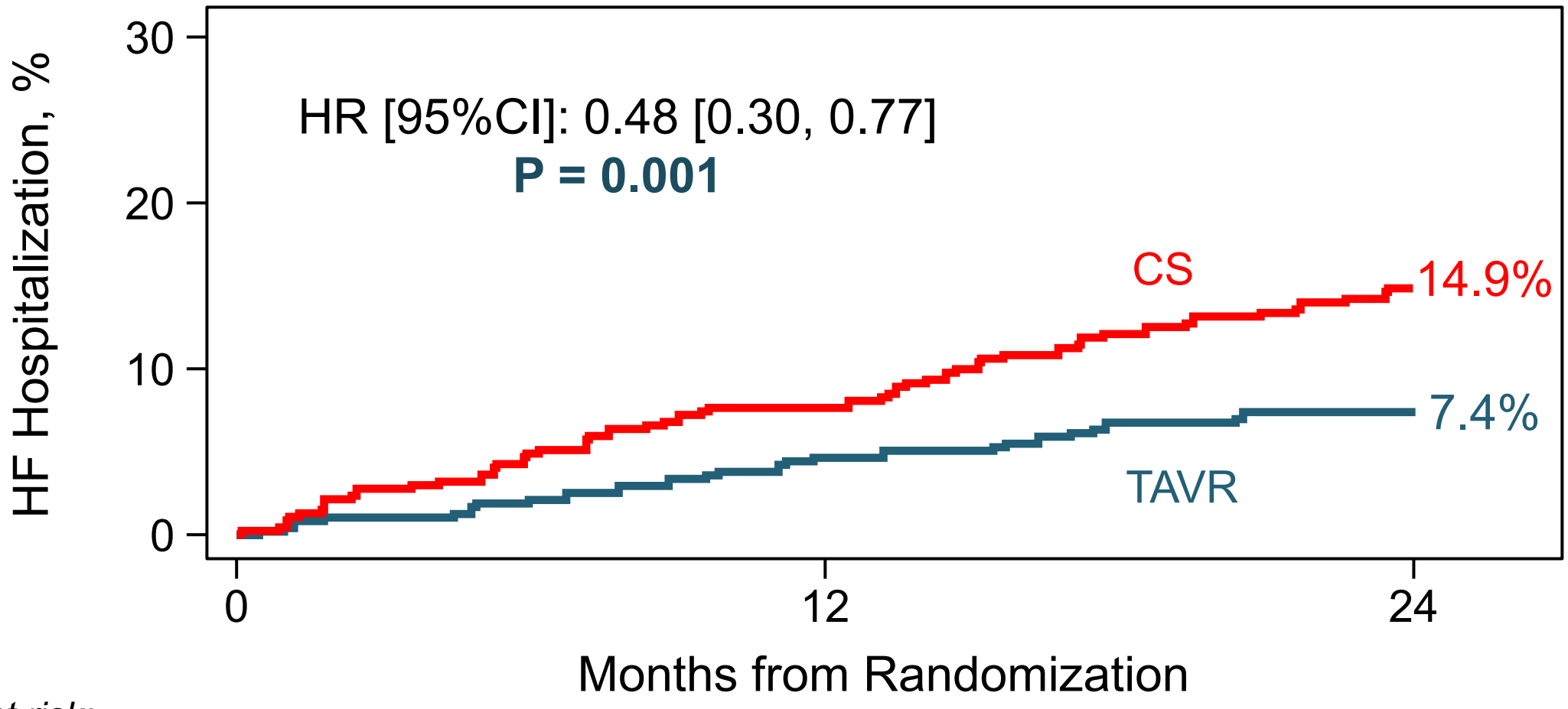

No. at risk:			
TAVR	373	333	308
CS	371	325	270

Nominal P value based on the rate difference for informative purposes

Primary Effectiveness Endpoint

The benefit of TAVR was consistent across all subgroups

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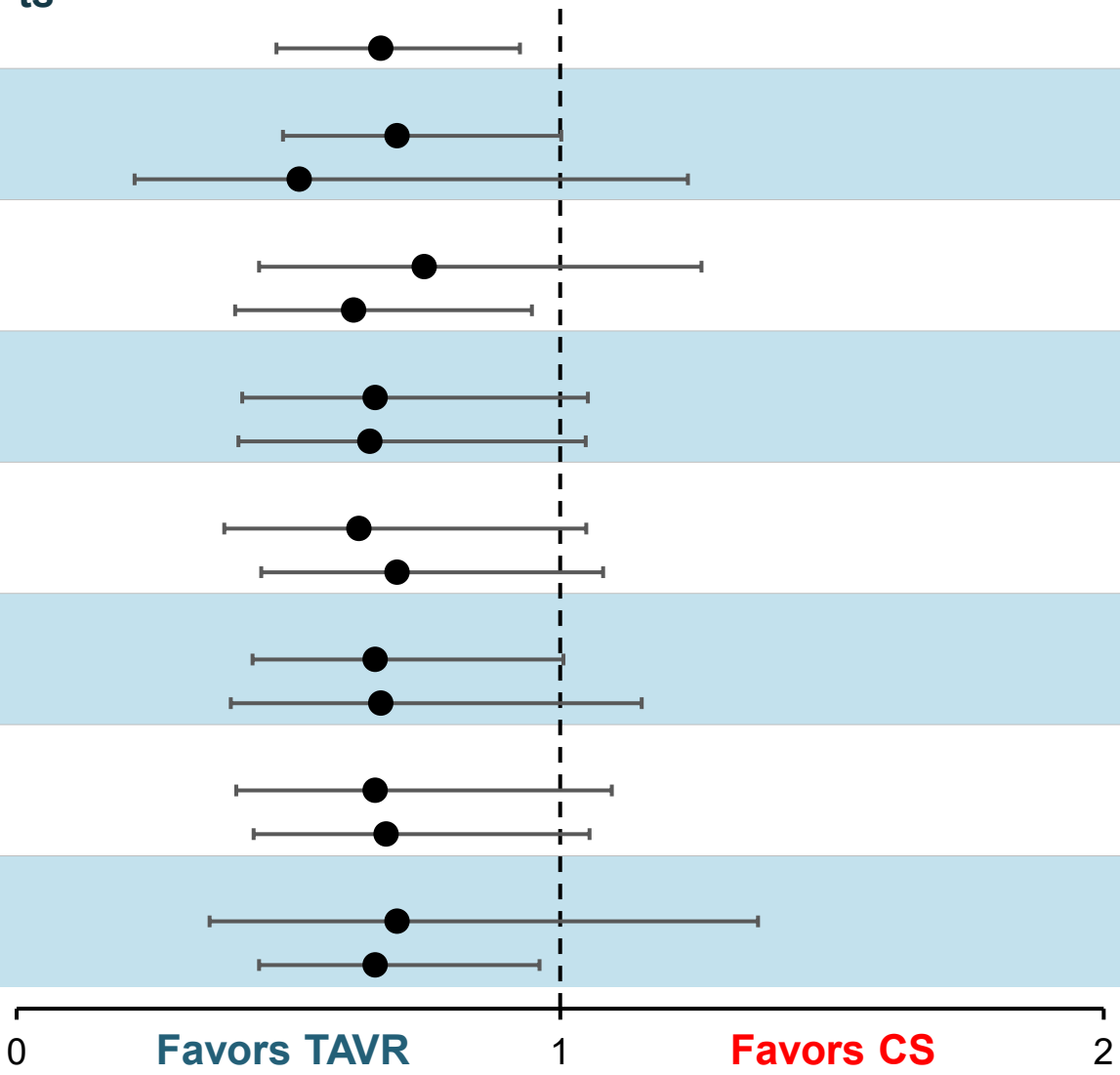
Subgroup (Baseline)	No. of Pts	HR [95% CI]	$P_{Interaction}$
ITT population	**744**	**0.67 [0.48, 0.93]**	
Age, y			0.54
≥ 75	548	0.70 [0.49, 1.00]	
< 75	196	0.52 [0.22, 1.24]	
Sex			0.58
Female	291	0.75 [0.45, 1.26]	
Male	453	0.62 [0.40, 0.95]	
STS score, %			0.97
≥ 3	270	0.66 [0.42, 1.05]	
< 3	474	0.65 [0.41, 1.05]	
NYHA class			0.77
III/IV	264	0.63 [0.38, 1.05]	
I/II	480	0.70 [0.45, 1.08]	
Aortic valve area, cm^2			0.94
≤ 1.2	436	0.66 [0.43, 1.01]	
> 1.2	308	0.67 [0.39, 1.15]	
NT-proBNP, pg/mL			0.97
≥ 3x normal	159	0.66 [0.40, 1.10]	
< 3x normal	585	0.68 [0.44, 1.05]	
AV calcium score, AU			0.88
Elevated	191	0.70 [0.36, 1.36]	
Not elevated	544	0.66 [0.45, 0.96]	



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/m^2, etc.

Pre-specified Secondary Endpoints

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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

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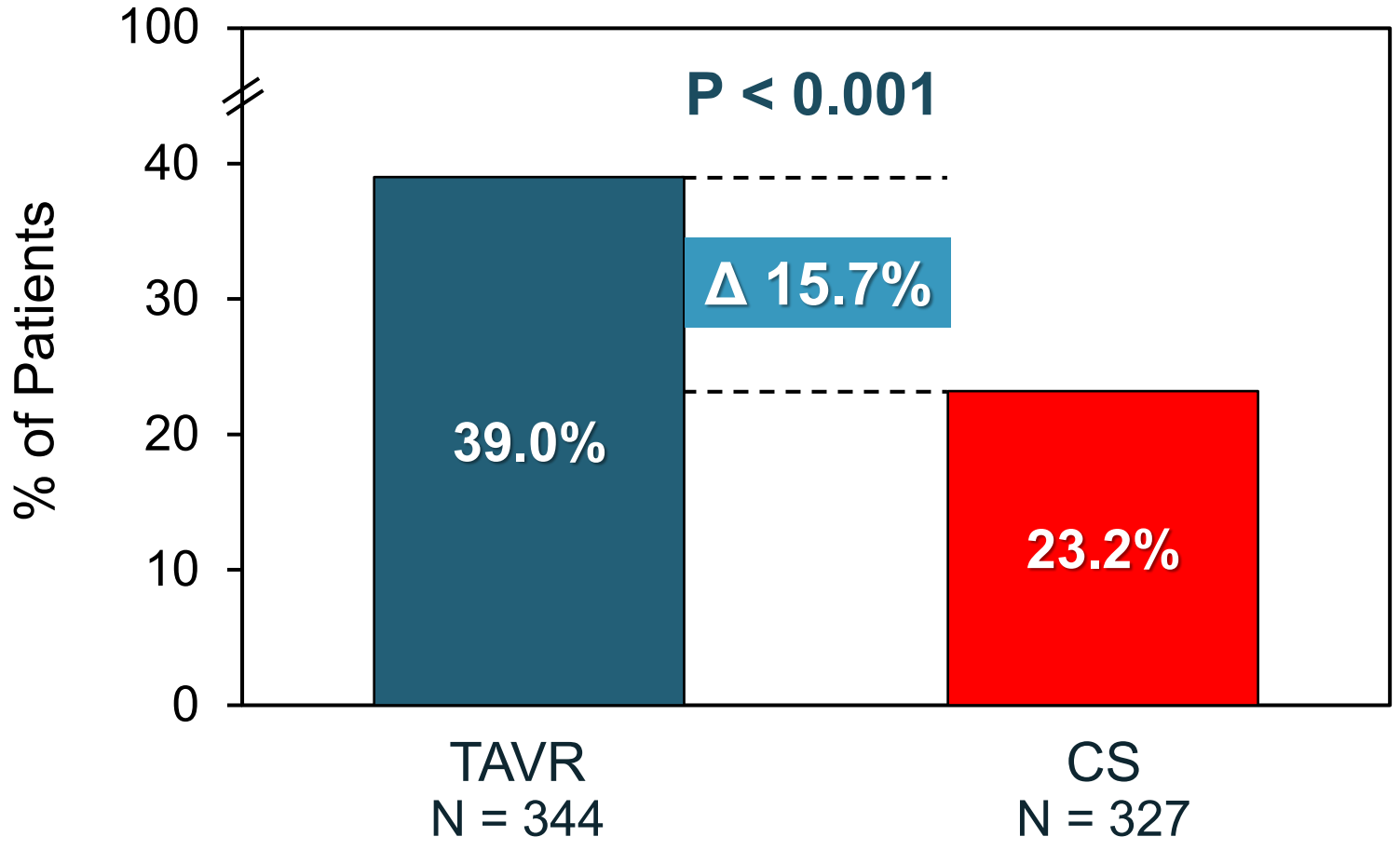
Proportion of patients alive with an improvement of ≥ 10 points in KCCQ score at 1 and 2 years



Nominal P value for informative purposes

Clinical Surveillance with Delayed AVR

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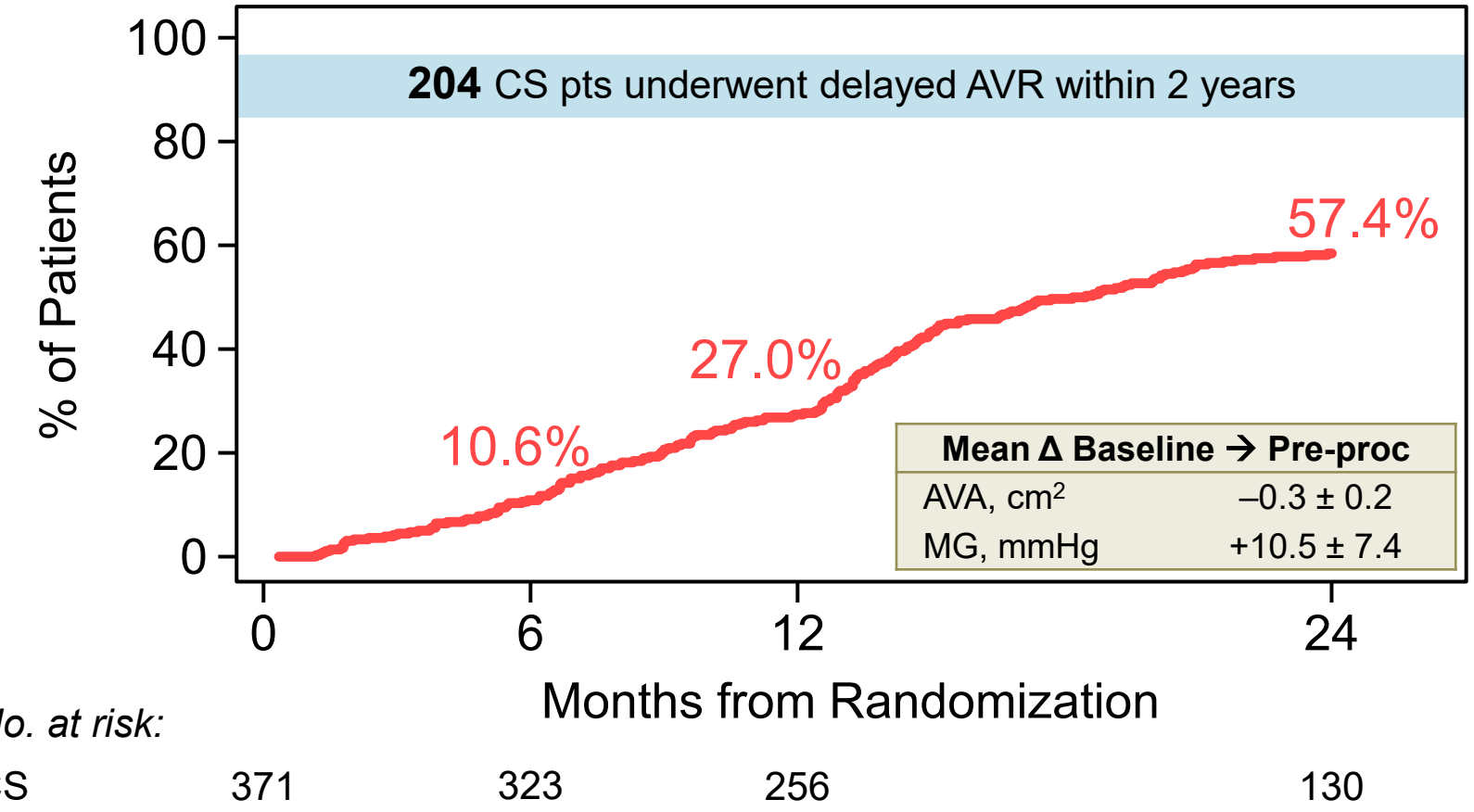
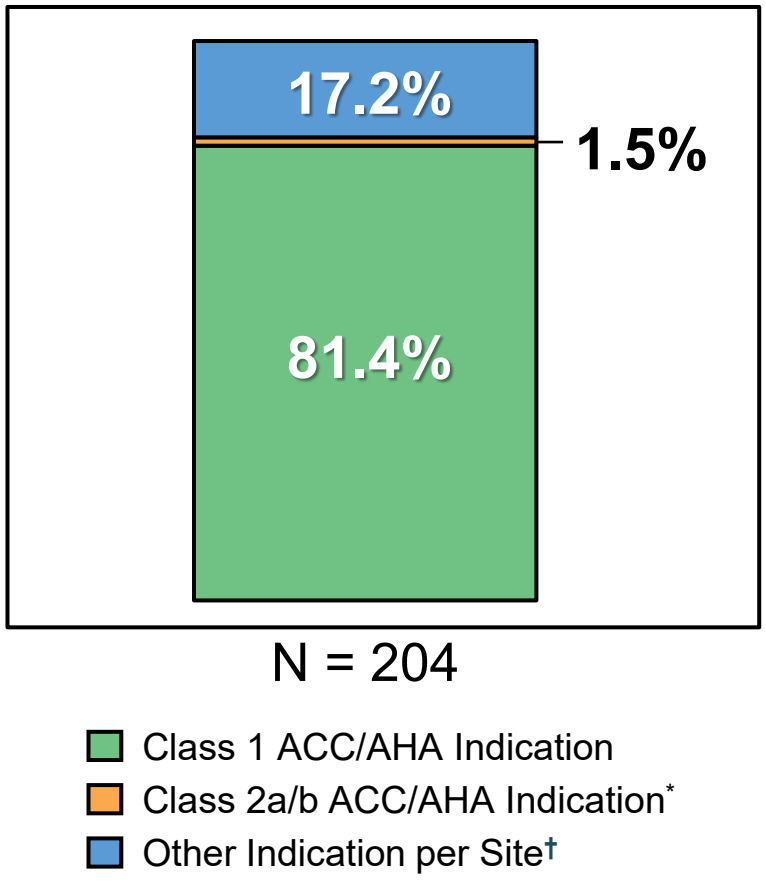
Timing of Delayed AVR



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

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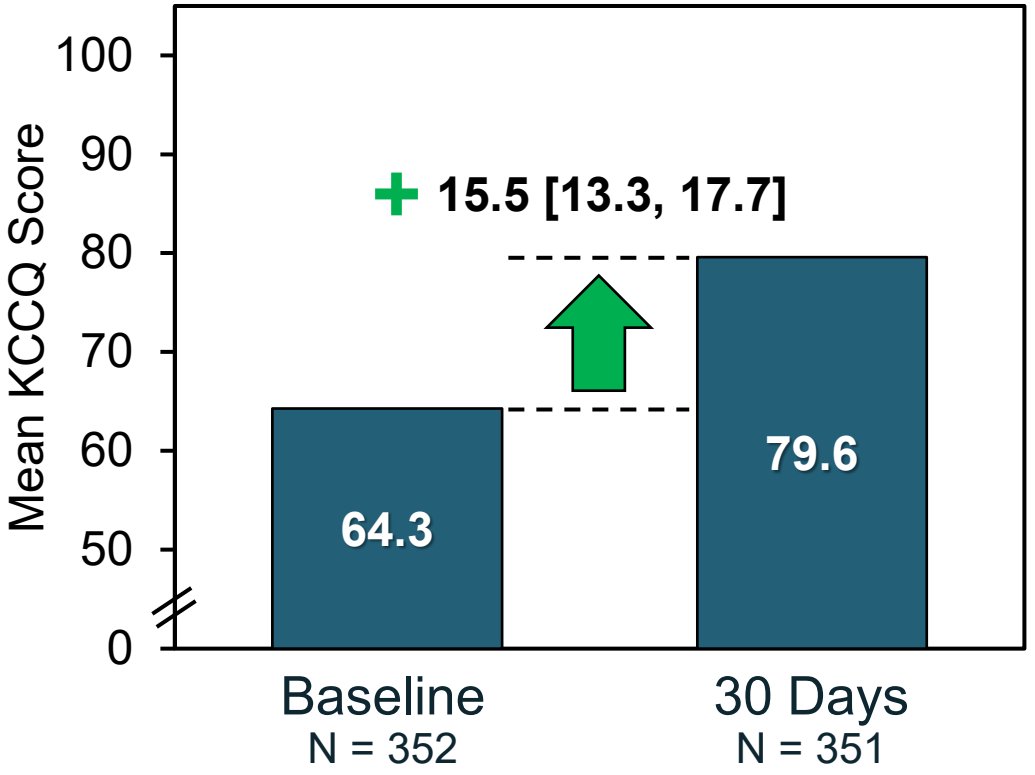
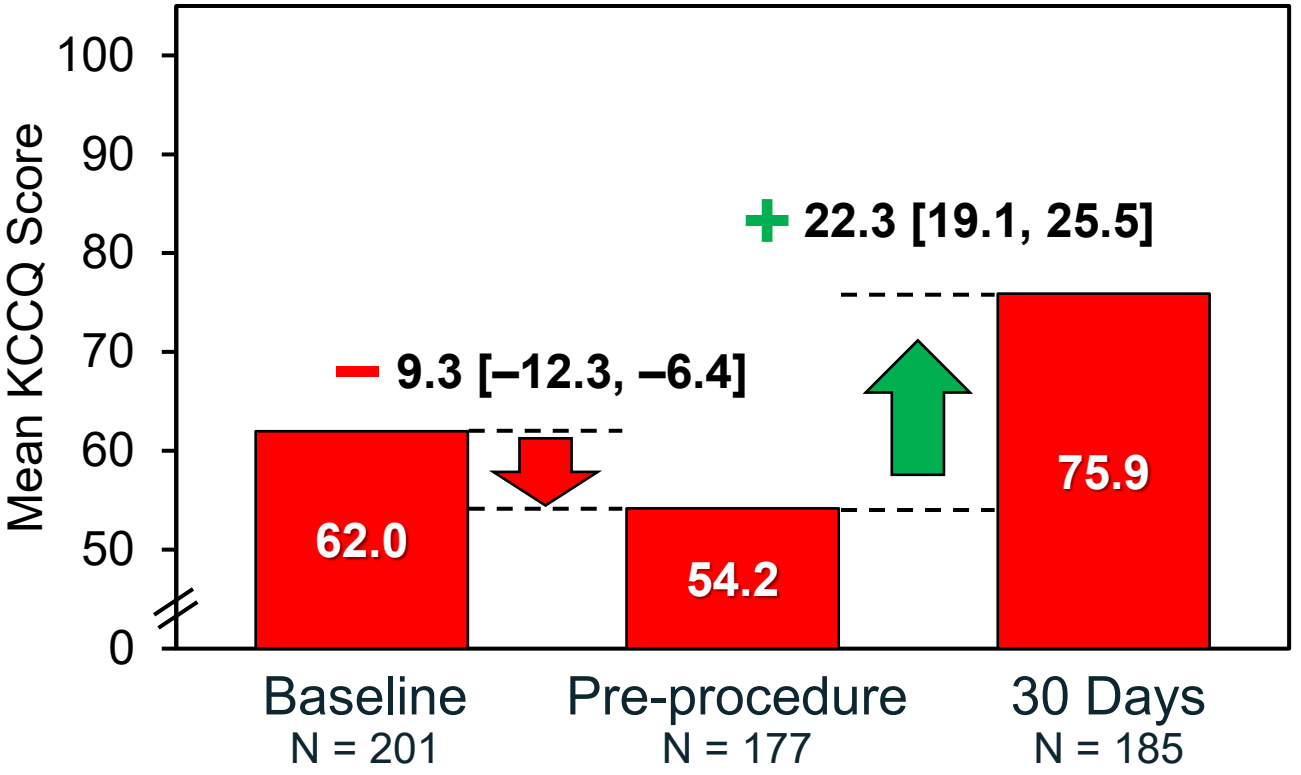
Randomized to TAVR*



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

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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

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- 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

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