TAVR for Asymptomatic Severe Aortic Stenosis:

Results of the EARLY TAVR Trial

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on behalf of the EARLY TAVR Investigators

Disclosures – Philippe Genereux, MD

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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, Abiomed, Edwards Lifesciences, Haemonetics, Pi-Cardia, Puzzle Medical Inc., Saranas, Shockwave Medical, Teleflex Incorporated, 4C Medical
• **Principal Investigator**	EARLY TAVR trial, PROGRESS trial, ECLIPSE trial, 4C Feasibility trial
• **Equity**	Puzzle Medical Inc., Pi-Cardia, Saranas

THE EARLY TAVR TRIAL

Background

- For patients with **asymptomatic severe AS** and preserved LVEF (≥ 50%), current ACC/AHA guidelines recommend clinical surveillance (CS) with routine follow-up every **6 to 12 months**

- Recently, 2 small RCTs[1,2] evaluating younger patients with very severe AS demonstrated a benefit for early surgical AVR compared to clinical surveillance

To date, no trial has explored a strategy of early TAVR compared to guideline-indicated clinical surveillance

[1]Kang et al. N Engl J Med 2020;382(2):111-119; [2]Banovic et al. Eur Heart J 2024;ehae585

THE EARLY TAVR TRIAL

Purpose

To determine the safety and effectiveness of a strategy of early intervention with TAVR compared to clinical surveillance in patients with asymptomatic severe AS.

THE EARLY TAVR TRIAL

Study Design

Prospective, multicenter RCT evaluating patients with asymptomatic, severe AS aged ≥ 65 years w/ an STS score ≤ 10% and LVEF ≥ 50%

Asymptomatic Assessment
Confirmed by negative treadmill stress test*

Randomization 1:1

Transfemoral-TAVR
(SAPIEN 3 or SAPIEN 3 Ultra THV)

Clinical Surveillance

PRIMARY ENDPOINT (Superiority)
Non-hierarchical composite of all-cause death, any stroke, or unplanned CV hospitalization at a minimum follow-up of 2 years

*Confirmed by detailed clinical history alone if patient was unable to perform stress test

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EARLY TAVR: 75 Clinical Sites

72 US Sites
97.6% (879 pts)

3 Canadian Sites
2.4% (22 pts)

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Key Inclusion Criteria

- **Age ≥ 65 years**
- **Severe aortic stenosis**
  - AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2 AND
  - Mean gradient ≥ 40 mmHg or peak jet velocity ≥ 4.0 m/s
- **LV ejection fraction ≥ 50%**
- **Asymptomatic status confirmed by:**
  - Negative treadmill stress test and detailed clinical history OR
  - If patient was unable to perform a stress test (e.g., due to orthopedic reasons), by detailed clinical history alone
- **STS score ≤ 10%**

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Key Exclusion Criteria

- **Class I indication for AVR**
- **Unsuitable anatomy for TF-TAVR** using the S3/S3 Ultra valve
  (Bicuspid valves w/ favorable anatomy for TAVR were permitted)
- Severe AR or MR (>3+) or ≥ moderate mitral stenosis
- Renal insufficiency (eGFR <30 mL/min/ 1.73 m^2) and/or renal replacement therapy
- Severe lung disease or severe pulmonary hypertension
- Pre-existing mechanical or bioprosthetic valve in any position
- Active COVID-19 infection or previous diagnosis with sequelae

Primary Endpoint

Composite of all-cause mortality, any stroke, or unplanned CV hospitalization

- Tested for **superiority** in the **intent-to-treat population** after a **minimum follow-up of 2 years**
- **Unplanned CV hospitalization** was defined as follows:
  - Any **CV hospitalization** through an ED or admission from clinic for therapy intensification* or lasting ≥ 24h
  - Any **aortic valve intervention** (CS arm) or **reintervention** (TAVR arm) that occurred within **6 months** (minimum guideline-indicated follow-up for CS)

*Includes IV diuretics, ≥50% increase in drug therapy dosages, or addition of new pharmacotherapy agents

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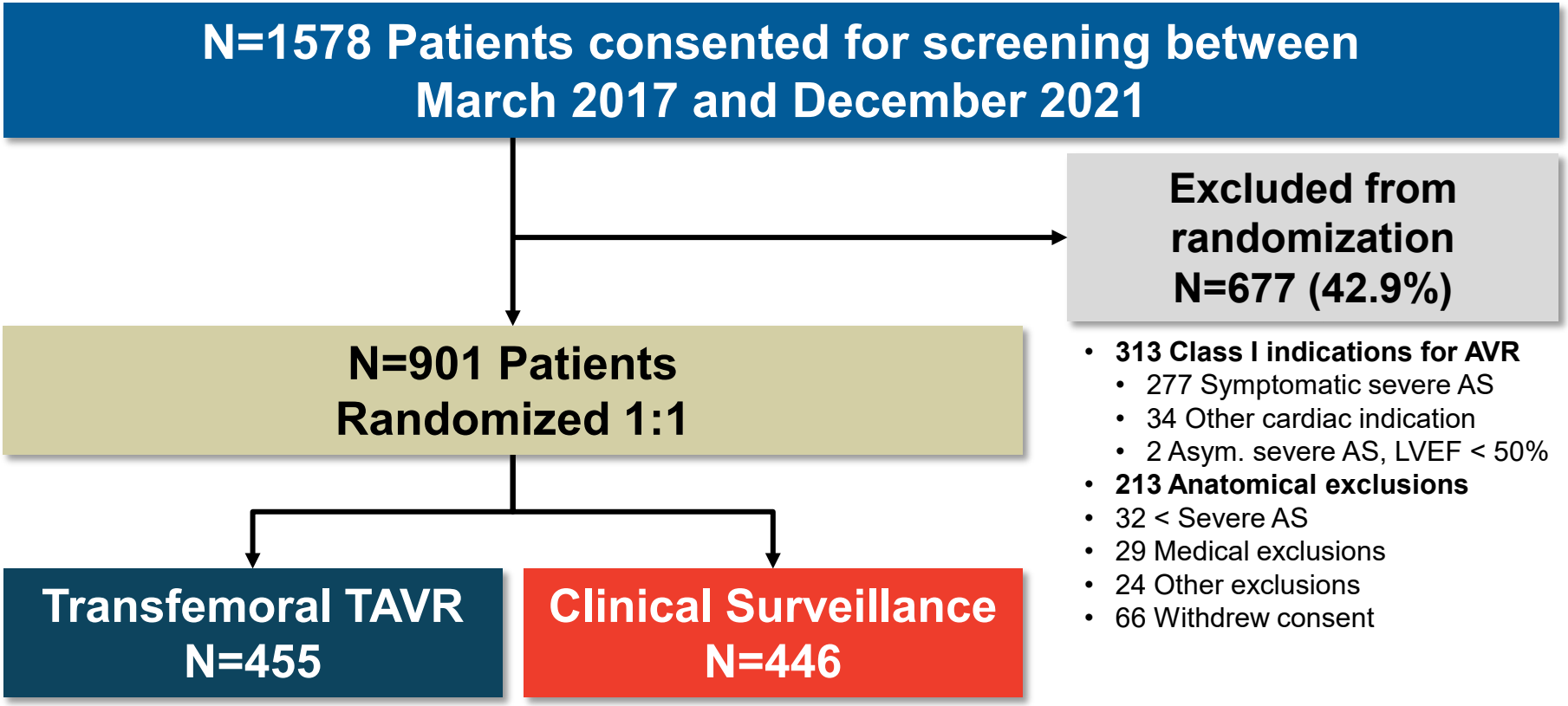
Secondary Endpoints (Hierarchical)

1. **Favorable Health Status Outcome***
   - Alive at 2Y w/ a KCCQ score ≥ 75 that did not decrease by > 10 points from baseline
2. **Integrated LV/LA health at 2 years** – composite of:
   - LV global longitudinal strain (GLS) ≥ 15% **and**
   - LV mass index < 115 g/m^2 for men or < 95 g/m^2 for women **and**
   - LA volume index ≤ 34 mL/m^2
3. **Change in LVEF from baseline to 2 years**
4. **New-onset atrial fibrillation**
5. **Death or disabling stroke**

*Evaluated at 2Y; If an AV intervention/reintervention occurred within 6M, pre-procedure (CS) or 30D (TAVR) KCCQ score was used

THE EARLY TAVR TRIAL

Patient Flow



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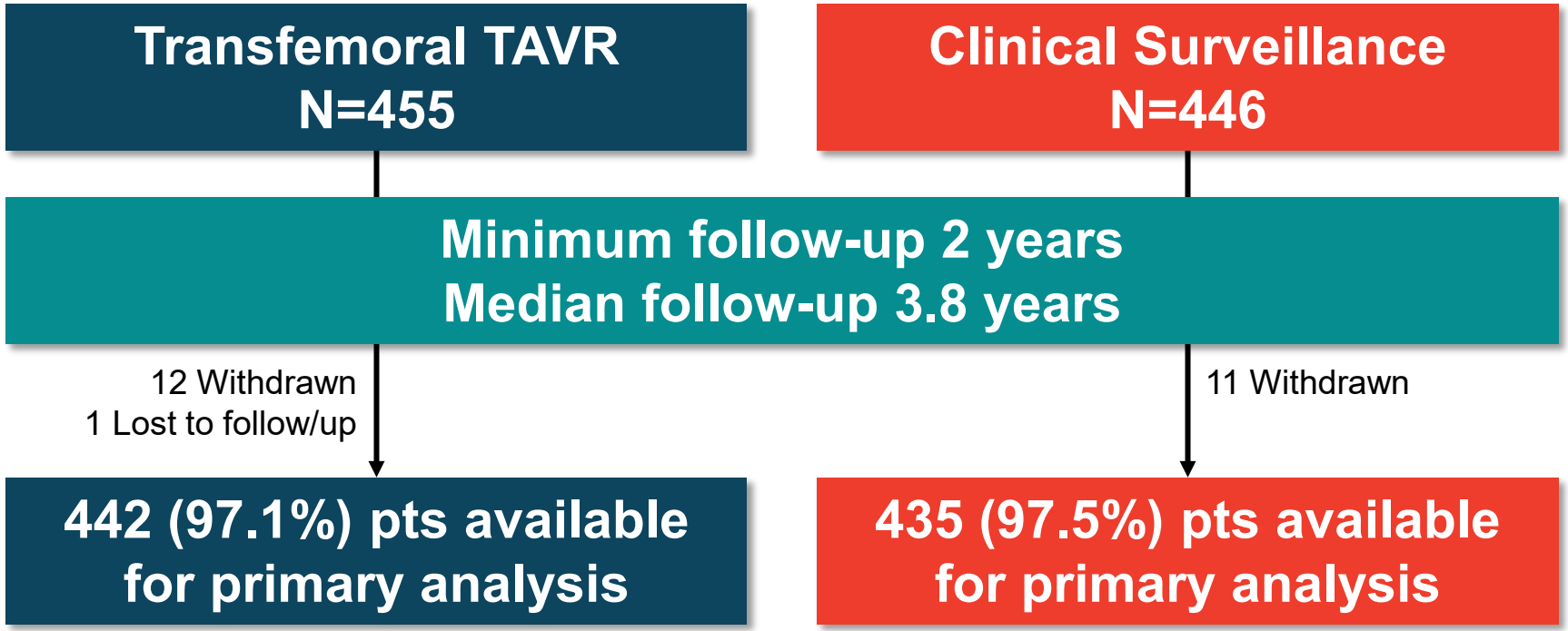
Patient Follow-up



Primary analysis evaluated in the ITT population

THE EARLY TAVR TRIAL

Baseline Characteristics

Characteristic	TAVR (N=455)	CS (N=446)	Characteristic	TAVR (N=455)	CS (N=446)
Age, y	76.0 ± 6.0	75.6 ± 6.0	Bicuspid valve	8.1%	8.8%
Female sex	28.8%	33.0%	Hx of afib	15.6%	13.2%
BMI, kg/m^2	28.4 ± 4.6	28.6 ± 4.8	Pacemaker†	4.6%	2.0%
STS score, %	1.8 ± 1.0	1.7 ± 1.0	Prior MI	5.1%	4.0%
Low-risk per Heart team	83.5%	83.9%	Prior stroke	4.2%	4.5%
Asymptomatic Criteria			CAD	29.2%	25.3%
Treadmill stress test	90.3%	90.8%	PVD	7.3%	4.7%
Clinical history only*	9.7%	9.2%	HTN	81.1%	81.8%
KCCQ Score	92.7 ± 8.7	92.7 ± 9.4	Diabetes	26.2%	25.6%
NT-proBNP, pg/mL	276 (139, 599)	297 (148, 608)	eGFR <45 mL/min/ 1.73 m^2	6.8%	4.5%

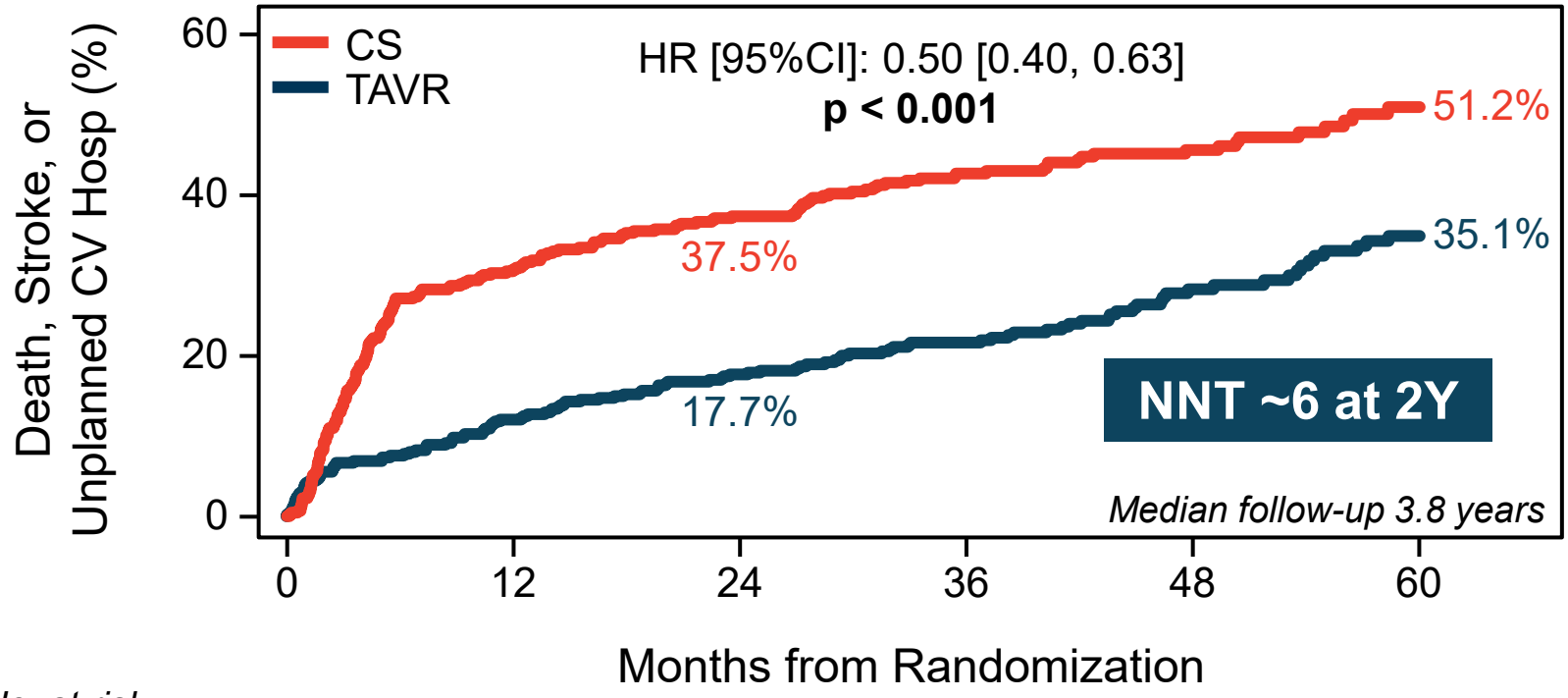
Values presented as %, mean ± SD, or median (IQR)
*Unable to take the stress test for orthopedic and/or neurologic reasons
†P<0.05 at baseline

Baseline Echo Characteristics

Characteristic	TAVR (N=455)	CS (N=446)
AVA, cm^2	0.9 ± 0.2	0.8 ± 0.2
Peak velocity, m/s	4.3 ± 0.5	4.4 ± 0.4
Mean gradient, mmHg	46.5 ± 10.1	47.3 ± 10.6
LVEF, %	67.4 ± 6.5	67.4 ± 6.7
LV diastolic dysfunction ≥ Grade II	42.7%	37.3%

Values presented as % or mean ± SD

Primary Endpoint



No. at risk:

TAVR	455	390	363	285	142	103
CS	446	305	266	187	117	46

Event rates are Kaplan-Meier estimates

Patients had a minimum follow-up of 2 years

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Primary Endpoint Components

Endpoint – % (no. of pts w/ an event)	TAVR (N=455)	CS (N=446)	P-value
Primary Endpoint	**26.8% (122)**	**45.3% (202)**	**<0.001**
All-cause Death	8.4% (38)	9.2% (41)	---
Any Stroke	4.2% (19)	6.7% (30)	---
Unplanned CV Hospitalization	20.9% (95)	41.7% (186)	---

Median follow-up of 3.8 years

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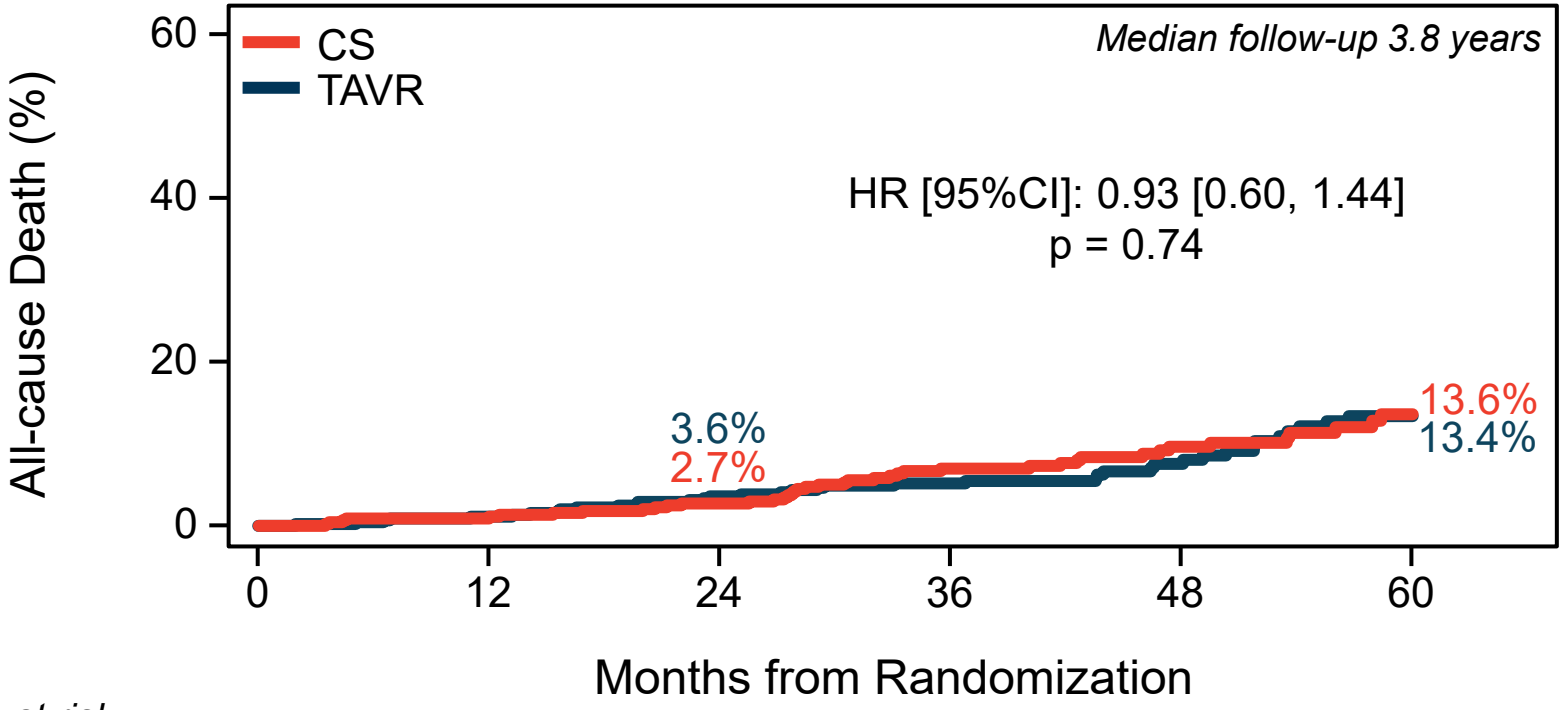
All-cause Death



No. at risk:

TAVR	455	439	425	346	187	136
CS	446	436	418	310	199	95

Event rates are Kaplan-Meier estimates

Patients had a minimum follow-up of 2 years

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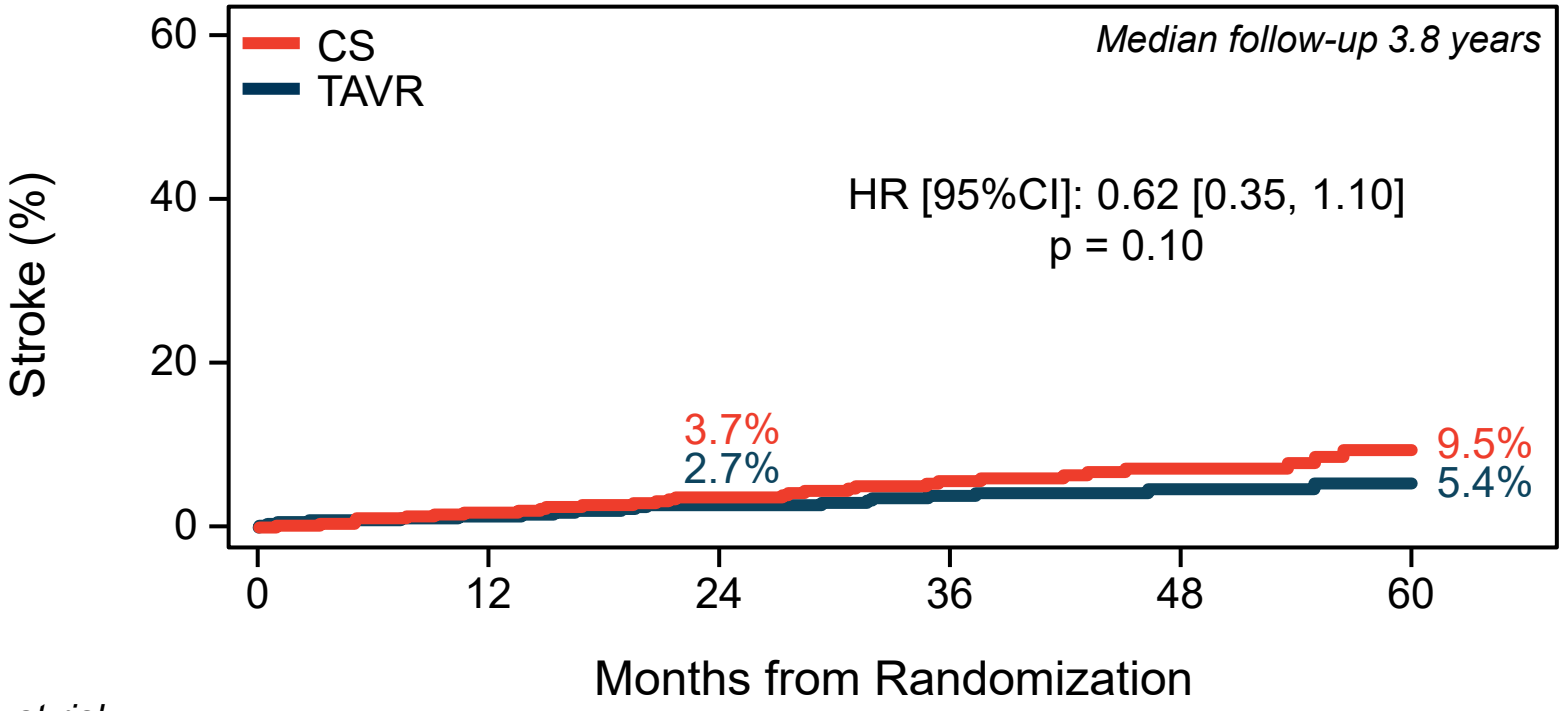
Stroke



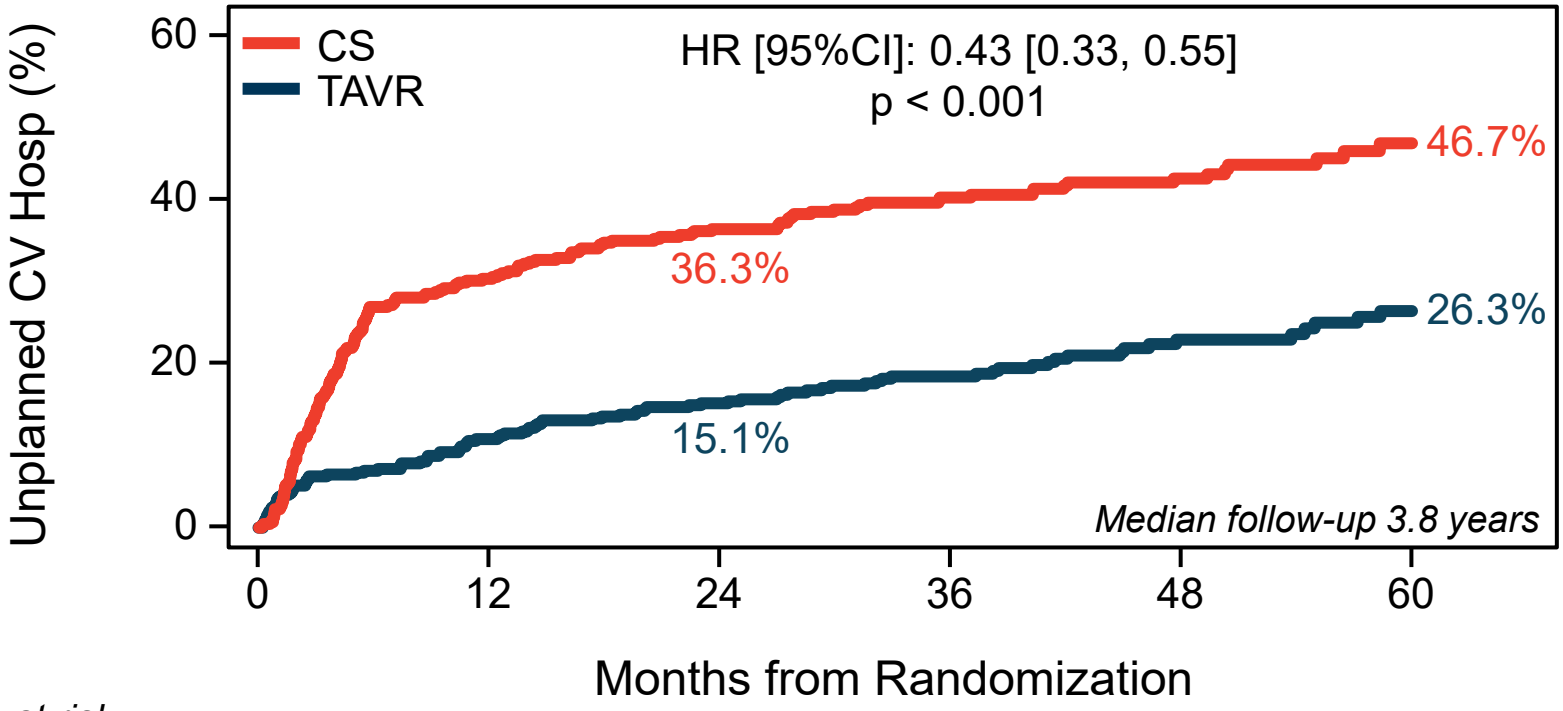
No. at risk:

TAVR	455	433	415	335	180	130
CS	446	429	406	295	185	87

Event rates are Kaplan-Meier estimates

Patients had a minimum follow-up of 2 years

Unplanned CV Hospitalization



No. at risk:

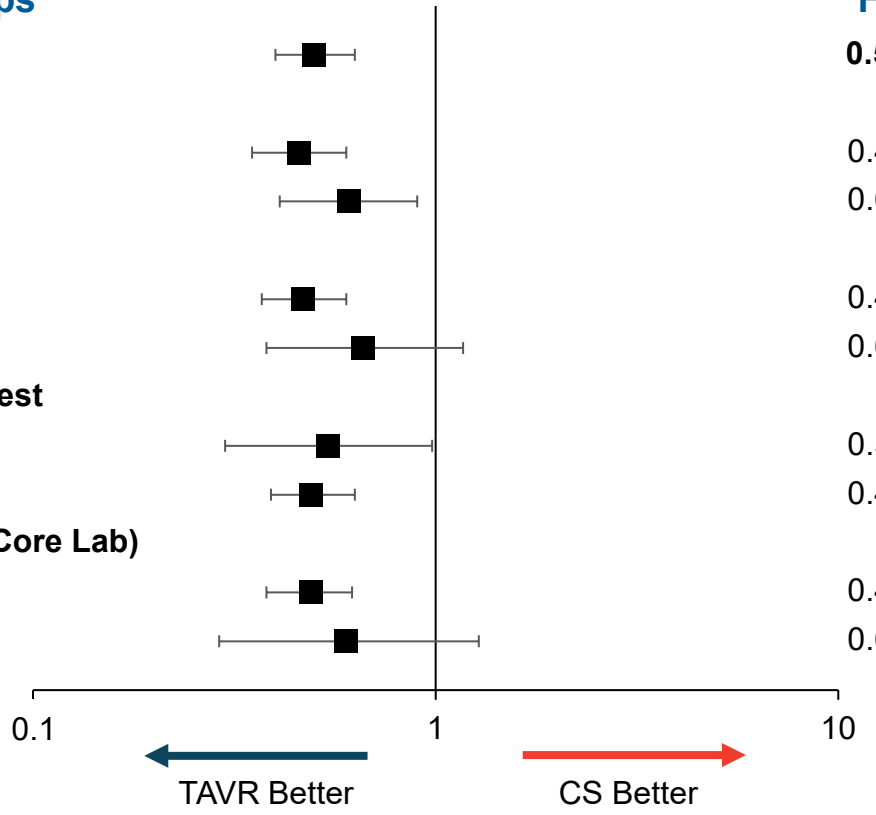
TAVR	455	392	365	287	142	103
CS	446	306	267	189	118	46

Event rates are Kaplan-Meier estimates

Patients had a minimum follow-up of 2 years

Subgroup Analyses: Primary Endpoint

Pre-specified Subgroups	HR [95% CI]	$P_{interaction}$
Intent-to-treat (N=901)	**0.50 [0.40, 0.63]**	
Sex		0.26
Male (n=623)	0.46 [0.35, 0.60]	
Female (n=278)	0.61 [0.41, 0.90]	
Baseline STS Score		0.24
< 3% (n=807)	0.47 [0.37, 0.60]	
≥ 3% (n=94)	0.66 [0.38, 1.17]	
Ability to Perform Stress Test		0.73
No (n=85)	0.54 [0.30, 0.98]	
Yes (n=816)	0.49 [0.39, 0.63]	
Baseline Jet Velocity (per Core Lab)		0.59
< 5 m/s (n=818)	0.49 [0.38, 0.62]	
≥ 5 m/s (n=74)	0.60 [0.29, 1.28]	



Consistent benefits of the early TAVR strategy for all pre-specified subgroups

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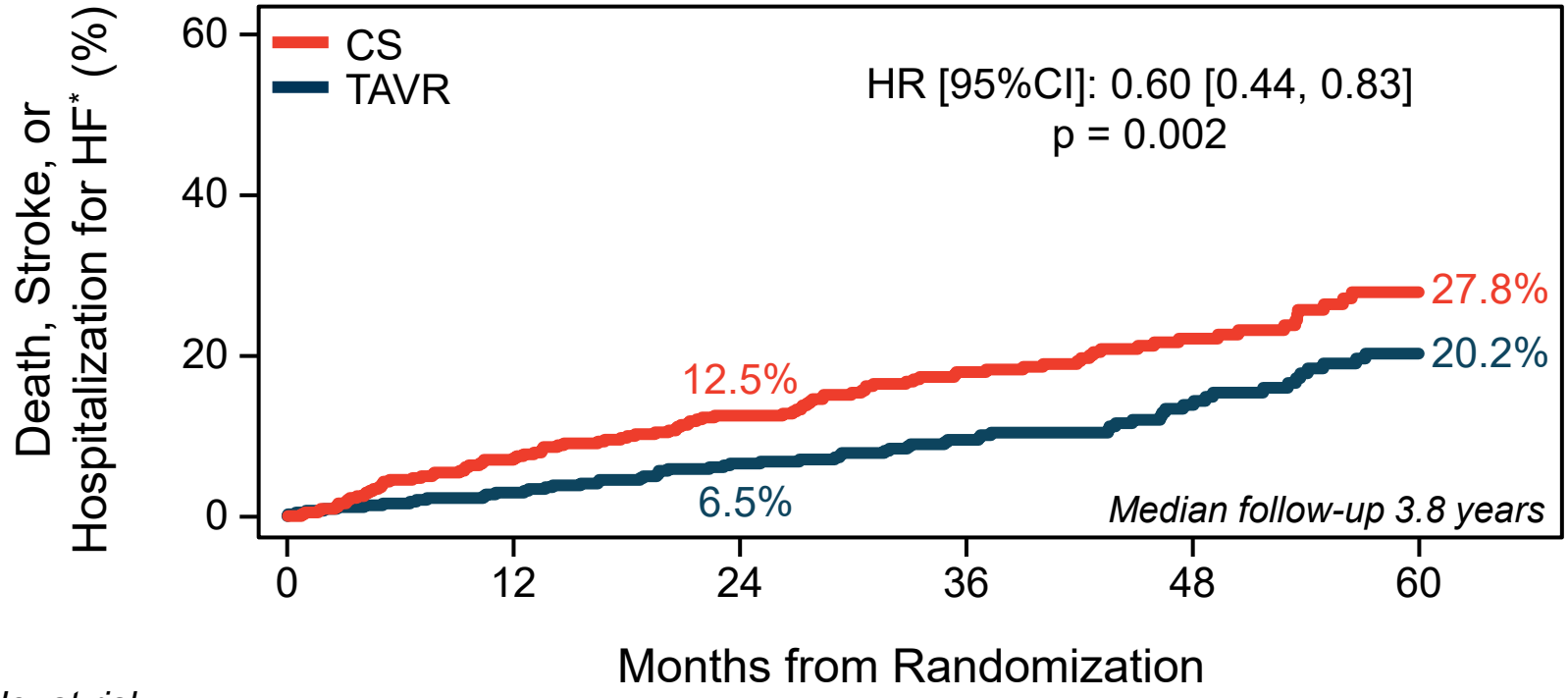
Death, Stroke, or Hosp. for HF*



No. at risk:

TAVR	455	431	412	331	175	128
CS	446	410	376	268	163	77

*Hosp for symptomatic CHF treated with IV diuresis, inotropic therapy, IABP, ventilation for pulmonary edema, or hemodialysis for vol. overload

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Pre-specified Secondary Endpoints

Endpoint — % or mean ± SE	TAVR (N=455)	CS (N=446)	Treatment Effect [95% CI]	P-value
1. Favorable Health Status Outcome*	86.6%	68.0%	Abs Δ: 18.5% [12.6%, 24.3%]	**<0.001**
2. Integrated LV/LA health at 2Y†	48.1%	35.9%	Abs Δ: 12.2% [4.4%, 19.4%]	**0.001**
3. Δ LVEF (%) from baseline to 2Y	-1.2 ± 0.4	-1.3 ± 0.4	Abs Δ: 0.1 [-0.8, 1.3]	0.66
4. New onset atrial fibrillation	13.0%	12.4%	HR: 1.08 [0.73, 1.60]	---
5. Death or disabling stroke	9.7%	11.2%	HR: 0.87 [0.58, 1.31]	---

*Evaluated at 2Y and defined as alive w/ a KCCQ score ≥ 75 that did not decrease > 10 points from baseline; if AV intervention/reintervention occurred w/in 6 mos, pre-procedure (CS) or 30-day (TAVR) KCCQ score was used

†Defined as meeting all of the following criteria: LV GLS ≥ 15%, LVMi < 115 g/m^2 for men or <95 g/m^2 for women, and LAVi ≤ 34 mL/m^2

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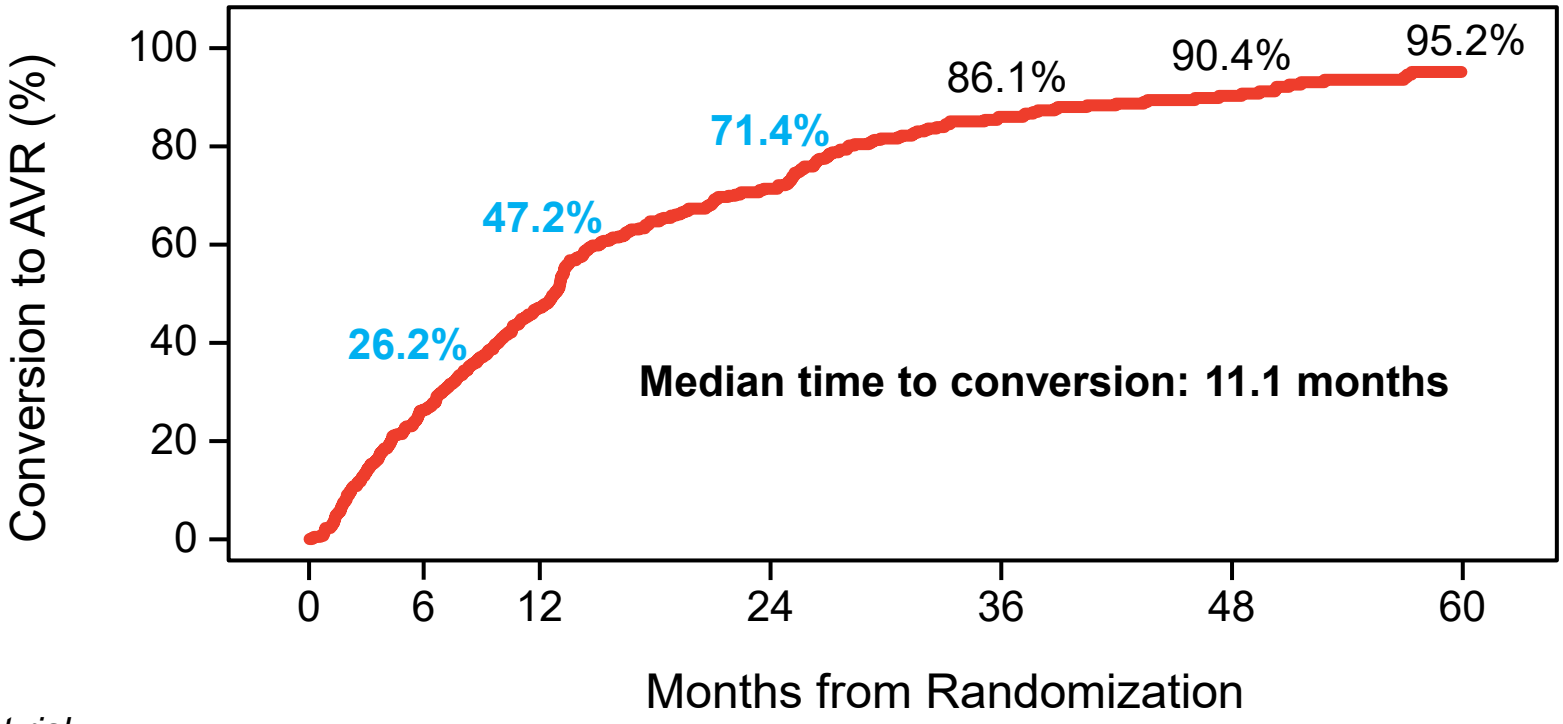
Conversion to AVR in CS



No. at risk:

Clinical Surveillance	446	326	231	119	45	22	9

Median follow-up 3.8 years; At the time of analysis, 30 patients were still on study but hadn't converted to AVR

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Symptoms at Time of Conversion to AVR

CS Patients who Converted to AVR with Symptoms	Total (N=377)
Most Common Symptoms*	
Dyspnea	**83.0%**
Angina	24.9%
Dizziness	24.7%
Fatigue	22.0%
Syncope	7.2%
Multiple Symptoms	
Experienced 2 symptoms	34.5%
Experienced ≥ 3 symptoms	13.3%
Symptom/HF Severity	
NYHA II	70.0%
NYHA III/IV	**30.0%**
Accompanying Signs of Worsening AS*	
Peak velocity > 5 m/s	22.3%
LVEF drops to < 50%	4.8%
≥ 3-fold increase in NT-proBNP	6.7%

*Categories are not mutually exclusive

Clinical Presentation at Time of AVR Conversion

Patients classified based on acuity and severity of signs/symptoms

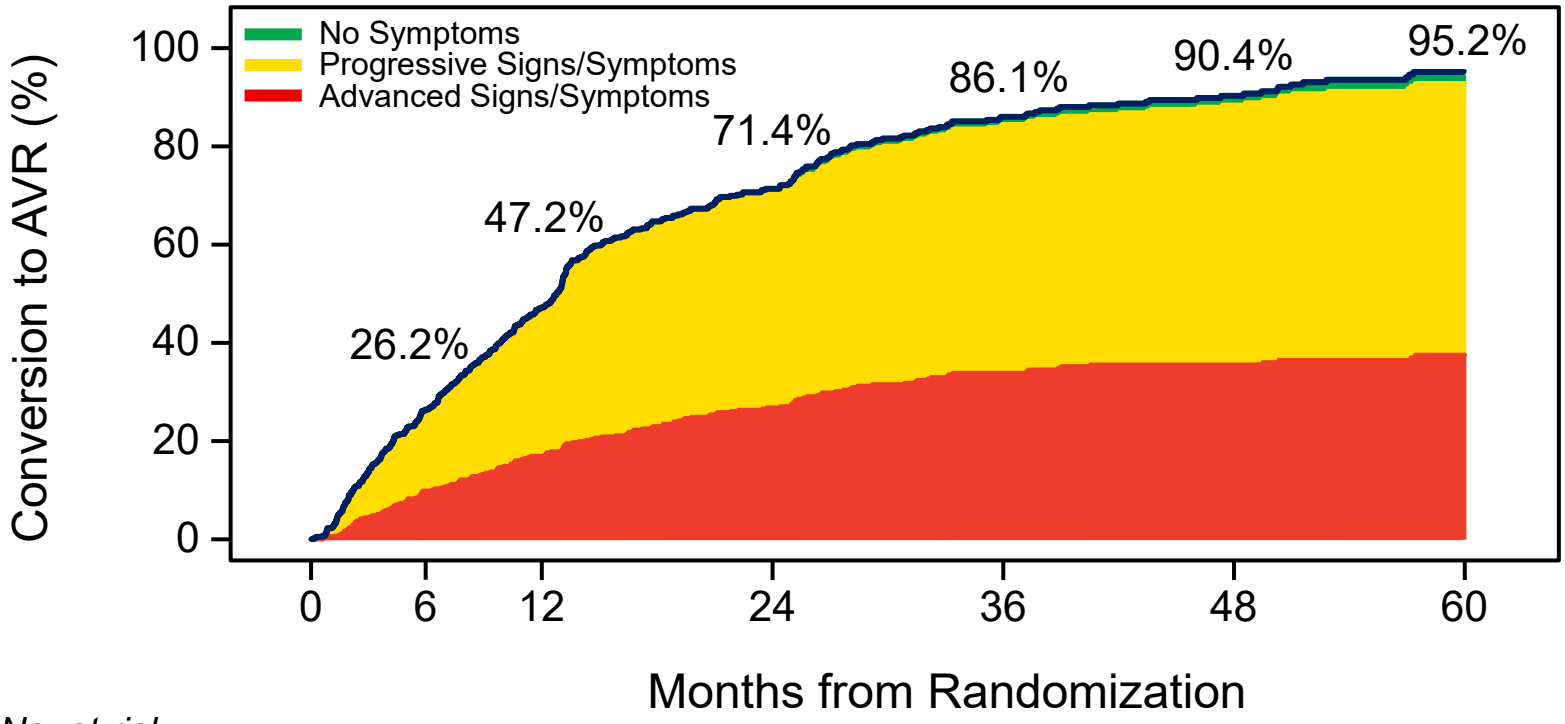
Asymptomatic
Includes pts who may have converted to AVR b/c they required additional medical procedures

Progressive Signs or Symptoms
NYHA II
Dyspnea
Angina
Fatigue
Dizziness
Increase in HF rx from baseline
≥ 1.5- to < 3-fold increase in NT-proBNP from baseline and age-specific threshold*

Advanced Signs or Symptoms / Acute Decompensation
NYHA III/IV
Dyspnea
Angina
Fatigue
Dizziness
Syncope
Atrial fibrillation
Ventricular arrhythmia
Resuscitated sudden death/cardiac arrest
Hospitalization for HF and/or pulmonary edema
LVEF drops to < 50%
≥ 3-fold increase in NT-proBNP from baseline and age-specific threshold*

*125 pg/mL for patients ≤ 75 years and 450 pg/mL for > 75 years

Signs & Symptoms at Time of Conversion to AVR



Median follow-up 3.8 years; At the time of analysis, 30 patients were still on study but hadn't converted to AVR

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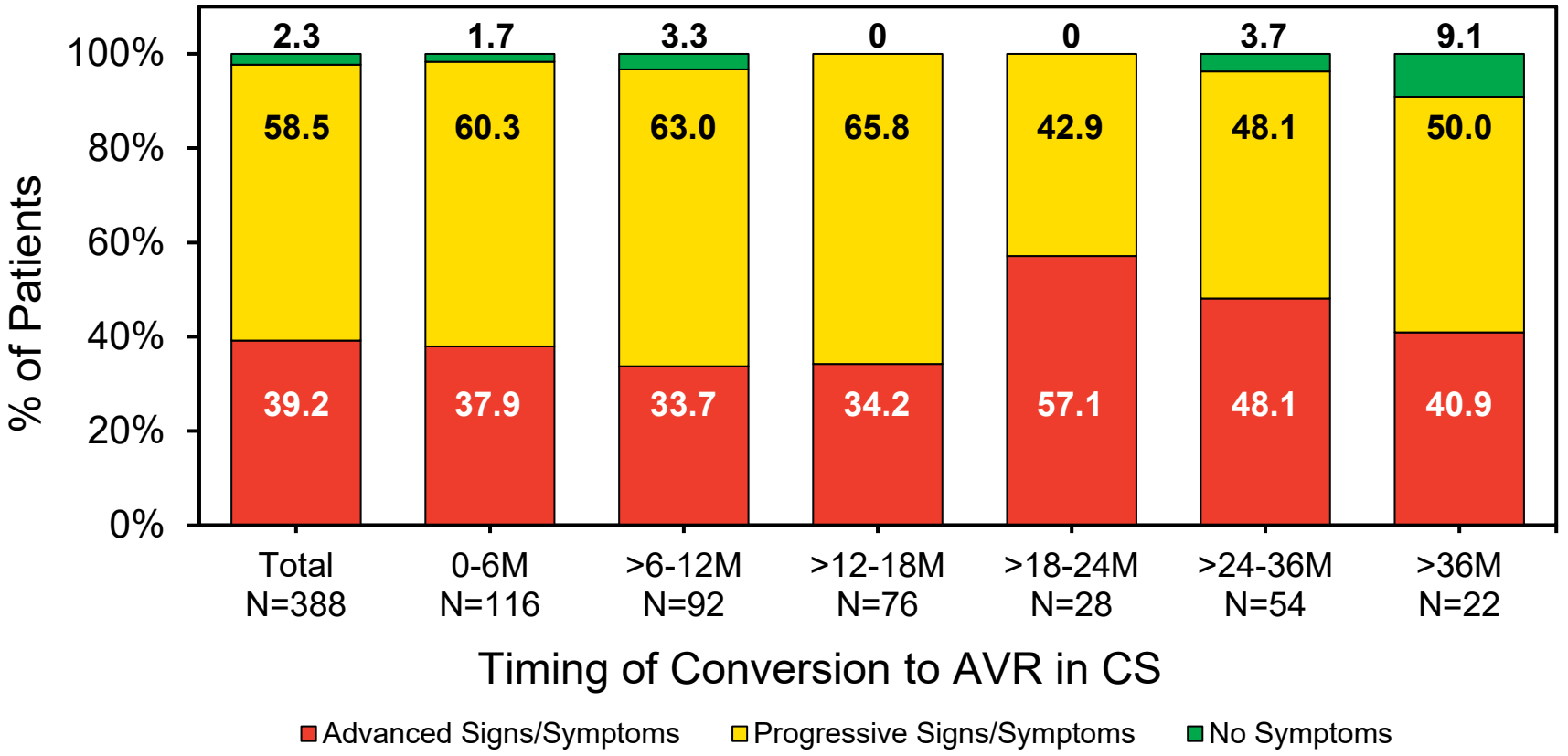
Proportion of Patients Presenting with Advanced Signs/Symptoms was Consistent Through Time



At the time of analysis, 30 patients were still on study but hadn't converted to AVR

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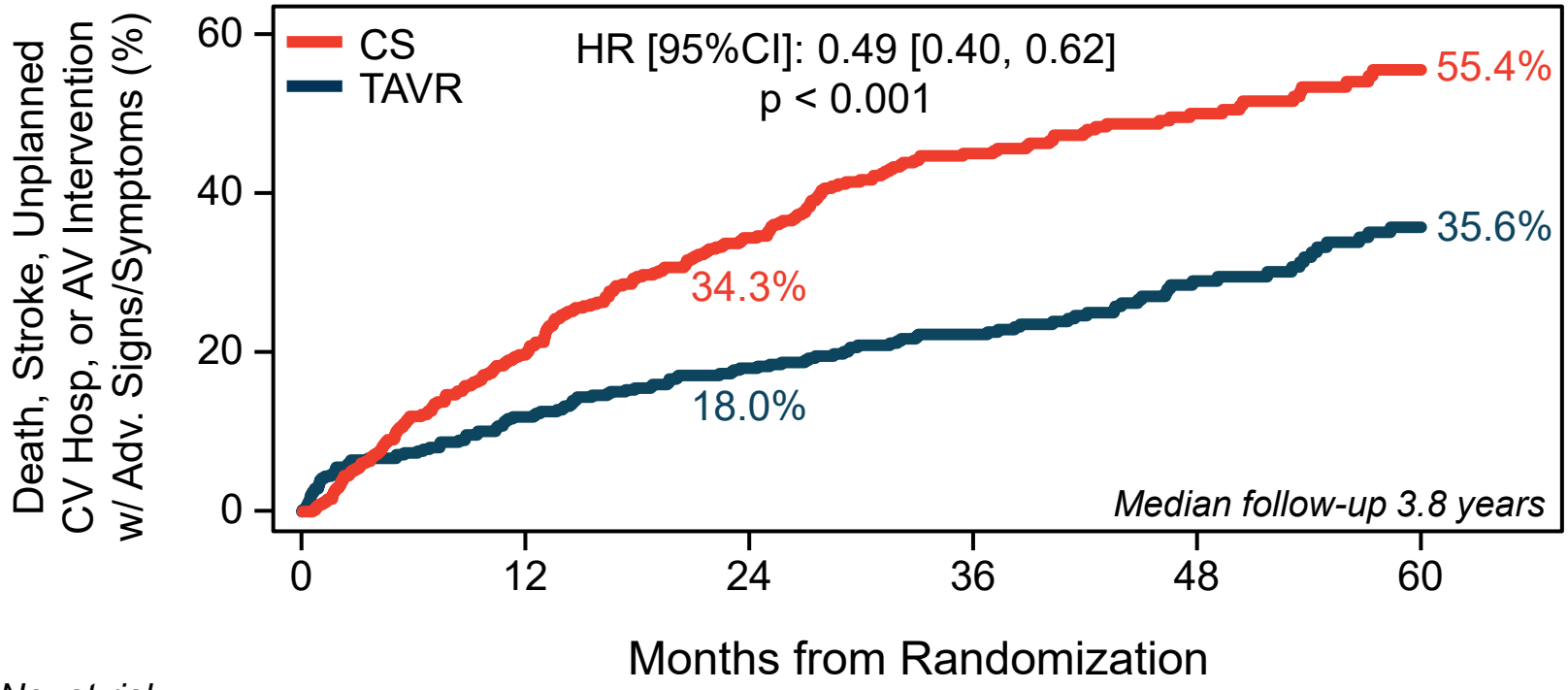
Exploratory Analysis of the PE



No. at risk:

TAVR	455	391	362	284	140	101
CS	446	354	281	186	108	52

Patients had a minimum follow-up of 2 years

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Promptness of Treatment

Median (IQR) timing from:	Early TAVR (N=444)	CS with AVR (N=388)
Randomization to early TAVR	14 (9, 24) days	-
AVR indication to conversion*	-	32 (18, 58) days

*N=381 (98.2%) underwent TAVR; N=7 (1.8%) underwent SAVR

87.9% of clinical surveillance patients who converted to AVR were treated within 3 months of indication for AVR

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Periprocedural* Outcomes

Outcome – Kaplan-Meier Estimates	TAVR (N=444)	CS with AVR (N=388)
All-cause death	0.2%	0%
CV death	0%	0%
Non-CV death	0.2%	0%
Stroke	0.9%	1.8%
Disabling stroke	0%	1.0%
Non-disabling stroke	0.9%	0.8%
New onset atrial fibrillation	4.5%	3.1%
New permanent pacemaker	5.7%	8.4%
Life-threatening/disabling or major bleeding	2.5%	3.6%
Acute kidney injury (site-reported)	2.5%	3.4%
Major vascular complications	1.4%	1.0%
Myocardial infarction	0.5%	0.5%
Coronary obstruction requiring intervention	0%	0%

*Periprocedural defined as ≤ 30 days from index procedure in the TAVR arm or date of conversion to AVR in the CS arm

Limitations

- Results apply only to the trial population, which included patients ≥ 65 years who were suitable for TF-TAVR
- Findings may not be applicable to other TAVR systems
- Less rigorous clinical surveillance and absence of early TAVR planning may result in different outcomes
- Trial was partly conducted during the COVID-19 pandemic, which may have affected outcomes

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Conclusions

In patients with asymptomatic, severe AS, a strategy of early TAVR compared with clinical surveillance:

- Resulted in a significant reduction of the primary endpoint (death, stroke, or unplanned CV hospitalization)
  - *Multiple endpoint variations demonstrated consistent results*
- Was not associated with excess mortality or stroke
- Prevented a clinically-meaningful decline in quality of life in clinical surveillance patients who subsequently converted to AVR
- Improved measures of LV and LA function

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Clinical Implications

Given the benefits observed and the lack of harm, early TAVR may be preferred to clinical surveillance in patients with asymptomatic severe AS, especially when combined with the challenges of timely symptom recognition and prompt treatment in real-world settings

THANK YOU!

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

THE EARLY TAVR TRIAL

Just Published!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis

P. Généreux, A. Schwartz, J.B. Oldemeyer, P. Pibarot, D.J. Cohen, P. Blanke, B.R. Lindman, V. Babaliaros, W.F. Fearon, D.V. Daniels, A.K. Chhatriwalla, C. Kavinsky, H. Gada, P. Shah, M. Szerlip, T. Dahle, K. Goel, W. O'Neill, T. Sheth, C.J. Davidson, R.R. Makkar, H. Prince, Y. Zhao, R.T. Hahn, J. Leipsic, B. Redfors, S.J. Pocock, M. Mack, and M.B. Leon, for the EARLY TAVR Trial Investigators*