

Expanding Role of TAVI to **Asymptomatic Severe Aortic Stenosis**

Philippe Généreux, MD, FACC

Interventional Cardiologist

Director, Structural Heart Program, Gagnon Cardiovascular Institute,
Morristown Medical Center, NJ



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Disclosure of Relevant Financial Relationships

Antegrade Medical: Equity, consultant; Abbott Vascular: Consultant, advisor, speaker Fees, PI Eclipse Trial; CARANX Medical: Consultant; Edwards LifeSciences: Consultant, advisor, speaker fees, proctor, research grant, PI EARLY-TAVR trial, PI PROGRESS trial; ECHOIQ: Equity, consultant; egnite inc.: Consultant, advisor; Haemonetics: Consultant, advisor, speaker Fees; Medtronic: Consultant, advisor, speaker fees; Pi-Cardia: Equity, consultant; Puzzle Medical: Equity, consultant; Spiralix: Equity, consultant; Teleflex: Consultant; 4C Medical: Consultant, PI Feasibility study



Krithika Loganath, MD¹; Neil J. Craig, MD^{1,2}; Russell J. Everett, PhD²; et al



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*



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Généreux et al. N Engl J Med. 2025 Jan 16;392(3):217-227

Study Design

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

Asymptomatic Status

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*

Patient Flow

N=1578 Patients consented for screening between March 2017 and December 2021

**Excluded from randomization
N=677 (42.9%)**

**N=901 Patients
Randomized 1:1**

**Transfemoral TAVR
N=455**

**Clinical Surveillance
N=446**

- **313 Class I indications for AVR**
 - 277 Symptomatic severe AS
 - 34 Other cardiac indication
 - 2 Asym. severe AS, LVEF < 50%
- **213 Anatomical exclusions**
 - 32 < Severe AS
 - 29 Medical exclusions
 - 24 Other exclusions
 - 66 Withdrew consent

Patient Flow

N=1578 Patients consented for screening between March 2017 and December 2021

**N=901 Patients
Randomized 1:1**

**Transfemoral TAVR
N=455**

**Clinical Surveillance
N=446**

**313 (~20%) Class 1 for
AVR (Excluded from
EARLY TAVR trial)**

**265 (~30%) Class 2a/2b
for AVR**

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

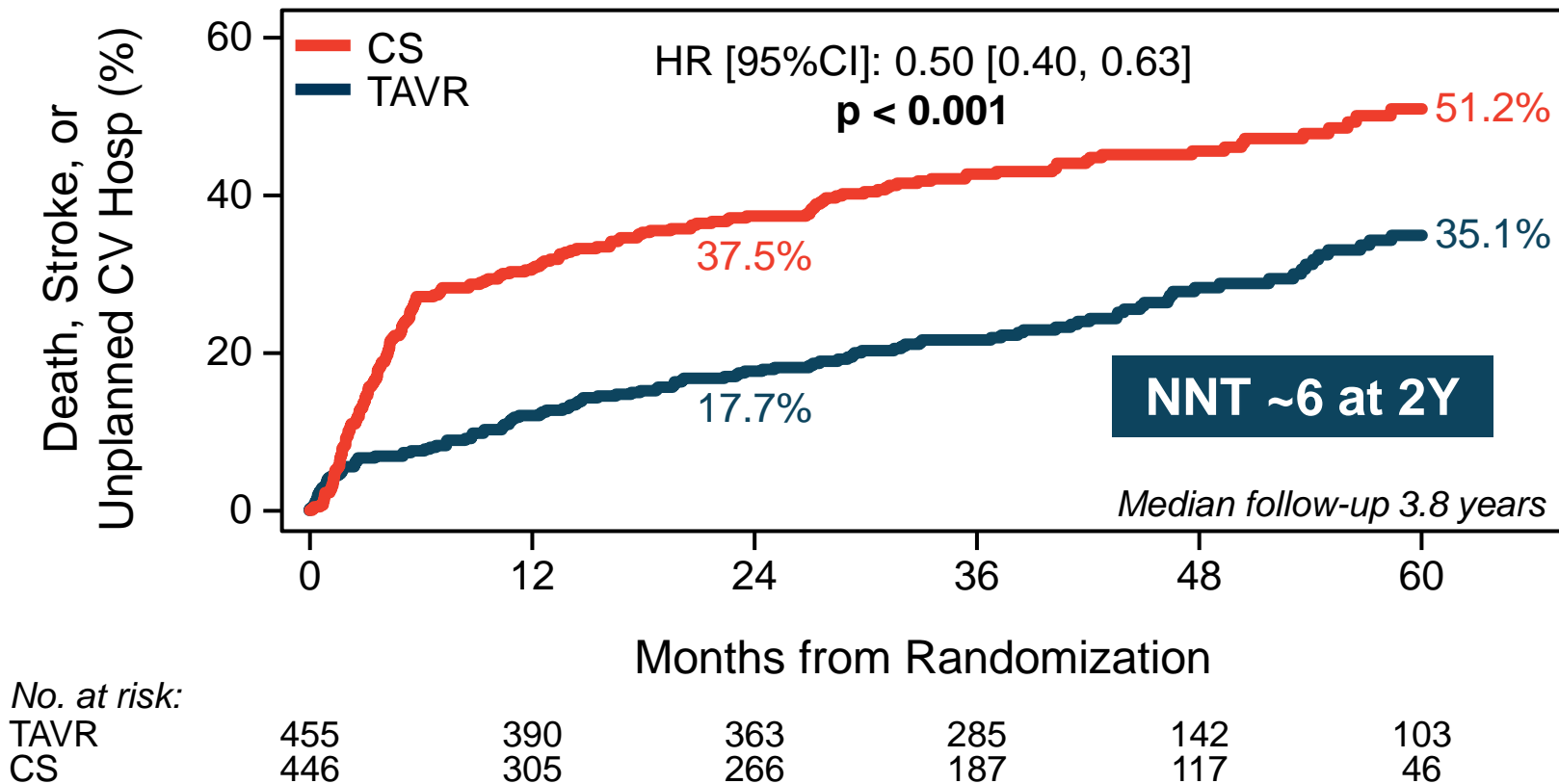
†P<0.05 at baseline

Baseline Echo Characteristics

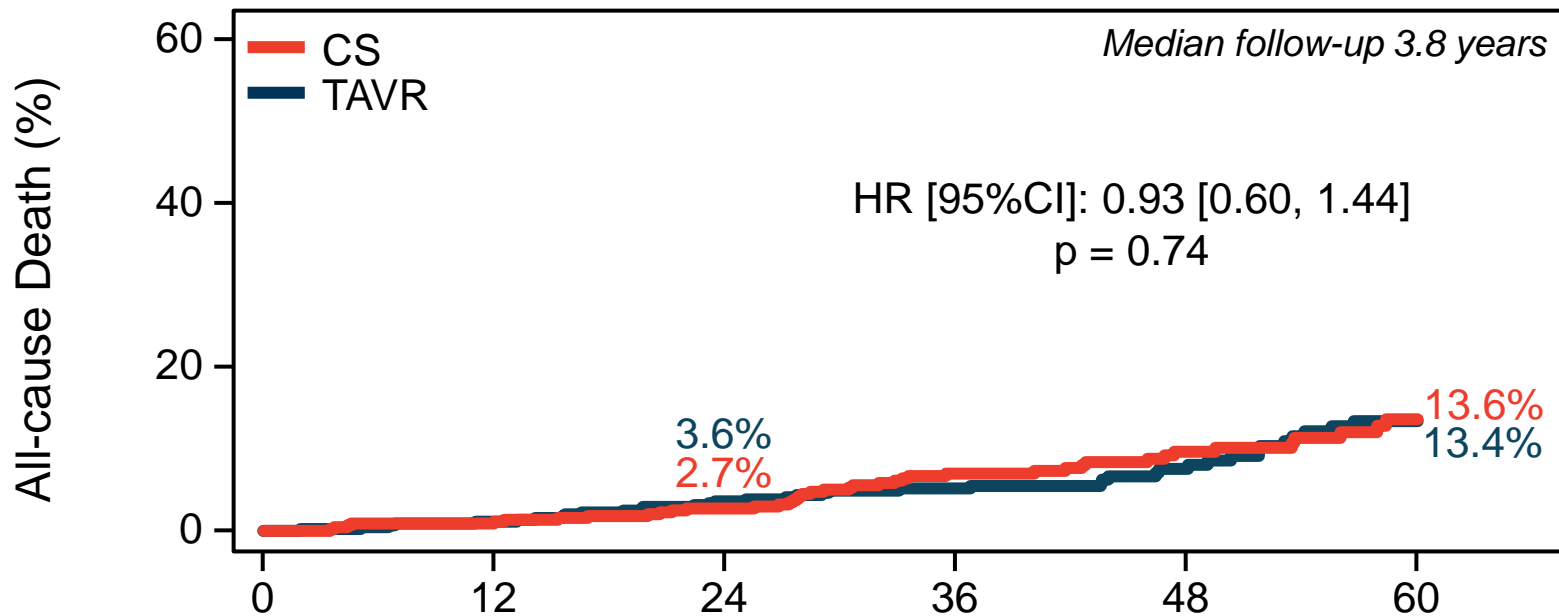
Characteristic	TAVR (N=455)	CS (N=446)
AVA, cm ²	0.9 ± 0.2	0.8 ± 0.2
Peak velocity, m/s	4.3 ± 0.5	4.4 ± 0.4
Mean gradient, mmHg	46.5 ± 10.1	47.3 ± 10.6
LVEF, %	67.4 ± 6.5	67.4 ± 6.7
LV diastolic dysfunction ≥ Grade II	42.7%	37.3%

Values presented as % or mean ± SD

Primary Endpoint



All-cause Death



No. at risk:

TAVR

455

439

425

346

187

136

CS

446

436

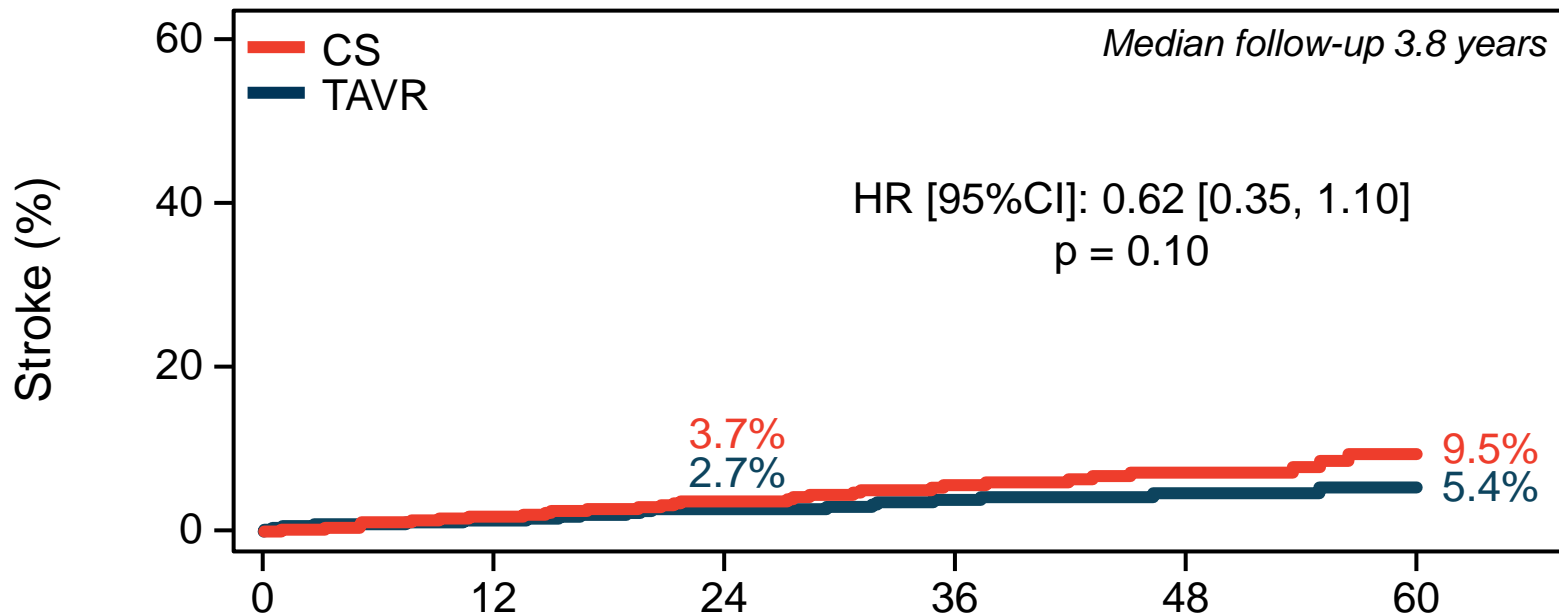
418

310

199

95

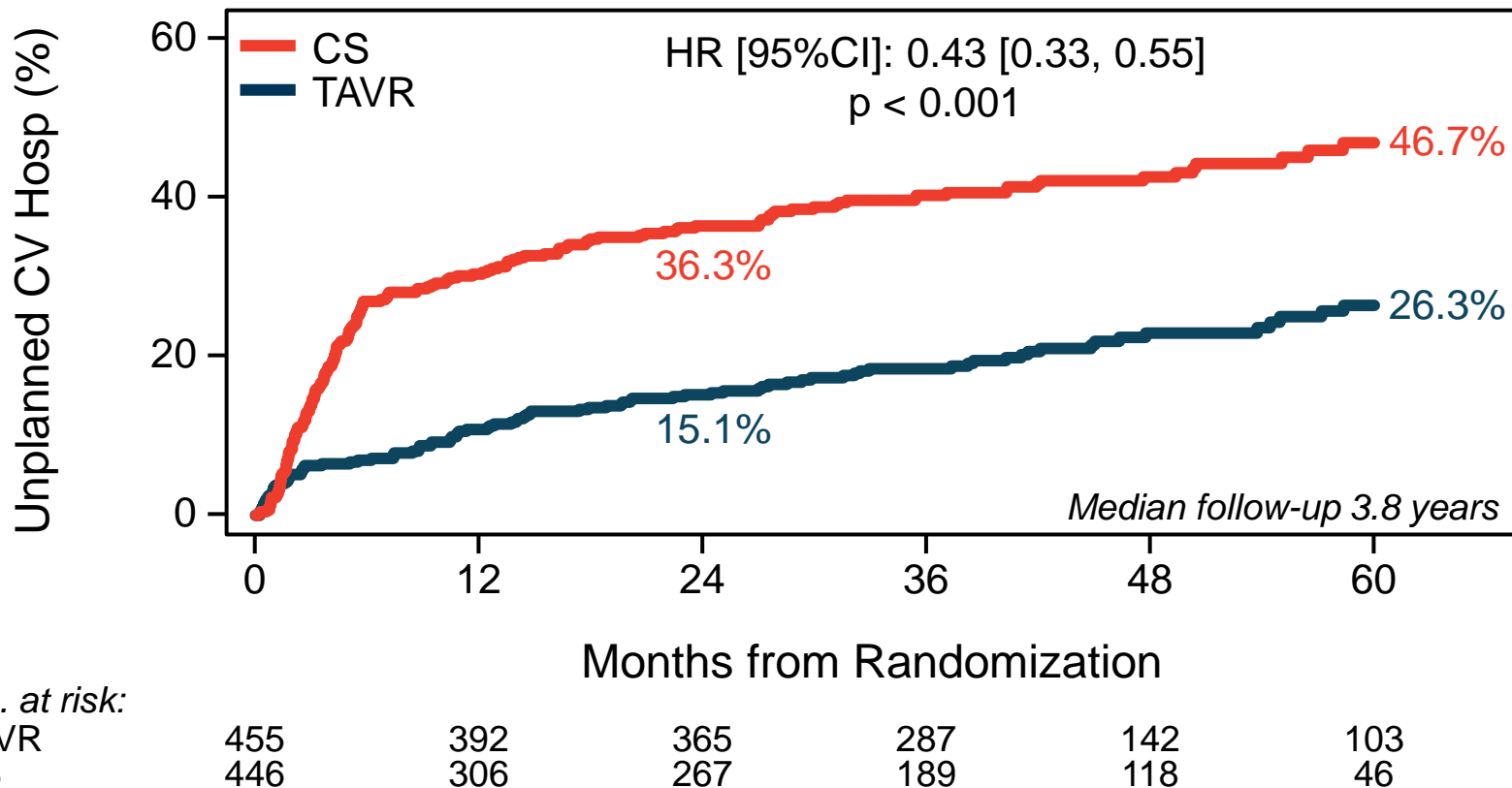
Stroke



No. at risk:

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

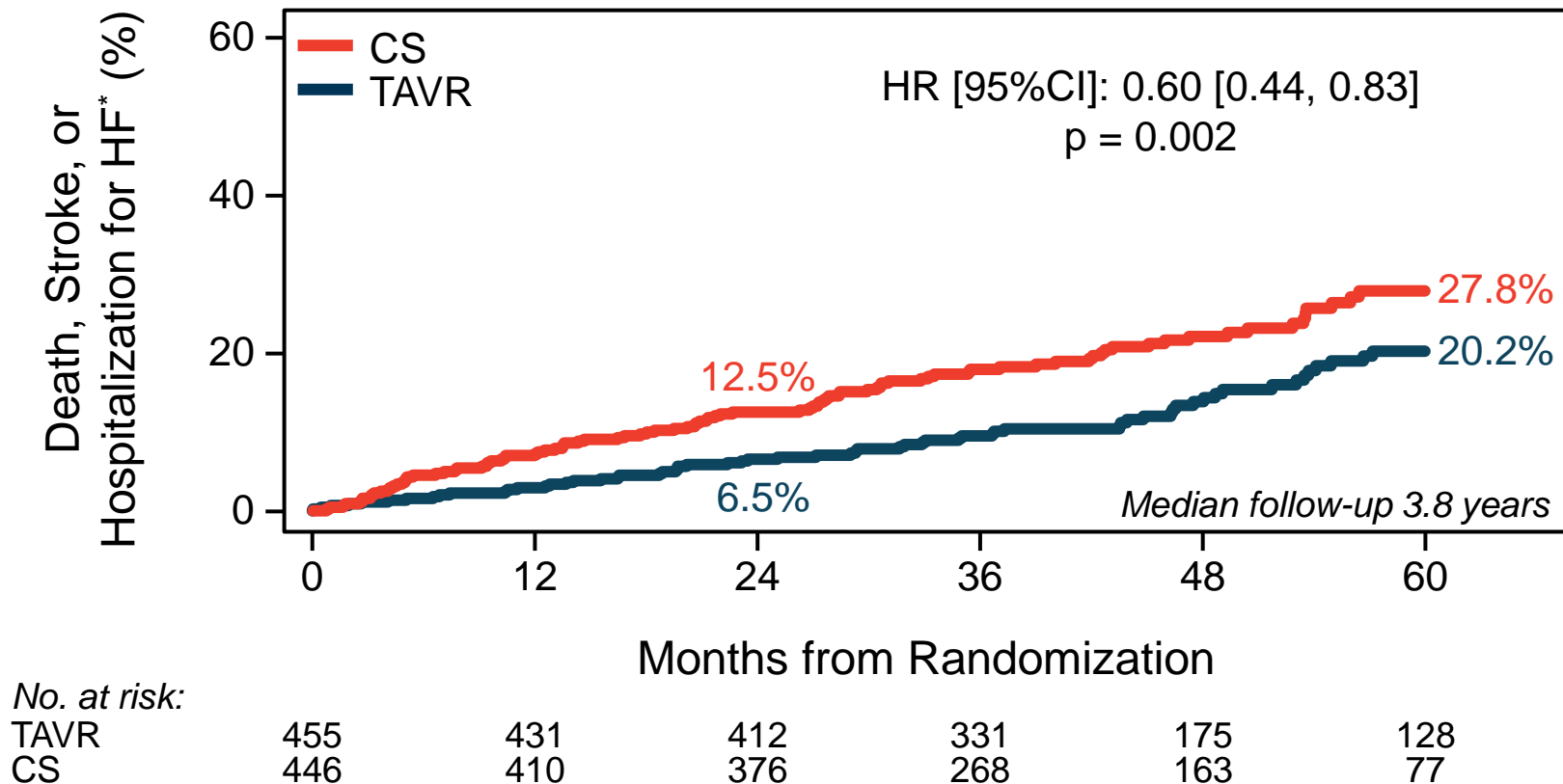
Unplanned CV Hospitalization



No. at risk:
TAVR
CS

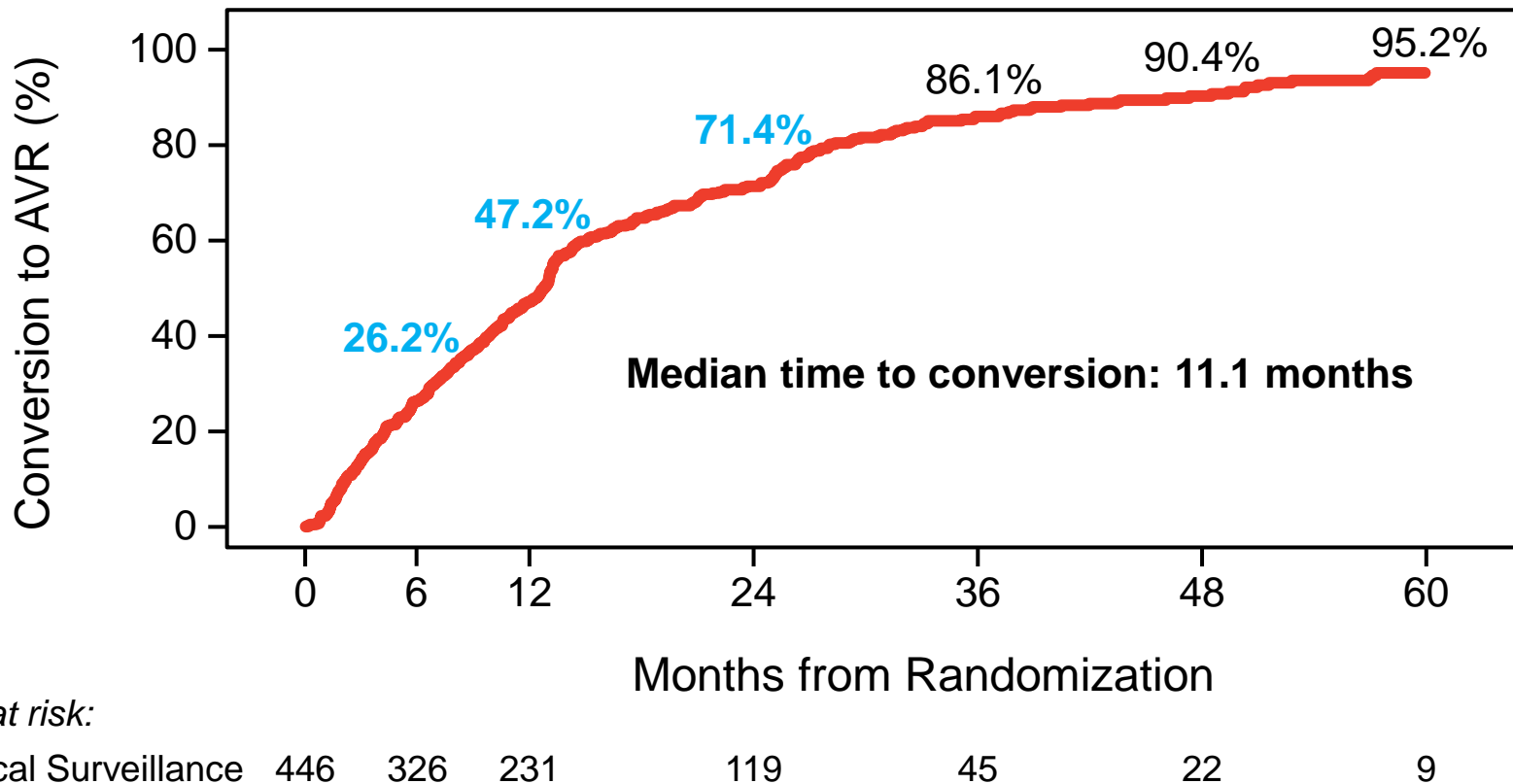
Months from Randomization

Death, Stroke, or Hosp. for HF*



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

Conversion to AVR in CS

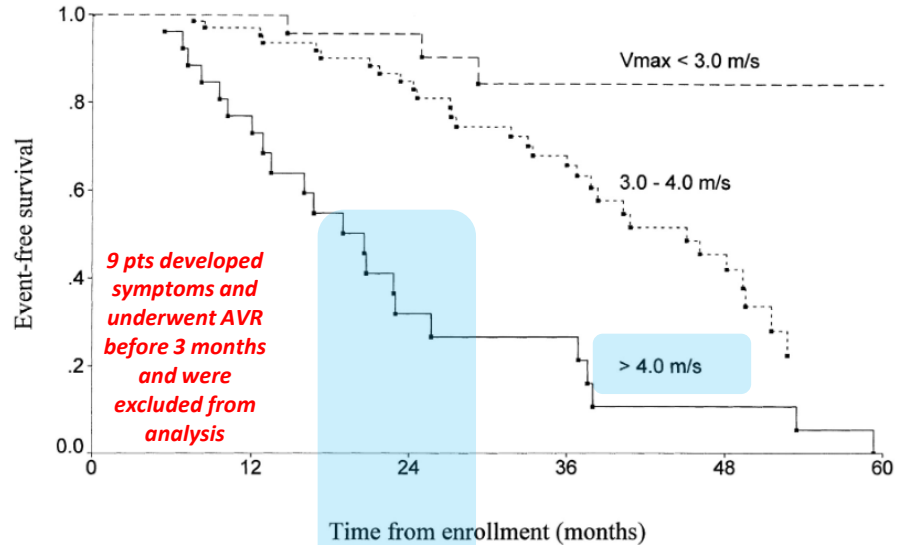


Circulation



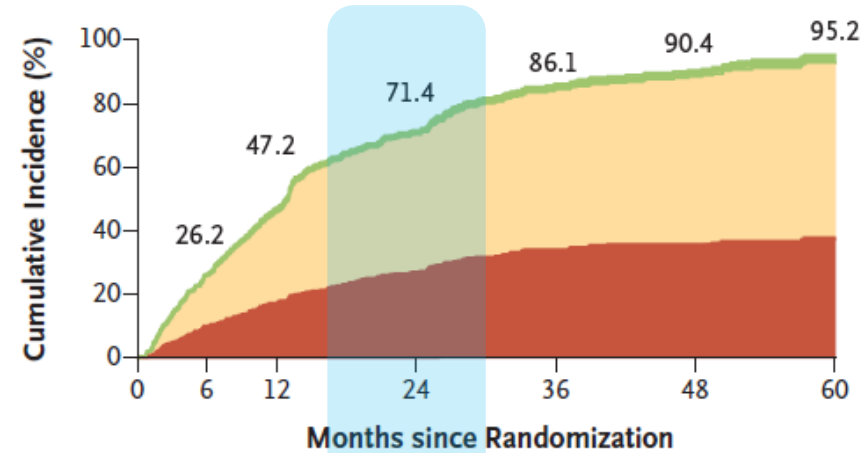
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1997; Otto et al.
Prospective Study of Asymptomatic Valvular AS
N=123 pts
AVR or Death



Time	Asymptomatic	Severe AS
1 year	~30%	
2 years	~70%	
3 years	75%	
4 years	90%	
5 years	95%	

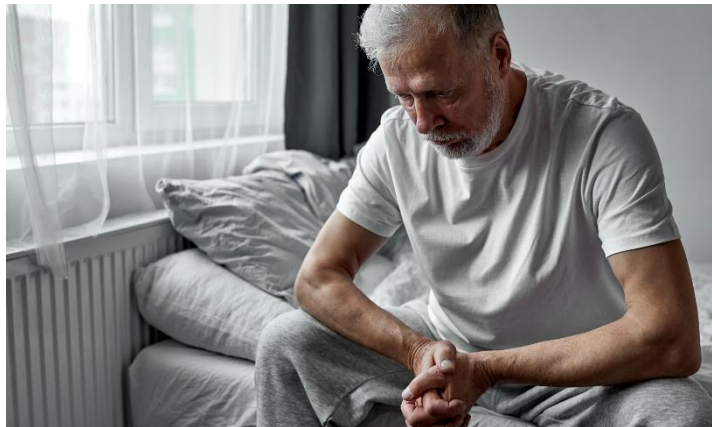
2025; G n reux et al.
TAVR for Asymptomatic Severe AS
N=901 pts
Conversion to AVR



Time	Asymptomatic	Severe AS
1 year	47.2%	
2 years	71.4%	
3 years	86.1%	
4 years	90.4%	
5 years	95.2%	

Natural History of Asymptomatic Severe AS: Otto et al. 1997 almost identical to G n reux et al. 2025 EARLY TAVR

Conversion to AVR due to Anxiety?



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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

ON MY MIND

New Classification to Describe Clinical Presentation in Aortic Stenosis: Stable, Progressive, and Acute Valve Syndrome

Philippe G  n  reux^{id}, MD; Brian R. Lindman^{id}, MD, MSc; Philippe Pibarot^{id}, DVM, PhD



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

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

Syncope

Atrial fibrillation

Ventricular arrhythmia

Resuscitated sudden death/cardiac arrest

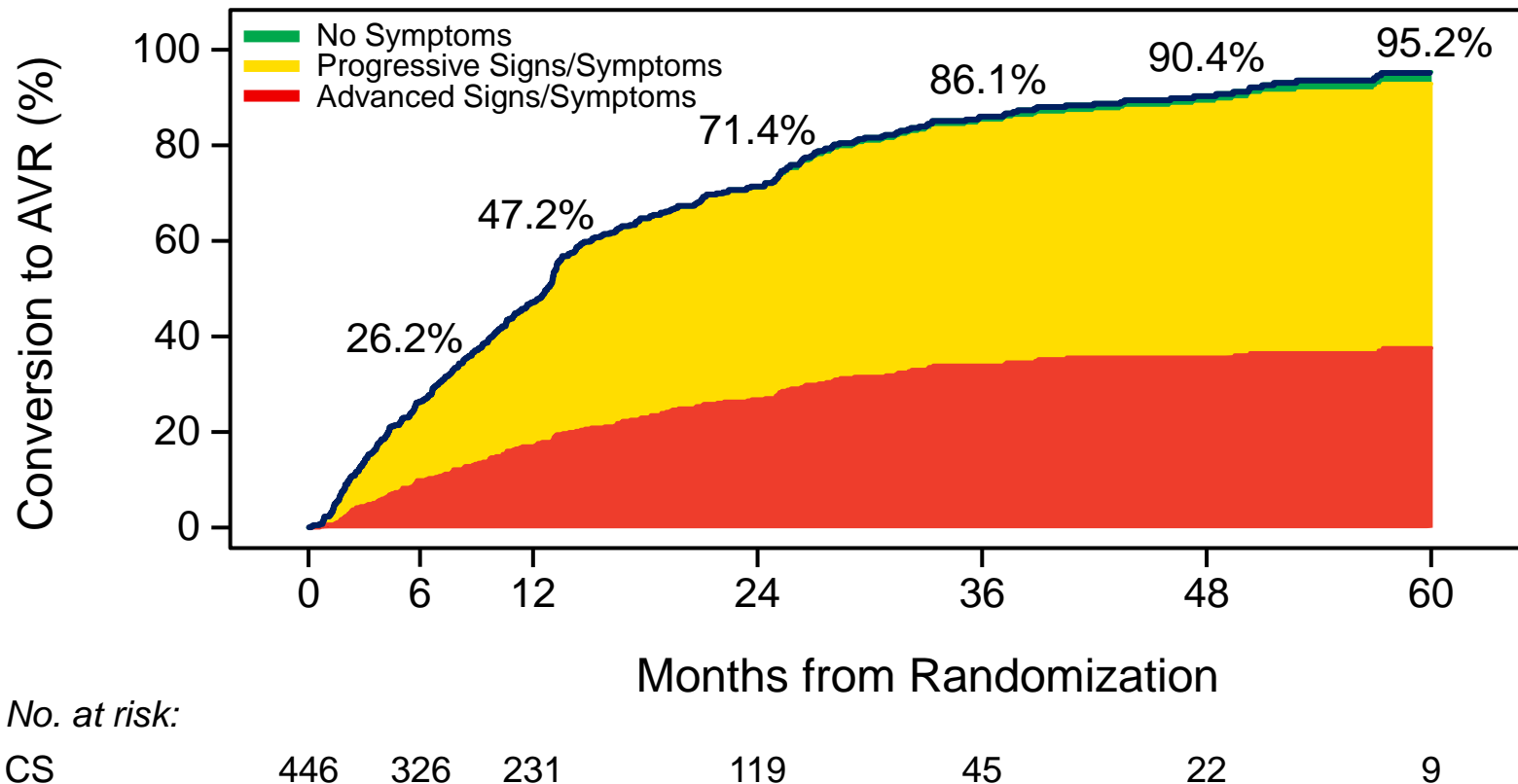
Hospitalization for HF and/or pulmonary edema

LVEF drops to < 50%

≥ 3-fold increase in NT-proBNP from baseline and age-specific threshold*

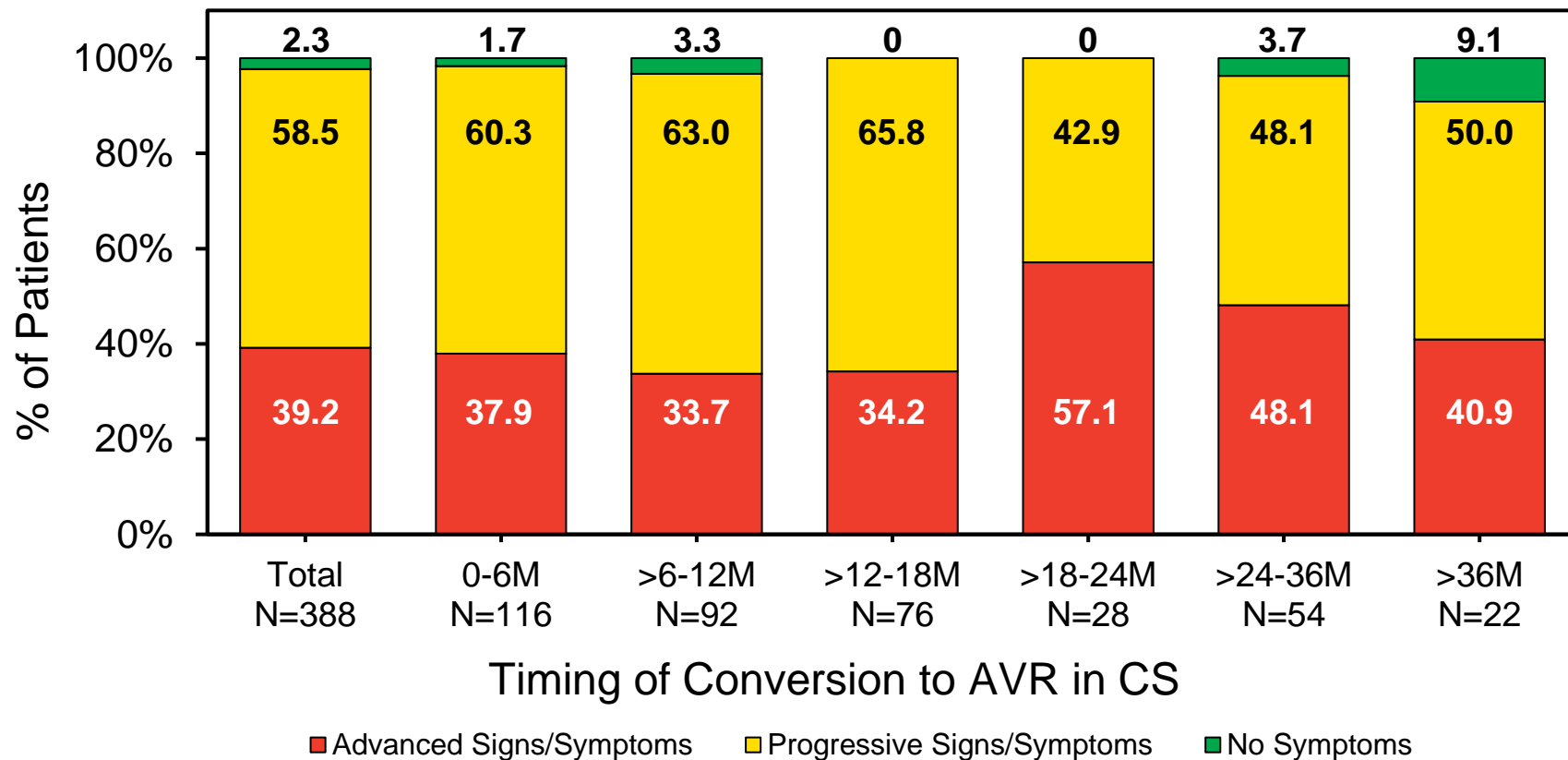
*125 pg/mL for patients ≤ 75 years and 450 pg/mL for > 75 years

Signs & Symptoms at Time of Conversion to AVR



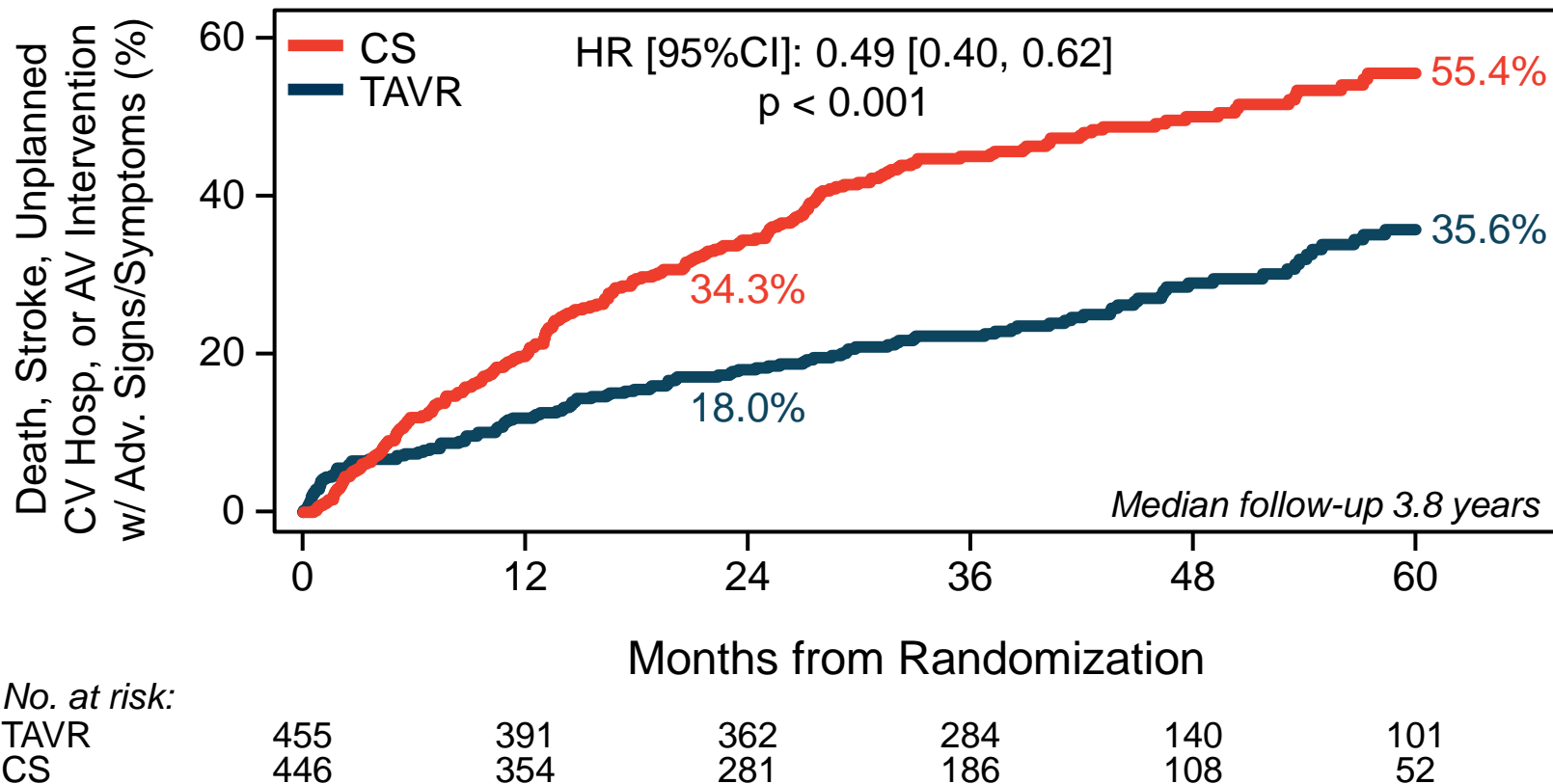
Median follow-up 3.8 years; At the time of analysis, 30 patients were still on study but hadn't converted to AVR

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

Exploratory Analysis of the PE



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**

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

Aortic Valve Replacement vs Clinical Surveillance in Asymptomatic Severe Aortic Stenosis

A Systematic Review and Meta-Analysis

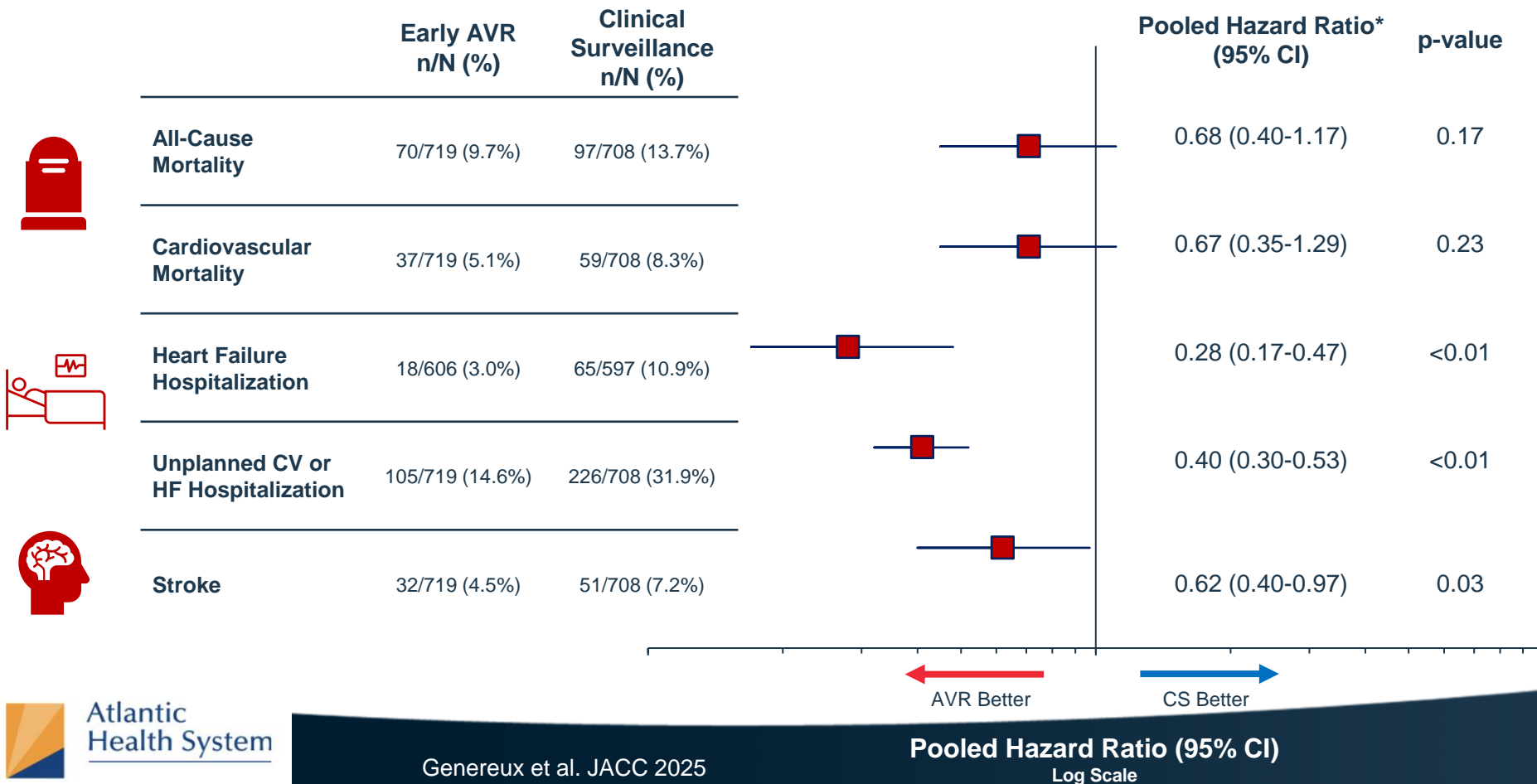
Philippe Généreux, MD,^a Marko Banovic, MD, PhD,^{b,c} Duk-Hyun Kang, MD, PhD,^d Gennaro Giustino, MD,^a Bernard D. Prendergast, MD,^{e,f} Brian R. Lindman, MD,^g David E. Newby, MD, PhD,^h Philippe Pibarot, DVM, PhD,ⁱ Björn Redfors, MD, PhD,^{j,k,l} Neil J. Craig, MD,^m Jozef Bartunek, MD, PhD,ⁿ Allan Schwartz, MD,^o Roxanna Seyedin, PhD, MPH,^p David J. Cohen, MD, MSc,^{q,r} Bernard Iung, MD,^s Martin B. Leon, MD,^{o,r} Marc R. Dweck, MD, PhD^h

EARLY TAVR, EVOLVED, AVATAR, RECOVERY



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Meta-Analysis 4 RCTs Asymptomatic Severe AS





European Society
of Cardiology

European Heart Journal (2025) 00, 1–102
<https://doi.org/10.1093/eurheartj/ehaf194>

ESC GUIDELINES

2025 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Fabien Praz *[†], (ESC Chairperson) (Switzerland), Michael A. Borger *[†], (EACTS Chairperson) (Germany), Jonas Lanz [‡], (ESC Task Force Co-ordinator) (Switzerland), Mateo Marin-Cuarteras [‡], (EACTS Task Force Co-ordinator) (Germany), Ana Abreu  (Portugal), Marianna Adamo (Italy), Nina Ajmone Marsan (Netherlands), Fabio Barili  (Italy), Nikolaos Bonaros  (Austria), Bernard Cosyns  (Belgium), Ruggero De Paulis  (Italy), Habib Gamra  (Tunisia), Marjan Jahangiri (United Kingdom), Anders Jeppsson  (Sweden), Robert J.M. Klautz  (Netherlands), Benoit Mores  (Belgium), Esther Pérez-David  (Spain), Janine Pöss (Germany), Bernard D. Prendergast (United Kingdom), Bianca Rocca  (Italy), Xavier Rossello  (Spain), Mikio Suzuki (Serbia), Holger Thiele  (Germany), Christophe Michel Tribouilloy  (France), Wojtek Wojakowski  (Poland), and ESC/EACTS Scientific Document Group

**ESC**European Society
of CardiologyEuropean Heart Journal (2025) **00**, 1–102<https://doi.org/10.1093/eurheartj/ehaf194>**ESC GUIDELINES****Asymptomatic patients with severe aortic stenosis**

Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause. ^{14,354–359}

I**B**

Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50% as an alternative to close active surveillance, if the procedural risk is low. ^{360–363,367,368}

IIa**A**

Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50% if the procedural risk is low and one of the following parameters is present:

- Very severe AS (mean gradient ≥60 mmHg or $V_{\max} > 5.0$ m/s). ^{14,362,363,482–484}
- Severe valve calcification (ideally assessed by CCT) and V_{\max} progression ≥0.3 m/s/year. ^{303,353,364}
- Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation). ^{97,365}
- LVEF <55% without another cause. ^{14,354,356–359}

IIa**B**

Intervention should be considered in asymptomatic patients with severe AS and a sustained fall in BP (>20 mmHg) during exercise testing.

IIa**C**

360. G  n  reux P, Schwartz A, Oldemeyer JB, Pibarot P, Cohen DJ, Blanke P, et al. Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *N Engl J Med* 2024;**392**:217–27. <https://doi.org/10.1056/NEJMoa2405880>

368. G  n  reux P, Banovic M, Kang DH, Giustino G, Prendergast BD, Lindman BR, et al. Aortic valve replacement vs clinical surveillance in asymptomatic severe aortic stenosis: a systematic review and meta-analysis. *J Am Coll Cardiol* 2024;**85**:912–22. <https://doi.org/10.1016/j.jacc.2024.11.006>

Just Published on-line

The image shows the cover of the journal 'Structural Heart'. It features a red background with a white wireframe illustration of a heart on the left. On the right, the text 'CRF®' is above the title 'Structural Heart' in a large, white, serif font. Below the title is the subtitle 'The Journal of the Heart Team' in a smaller, white, sans-serif font. At the bottom right of the red section, the words 'Open Access' are written in a small, white, italicized font.

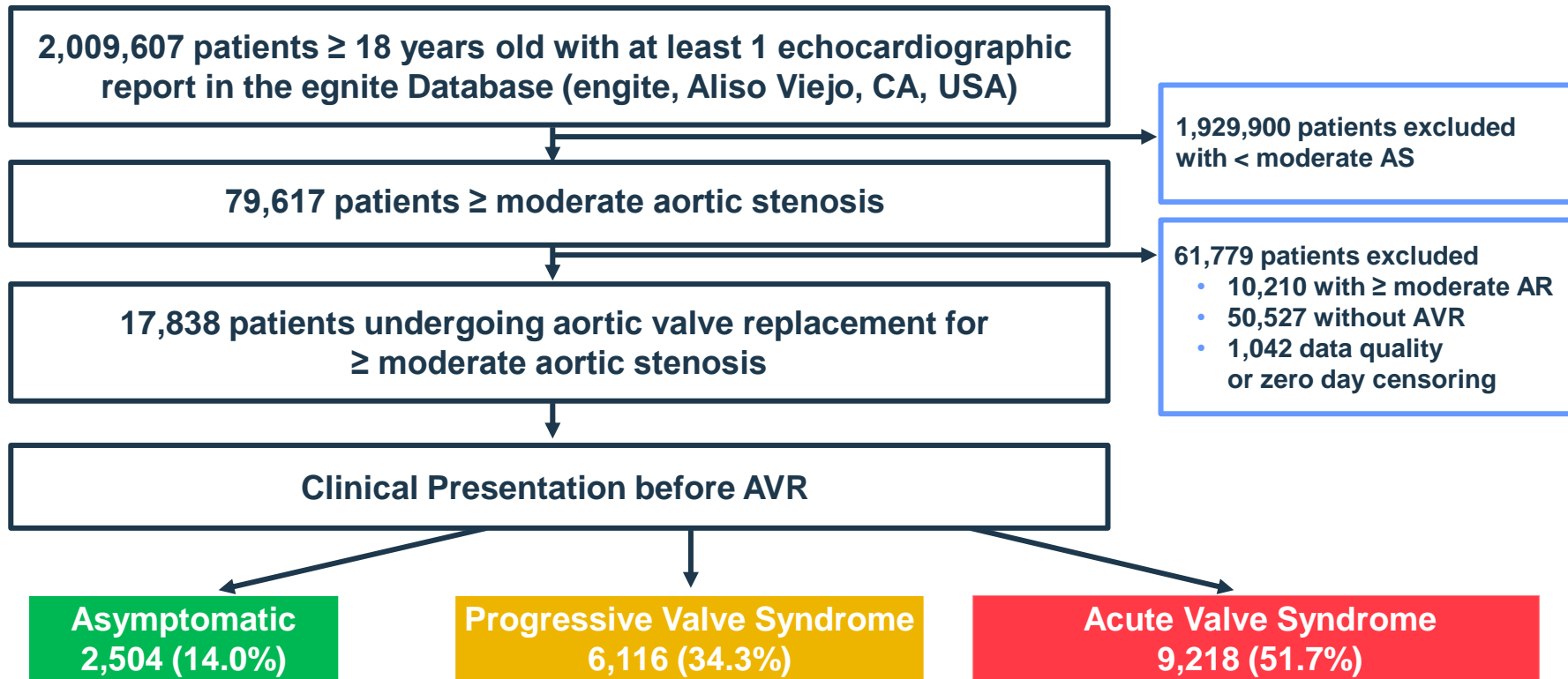
Acute Valve Syndrome in Aortic Stenosis

Philippe Généreux, MD Patricia A. Pellikka, MD, Brian R. Lindman, MD, MSCI, Philippe Pibarot, DVM, PhD, Santiago Garcia, MD, Konstantinos P. Koulogiannis, MD, Evelio Rodriguez, MD, Vinod H. Thourani, MD, Michael Dobbles, MS, Gennaro Giustino, MD, Rahul P. Sharma, MBBS, David J. Cohen, MD, MSc, Allan Schwartz, MD, Martin B. Leon, MD, Linda D. Gillam, MD, MPH



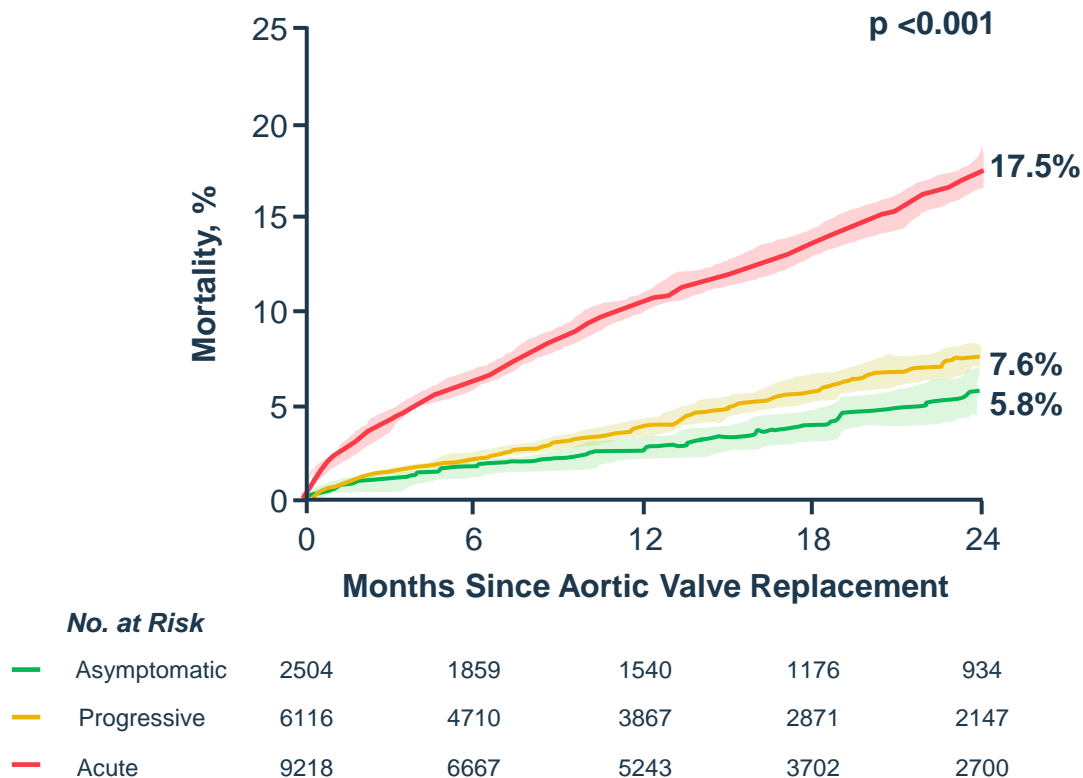
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Study Flow Chart



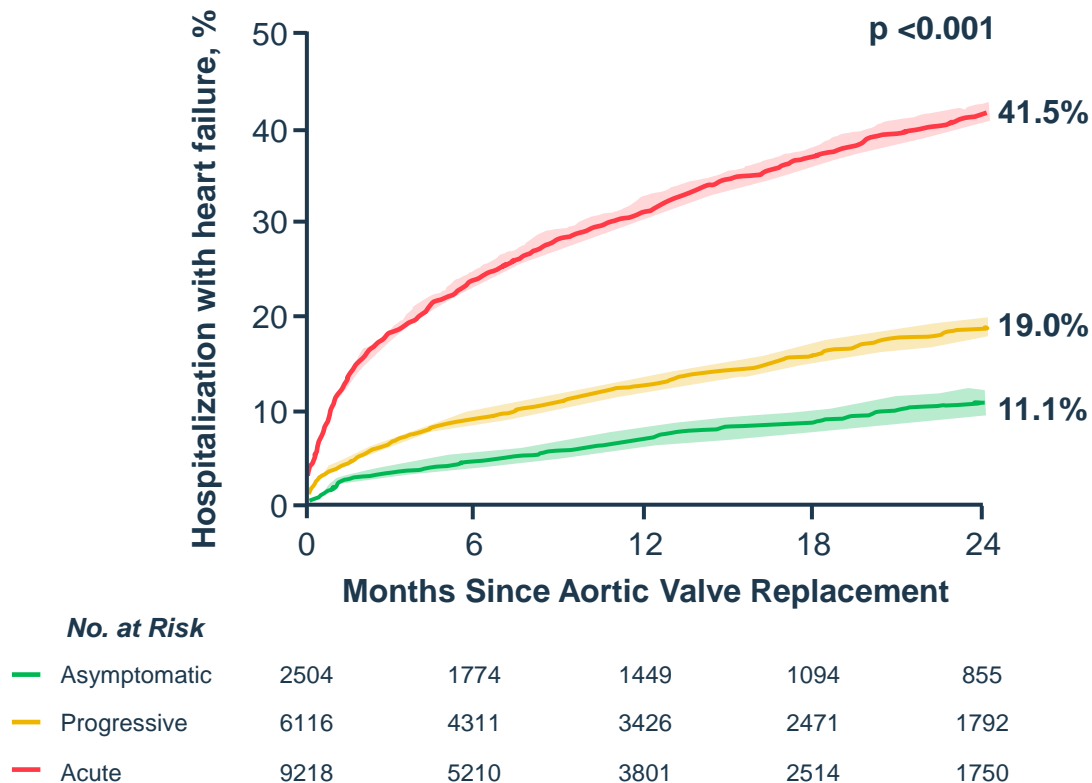
2-Year Mortality After AVR Per Clinical Presentation

ASx vs. Progressive vs. **Acute Valve Syndrome**

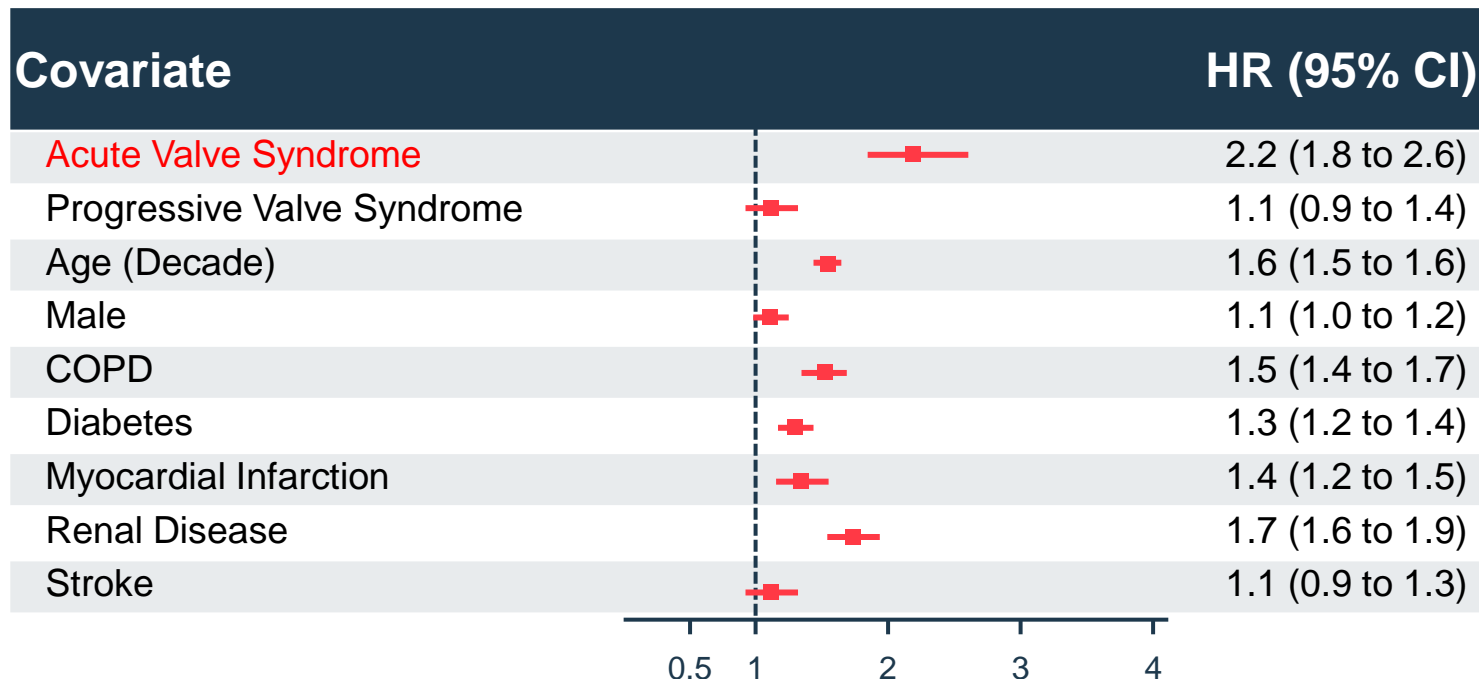


2-Year HF Hospitalization After AVR Per Clinical Presentation

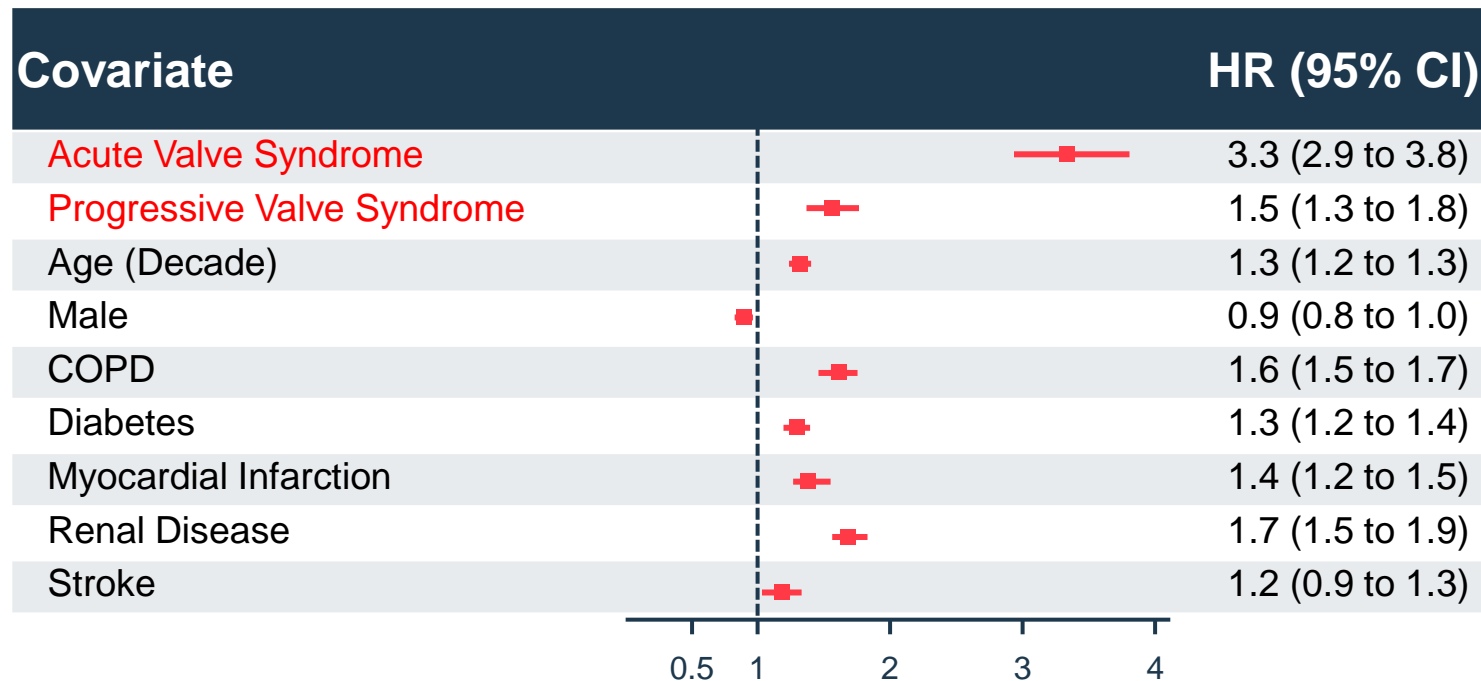
ASx vs. Progressive vs. **Acute Valve Syndrome**



Predictor of 2-Year Mortality after AVR
















2-Year Hospitalization with Heart Failure after AVR



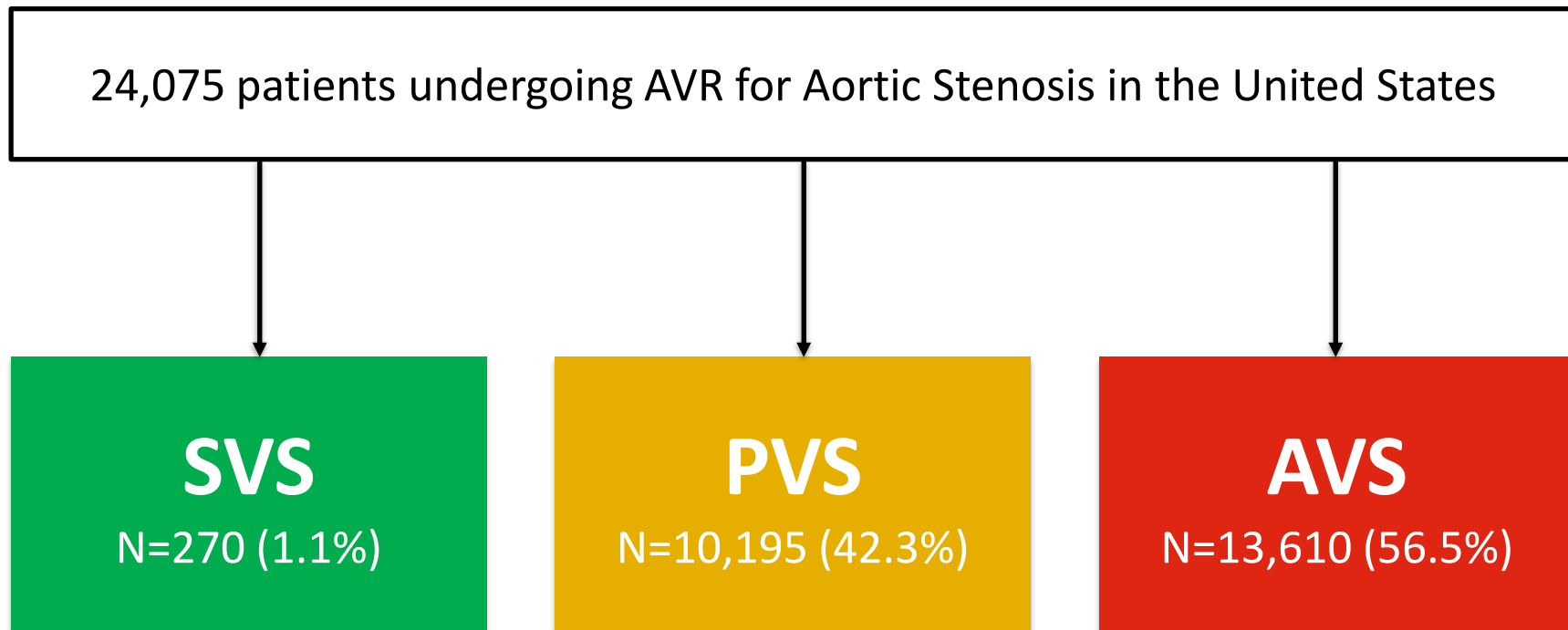
ORIGINAL RESEARCH

Acute Valve Syndrome Before Aortic Valve Replacement: Impact on Clinical Outcomes, Health Care Costs, and Resource Use

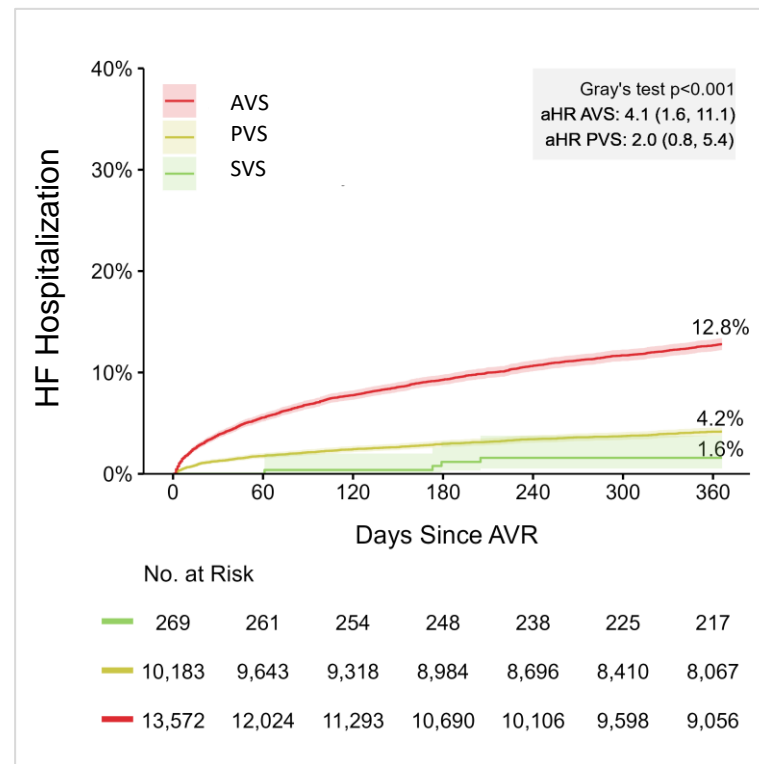
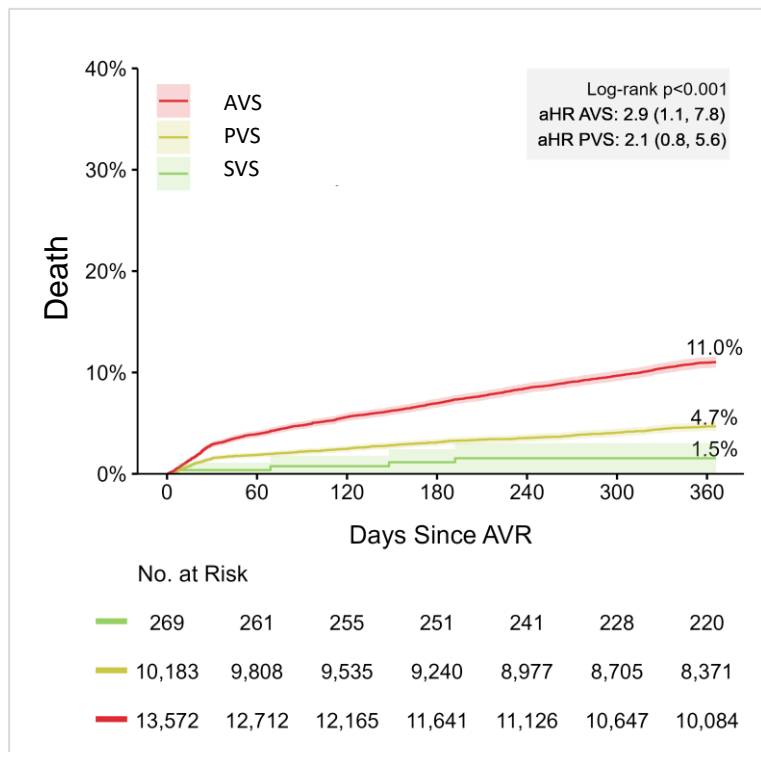
Philippe G  n  reux , MD; Gennaro Giustino, MD; Brian R. Lindman , MD; Philippe Pibarot , DVM, PhD; Suzanne J. Baron , MD, MSc; Chantal Asselin , MD; Alissa Dratch , MPH; Shannon M. E. Murphy , MA; Soumya Chikermane , PhD; Vinod H. Thourani, MD; Kostantinos P. Koulogiannis , MD; Allan Schwartz , MD; Martin B. Leon , MD; Patricia P. Pellikka , MD; Linda D. Gillam , MD, MPH



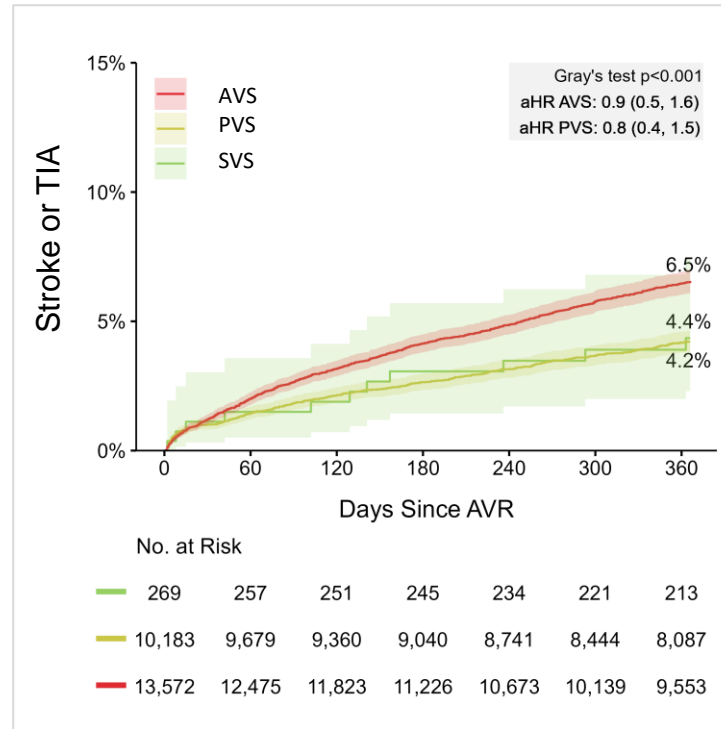
Study Cohort: Clinical Presentation Before AVR



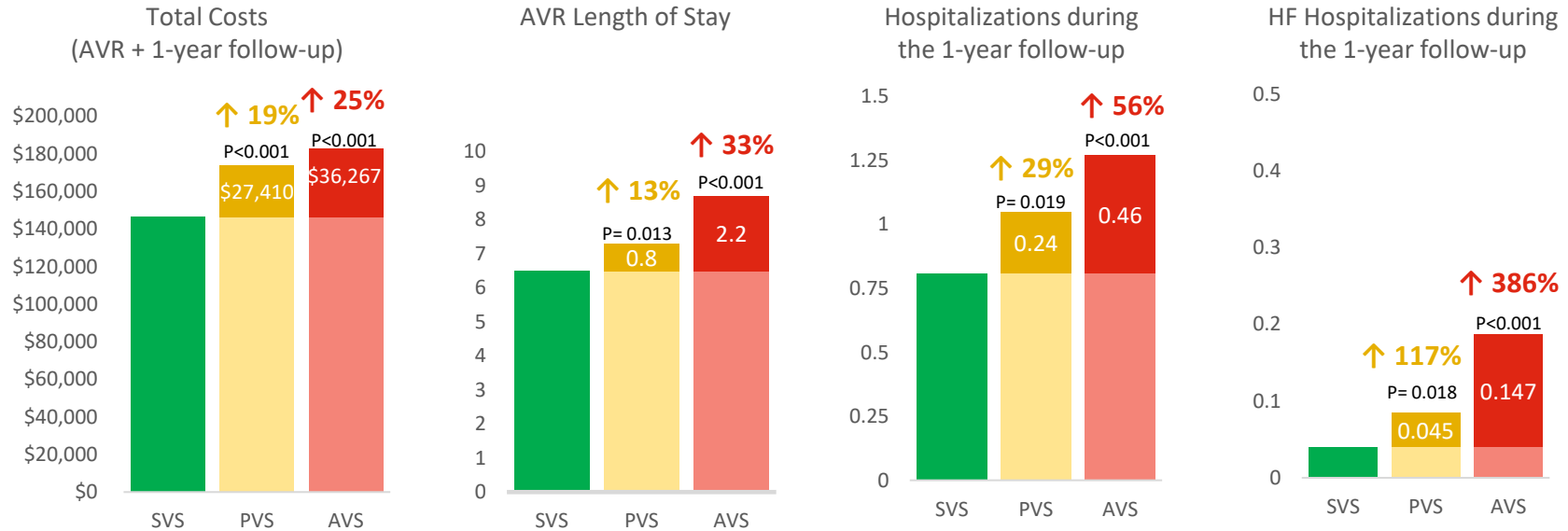
Acute Valve Syndrome is Associated with Increased Risk of Death and HF Hospitalization Post-AVR



Acute Valve Syndrome is Associated with Increased Risk of Stroke Post-AVR

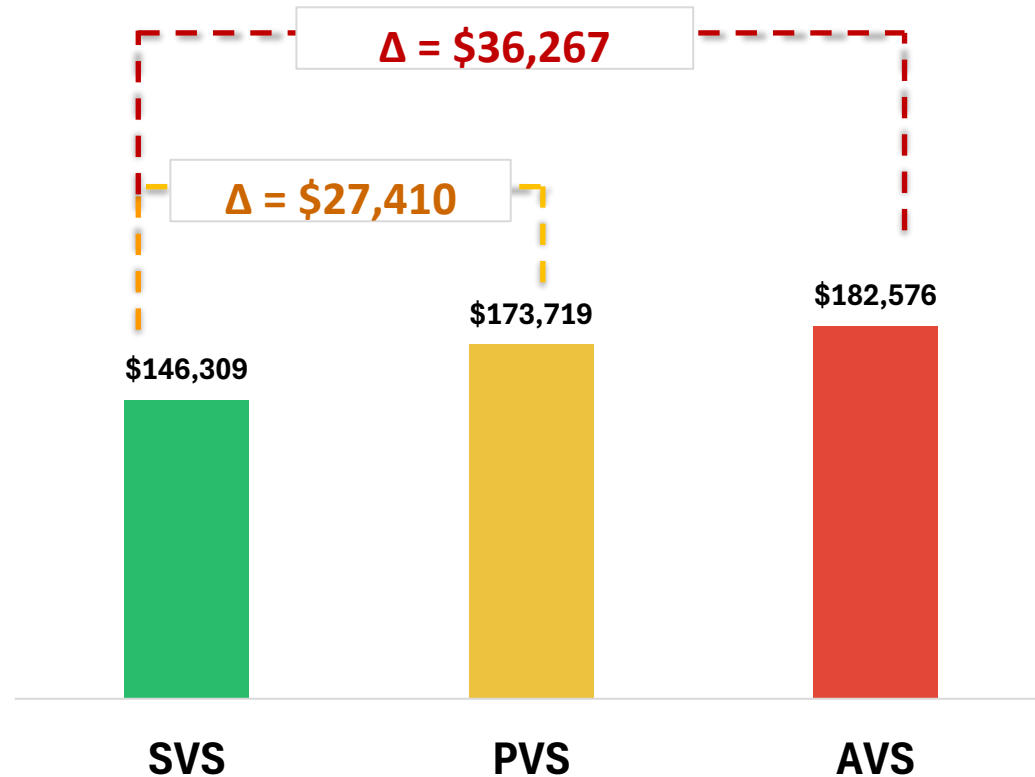


Healthcare Cost and Utilization by Clinical Presentation before AVR



AVS and PVS before AVR are associated with higher total costs, increased LOS, higher all-cause and HF hospitalizations post AVR.

Total Healthcare Cost Up to 1 year after AVR Across Clinical Presentation



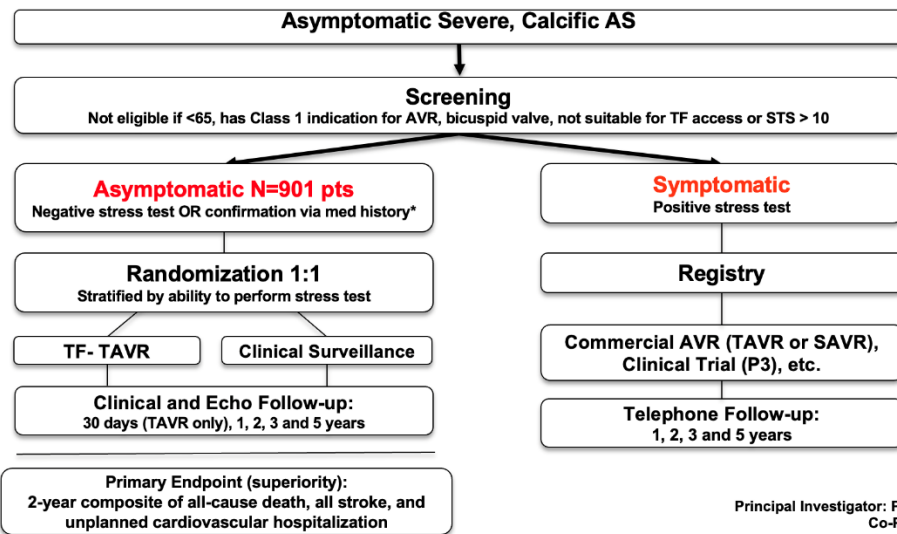
Post EARLY TAVR:

What do I say to My Patients? To Referring Physicians?

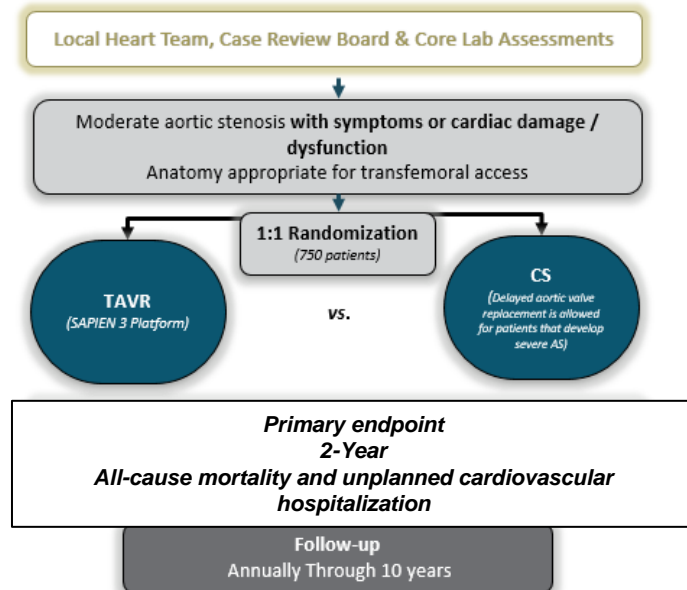
- **Refer early** (Severe AS no symptoms or Moderate AS)
- **Complete workup for AS treatment**
 - CT-Scan for procedural planning
 - Dental work
 - Plan your AVR date ahead of time **to avoid AVS**
 - If you wait for symptoms, **treat within 3 months of symptoms onset** to mitigate mortality risk of longer waiting period
- **There was no penalty to early intervention**
 - Prompt Treatment will save heart failure hospitalization, stroke, and AVS
 - Prompt Treatment will save cardiac damage and \$\$\$ to the Health Care System

The Future of TAVR?

Prevention of Cardiac Damage



Principal Investigator: Philippe Généreux, MD
Co-PI: Allan Schwartz, MD
Chair: Martin B. Leon, MD



Conclusion

Future of Aortic Stenosis Management

- Screening will become key to detect significant (moderate, severe) AS
- Early Referral to ensure adequate and preemptive procedural planning
- Timely and prompt AVR is key; don't wait for symptoms >3 months
- Lifetime management is important while planning the first intervention

