

Asymptomatic Severe Aortic Stenosis: Ongoing Trials and Updated Evidence

Duk-Woo Park, MD., PhD.

Division of Cardiology, University of Ulsan College of Medicine,
Heart Institute, Asan Medical Center, Seoul, Korea

Conflict of Interest Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Consulting Fees/Honoraria

Company

Edwards LifeSciences

Medtronic Inc

Boston Scientific

>15 Years of TAVR



15 min Post-TAVR

April 16, 2002; FIM-TAVR, Trans-septal

Clinical Trials

Trial Name	STS Score	Age
Inoperable Population		
PARTNER IB Trial (2010)	11.6	83
High Risk Population (>8)		
PARTNER IA Trial (2011)	11.8	84
CoreValve US Pivotal Trial (2014)	7.4	83
Intermediate Risk Population (4-8)		
PARTNER II Trial (2016)	5.8	82
Low Risk Population (<4)		
NOTION Trial (2015)	3.0	79
PARTNER III (2019)	1.9	73
Evolut Low Risk Trial (2019)	1.9	74

Innovation in TAVR

**Remaining
Clinical Needs**

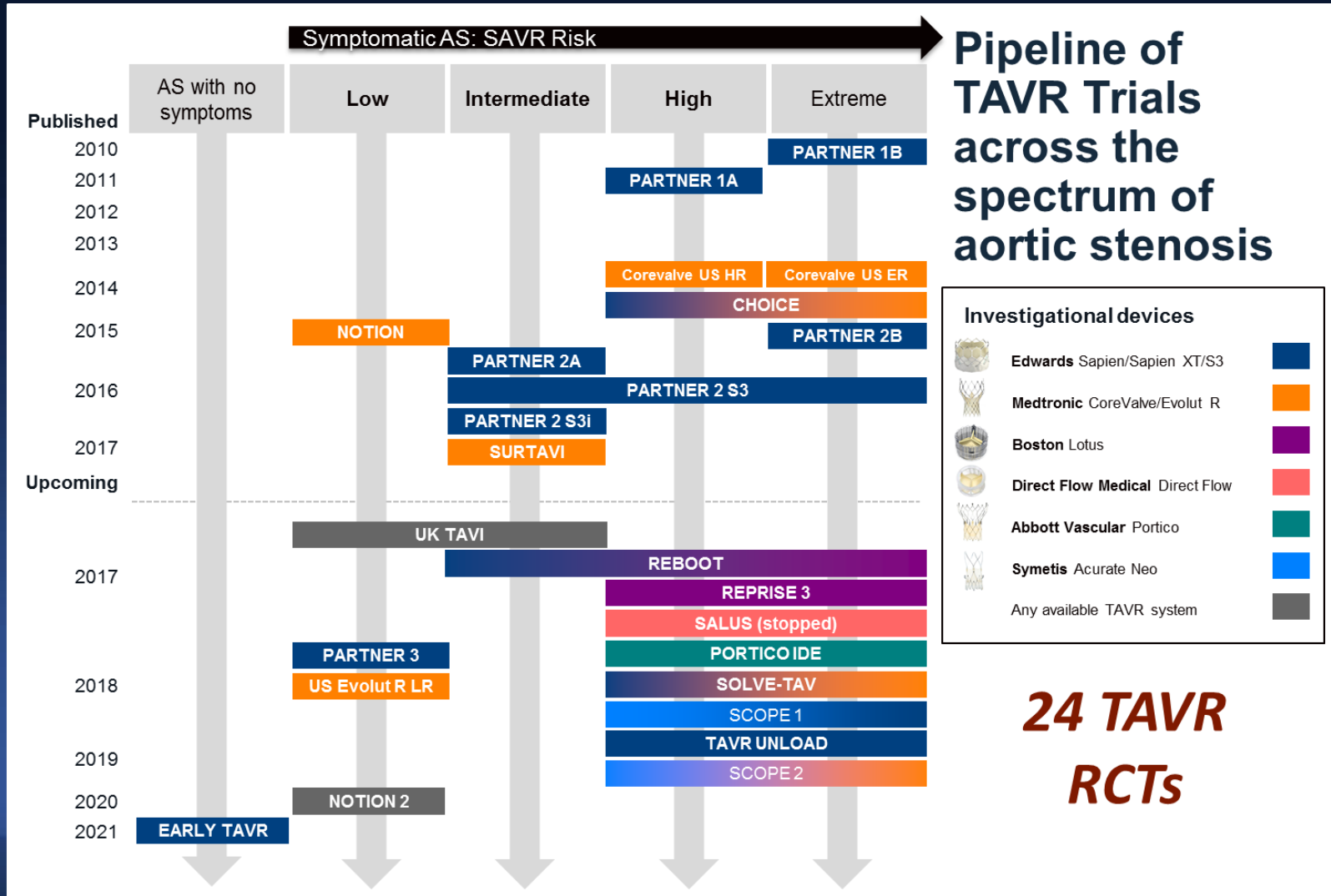
Innovation in TAVR

Remaining Clinical Needs

- Bicuspid AV disease
- AS + concomitant disease (CAD, MR, AF)
- Severe asymptomatic AS
- Moderate AS + CHF
- Durability concerns (including valve leaflet thrombosis) and coronary obstruction/access
- Adjunct Pharmacotherapy
- High-risk severe AR

Landscape of TAVR - 2019

Clinical Research



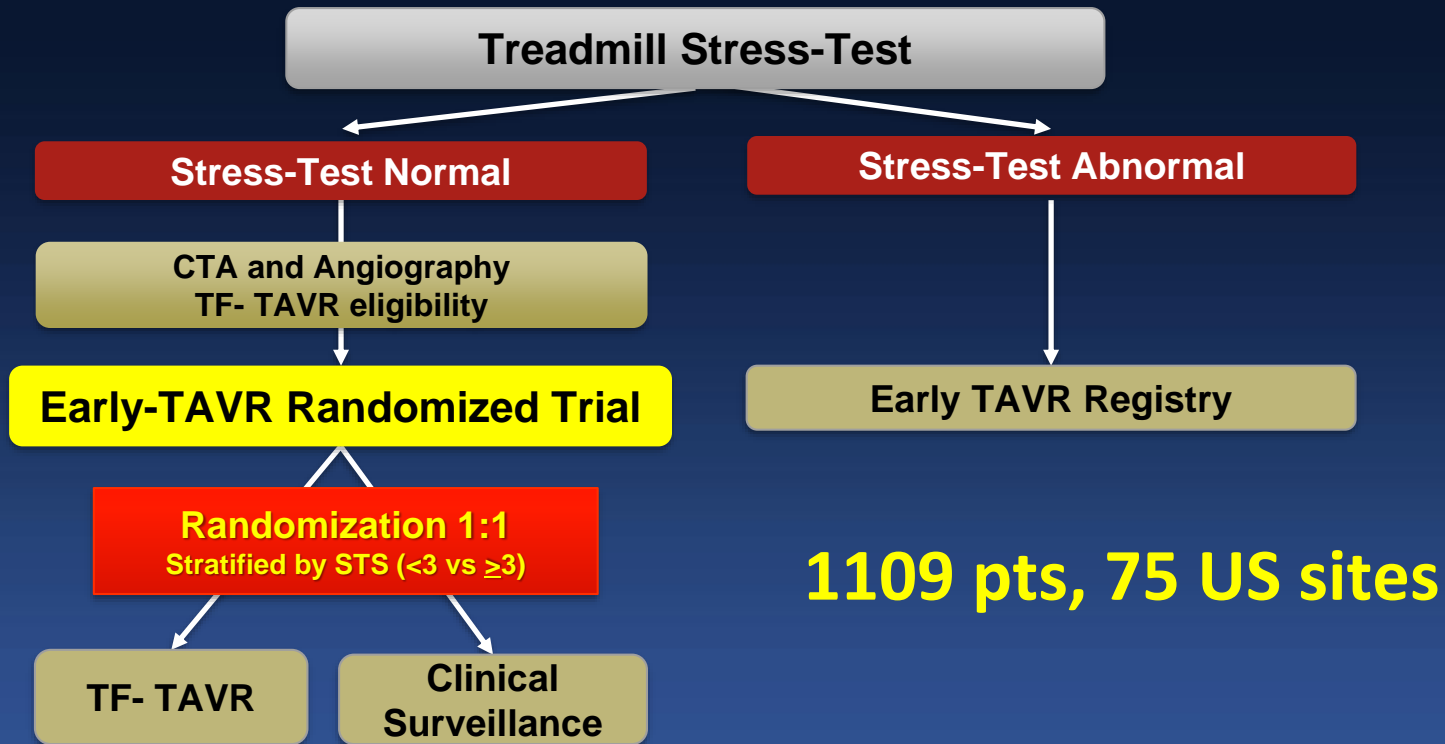
Severe Asymptomatic AS

- In “truly” asymptomatic severe AS patients (negative stress tests), the **CV event rate is ~50% at two years** with conservative management
- The strategy of **“watching waiting” is problematic** resulting in many lost opportunities for optimal outcomes (preservation of LV mechanics, clinical benefits)
- **In the “modern era” of TAVR (1% mortality, 1% strokes) earlier intervention is now possible, but more robust clinical evidence in the form of careful RCTs is clearly needed to support a strong recommendation!**

EARLY TAVR Trial: Severe Asymptomatic AS

Study Flow

Asymptomatic Severe AS and 2D-TTE (PV $\geq 4\text{m/s}$ or AVA $\leq 1\text{ cm}^2$)
Exclusion if patient is symptomatic, age < 65 yo, EF $< 50\%$, concomitant surgical indications, or STS > 8



Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)

Principal Investigators:
Philippe G n reux, Allan Schwartz
Chair: Martin B. Leon

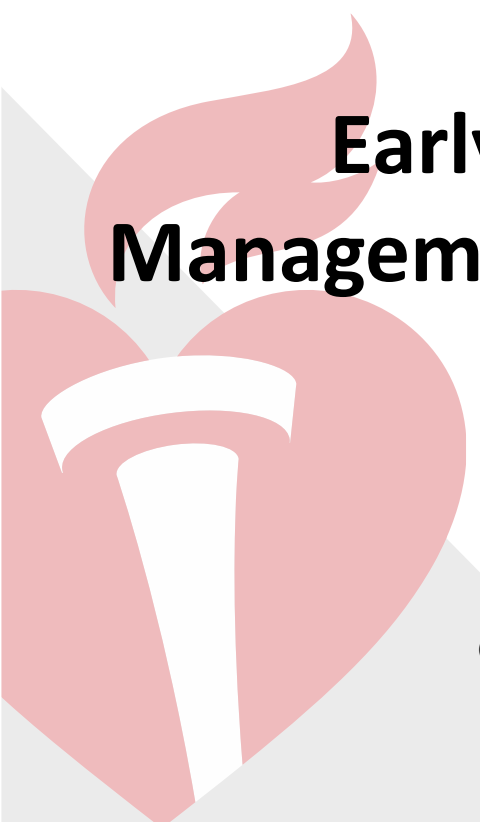


The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

Duk-Hyun Kang, M.D., Ph.D., Sung-Ji Park, M.D., Ph.D., Seung-Ah Lee, M.D.,
Sahmin Lee, M.D., Ph.D., Dae-Hee Kim, M.D., Ph.D.,
Hyung-Kwan Kim, M.D., Ph.D., Sung-Cheol Yun, Ph.D.,
Geu-Ru Hong, M.D., Ph.D., Jong-Min Song, M.D., Ph.D.,
Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D.,
Jae-Won Lee, M.D., Ph.D., and Seung-Woo Park, M.D., Ph.D.

A stylized graphic on the left side of the slide. It features a light red heart shape with a white aortic valve in the center. The valve is depicted with a white leaflet and a white stent-like structure. The heart and valve are set against a light gray background that transitions into a white background for the rest of the slide.

Early Surgery versus Conventional Management for Asymptomatic Severe Aortic Stenosis

Duk-Hyun Kang MD PhD

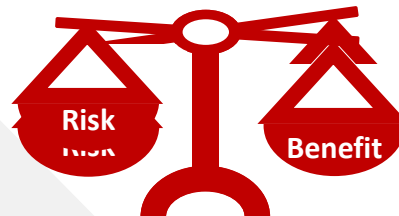
on behalf of the RECOVERY Investigators

**Asan Medical Center
Seoul, Korea**

AHA 2019 Late Breaking Trial

Introduction

- Although aortic valve replacement (AVR) is the only effective therapy for symptomatic severe aortic stenosis (AS), optimal timing for AVR in *asymptomatic* severe AS remains controversial
- In asymptomatic patients, the potential benefit of preventing sudden death may not be greater than the risk of AVR
- Watchful observation is recommended for the majority of asymptomatic patients, with AVR planned once symptoms develop
- Recent advances in surgery may change the risk-to-benefit ratio



Method: Study Design and Patients

RECOVERY A prospective, multicenter, open-label, randomized trial to compare long-term clinical outcomes of early surgical AVR vs. conservative management in asymptomatic pts with very severe AS

Inclusion	Exclusion
<ul style="list-style-type: none">▪ Age 20-80 years	<ul style="list-style-type: none">▪ Presence of symptoms (exertional dyspnea, syncope, or angina)
<ul style="list-style-type: none">▪ Very severe AS (defined as $AVA \leq 0.75 \text{cm}^2$ with peak aortic jet velocity $\geq 4.5 \text{m/s}$ or mean trans-aortic gradient $\geq 50 \text{mmHg}$)	<ul style="list-style-type: none">▪ LV ejection fraction $< 50\%$▪ Significant aortic regurgitation▪ Significant mitral valve disease
<ul style="list-style-type: none">▪ Candidates for early surgery	<ul style="list-style-type: none">▪ Previous cardiac surgery
<ul style="list-style-type: none">▪ Informed consent	<ul style="list-style-type: none">▪ Positive exercise test

Clinicaltrials.gov NCT01161732

Method: Study Procedures

- Patients were randomly assigned on a 1:1 basis to early surgery or conventional treatment using a Web-based interactive response system
- **In the early surgery group**, AVR should be performed within 2 months of randomization
- **Patients in the conventional treatment group** were treated according to the current guidelines and referred for AVR if they became symptomatic, LV EF < 0.50 or an increase in peak aortic velocity > 0.5 m/s per year

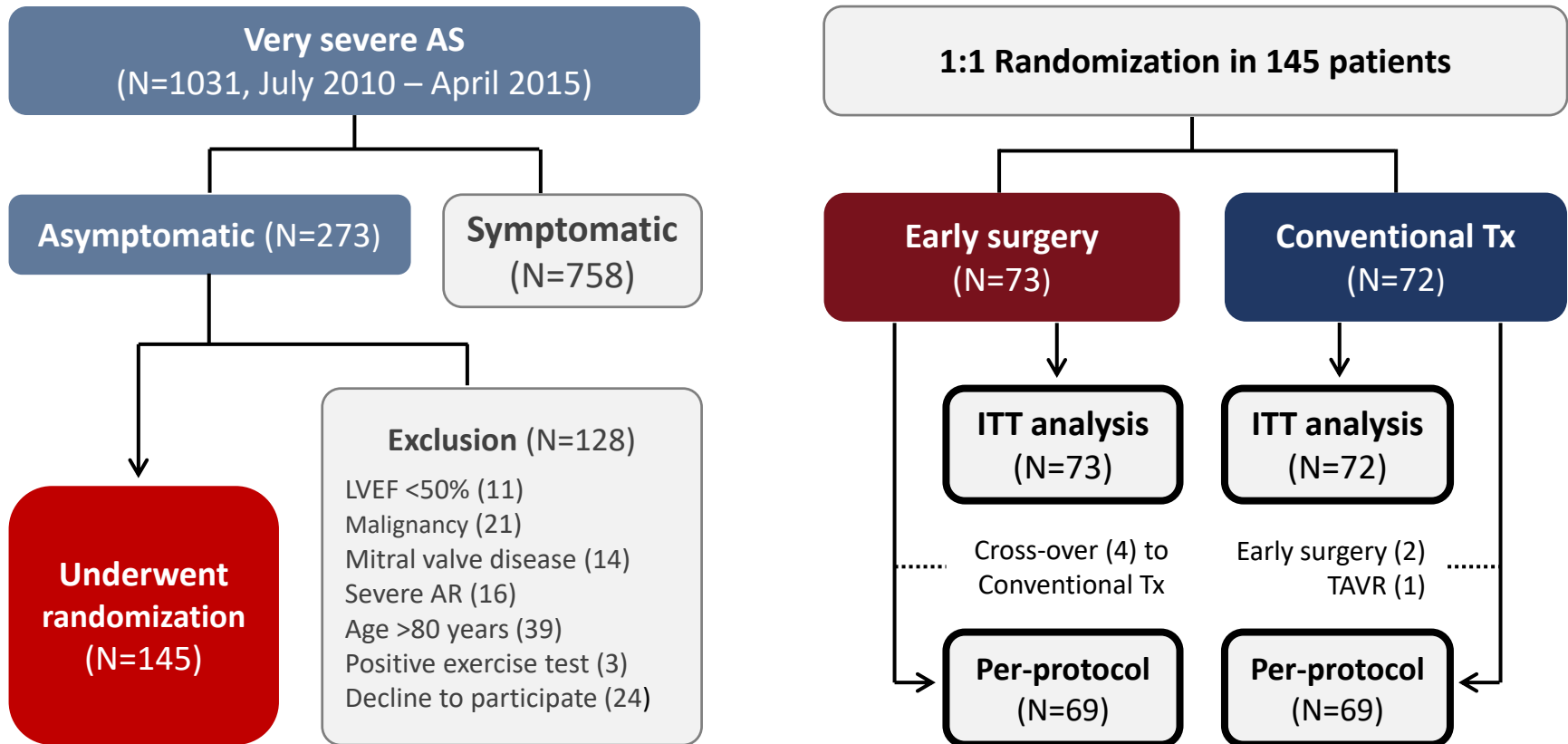
Method: Endpoints

Hypothesis Early surgery would reduce the risk of cardiovascular mortality as compared with conservative management

End point	Sample size
<ul style="list-style-type: none">▪ Primary end point*<ul style="list-style-type: none">- Operative mortality- Cardiovascular death▪ Secondary end point*<ul style="list-style-type: none">- All-cause death- Repeat aortic valve surgery- Clinical thromboembolic event- Hospitalization for CHF	<ul style="list-style-type: none">▪ Assumptions<ul style="list-style-type: none">- Event rate of 2% in early surgery vs. 16% in conventional group during minimum follow-up of 4 years (<i>Kang DH et al. Circulation 2010</i>)- 80% Power at 2-sided significance level of 0.05▪ Estimated sample N=144

*occurred during 4-year follow-up period after enrollment of the last patient

Results: Study Flow



Clinicaltrials.gov NCT01161732

Results: Baseline Characteristics

Patient characteristics			Echocardiographic Findings		
	Conventional (n=72)	Early AVR (n=73)		Conventional (n=72)	Early AVR (n=73)
Age (years)	63±11	65±8	Peak AV jet velocity (m/s)	5.0±0.4	5.1±0.5
Male	34 (47%)	37 (51%)	Mean AV PG (mmHg)	63±12	64±14
Diabetes	7 (10%)	13 (18%)	Aortic valve area (cm ²)	0.64±0.09	0.63±0.09
Hypertension	39 (54%)	40 (55%)	LV mass index (g/m ²)	134±31	136±38
Coronary disease	1 (2%)	5 (7%)	LV ejection fraction (%)	65±4	65±5
Previous stroke	3 (4%)	3 (4%)	Cause of AS		
Atrial fibrillation	6 (8%)	3 (4%)	Bicuspid	39 (54%)	49 (67%)
Creatinine (mg/dl)	0.8±0.2	0.8±0.2	Degenerative	26 (36%)	22 (30%)
EuroSCORE II (%)	0.9±0.4	0.9±0.3	Rheumatic	7 (10%)	2 (3%)

Results: AVR Procedures

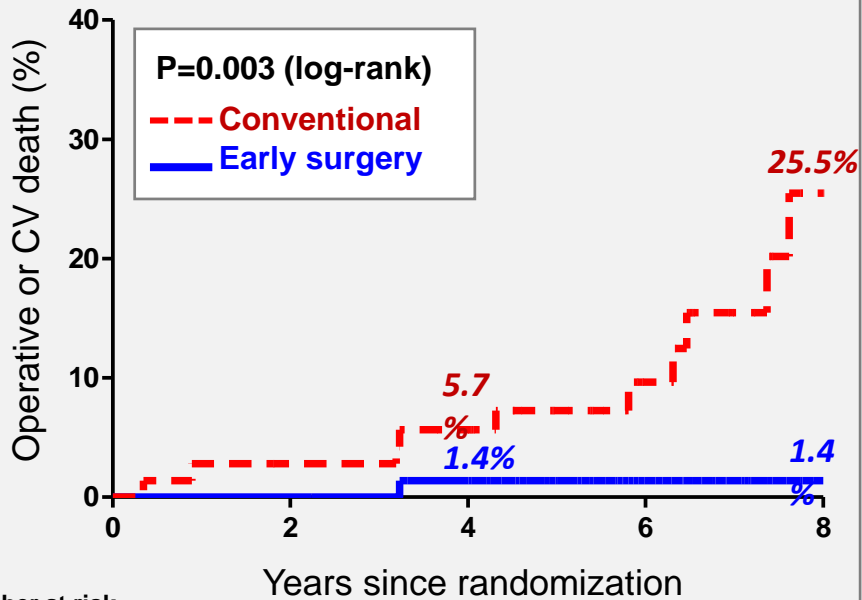
	Conventional Treatment (n=72)	Early Surgery (n=73)
Performance of AVR	53 (74%)	72 (99%)
Early surgery	2 (4%)	69 (96%)
Urgent surgery	9 (17%)	0 (0%)
Mechanical prosthesis	21 (40%)	36 (50%)
CABG	1 (2%)	5 (7%)
Replacement of aorta	8 (15%)	7 (10%)
Operative mortality	0 (0%)	0 (0%)
Stroke	0 (0%)	1 (1%)
Myocardial infarction	1 (2%)	0 (0%)
Reoperation	0 (0%)	0 (0%)

Results: End Points

	Conventional	Early surgery	Hazard ratio	P value
Primary end point (Operative or CV death)	11 (15.3%)	1 (1.4%)	0.09 (0.01-0.67)	0.003
Secondary end point				
▪ All-cause mortality	15 (20.8%)	5 (6.8%)	0.33 (0.12-0.90)	0.030
▪ Thromboembolic events	4 (5.6%)	1 (1.4%)	0.30 (0.04-2.31)	0.25
- Stroke	3	1		
- Myocardial infarction	1	0		
▪ Repeat AV surgery	2 (2.8%)	0 (0%)	0.19 (0.10-8.00)	0.39
▪ CHF hospitalization	8 (11.1%)	0 (0%)	0.05 (0.00-1.05)	0.054

Results: Primary Analysis

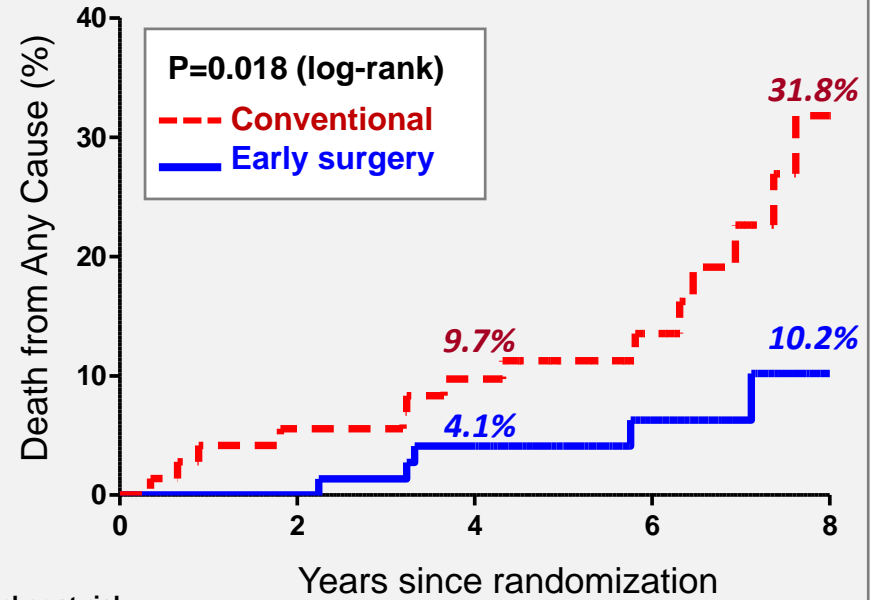
Operative or CV Death



Number at risk

	0	2	4	6	8
Early Surgery	73	73	70	38	13
Conventional	72	68	65	36	12

Death from Any Causes

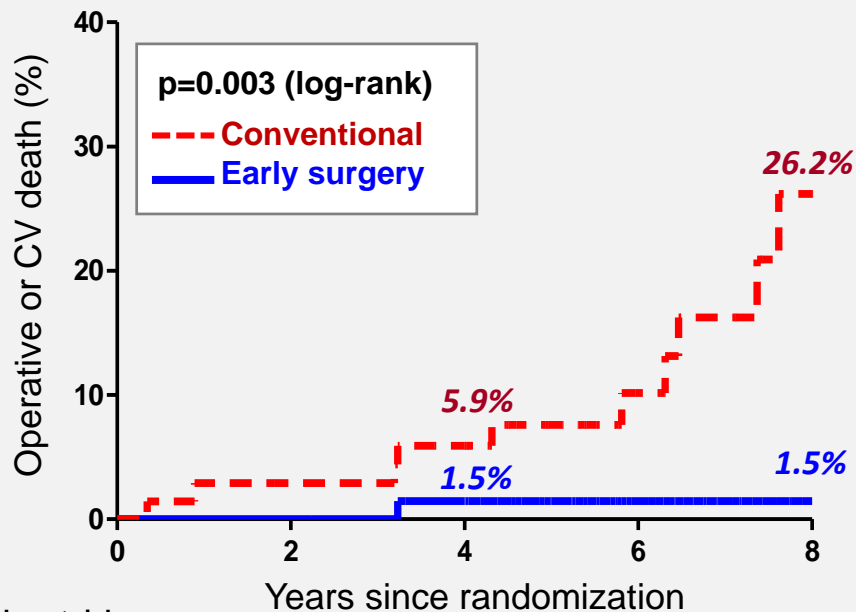


Number at risk

	0	2	4	6	8
Early Surgery	73	73	70	38	13
Conventional	72	68	65	36	12

Results: Secondary Per-Protocol Analysis

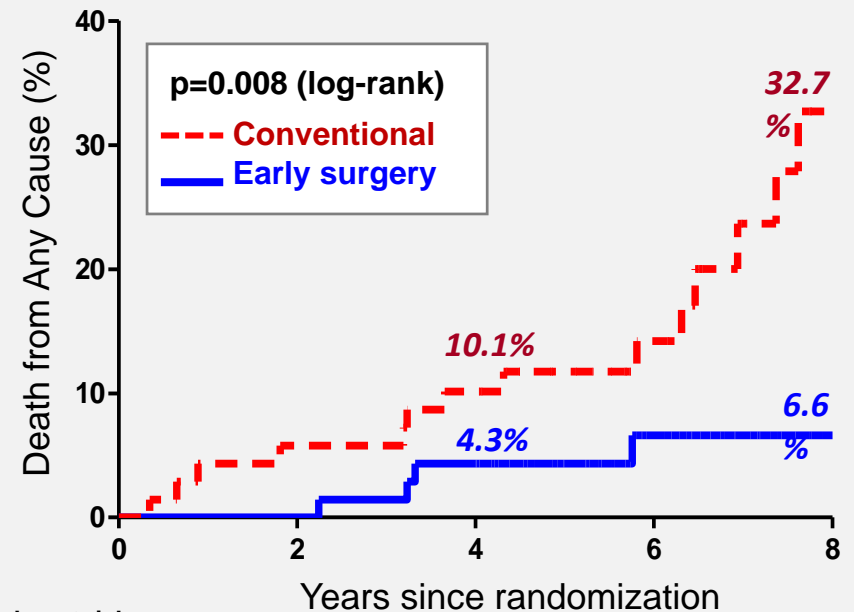
Operative or CV Death



Number at risk

	0	2	4	6	8
Early Surgery	69	69	67	38	14
Conventional	69	66	63	34	13

Death from Any Causes



Number at risk

	0	2	4	6	8
Early Surgery	69	69	67	38	14
Conventional	69	66	63	34	13

Limitations

- Patients with very severe AS (aortic velocity > 4.5 m/s)
- Cross-over in 4%: Similar results in per-protocol analysis
- Selective performance of exercise test
- Younger patients with low operative risk and higher incidence of bicuspid AV: Our results cannot be directly applied to early TAVR for asymptomatic severe AS

Conclusions

Early surgical AVR (vs. conservative management) significantly reduced the rates of operative or cardiovascular death, and death from any cause in asymptomatic patients with very severe AS

The RECOVERY trial provides the evidence for early preemptive AVR



American Heart Association®

Scientific Sessions

AHA 2019 Late Breaking Trial