#AHA21

*A*ortic *V*alve Repl*A*cemen*T* versus Conservative Treatment in *A*symptomatic Seve*R*e Aortic Stenosis: The *AVATAR* Trial

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On behalf of AVATAR trial Investigators

American Heart Association.

Conflict of Interest

Nothing to Disclose

Background

- Decision to operate on an asymptomatic patient with severe aortic stenosis and normal LV function remains a matter of debate, still a significant unmet need

- Observational studies challenged watchful waiting in such patients by noting increased mortality and morbidity

- Recent randomized trial suggested a benefit of early valve surgery in patients with critical aortic stenosis and high prevalence of bicuspid aortic valves

Otto C, et al. ACC/AHA valvular guidelines 2021
Vahanian A, et al. ESC valvular guidelines 2021

Iung B, et al. Circulation 2019
Kang DH, et al. NEJM 2020

Objective

To evaluate the efficacy and safety

of early surgical valve replacement in asymptomatic patients

with severe aortic stenosis and normal LV function

AVATAR Trial Design

- Physician-initiated, prospective, multicenter, randomized, open-label, parallel group

- Patients with asymptomatic severe aortic stenosis randomized to:
  - ➢ Elective surgery arm: aortic valve replacement
  - ➢ Conservative treatment arm: watchful waiting with guidelines directed management

- Performed in 9 medical centers in 7 EU countries

AVATAR Trial

Inclusion Criteria

Main Inclusion Criteria

- Age $\geq$ 18 years
- Severe aortic stenosis:
  - V_{max} > 4 m/s or mean PG $\geq$ 40 mmHg
  - AVA $\leq$ 1 cm^2 or AVA_i $\leq$ 0.6 cm^2/m^2
- Without symptoms: confirmed exercise testing
- Society of Thoracic Surgeons (STS) score < 8%

Main Exclusion Criteria

- Positive exercise testing
- LV ejection fraction < 50% at rest
- Very severe, critical aortic stenosis:
  - V_{max} > 5.5 m/s
- Need for aortic or other valve surgery
- Previous cardiac surgery
- Major co-morbidities or life expectancy <3 year

AVATAR Trial

Exercise Testing

- Mandatory, according to standardized protocol
- Negative if reaching age-predicted submaximal heart rate
- Positive if:
  - ➢ Onset of aortic stenosis-related symptoms (chest pain, dizziness, syncope, pronounced dyspnea)
  - ➢ Fall in systolic blood pressure ≥ 20mmHg from baseline
  - ➢ Signs of myocardial ischemia

Pellikka PA, et al.. J Am Soc Echocardiogr 2007

AVATAR Trial Endpoints

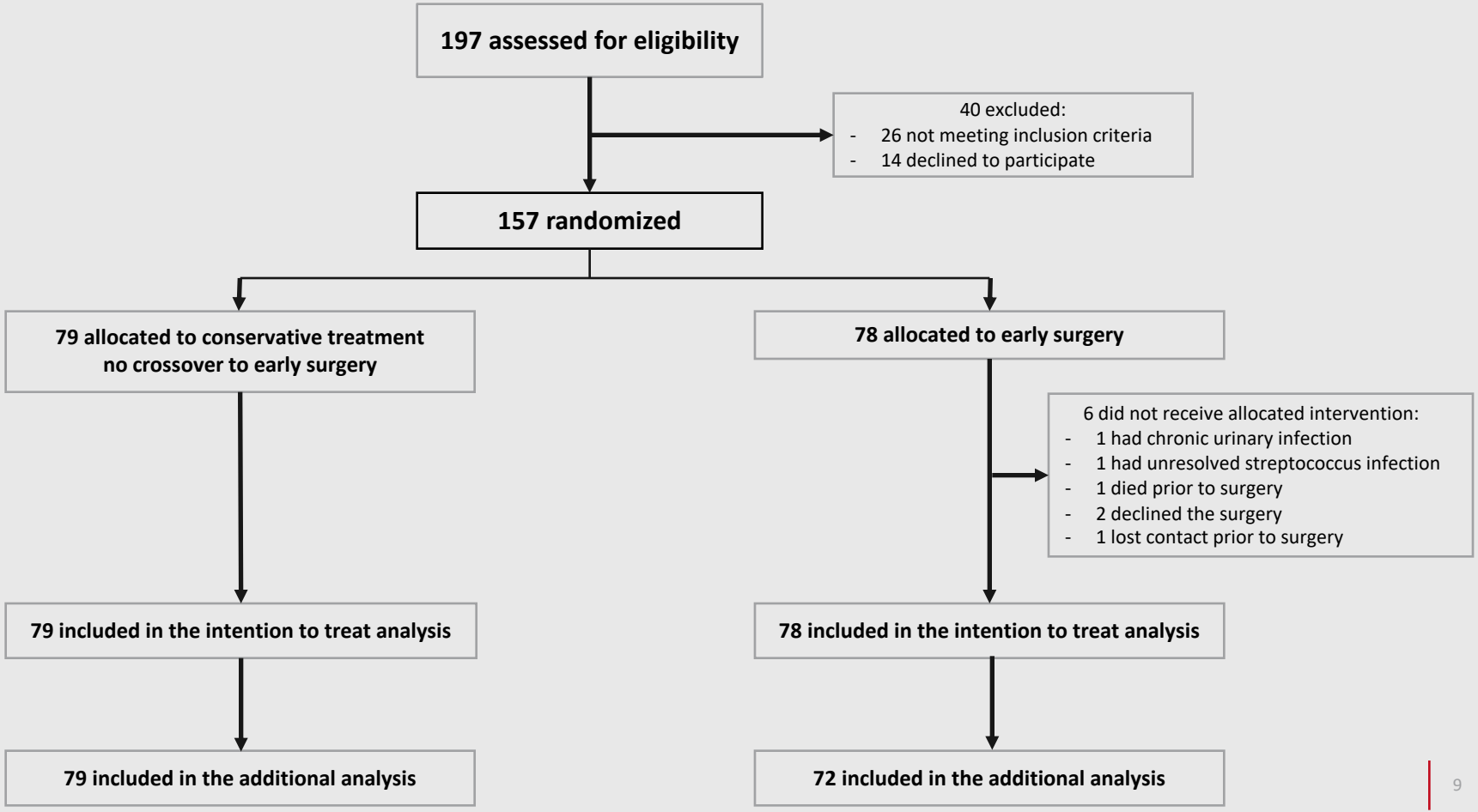
Primary endpoint: Composite of all cause death and MACE comprising acute MI, stroke and unplanned HF hospitalization requiring iv diuretics or inotropes

Secondary endpoints:

- in-hospital operative mortality
- repeated MACE
- major bleeding as defined by Bleeding Academic Research Consortium
- thromboembolic complication
- time to death
- time to HF hospitalization

Event-driven design: target of 35 events assuming need for 24 month enrollment of 312 patients

AVATAR Trial Flowchart



Baseline Characteristics

	Early surgery (n=78)	Conservative (n=79)
Age (years)	65.4±11.7	68.9±8.1
Sex (female)	32 (41.0%)	35 (44.3%)
STS score	2.1±1.7	2.2±1.6
Days from randomization to surgery (median ,IQR)	55 (36-79)	400 (191-619)
Diabetes mellitus	14 (17.9%)	23 (29.1%)
History of coronary artery disease	1 (1.3%)	3 (3.8%)
Degenerative etiology (%)	64 (82%)	69 (87%)
LV ejection fraction (%)	69.6±7.3	67.9±8.2
LV end-diastolic volume (mL)	114.6±39.2	109.3±26.3
Stroke volume indexed (mL/m^2)	41.2±13.4	42.4±10.6
PG mean (mmHg)	53.7±14.0	51.1±8.9
Aortic valve area indexed (cm^2/m^2)	0.36±0.09	0.38±0.08
BNP (pg/ml)	105.7±85.3	114.6±86.5
Beta-blockers	48/73 (66%)	50/77 (65%)
ACE inhibitors	43/73 (59%)	44/77 (57%)
Calcium channel blockers	30/73 (41%)	30/77 (39%)
Diuretics	27/73 (37%)	30/77 (39%)
Statins	40/73 (55%)	48/77 (62%)
Angiotensin receptor blockers	5/73 (7%)	15/77 (19%)
Antiplatelet agents	44/73 (60%)	45/77 (58%)

AVATAR Trial Follow-up

- Per protocol 6 months follow-up visits
- Number of pre-specified events reached October 2020 at 157 randomized patients
- DSMB recommended to stop enrollment November 1, 2020
- The overall median follow-up: 32 months
  - ➢ early surgery group: 28 months
  - ➢ conservative treatment group: 35 months

AVATAR Trial

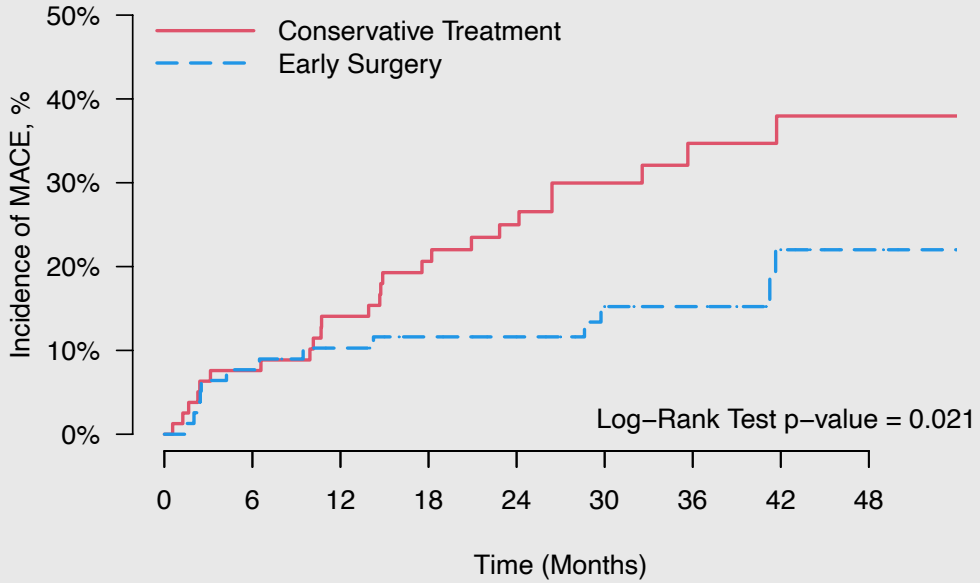
Components of the Primary Endpoint

Primary Endpoint Components	Group	
	Early Surgery n	Conservative n
All cause death	9	16
Heart Failure	1	7
Acute MI	1	2
Stroke	2	1
Total	**13**	**26**

Operative mortality in early surgery group = 1.4% (1/72)

AVATAR Trial

Primary Endpoint



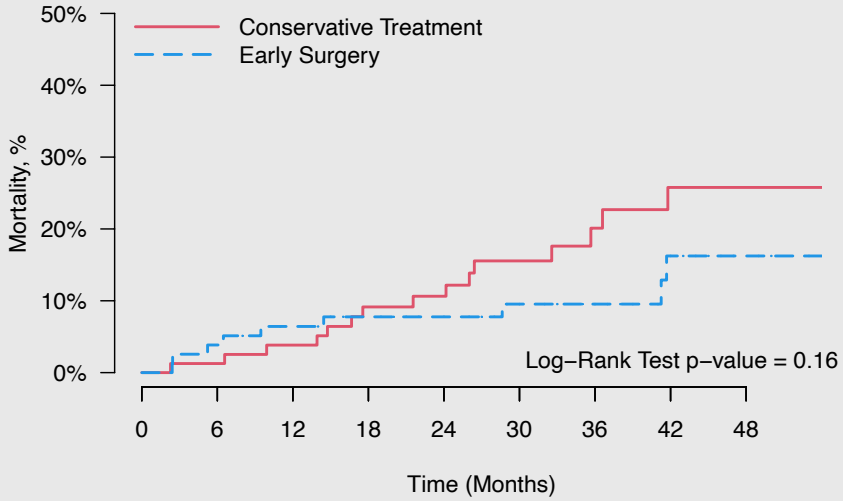
Patients, n									
Conservative Treat.	79	73	66	59	49	36	25	19	12
Early Surgery	78	72	68	63	56	46	38	23	13

HR 0.46; 95% CI 0.23 - 0.90

AVATAR Trial

Secondary Endpoints

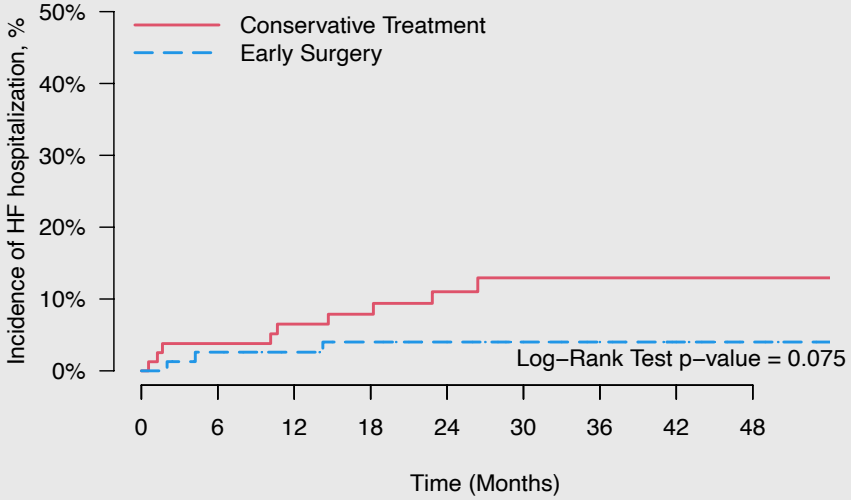
All-cause death



Patients, n									
Conservative Treat.	79	78	74	67	59	45	32	24	16
Early Surgery	78	75	71	66	59	49	41	25	14

HR 0.56; 95% CI 0.24 - 1.27

HF hospitalization

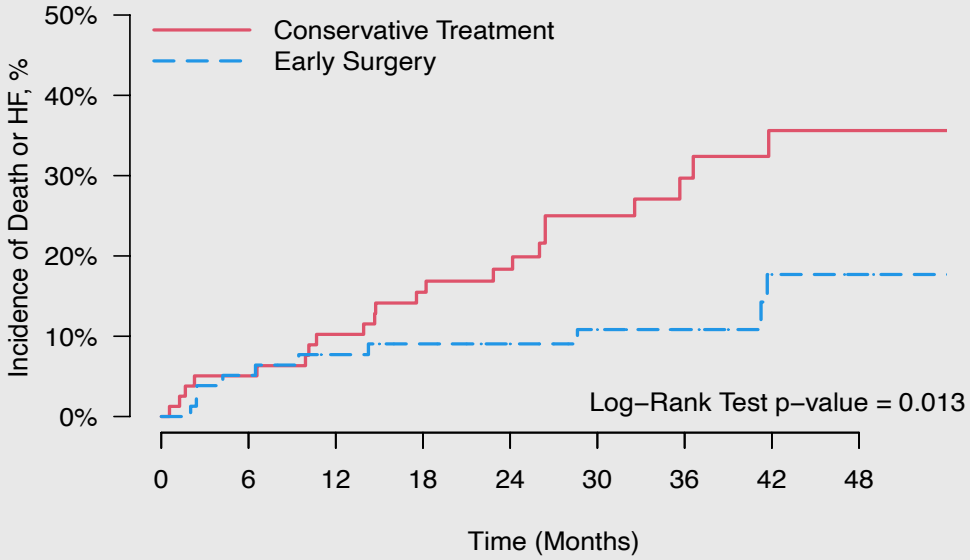


Patients, n									
Conservative Treat.	79	75	69	63	54	39	27	20	13
Early Surgery	78	74	70	65	58	48	40	24	14

HR 0.32; 95% CI 0.18 - 1.19

AVATAR Trial

All Cause Death and HF hospitalization



Patients, n									
Conservative Treat.	79	75	69	63	54	39	27	20	13
Early Surgery	78	74	70	65	58	48	40	24	14

HR 0.40; 95% CI 0.19 - 0.84

AVATAR Trial

Secondary Endpoints

Endpoint	Early surgery n (%)	Conservative treatment n (%)	Odds Ratio [95% CI]
Intraoperative mortality	1 (1.4%)	1 (4%)	OR 0.34 95% CI 0.02 – 5.61
Repeated MACE	3 (3.8%)	7 (8.9%)	OR 0.41 95% CI 0.10 – 1.65
Thromboembolic complication	2 (2.6%)	2 (2.3)	OR 1.03 95% CI 0.14 – 7.67
Major bleeding	4 (5.1%)	1 (1.3%)	OR 3.52 95% CI 0.37 –32.68

AVATAR Trial

Summary

- The largest randomized trial in low-risk, asymptomatic patients with severe, mainly degenerative aortic stenosis and normal LV function

- Early surgery associated with lower incidence of primary composite outcome comprising all cause death, acute MI, stroke or unplanned HF hospitalization

- Intra-operative mortality in early surgery group in line with anticipated mortality for elective isolated surgical aortic valve replacement

AVATAR Trial

Conclusion

The AVATAR trial demonstrates the preliminary efficacy and safety of early surgical aortic valve replacement in improving clinically relevant composite end-point.

The findings advocate for early surgery once aortic stenosis becomes significant regardless of symptoms.

Acknowledgment

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Steering Committee: Bernard Iung (Chairman, France), Jozef Bartunek (Co-chairman, Belgium), Marko Banovic (Serbia), Svetozar Putnik (Serbia), Marek Deja (Poland), Martin Penicka (Belgium), Guy Van Camp (Belgium), Wojtek Wojakowski (Poland)

Avatar Data Safety Monitoring Board: Serge Nikolic (chairman, USA), Michael D Laufer (USA), Sinisa Gradinac (Kuwait), Gheorghe Doros (USA)

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AORTIC VALVE REPLACEMENT VERSUS CONSERVATIVE TREATMENT IN ASYMPTOMATIC SEVERE AORTIC STENOSIS: THE AVATAR TRIAL

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THANK YOU

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