Early Intervention in Patients with Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis

The EVOLVED Randomized Clinical Trial

Professor Marc Dweck MD PhD, University of Edinburgh UK
on behalf of the EVOLVED Investigators

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EvoLVed

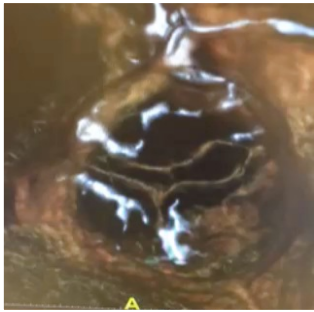
Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant/Research Support	Company Name(s)
Consultant Fees/Honoraria	Novartis, Astra-Zeneca, Pfizer, Bristol Myers Squibb, Amarin, Jupiter Bioventures, Beren, Silence Therapeutics
Individual Stock(s)/Stock Options	None
Royalties/Patent Beneficiary	None
Executive Role/Ownership Interest	None
Other Financial Benefit	None

All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app

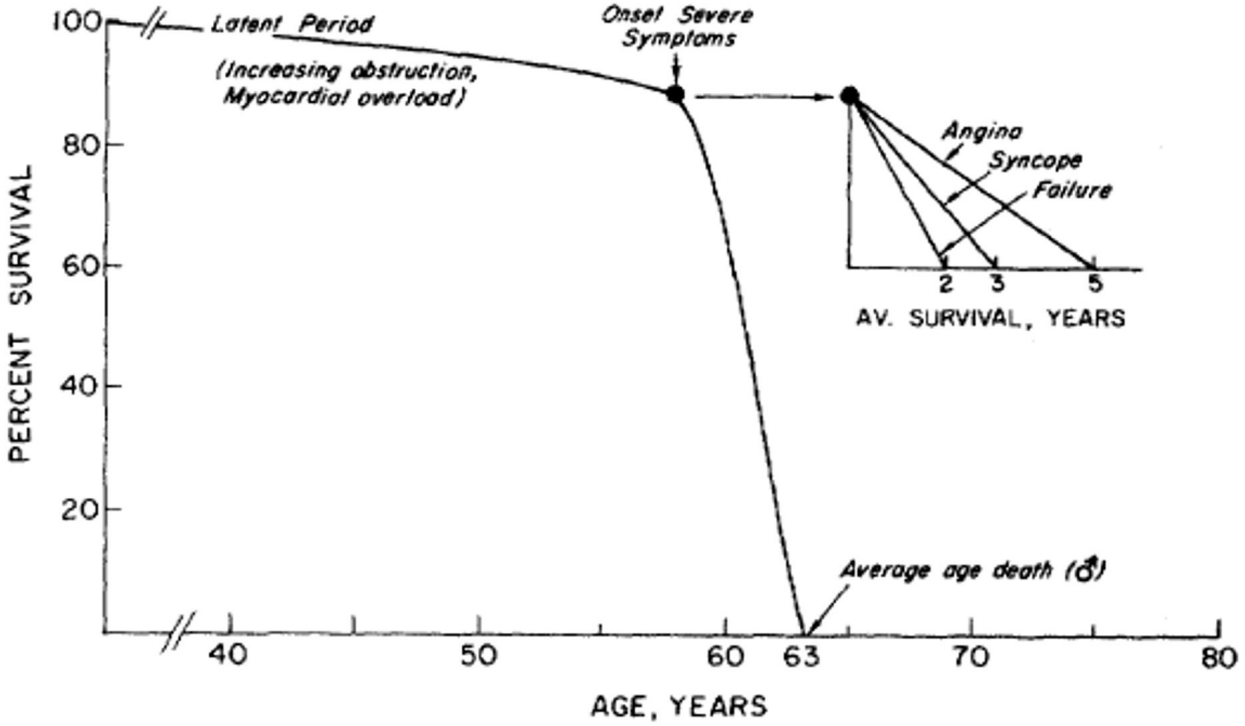
When Should We Offer Aortic Valve Intervention



A) Symptomatic aortic stenosis	Class[b]	Level[c]
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1.0 cm^2 (or ≤0.6 cm^2/m^2)].[235,236]	I	B

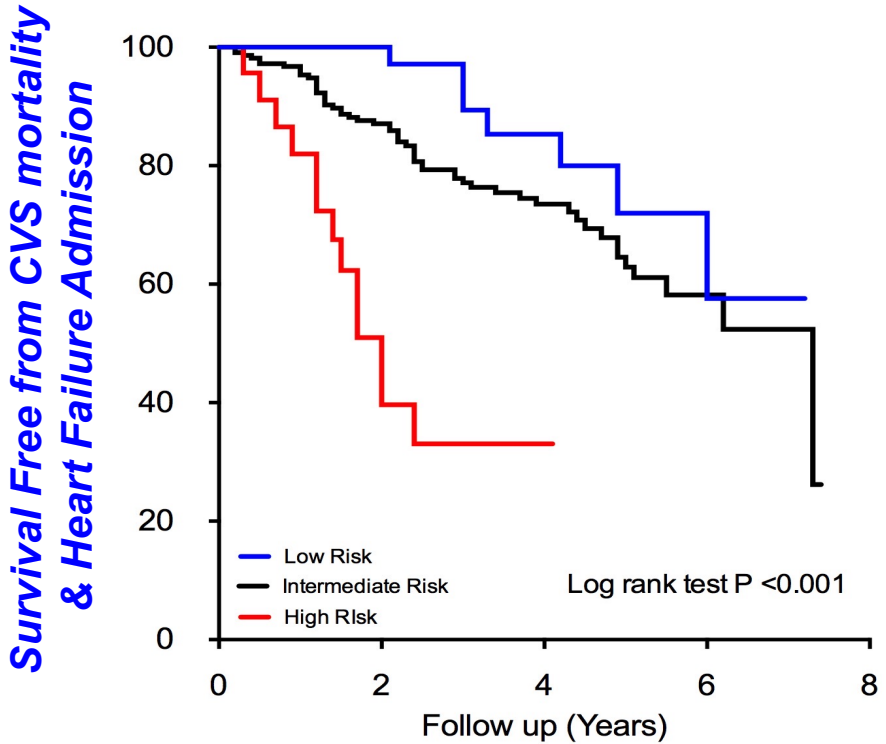
ESC Heart Valve Guidelines 2021

Symptoms & Aortic Stenosis



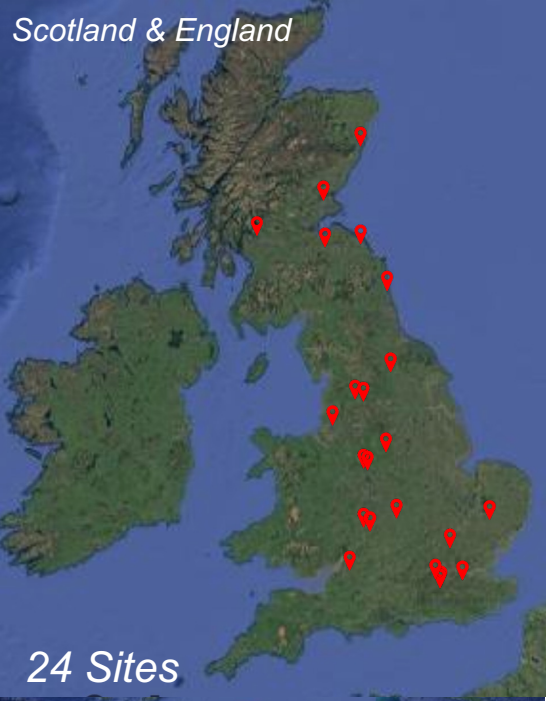
Ross J Jr, Braunwald E. Circulation 1968

Symptoms Often Hard to Assess & Post AVR Patients Have High Rates of Heart Failure



Chin European Heart Journal 2016

Objective: To investigate whether early aortic valve intervention can improve outcomes in patients with asymptomatic severe aortic stenosis who had myocardial fibrosis



EvoLVed

- **Trial Design:** Investigator-led, international multicenter trial with a prospective randomized open-label blinded-endpoint (PROBE) design
- **Edinburgh Clinical Trials Unit**
- **Sponsor:** University of Edinburgh
- **Funding:** Sir Jules Thorne Charitable Trust

The Sir Jules Thorn CHARITABLE TRUST

Study Population

Inclusion Criteria

- Asymptomatic Severe Aortic Stenosis (Vmax ≥ 4.0 m/s, or ≥ 3.5 m/s with iAVA <0.6cm^2/m^2)
- Symptomatic status assessed by attending cardiologist who could use exercise stress testing at their discretion.

Exclusion Criteria

- Left ventricular ejection fraction <50%
- Concomitant severe aortic or mitral regurgitation
- eGFR <30 mL/min/1.73 m^2
- Contraindications to magnetic resonance
- Deemed unfit for intervention

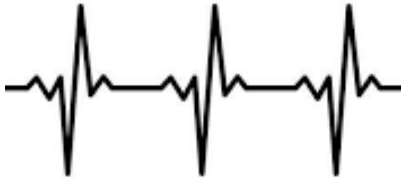
Advanced Diagnostics to Enrich a High Risk Population

1) Screening

Exclusion of low-risk patients

with normal ECG (no LVH) and / or normal high sensitivity troponin I <6 ng/L

High sensitivity troponin I



ECG

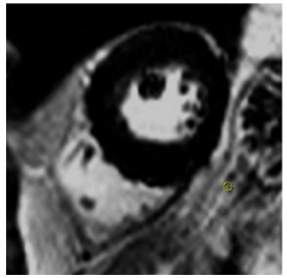
2) Cardiovascular Magnetic Resonance

- Inclusion of high-risk patients with non-infarct myocardial fibrosis on CMR

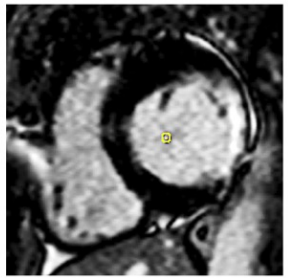
Cardiovascular Magnetic Resonance (CMR)

Cardiac Magnetic Resonance

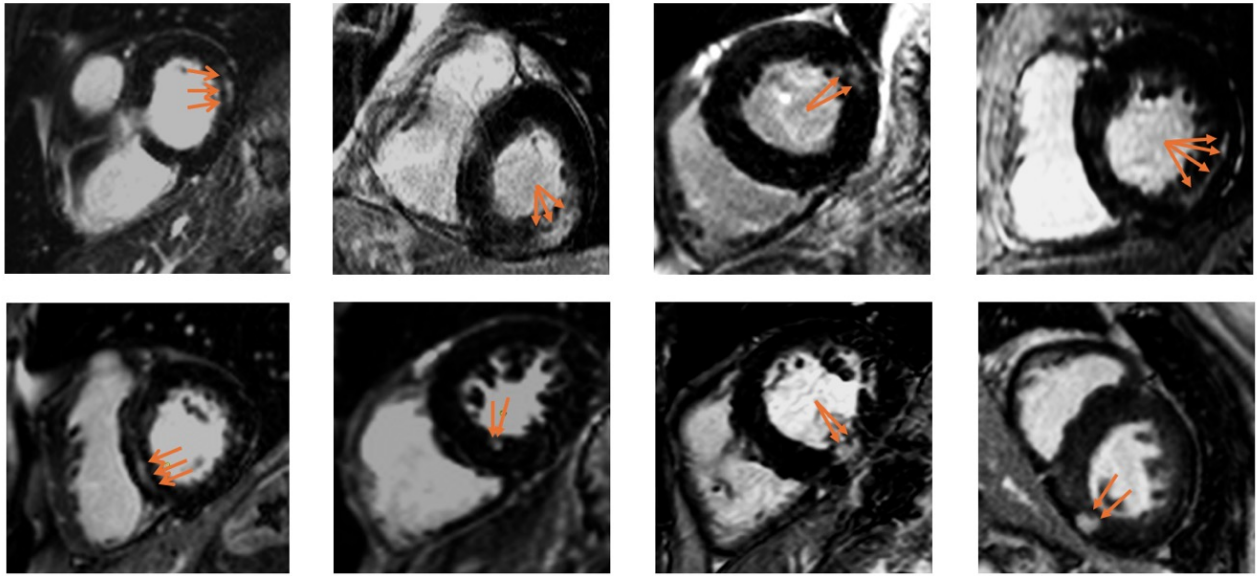
Normal myocardium



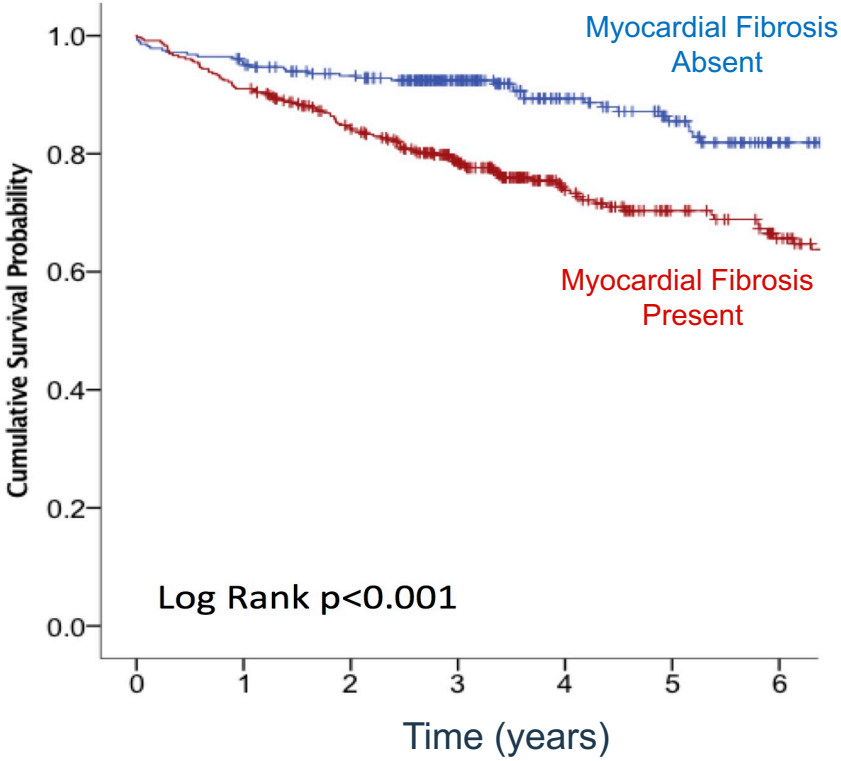
Infarct-related fibrosis

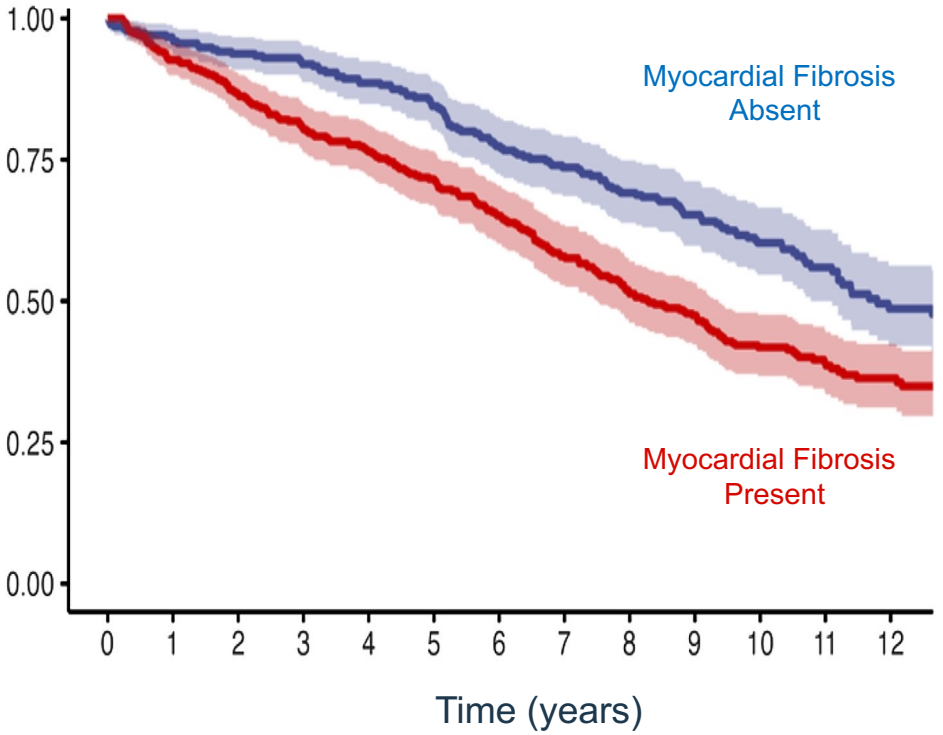


Midwall fibrosis



Myocardial Fibrosis in Aortic Stenosis
Powerful Predictor of Death Post Intervention





Randomization and Procedures

- Patients with asymptomatic severe aortic stenosis and midwall fibrosis were randomized to **early aortic valve intervention** or **routine care**
- Patients without midwall fibrosis entered into an observational registry with identical follow up to maintain blinding in the routine care arm and reduce cross-over
- Choice of SAVR versus TAVR was determined by the local heart valve team

Endpoints

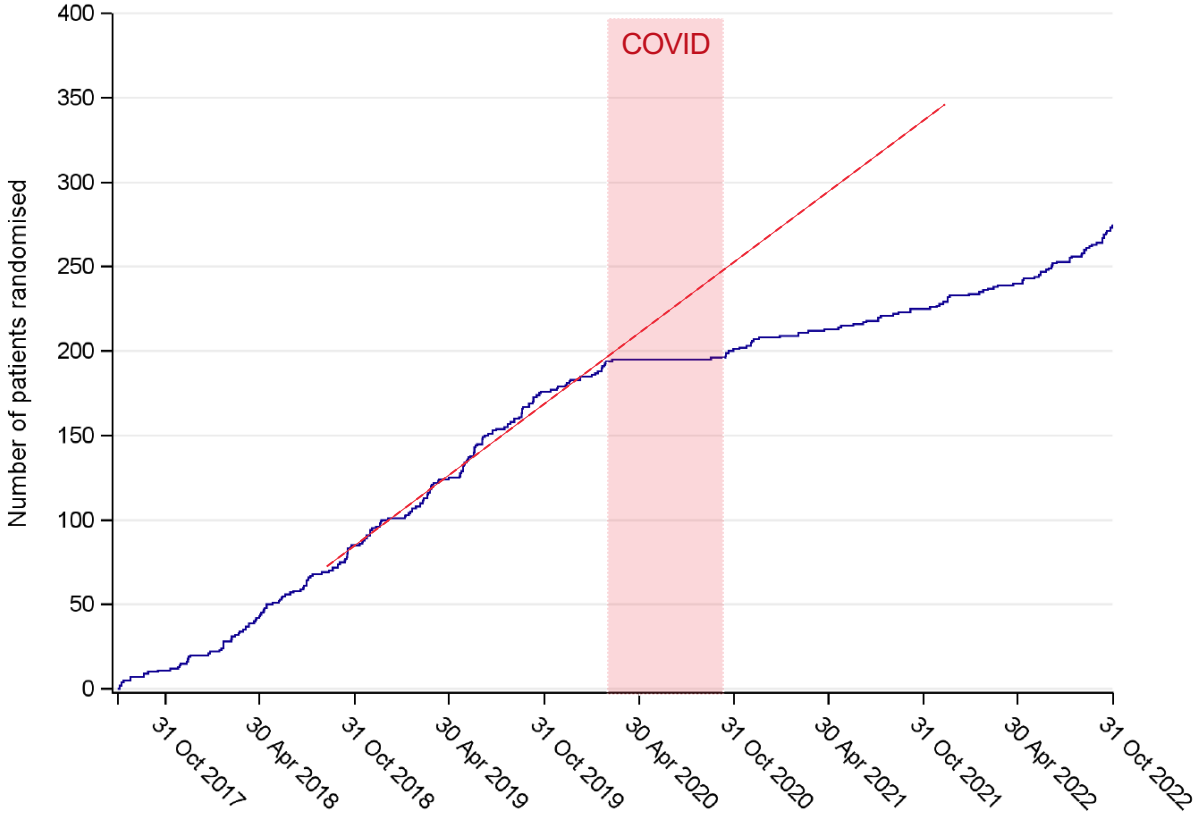
- **Primary Outcome:** Composite of **all-cause mortality** or **unplanned aortic stenosis-hospitalization***
- **Secondary Outcomes:** included all cause mortality and unplanned aortic stenosis-hospitalization considered separately
- **Events adjudicated by an Independent Blinded Committee**

**unplanned admission before of after aortic valve replacement with syncope, heart failure, chest pain ventricular arrythmia or second or third degree heart block attributed to aortic valve disease*

Sample Size

- Planned Sample Size = 356 patients to achieve 88 events after a median expected follow up of 2 years
- Power 80%
- $\alpha = 0.025$
- Expected hazard ration of 0.5
- Assumed incidence of 25% with guideline directed conservative management versus 13.4% with early intervention

Recruitment

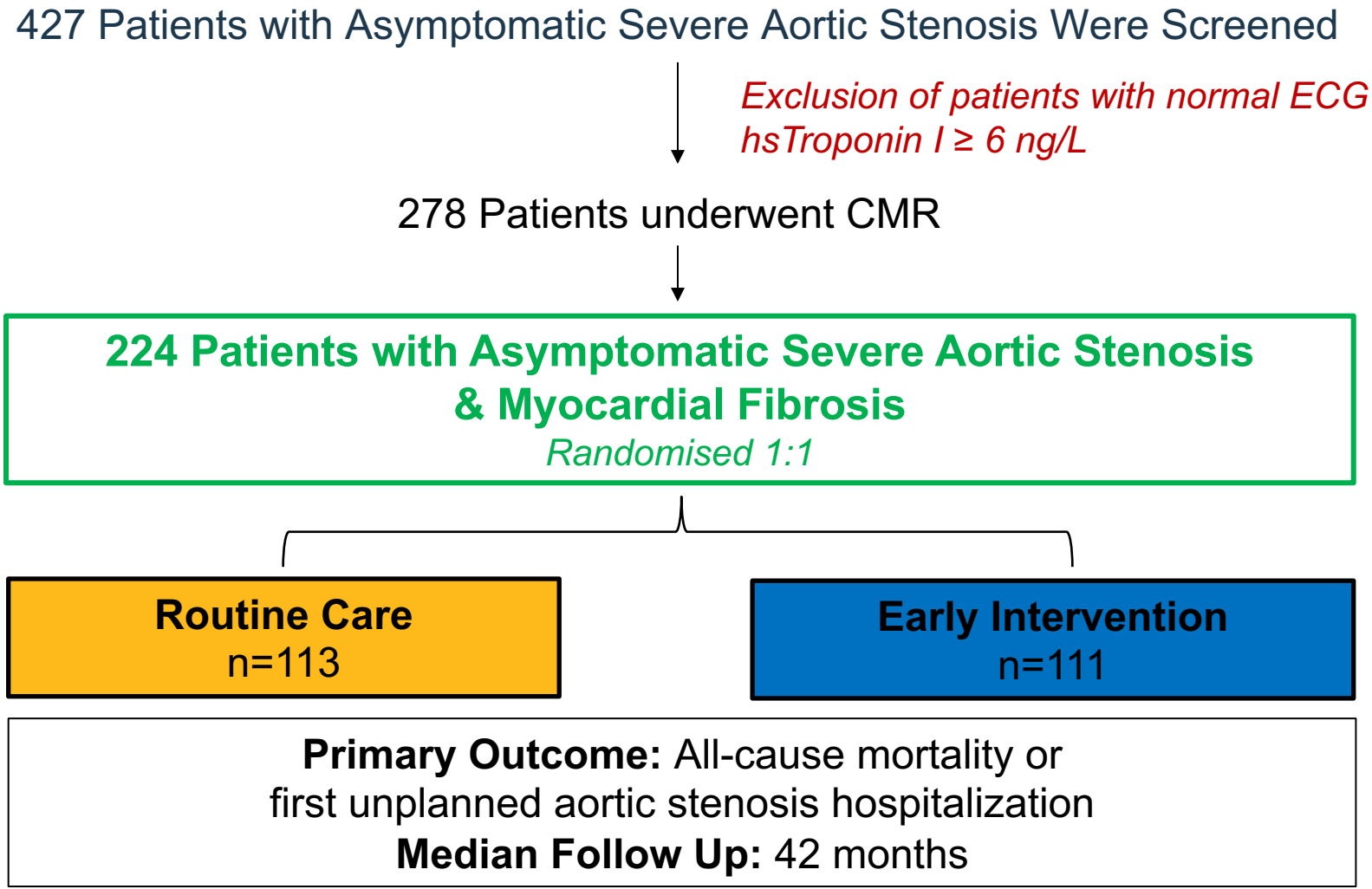


First patient was randomised on 04-AUG-2017 and last patient was randomised on 31-OCT-2022.

Trial recruitment was suspended during the COVID-19 pandemic & post-pandemic the recruitment rates did not fully recover

RECOVERY & AVATAR were reported suggesting a larger treatment effect than had been assumed, such that only 35 events would be required to achieve a HR of 0.33 at 90% power

Trial Steering Committee recommended to halt recruitment on 31 October 2022


427 Patients with Asymptomatic Severe Aortic Stenosis Were Screened
Exclusion of patients with normal ECG and hsTroponin I ≥ 6 ng/L
278 Patients underwent CMR
224 Patients with Asymptomatic Severe Aortic Stenosis & Myocardial Fibrosis
Randomised 1:1
Routine Care
n=113
Early Intervention
n=111
Primary Outcome: All-cause mortality or first unplanned aortic stenosis hospitalization
Median Follow Up: 42 months

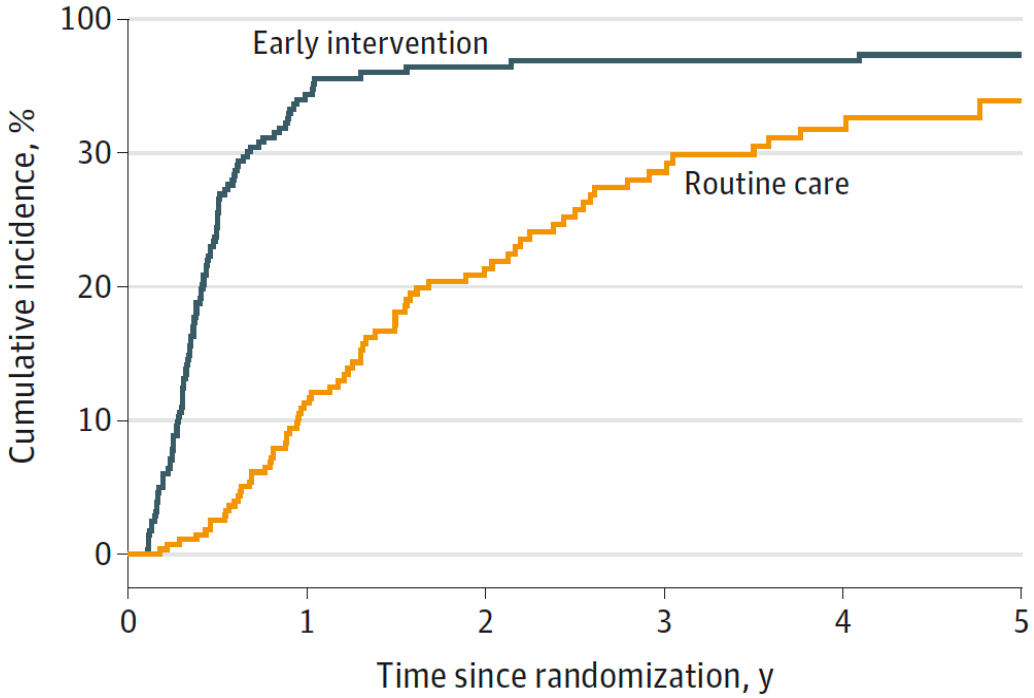
Selected Baseline Characteristics

	Routine Care n = 111	Early Intervention n = 113
Age, median [IQR]	76 [68 – 80]	75 [68 – 79]
Male sex, No. (%)	79 (71)	82 (73)
Body-mass index, median [IQR], kg/m^2	27.8 [24.8 – 31.1]	27.2 [24.1 – 31.1]
Prior myocardial infarction, No. (%)	9 (8)	10 (9)
Peak Velocity, mean ± SD, m/s	4.4 ± 0.5	4.3 ± 0.5
Aortic Valve Area, mean ± SD, cm^2	0.8 ± 0.2	0.8 ± 0.2
LVEF, mean ± SD, %	68 (8)	68 (9)

Time to Intervention

15-month difference in median time-to-intervention

Median time to intervention
- Early intervention 5 months
- Routine care 20 months



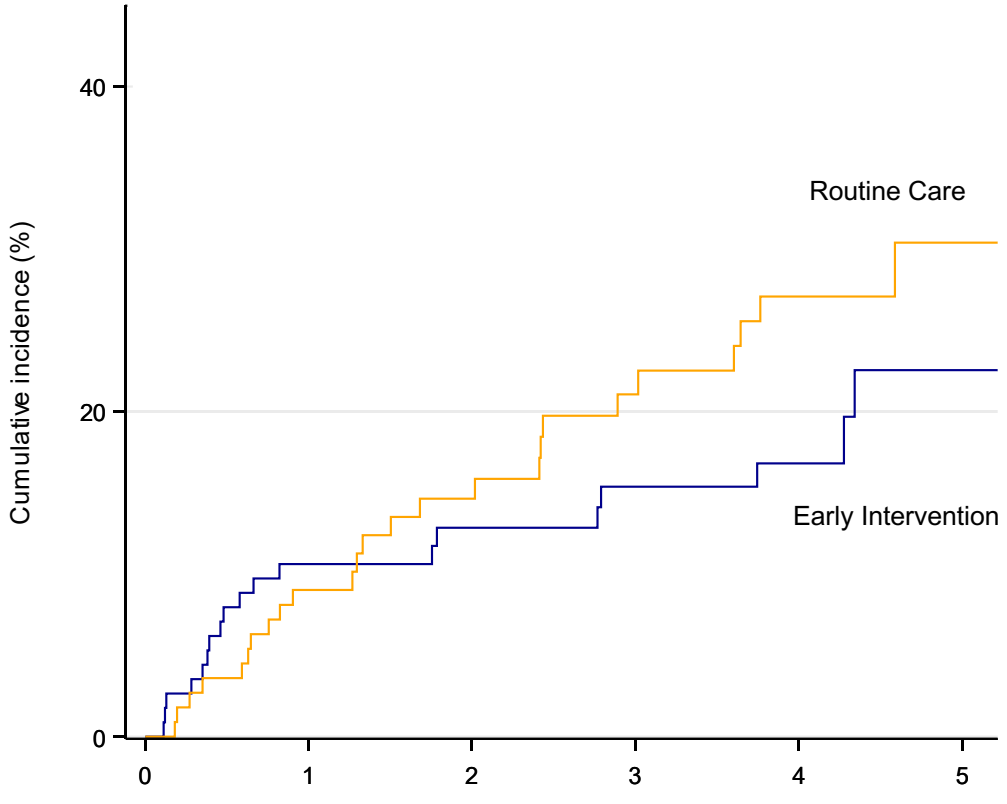
No. of patients at risk						
Early intervention	113	16	8	7	7	6
Routine care	111	77	37	18	12	4

Did the clear separation in time to intervention between the two study arms result in improved clinical outcomes?

Primary Endpoint

All-cause death or unplanned aortic stenosis hospitalization

Hazard Ratio 0.79
(95% CI 0.44 to 1.43)
P=0.44



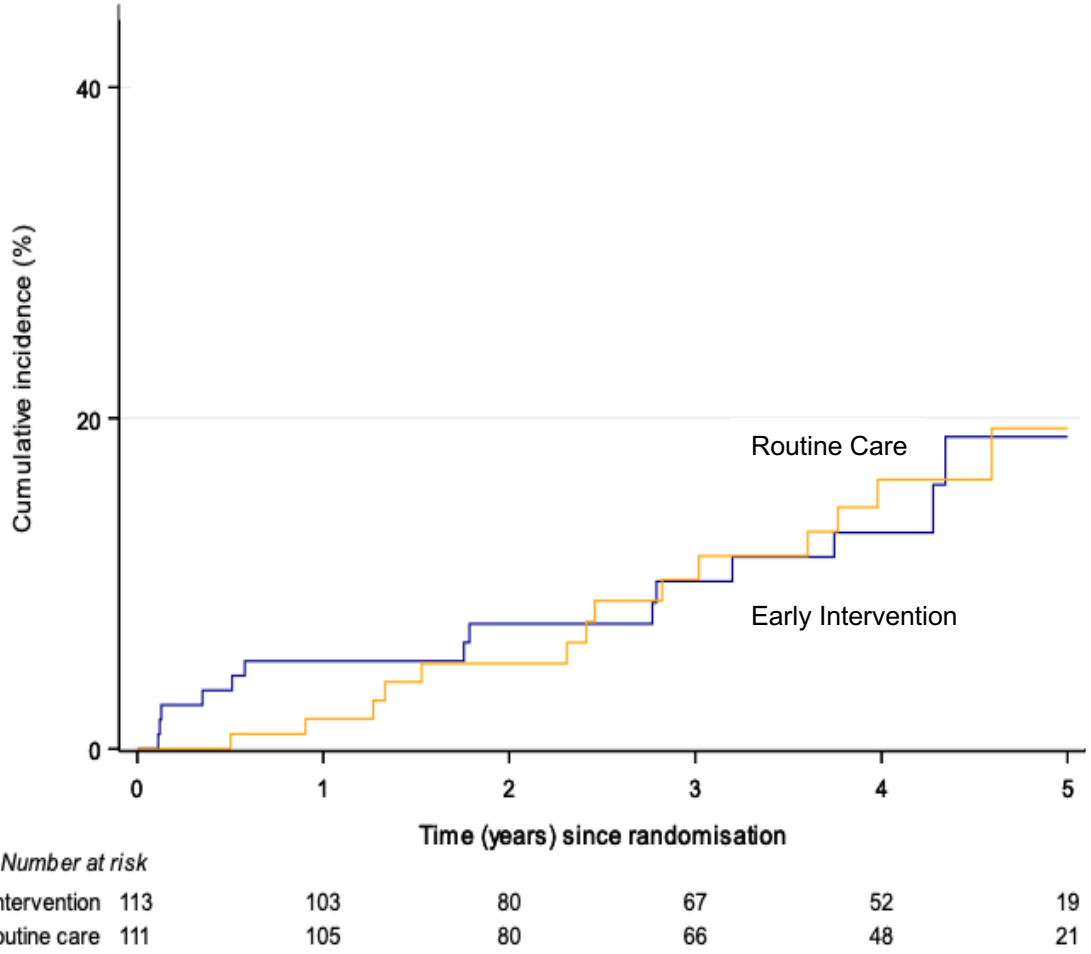
Number at risk

Early intervention	113	97	76	65	51	18
Routine care	111	97	71	57	40	17

Secondary Endpoint

All-cause death

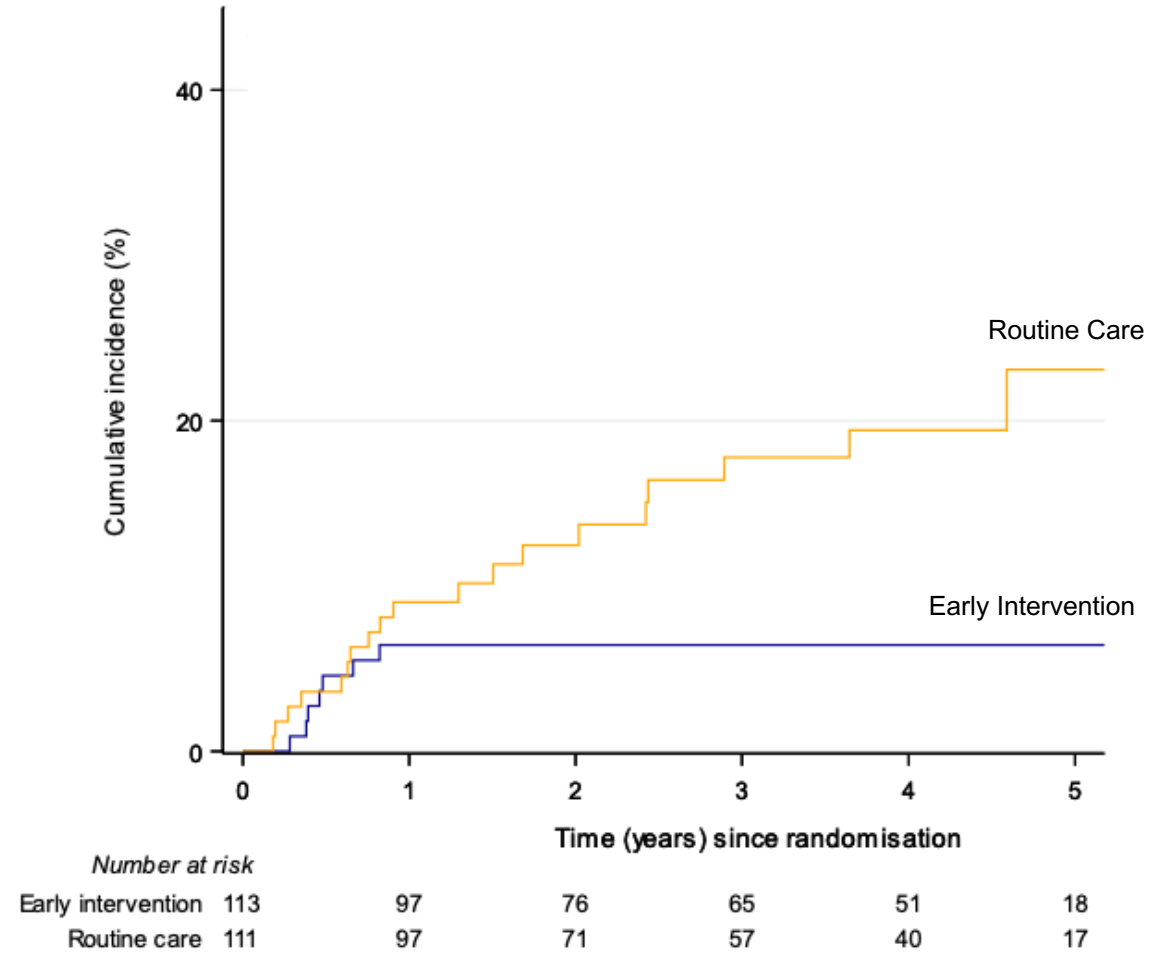
Hazard Ratio 1.22
(95% CI 0.59 to 2.51)



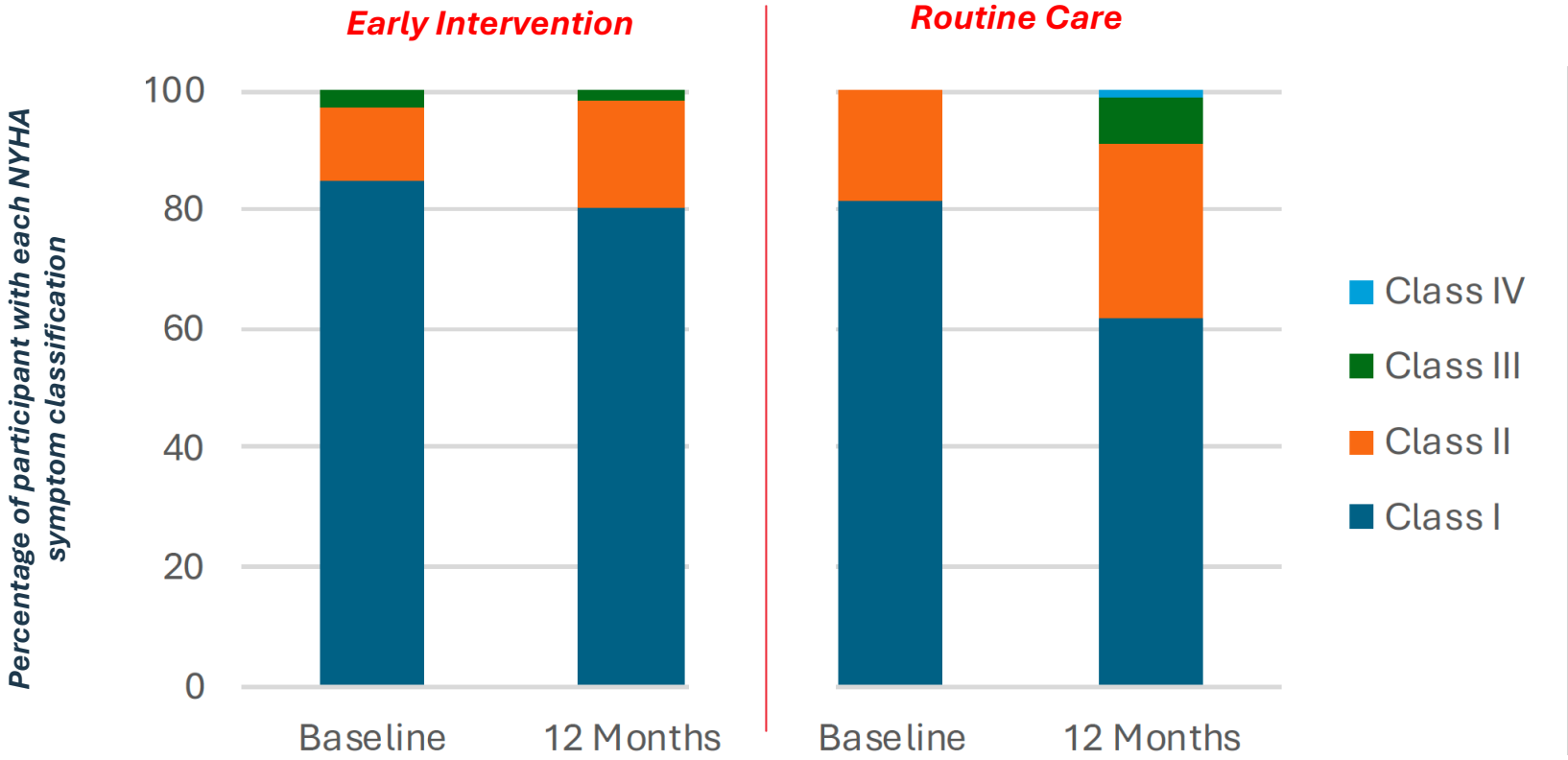
Secondary Endpoint

Unplanned aortic hospitalization

Hazard Ratio 0.37
(95% CI 0.16 to 0.88)



Secondary Endpoint: NYHA Symptom Class at 12 months



Odds Ratio 0.37 (95% CI 0.20 to 0.70)

Secondary Endpoints

All-cause death	16 (14)	14 (13)	1.55 (−7.37 to 10.46)	1.22 (0.59 to 2.51)
Cardiovascular death	10 (9)	8 (7)	1.64 (−5.47 to 8.75)	1.33 (0.52 to 3.36)
Aortic stenosis-related death	6 (5)	5 (5)	0.81 (−4.85 to 6.46)	1.25 (0.38 to 4.10)
Unplanned aortic stenosis-related hospitalization	7 (6)	19 (17)	−10.92 (−19.22 to 2.62)	0.37 (0.16 to 0.88)
Permanent pacemaker, cardiac resynchronization therapy, or automated cardiac defibrillator implantation	5 (4)	7 (6)	−1.88 (−7.78 to 4.02)	0.75 (0.24 to 2.37)
Stroke	8 (7)	14 (13)	−5.53 (−13.31 to 2.25)	0.62 (0.26 to 1.49)
Endocarditis	1 (1)	3 (3)	−1.82 (−5.29 to 1.66)	0.33 (0.03 to 3.14)
Development of left ventricular systolic impairment	8 (7)	11 (10)	−2.83 (−10.13 to 4.47)	0.72 (0.29 to 1.80)
Peri- or postoperative complications within 30 d of surgery or transcatheter aortic valve intervention	15 (14)	9 (11)	5.17 (−2.89 to 13.22)	Odds ratio for ≥1 specified complication, 1.20 (95% CI, 0.50 to 2.93)
WHODAS total score at 1 y, adjusted mean	3.3	4.1		Adjusted mean difference, −0.8 (95% CI, −2.0 to 0.4)

Limitations

- **Recruitment**
  - Did not achieve originally planned sample size of 356 patients
  - Wide confidence intervals- findings require confirmation in further trials
- **Primary End Point not met**
  - Findings in secondary endpoints require confirmation in further trials
- **Time-to-intervention**
  - 5 months in early intervention vs. 20 months in routine care arm
- **TAVR rate higher in routine care arm (45% vs 25%)**
  - TAVR more likely to be used in patients admitted emergently

Conclusions

- In patients with asymptomatic severe aortic stenosis and myocardial fibrosis, early intervention did not reduce the incidence of the composite primary endpoint of all-cause death or unplanned aortic stenosis hospitalization.

- The principal benefit of early intervention appears to be in the reduction of unplanned hospitalizations and in preventing the development of limiting symptoms.

JAMA | Original Investigation

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