ORIGINAL RESEARCH ARTICLE

Early Intervention in Patients with Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis: The EVOLVED Randomized Clinical Trial

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Summary:	350/350
Word count:	3169/3000
Tables and Figures:	5/5
References:	33/50

Key Points

Question: Is early aortic valve intervention superior to guideline-directed conservative management in asymptomatic patients with severe aortic stenosis and myocardial fibrosis?

Findings: In this multicenter randomized controlled trial of 224 patients with asymptomatic severe aortic stenosis and myocardial fibrosis, patients allocated to early intervention experienced the primary composite endpoint of all-cause death or unplanned aortic-stenosis related hospitalization as frequently as patients allocated to guideline-directed conservative management: 18% versus 23% respectively.

Meaning: Amongst patients with asymptomatic severe aortic stenosis and myocardial fibrosis, early aortic valve intervention did not improve clinical outcomes compared with guideline-directed conservative management.

Abstract

Importance: Development of myocardial fibrosis in patients with aortic stenosis precedes left ventricular decompensation and is associated with an adverse long-term prognosis.

Objective: To investigate whether early valve intervention reduced the incidence of all-cause death or unplanned aortic stenosis-related hospitalization in asymptomatic patients with severe aortic stenosis and myocardial fibrosis.

Design: Prospective randomized open label blinded endpoint trial conducted between August 2017 and October 2022.

Setting: Twenty-four Cardiac Centers across the United Kingdom and Australia.

Participants: Asymptomatic patients with severe aortic stenosis and myocardial fibrosis.

Interventions: Early valve intervention with transcatheter or surgical aortic valve replacement.

Main Outcomes and Measures:

The primary outcome was a composite of all-cause death or unplanned aortic stenosis-related hospitalization in a time-to-first event intention-to-treat analysis. There were 9 secondary outcomes including the components of the primary outcome and symptom status at 12 months.

Results:

The trial enrolled 224 eligible patients (mean age 73 (standard deviation 9) years, 28% women and mean aortic valve peak velocity 4.3 (0.5) m/s) of the originally planned sample size of 356 patients. The primary endpoint occurred in 20/113 (18%) patients in the early intervention group and 25/111 (23%) patients in the guideline-directed conservative management group (hazard ratio, 0.79 [95% confidence interval 0.44 to 1.43], *P*=0.44; between-group difference -4.82 [95% confidence interval -15.31 to 5.66]). Of 9 prespecified secondary endpoints, 7 showed no significant difference. All-cause death occurred in 16/113 (14%) and 14/111 (13%) patients (hazard ratio, 1.22 [95% confidence interval 0.59 to 2.51]) and unplanned aortic stenosis hospitalization occurred in 7/113 (6%) and 19/111 (17%) patients (hazard ratio, 0.37 [95% confidence interval 0.16 to 0.88]) respectively. Early intervention was associated with a lower 12-month rate of New York Heart Association class II-IV symptoms than guideline-directed conservative management (21 (19.7%) versus 39 (37.9%); odds ratio 0.37 [95% confidence interval 0.20 to 0.70]).

Conclusions and Relevance:

In asymptomatic patients with severe aortic stenosis and myocardial fibrosis, early aortic valve intervention had no demonstrable effect on all-cause death or unplanned aortic stenosis-related hospitalization. The trial had a wide 95% confidence interval around the primary endpoint, with further research needed to confirm these findings.

Trial Registration:

Clinicaltrials.gov Identifier: NCT03094143

INTRODUCTION

Aortic stenosis is the commonest heart valve disease in developed countries, with an increasing prevalence in the aging population.[1] Aortic valve replacement via surgical or transcatheter approaches remains the cornerstone of treatment but is reserved for patients with severe aortic stenosis who are symptomatic, or those with a left ventricular ejection fraction below 50%.[2,3] Based on expert opinion and non-randomized data, guidelines recommend that asymptomatic patients are observed, and that aortic valve intervention is deferred until the onset of symptoms. In clinical practice, assessment of symptoms in patients with severe aortic stenosis is challenging due to limited mobility or multiple co-morbidities.[4,5] Two small randomized controlled trials have suggested that early surgical aortic valve replacement may improve clinical outcomes in selected younger patients with asymptomatic severe aortic stenosis and normal left ventricular ejection fraction. [6,7]

The potential benefits of early aortic valve intervention are most likely to be apparent in patients who are at the highest risk of aortic stenosis-related clinical events. In patients with aortic stenosis, plasma high-sensitivity cardiac troponin I concentration and left ventricular hypertrophy on electrocardiography are sensitive markers of myocardial health and adverse left ventricular remodeling that are associated with worse outcomes.[8-11] Midwall late gadolinium enhancement on cardiac magnetic resonance provides a more definitive specific measure of cardiac damage through the identification of myocardial fibrosis, the key pathological process driving the transition from left ventricular hypertrophy to heart failure in aortic stenosis.[12-19] Multiple observational studies demonstrate that myocardial fibrosis progresses rapidly once established and is a strong independent predictor of incident heart failure and all-cause and cardiovascular mortality in patients with aortic stenosis.[20-23] We

therefore developed an enrichment approach using these biomarkers to identify asymptomatic patients with severe aortic stenosis who had evidence of myocardial fibrosis and who would be at heightened risk of cardiac decompensation. We hypothesized that the potential benefits of early aortic valve intervention would be maximized in this high-risk population of patients.

The Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial was designed to investigate whether early aortic valve intervention can improve clinical outcomes in patients with asymptomatic severe aortic stenosis and myocardial fibrosis. We hypothesized that the incidence of all-cause death or unplanned aortic stenosis-related hospitalization would be reduced in patients who underwent early aortic valve intervention compared to those receiving guideline-directed conservative management.

METHODS

Trial Design and Oversight

The EVOLVED trial is a parallel-group multicenter prospective randomized open-label blinded endpoint trial conducted across 24 Cardiac Centers in the United Kingdom and Australia (Supplement 1).[24] The study was approved by the South-East Scotland Research Ethics Committee. The trial protocol (Supplement 2) was designed by the Chief Investigator and approved by the Principal Investigators and institutional review boards at each participating site. All participants provided written informed consent. A Trial Steering Committee oversaw trial conduct and progress, including data and safety monitoring as this was an open label trial where the risks and benefits of all trial related procedures and interventions are well known. This report follows the CONSORT reporting guideline for parallel group randomized trials.[25]

Participant Selection

Patients aged 18 years of age or older with severe aortic stenosis and without symptoms attributable to their valve disease were invited to participate. Severe aortic stenosis was defined as aortic valve peak velocity ≥ 4.0 m/s, or an aortic valve peak velocity ≥ 3.5 m/s with an indexed aortic valve area <0.6 cm^2/m^2.[2,26] The attending physician assessed for the presence of aortic stenosis-related symptoms with the option of exercise stress testing according to their clinical practice. Routine exercise stress testing was not mandated because of the challenges of interpretation and consequent exclusion of many patients who would be unable to perform exercise stress due to poor mobility or co-morbidities. Patients were excluded if they had symptoms attributable to aortic stenosis, a left ventricular ejection fraction <50%, concomitant severe aortic or mitral regurgitation, estimated glomerular

filtration rate <30 mL/min/1.73 m^2, contraindications to magnetic resonance, or if deemed unfit for surgery or transcatheter aortic valve implantation (eMethods in Supplement 1).

Participant Eligibility

Patients were initially screened for adverse left ventricular remodeling by plasma cardiac troponin I concentration ≥ 6 ng/L measured using a high-sensitivity assay (Abbott Laboratories, Abbott Park, IL, USA) or the presence of left ventricular hypertrophy on electrocardiography.[8-11] Potentially eligible participants meeting one of these criteria underwent cardiac magnetic resonance with gadolinium contrast using a standardized protocol (eTable 1 in Supplement 1). The presence or absence of midwall late gadolinium enhancement was assessed by the core laboratory blinded to clinical details (eMethods and eFigure 1 in Supplement 1). Site investigators and attending physicians were blinded to the cardiac magnetic resonance findings other than any unexpected clinically urgent findings.

Randomization

Eligible participants with midwall myocardial fibrosis were randomly assigned in a 1:1 ratio to early aortic valve intervention or guideline-directed management using a computer-generated randomization process employing minimization incorporating age, sex, aortic valve peak velocity, ischemic heart disease and screening method. To reduce bias, participants without detectable myocardial fibrosis were entered into an observational registry, such that site investigators were blinded to the presence or absence of myocardial fibrosis in patients allocated to guideline-directed conservative management.

The EASY-AS trial (NCT04204915) was launched in the United Kingdom in 2020 and randomized all patients with asymptomatic severe aortic stenosis to early intervention or

guideline-directed conservative management. Patients could be co-enrolled and randomized into both the EVOLVED and EASY-AS trials after cardiac magnetic resonance imaging had been performed as stipulated by the EVOLVED protocol. Treatment allocation was based upon randomized treatment allocation in the EASY-AS trial (see eMethods in Supplement 1 for more details).[27]

Trial Intervention

The choice of surgical aortic valve replacement or transcatheter aortic valve implantation was made by the local heart valve team, with the procedure performed as soon as possible (ideally within 2 months) within the constraints of the local health care setting. Patients assigned to guideline-directed conservative management received treatment and were referred for aortic valve intervention at the discretion of their treating physician and local heart valve team.

Trial Endpoints

The primary endpoint was a composite of all-cause mortality or unplanned aortic stenosis-related hospitalization during the follow-up period. Aortic stenosis-related hospitalization was defined as any unplanned admission before or after aortic valve replacement with syncope, heart failure, chest pain, ventricular arrythmia or second- or third-degree heart block, attributed to aortic valve disease and adjudicated independently by two investigators blinded to the details of trial arm allocation. Secondary endpoints included the individual components of the composite primary endpoint, symptom burden assessed by the New York Heart Association (NYHA) classification and the development of left ventricular systolic dysfunction (ejection fraction less than 50%) at 12 months following randomization. Health and disability burden were assessed using the World Health Organization Disability

Assessment Schedule (WHODAS) 2.0 score at 12 months following enrolment. Other prespecified secondary endpoints included cardiovascular, aortic stenosis-related death, sudden cardiac death, stroke, endocarditis, or implantation of a cardiac pacemaker, resynchronization device or automated cardioverter defibrillator and post-operative complications occurring within 30 days.

Statistical Analysis

We estimated that a sample of 356 participants would provide the trial with 80% power at a two-sided significance level of 0.05 to detect a significant difference in the primary endpoint, assuming the incidence of the primary endpoint would be 25.0% with guideline-directed conservative management and 13.4% with early aortic valve intervention during a follow up period that continued for a minimum of 12 months after the last patient was enrolled.[13] During the COVID-19 pandemic, recruitment into the EVOLVED trial was suspended for five months to comply with a United Kingdom Government directive. After the pandemic, recruitment rates did not fully recover (eFigure 2 in Supplement 1). The results of two emerging randomized trials suggested a larger treatment effect of early intervention than had been assumed in the original power calculation, such that only 35 events would be required to achieve a hazard ratio of 0.33 at 90% power.[6,7] A decision to halt recruitment into the trial on the pre-specified date of 31 October 2022 was made by the Trial Steering Committee.

Analyses were performed on an intention-to-treat basis. Ineligible randomized participants were excluded from the primary analysis group (eMethods in Supplement 1). Cox proportional hazard regression was used for analysis of the primary endpoint and pre-specified secondary endpoints. The NYHA classification was assessed by a proportional odds regression model and the WHODAS score with a linear regression model. All analyses were

adjusted for age, sex and treatment arm. Estimates of cumulative incidences were calculated in a time-to-first event Kaplan-Meier analysis. Because there was no adjustment for multiplicity of testing, secondary endpoints are reported as point estimates and 95% confidence intervals. The confidence intervals have not been adjusted for multiplicity and should not be used in place of a hypothesis test. All reported *P* values were two-sided and a value of less than 0.05 was considered statistically significant. SAS software (version 9.4) was used for statistical analysis.

RESULTS

Between 4 August 2017 and 31 October 2022, 427 asymptomatic patients with severe aortic stenosis were screened, of whom 275 were eligible based upon high-sensitivity troponin I concentrations or 12-lead ECG criteria and underwent cardiac magnetic resonance imaging which was well tolerated and incurred no adverse reactions. Cardiac magnetic resonance imaging identified that 226 of the 275 patients had midwall myocardial fibrosis and were randomized (Figure 1). Two participants were excluded as they were randomized after they had been referred for surgery (Supplement eMethods). Of the 224 eligible participants with myocardial fibrosis who had been randomized, 113 patients were allocated to early aortic valve intervention and 111 to guideline-directed conservative management. Forty-nine patients did not have midwall myocardial fibrosis and were entered into the observational registry. Data collection ended in July 2024, 21 months after the last enrolled patient was randomized. Median follow up was 42 months with a total follow up of 722 patient-years.

Baseline characteristics were comparable between groups. The mean age was 73 (9) years, 63 (28%) were female, and 64 (29%) had a bicuspid aortic valve. Mean aortic valve peak velocity was 4.3 (0.5) m/s and the mean aortic valve area was 0.8 (0.2) cm^2 (Table 1).

In the early intervention group, 106 (94%) patients received aortic valve intervention and 86% received it within 12 months of randomization (Figure 2). The median time to intervention was 5.0 [interquartile interval 3.4 to 8.0] months: 4.2 [interquartile interval 3.0 to 6.0] and 6.5 [interquartile interval 4.6 to 10.9] months before and after the COVID-19 pandemic respectively. Seven (6%) patients randomized to early intervention did not undergo any intervention, of whom 6 died before their procedure at a median of 5.5 [interquartile

interval 1.6 to 7] months following randomization. Surgical aortic valve replacement was performed in 80 (75%) patients and transcatheter aortic valve intervention in 26 (25%) patients (eTable 3 in Supplement 1). Seven (7%) participants received a mechanical valve and 3 (3%) patients required urgent inpatient surgery 4.8, 5.6 and 6.1 months following randomization. Thirty-day mortality was 1%.

In the guideline-directed conservative management group, the median time to intervention was 20.2 [interquartile interval 11.4 to 42.0] months: 85 (77%) patients received aortic valve intervention and 28% received it within 12 months of randomization (Figure 2). Surgical aortic valve replacement was performed in 47 (55%) patients and 38 (45%) patients underwent transcatheter aortic valve intervention. Symptom development was the primary indication for aortic valve intervention in 61 (72%) patients, and 13 (15%) patients required urgent inpatient surgery. Thirty-day mortality was 0%. Additional surgical procedural information is provided in eTable 3 in Supplement 1.

Twenty (18%) patients allocated to early aortic valve intervention and 25 (23%) patients allocated to guideline-directed conservative management experienced the primary composite endpoint of all-cause death or unplanned aortic stenosis hospitalization (hazard ratio 0.79 [95% confidence interval 0.44 to 1.43], *P*=0.44; between-group difference -4.82 [95% confidence interval -15.31 to 5.66]) (Table 2, Figure 3).

Pre-specified secondary endpoints are listed in Table 2. A total of 16 (14%) deaths occurred in the early intervention group and 14 (13%) deaths in the guideline-directed conservative management group: hazard ratio 1.22 [95% confidence interval 0.59 to 2.51] (Figure 3). Six of the 16 deaths in the early intervention group and 5 of the 14 deaths in the guideline-

directed conservative management group were adjudicated to be related to aortic stenosis (eTable 4 in Supplement 1). Only one participant died due to COVID-19 and had been allocated to early aortic valve intervention. The frequency of peri-procedural complications was low and similar in the two groups (eTable 3 in Supplement 1).

Seven (6%) patients in the early aortic valve intervention group and 19 (17%) patients in the guideline-directed conservative management group experienced an unplanned aortic stenosis-related hospitalization: hazard ratio 0.37 [95% confidence interval 0.16 to 0.88] (Figure 3). At one year of follow up, 21 (20%) participants allocated to early intervention and 39 (38%) allocated to guideline-directed conservative management had New York Heart Association class II-IV symptoms (adjusted odds ratio 0.37, 95% confidence interval 0.20 to 0.70) (eFigure 3 in Supplement 1). The adjusted mean WHODAS score at 1 year was 3.3 in patients allocated to early intervention compared to 4.1 in the those allocated to guideline-directed conservative management: adjusted means difference -0.8 [95% confidence interval -2.0 to 0.4].

DISCUSSION

We have compared early aortic valve intervention with guideline-directed conservative management in asymptomatic patients with severe aortic stenosis and subclinical evidence of cardiac decompensation. There was no demonstrable difference in the primary composite endpoint of all-cause mortality or unplanned aortic stenosis-related hospitalization. However, the 95% confidence interval around the primary endpoint is wide and encompasses potential clinically meaningful benefits or harms from early intervention. Our findings are not definitive, and further research will be required to confirm our findings.

In our trial, we enriched our population for increased cardiac risk using cardiac biomarkers and cardiac magnetic resonance, and selected a patient population with aortic stenosis in whom the left ventricle was starting to decompensate due to their severe valve disease. Our hypothesis was that these high-risk asymptomatic patients would have the most to gain from a strategy of earlier aortic valve intervention. Despite this, we were still unable to demonstrate an impact of the trial intervention on the primary outcome.

It could be argued that our median time to early intervention was too long in the early intervention arm and some patients may not have had a primary outcome event had they undergone more rapid early intervention. However, the time delay to intervention is representative of contemporary practice in the United Kingdom and Australia and indeed many other healthcare systems around the world including Canada, France and Sweden.[28-31] Nonetheless, there was a large difference of 15 months in the time to intervention between trial arms. This occurred despite a marginally shorter time to intervention from referral in the

guideline-directed conservative management group which was likely driven by the development of symptoms, and the higher rates of hospitalization and inpatient procedures.

The decision to undertake aortic valve intervention in an asymptomatic patient requires careful consideration, because the early procedural risks need to be weighed against those associated with progressive and potentially irreversible adverse left ventricular remodeling, heart failure and death with continued conservative management. International guidelines suggest that conservative management and watchful waiting for the onset of symptoms is a safe strategy, and this is supported by our data. The risk of procedural death and sudden cardiac death were very low even in our enriched elderly population of patients with severe aortic stenosis and myocardial fibrosis. Moreover, there were no differences in all-cause or cardiovascular mortality between trial groups across 722 patient-years of follow-up.

Our mortality data conflict with the results of the RECOVERY trial which demonstrated a mortality benefit of early intervention in a highly selected cohort of younger and otherwise healthy patients with predominantly bicuspid valve disease. These patients had critical aortic stenosis with a mean aortic valve peak velocity of over 5 m/s, meaning most would have met the Class IIb level recommendation for aortic valve intervention at trial inclusion.[2,3,6] The AVATAR trial demonstrated a long-term benefit in all cause but not cardiovascular mortality but again recruited a younger patient population that also included patients with very severe aortic stenosis. Even after enriching for a high-risk population with myocardial fibrosis, our trial suggests that their findings of improved mortality with early intervention cannot be extrapolated to the broader older population with asymptomatic severe aortic stenosis who have a greater burden of co-morbidities. Indeed, in our study, only a third of deaths were

attributed to the patients' underlying aortic valve disease, meaning that most deaths were not modifiable by aortic valve intervention.

Although focus on mortality is important, it is also crucial to consider the impact of intervention in reducing symptoms and preventing emergency hospitalizations in an older population. We observed a higher burden of heart failure symptoms at 12 months in patients allocated to guideline-directed conservative management which was not apparent in those who underwent early aortic valve intervention. Consistent with this, early aortic valve intervention also resulted in fewer unplanned aortic stenosis-related hospitalizations compared to guideline-directed conservative management. These are primary treatment goals for many older patients and thus represent an important finding, particularly given the low peri-procedural risk associated with early intervention.[6,7] . Our findings that early intervention was associated with a lower incidence of unplanned aortic stenosis-related hospitalization and improved symptom burden should be considered hypothesis generating given that we failed to meet our primary endpoint and we did not adjust for multiple comparisons. If confirmed, the principal benefits of early intervention in asymptomatic patients with subclinical cardiac decompensation may be to avoid the development of symptoms and unplanned hospitalizations rather than to reduce mortality. These hypotheses need to be addressed in future larger trials, such as the EASY-AS trial (NCT04204915).[27]

Our trial has several limitations. First, because the primary endpoint is null, any conclusions about the secondary endpoints must be designated as hypothesis generating. Second, recruitment was heavily impacted by the COVID-19 pandemic and prevented the achievement of our original sample size. For these reasons, further research is needed to confirm our findings. Third, the rate of transcatheter aortic valve intervention was higher in

the guideline-directed conservative management group than the early intervention group, reflecting better access to transcatheter aortic valve intervention during study conduct and urgent intervention following unplanned aortic stenosis-related hospitalizations where patients may have been too unwell to undergo surgical aortic valve replacement. Finally, the rate of female participants in this trial was low (28%) which could reflect that women may have less advanced myocardial remodeling than men in response to the same level of valvular stenosis,[32,33] and this limits the generalizability of the trial findings.

CONCLUSIONS

Early aortic valve intervention has no demonstrable effect on the combined primary endpoint of all-cause death or unplanned aortic stenosis-related hospitalization compared with guideline-directed conservative management among patients with asymptomatic severe aortic stenosis and myocardial fibrosis. There was a wide 95% confidence interval around the primary endpoint, with further research needed to confirm these findings.

ARTICLE INFORMATION

Author Contributions: Dr Craig, Prof. Dweck, Ms Graham and Prof. Lewis had fully access to all of the data in the study and take responsibilituy for the integrity of the data and the accurary of the data analysis.

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Administrative, technical, or material support: White, MacGillivray, Tuck, Rayson, Cranley, Irvine, Armstrong, Milne.

Supervision: Dweck, Newby, Singh, Prendergast, McCann, Ripley, Rajani, Miller, Motwani, Treibel, Dawson, Keenan, Prasad, Boon, Hothi, Dungu, Vassiliou, Kunadian, Joshi, Bucciarelli-Ducci, Lang, Leslie, Steeds, Greenwood, Fairbairn, Hillis.

Declaration of interests

We have no competing interests.

Funding/Support: Sir Jules Thorne Charitable Trust funded the trial.

Role of the Funder/Sponsor: The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

REFERENCES

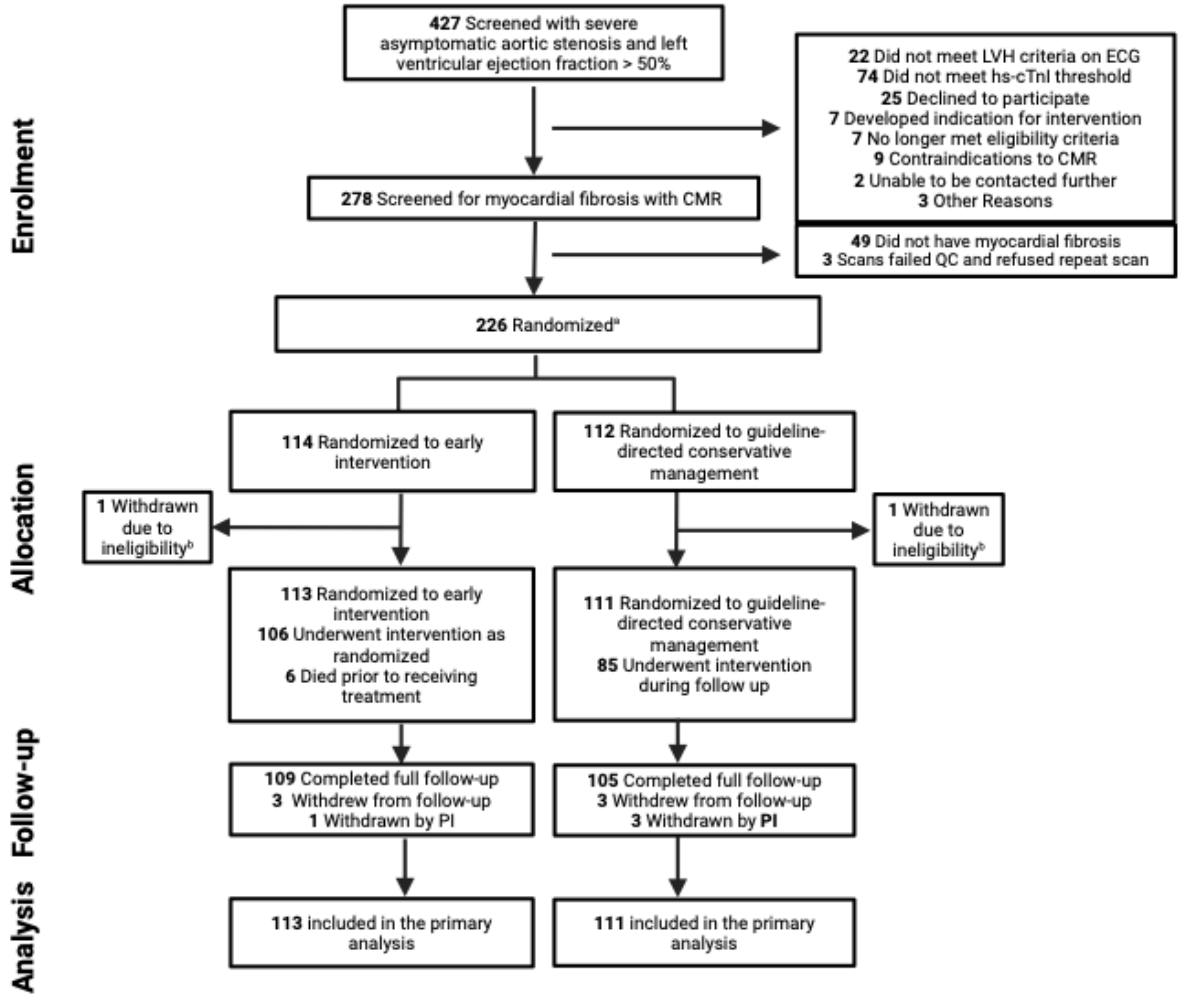
1. Osnabrugge R, Mylotte D, Head S et al. Aortic stenosis in the elderly. *J Am Coll Cardiol* 2013;61:1002-12.
2. Baumgartner H *et al*. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739-91.
3. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-e185.
4. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic severe aortic stenosis in the elderly. *JACC Cardiovasc Imaging* 2017;10:43-50.
5. Iung B, Cachier A, Baron G et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714-20.
6. Kang DH, Park SJ, Lee SA et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;382:111-19
7. Banovic M, Putnik S, Penicka M et al. Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: The AVATAR Trial. *Circulation* 2022;145:648-658.
8. Shah AS, Griffiths M, Lee KK et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ*. 2015;350:g7873.

9. Chin CW, Shah AS, McAllister DA et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;35:2312-21.
10. Shah AS, Chin CW, Vassiliou V et al. Left ventricular hypertrophy with strain and aortic stenosis. *Circulation* 2014;130:1607-16.
11. Greve AM, Boman K, Gohlke-Baerwolf C et al. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. *Circulation* 2012;125:346-53.
12. Azevedo CF, Nigri M, Higuchi ML et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol*. 2010;56:278-87.
13. Dweck MR, Joshi S, Murigu et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol*. 2011;58:1271-9.
14. Vassiliou VS, Perperoglou A, Raphael CE et al. midwall fibrosis and 5-year outcome in moderate and severe aortic stenosis. *J Am Coll Cardiol* 2017;69:1755-1756.
15. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol* 2012;60:1854-63.
16. Hein S, Arnon E, Kostin S et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation* 2003;107:984-91.
17. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation* 1989;79:744-55.

18. Kong WKF, Bax JJ, Delgado V. Left ventricular myocardial fibrosis: a marker of bad prognosis in symptomatic severe aortic stenosis. *Eur Heart J* 2020 21;41:1915-1917.
19. Milano AD, Faggian G, Dodonov M et al. Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. *J Thorac Cardiovasc Surg* 2012;144:830-7.
20. Barone-Rochette G, Piérard S, De Meester de Ravenstein C et al. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J Am Coll Cardiol*. 2014;64:144-54.
21. Chin CWL, Everett RJ, Kwiecinski J et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging*. 2017;10:1320-33.
22. Musa TA, Treibel TA, Vassiliou VS et al. Myocardial scar and mortality in severe aortic stenosis. *Circulation*. 2018;138:1935-47.
23. Thornton GD, Vassiliou VS, Musa TA et al. Myocardial scar and remodelling predict long-term mortality in severe aortic stenosis beyond 10 years. *Eur Heart J* 2024 7;45:2019-2022.
24. Bing R, Everett RJ, Tuck C et al. Rationale and design of the randomized, controlled Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial. *Am Heart J*. 2019;212:91-100.
25. Schultz K, Altman D, Moher D, CONSORT Group. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c332.
26. Baumgartner H, Hung J, Bermejo J et al. American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1-23.

27. Richardson C, Gilbert T, Aslam S et al. Rationale and design of the early valve replacement in severe asymptomatic aortic stenosis trial. *Am Heart J* 2024;275:119-127.
28. Elbaz-Greener G, Masih S, Fang J et al. Temporal Trends and Clinical Consequences of Wait Times for Transcatheter Aortic Valve Replacement: A Population-Based Study. *Circulation* 2018; 138(5):483-493.
29. Henning K, Ranvindran M, Qiu F et al. Impact of procedural capcity on transcatheter aortic valve replacement wait times and outcomes: a study of regional variation in Ontario, Canada. *Open Heart* 2020:7:e001241.
30. Nilsson K, Lindholm D, Backes J et al. Regional assessment of availability for transcatheter aortic valve implantation in Sweden: a long-term observational study. *Eur Heart J Qual Care Clin Outcomes* 2023;qcad076.
31. Roule V, Rebouh I, Lemaitre A et al. Impact of wait times on late postprocedural mortality after successful transcatheter aortic valve replacement. *Sci Rep* 2022; 12(1)5967.
32. Treibel T, Kozor R, Fontana M et al. Sex dimorphism in the Myocardial Response to Aortic Stenosis. *JACC Cardiovasc Imaging* 2018 11(7):962-973.
33. Singh A, Musa T, Treibel T et al. Sex differences in left ventricular remodelling, myocardial fibrosis and mortality after aortic valve replacement. *Heart* 2019; 105(23):1818-1824.

Figure 1. Recruitment, Randomization and Follow-up in the EVOLVED Trial

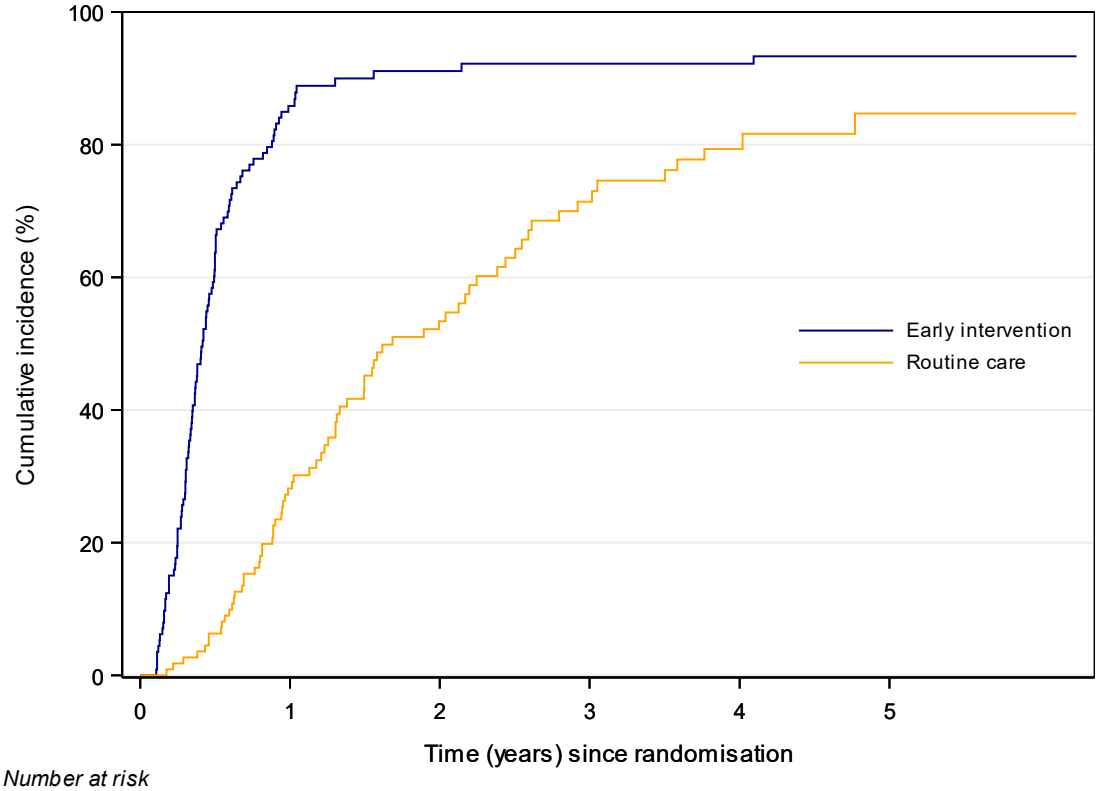


[a] Randomization used minimization, with stratification for age, sex, aortic valve peak velocity, ischemic heart disease and screening method.

[b] Two participants were excluded as they were randomized after having already been referred for surgery (see eMethods in Supplement 1 for details).

* LVH = left ventricular hypertrophy, ECG = electrocardiogram, hs-cTnI = plasma high-sensitivity cardiac troponin I concentration, CMR = cardiac magnetic resonance, QC =Quality Control.

Figure 2: Cumulative Incidence of Aortic Valve Intervention

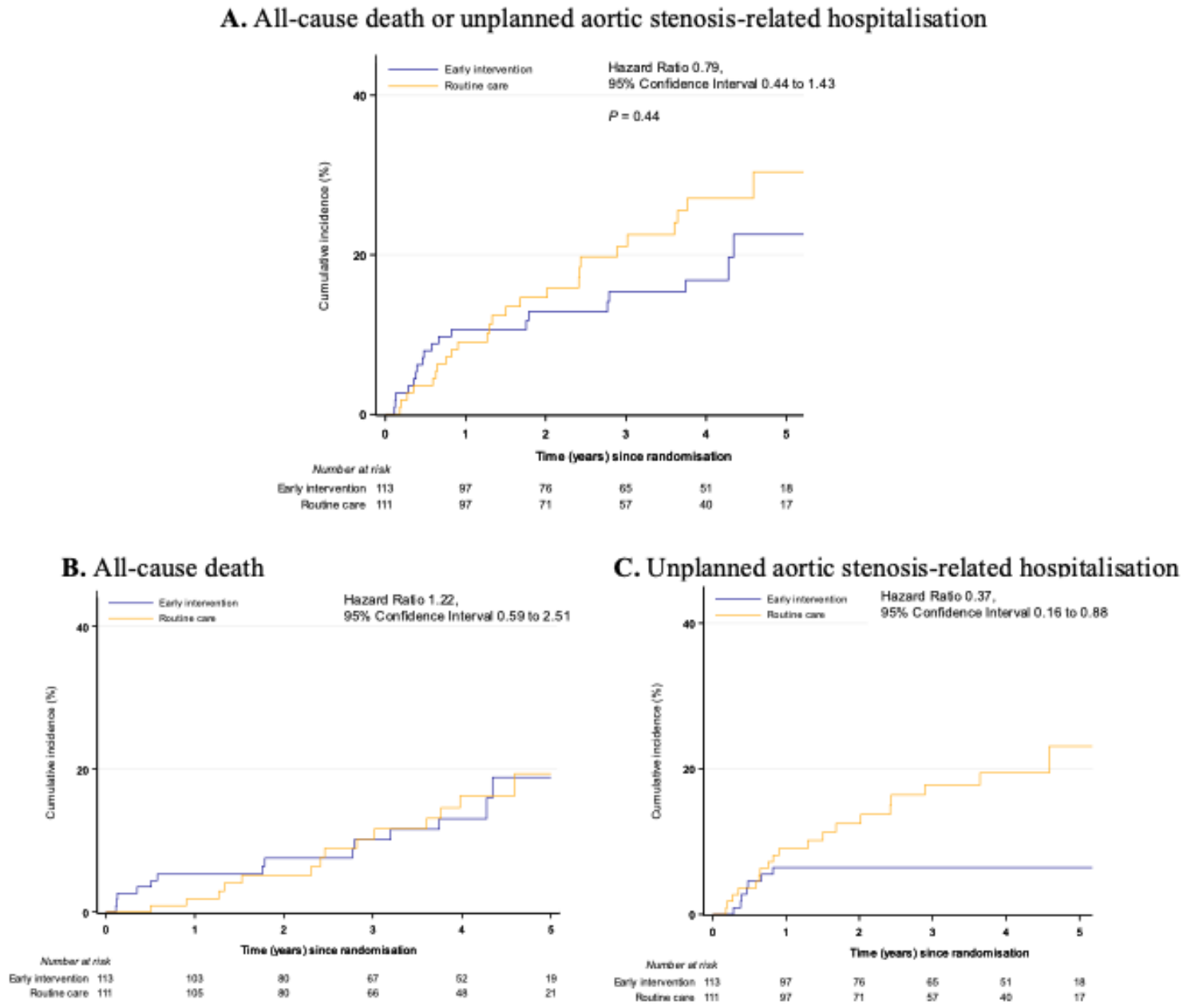


Number at risk

Early intervention	113	16	8	7	7	6
Routine care	111	77	37	18	12	4

At 12 months, 86% of patients in the early intervention arm (blue) received aortic valve intervention compared with 28% of patients in the guideline-directed conservative management arm (orange).

Figure 3. Cumulative Incidence of the Primary Composite Endpoint and its Components



Time-to-first event Kaplan-Meier Analysis. The median observation time [interquartile interval] for each curve is as follows:

A. Early Intervention: 48.2 [12.6 to 52.1] months; Routine Care 36.5 [13.8 to 49.6] months
B. Early Intervention: 48.5 [15.9 to 52.9] months; Routine Care 48.1 [23.7 to 55.3] months
C. Early Intervention: 48.2 [12.6 to 52.1] months; Routine Care 36.5 [13.8 to 49.6] months

Table 1. Clinical Characteristics of the Study Population

	Early Intervention (n=113)	Conservative Management (n=111)
Demographics		
Age, median [IQR], years	75 (68 - 79)	76 [68 – 80]
Age ≥75 years, No. (%)	57 (50)	60 (54)
Sex, No. (%)		
Male	82 (73)	79 (71)
Female	31 (27)	32 (29)
Body-mass index, median (IQR), kg/m^2	27.2 [24.4 – 31.1]	27.8 [24.8 – 31.1]
Body-mass index ≥30 kg/m^2, No. (%)	35 (31)	33 (30)
Smoking history (current or ex-smoker), No. (%)	51 (45)	55 (50)
Comorbidities, No. (%)		
Hypertension, No. (%)	76 (67)	70 (63)
Hyperlipidaemia, No. (%)	55 (49)	56 (50)
Diabetes mellitus, No. (%)	15 (13)	26 (23)
Cerebrovascular disease, No. (%)	8 (7)	14 (13)
History of angina, No. (%)	5 (4)	8 (7)
Peripheral vascular disease, No. (%)	4 (4)	9 (8)
Past Procedures, No. (%)		
Previous percutaneous coronary intervention, No. (%)	7 (6)	7 (6)
Previous coronary artery bypass graft surgery, No. (%)	3 (3)	3 (3)
Medication, No. (%)		
- Statin	70 (62)	73 (66)
- Beta-blocker	33 (29)	17 (15)
- Angiotensin-converting enzyme inhibitor	30 (27)	31 (28)
- Diuretic	27 (24)	18 (16)
- Angiotensin-receptor blocker	25 (22)	21 (19)
High-sensitivity cardiac troponin I concentration[a], median [IQR], ng/L	11.0 [9.0 - 18.0]	9.0 [6.0 - 16.5]
Presence of left ventricular hypertrophy on electrocardiogram, No (%).	88 (78)	87 (78)
Echocardiography, mean (SD)		
- Aortic valve peak velocity, m/s	4.3 (0.5)	4.4 (0.5)
- Mean gradient, mmHg	45.2 (11.5)	45.0 (10.2)
- Aortic valve area, cm^2	0.8 (0.2)	0.8 (0.2)
Cardiac magnetic resonance		
- Bicuspid aortic valve, No. (%)	36 (32)	28 (25)
- Indexed left ventricular mass, mean (SD), g/m^2	85.5 (18.4)	81.5 (16.4)
- Indexed left ventricular end diastolic volume, mean (SD), mL/m^2	75.0 (18.4)	74.3 (18.5)
- Indexed left ventricular stroke volume, mean (SD), mL/m^2	50.2 (11.5)	49.9 (11.7)

	Early Intervention (n=113)	Conservative Management (n=111)
- Left ventricular ejection fraction, mean (SD), %	68 (9)	68 (8)
- Prior myocardial infarction, No. (%)	10 (9)	9 (8)

[a] High-sensitivity cardiac troponin I concentration ≥6 ng/L was in the inclusion criteria for sites screening with ECG and Troponin.

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Outcome	Early Intervention (n=113)	Conservative Management (n=111)	Absolute Difference [95% Confidence Interval]	Hazard Ratio [95% Confidence Interval]
Primary endpoint				
- All-cause death or unplanned aortic stenosis-related hospitalization, No. (%)	20 (18)	25 (23)	-4.82 [-15.31 to 5.66] *P*=0.37	0.79 [0.44 to 1.43] *P*=0.44
Secondary endpoints				
- All-cause death, No. (%)	16 (14)	14 (13)	1.55 [-7.37 to 10.46]	1.22 [0.59 to 2.51]
- Cardiovascular death, No. (%)	10 (9)	8 (7)	1.64 [-5.47 to 8.75]	1.33 [0.52 to 3.36]
- Aortic stenosis-related death, No. (%)	6 (5)	5 (5)	0.81 [-4.85 to 6.46]	1.25 [0.38 to 4.10]
- Unplanned aortic stenosis-related hospitalization, No. (%)	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, No. (%)	5 (4)	7 (6)	-1.88 [-7.78 to 4.02]	0.75 [0.24 to 2.37]
- Stroke, No. (%)	8 (7)	14 (13)	-5.53 [-13.31 to 2.25]	0.62 [0.26 to 1.49]
- Endocarditis, No. (%)	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]

Outcome	Early Intervention (n=113)	Conservative Management (n=111)	Absolute Difference [95% Confidence Interval]	Odds Ratio for experiencing at least one specified complication
- Peri- or post-operative complications within 30 days of surgery or transcatheter aortic valve intervention, No. (%)	15 (14)	9 (11)	5.17 [-2.89 to 13.22]	1.20 [0.50 to 2.93]
-				**Adjusted means for WHODAS total score at one year follow-up and difference in adjusted means**
- WHODAS Total Score, No. (%)	3.3	4.1		-0.8 [-2.0 to 0.4]
- NYHA Classification at 1 year, No. (%)				**Odds Ratio for higher NYHA Classification (95% Confidence Interval**
- Class I - Class II - Class III - Class IV	86 (80) 19 (18) 2 (2) 0 (0)	64 (62) 30 (29) 8 (8) 1 (1)		0.37 [0.20 to 0.70]

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*Cardiovascular death is defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, or other cardiovascular causes, death due to cardiovascular procedures, and death due to other cardiovascular causes. Aortic stenosis-related death is a death where aortic stenosis has been listed as a contributory cause by the clinical care team on the patient's official death certificate. Sudden cardiac death is defined as any death that occurs unexpectedly and not within 30 days of acute myocardial infarction. This includes unsuccessful resuscitation following an arrhythmia.