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

Insights From the EVOLVED Randomized Clinical Trial

ORIGINAL RESEARCH ARTICLE

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

Insights from The EVOLVED Randomized Controlled Trial

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Key Points

Question. In asymptomatic patients with severe aortic stenosis, is myocardial fibrosis burden associated with adverse events, and potential benefits of early valve intervention?

Findings. In this *post hoc* analysis, higher midwall fibrosis burden was associated with increasing incidence of the primary composite endpoint of all-cause death or unplanned aortic stenosis-related hospitalization. However, the potential beneficial effects of early valve intervention demonstrated no significant heterogeneity by the degree of midwall fibrosis.

Meaning. In asymptomatic patients with severe aortic stenosis, higher fibrosis burden was associated with adverse outcomes. Benefits of early intervention were similar between patients with high and low fibrosis burden.

Abstract

Importance. Myocardial fibrosis burden has been associated with adverse clinical outcomes in symptomatic patients with aortic stenosis.

Objectives. To determine whether midwall myocardial fibrosis burden is associated with adverse clinical outcomes in asymptomatic patients, and whether those with more fibrosis derive greater benefit from early intervention.

Design. *Post-hoc* analysis of a randomized controlled 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 midwall fibrosis on cardiac magnetic resonance.

Intervention. Early intervention with transcatheter or surgical aortic valve replacement.

Main Outcomes and Measures. Primary outcome was all-cause death or unplanned aortic stenosis-related hospitalization. Secondary outcomes included the individual components of the primary outcome.

Results. In 224 trial participants (mean age 73 (standard deviation 9) years, 28% women and mean aortic valve peak velocity 4.3 (0.5) m/s) with median follow-up of 42 months, fibrosis burden (per 1% increase) was associated with an increase in the primary endpoint (hazard ratio (HR), 1.23 [95% confidence interval 1.08-1.37]) and its component of unplanned aortic stenosis-related hospitalizations (HR 1.22 [1.03-1.40]) but not all-cause death (HR 1.17 [0.98-1.35]).

There were no interactions between randomization arm and the midwall fibrosis burden for the primary ($P_{interaction}$=0.39) or secondary endpoints. In patients with high fibrosis

burden above the median, the primary endpoint occurred in 12/59 (20%) of those randomized to early intervention and 17/53 (32%) of those randomized to guideline-directed conservative management (HR 0.62 [0.29–1.28]). For the individual components, all-cause death occurred in 9 (15%) and 10 (19%) patients respectively (HR 0.84 [0.33-2.07]), and unplanned aortic stenosis-related hospitalization in 4 (7%) and 13 (25%) patients respectively (HR 0.27 [0.08-0.77]). In patients with low fibrosis burden below the median, there were no differences in the primary outcome (HR 1.05 [0.39-2.86]) or its components between intervention groups.

Conclusions and Relevance. In asymptomatic patients with severe aortic stenosis, higher midwall fibrosis burden was associated with adverse outcomes. There was no demonstrable heterogeneity by the degree of midwall fibrosis for the treatment effects of early surgical or transcatheter aortic valve replacement compared to clinical surveillance.

Trial Registration:

Clinicaltrials.gov Identifier: NCT03094143

INTRODUCTION

Aortic valve replacement remains the cornerstone of treatment for severe aortic stenosis, although debate continues about its optimal timing.(1) Asymptomatic patients may undergo irreversible adverse left ventricular remodeling whilst waiting for intervention.(2) Specifically, myocardial fibrosis ultimately leads to heart failure and adverse events.(3,4) Midwall late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) identifies regions of non-infarct replacement fibrosis, with observational studies from predominantly symptomatic patients with severe aortic stenosis demonstrating that it provides objective assessment of left ventricular decompensation, increases over time, and predicts heart failure and mortality.(3,5–9)

The Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial randomized asymptomatic patients with severe aortic stenosis and midwall LGE to early aortic valve intervention or guideline-directed conservative management.(10) In both arms, the choice of surgical or transcatheter aortic valve replacement was made by the local heart valve team. There was no demonstrable difference in the incidence of the composite primary endpoint of all-cause death or unplanned aortic stenosis-related hospitalization, although early intervention resulted in fewer such hospitalizations. This *post-hoc* analysis was designed to confirm whether asymptomatic patients with a higher burden of midwall fibrosis developed more adverse events. We further hypothesized that benefits of early intervention would be greater in patients with greater midwall fibrosis.

METHODS

Study Design and Patient Selection

The EVOLVED trial (NCT03094143) was a parallel-group multicenter prospective randomized open-label blinded endpoint trial, performed at 24 sites across the United Kingdom and Australia. The study design and population have been described previously (10) (eMethods in the Supplement). The study was conducted following Research Ethics Committee approval and the written informed consent of participants. This report follows the CONSORT reporting guideline for parallel-group randomized trials.

CMR was performed on 1.5 or 3-Tesla scanners using standardized protocols (eMethods and eFigures 1 and 2 in the Supplement) with images assessed by a core laboratory blinded to clinical details.

The primary endpoint was a composite of all-cause mortality or unplanned aortic stenosis-related hospitalisation during the follow-up period. Aortic stenosis-related hospitalisation 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 2 investigators blinded to trial arm allocation. Secondary endpoints included the components of the primary endpoint.(10) Statistical methods are described in eMethods in the Supplement.

RESULTS

Study Population

Overall, 224 asymptomatic participants with severe aortic stenosis were followed up for a median of 42 months. The mean age was 73 (standard deviation 9) years and 63 (28%) were female. The mean aortic valve peak velocity was 4.3 (0.5) m/s, mean aortic valve area 0.8 (0.2) cm^2 and median midwall fibrosis burden 1.0% [interquartile interval 0.5-2.0%]. Baseline characteristics were comparable between those in the high (>1.0%) and low (<1.0%) midwall fibrosis burden groups (Table 1).

Midwall Fibrosis and Clinical Events

Twenty-nine (26%) patients with a high midwall fibrosis burden above the median and 16 (14%) patients with the low midwall fibrosis burden below the median experienced the primary composite endpoint (hazard ratio (HR) 1.86 [95% confidence interval (CI) 1.20-3.50]) (eTable 1 in the Supplement, Figure 1). Across the cohort, each 1% increase in midwall fibrosis burden was associated with an increased incidence of the primary composite endpoint (HR 1.23 [1.08–1.37]) and unplanned aortic stenosis-related hospitalization (HR 1.22 [1.03–1.40]).

Early Intervention and Midwall Fibrosis Burden

For the primary endpoint, the interaction between trial allocation and midwall fibrosis burden was not significant ($P_{interaction}$=0.39). In the high midwall fibrosis burden group, 12 (20%) patients randomized to early intervention and 17 (32%) randomized to guideline-directed conservative management experienced the composite primary endpoint (HR 0.62 [95% CI 0.29-1.28]) (eTable 2 in the Supplement, Figure 2). There was no difference in all-cause mortality (HR 0.84 [95% CI 0.33-2.07]), but unplanned aortic stenosis-related hospitalizations were lower (HR 0.27 [95% CI 0.08-0.77]) with early intervention.

In the low midwall fibrosis burden group, 8 (15%) patients randomized to early intervention and 8 (14%) patients randomized to guideline-directed conservative management experienced the composite primary endpoint (HR 1.05 [95% CI 0.39-2.86]) (eTable 2 in the Supplement, Figure 2). There were no differences in all-cause mortality (HR 1.87 [95% CI 0.56-7.12]) or unplanned aortic-stenosis related hospitalization (HR 0.54 [95% CI 0.11-2.04]).

DISCUSSION

In this *post-hoc* analysis of EVOLVED, we examined the relationship between midwall fibrosis burden and clinical outcomes in an asymptomatic population with severe aortic stenosis. Greater midwall fibrosis was associated with a higher incidence of the composite primary endpoint of all-cause death or unplanned aortic stenosis-related hospitalization. However, for the primary outcome and its components, there was no demonstrable heterogeneity by the degree of midwall fibrosis for the treatment effects of early surgical or transcatheter aortic valve replacement compared to clinical surveillance.

Observational retrospective data have demonstrated that patients with higher midwall fibrosis experience more adverse events, but included symptomatic patients already referred for valve replacement.(3,6) We report the first prospective multicenter randomized trial data, confirming that higher midwall fibrosis is associated with increased death or hospitalization in asymptomatic patients. Our data support assessment of midwall fibrosis as a useful prognostic marker in patients with asymptomatic severe aortic stenosis in whom early intervention may play an increasing clinical role.

In meta-analysis of the 4 randomized trials evaluating timing of aortic valve intervention in asymptomatic patients with severe aortic stenosis, early intervention resulted in a lower incidence of emergency hospitalizations without a reduction in all-cause or cardiovascular mortality.(11) However, asymptomatic patients with severe aortic stenosis are a heterogenous population with a spectrum of risk. For example, the RECOVERY trial enriched their study population with high-risk patients with very severe aortic stenosis by echocardiography (12) whilst EVOLVED enriched via the presence of midwall fibrosis. Some commentators have

suggested that earlier valve intervention may still be "too late" for these high-risk patients with established midwall fibrosis, proposing that earlier intervention during the stage of milder diffuse interstitial fibrosis might be more beneficial.(13,14) Although EVOLVED only randomized patients with replacement fibrosis, our data do not support this view. Indeed our data indicate that patients with more advanced replacement fibrosis have at least as much to gain from early intervention as those with a low burden of fibrosis. While our findings are exploratory and hypothesis-generating, they suggest that future work examining the optimal timing of aortic valve implantation in asymptomatic patients and the interaction with myocardial fibrosis is warranted.

In the absence of symptoms, decisions to undertake intervention require careful consideration, balancing early procedural risks against progressive irreversible adverse remodeling. Many patients may take a proactive view and proceed with early intervention to remain well and prevent emergency, arguably higher risk hospitalization. Other patients may prefer to avoid the risks of intervention whilst feeling healthy. Some may remain uncertain about their individual risk and wish more information before committing to a certain treatment pathway. CMR has established its powerful prognostic power in aortic stenosis across multiple data sets now including the asymptomatic patients in EVOLVED and may fulfil this role. In EVOLVED, pre-screening by high-sensitivity cardiac troponin I concentration or left ventricular hypertrophy on electrocardiography successfully identified patients likely to have midwall fibrosis. These quick inexpensive tests might also be useful to identify patients in whom CMR may be most helpful.

Recruitment to EVOLVED was impacted by COVID-19 and the consequent modest sample size resulted in reduced statistical power to assess potential interaction effects between

randomization arms and fibrosis burden. Whilst some trends in the data were apparent, we observed no significant interaction between the primary endpoint and fibrosis burden. Longer term follow-up for the EVOLVED trial is ongoing and more primary outcome events may further clarify our findings. Although not a pre-specified secondary analysis, others have highlighted the importance of our fibrosis data.(13,15) We chose not to include infarct-pattern fibrosis as this relates to a different pathological condition which is less likely to be impacted by the timing of aortic valve intervention. However, we acknowledge that this limits comparison of our findings with prior observational data.(3,6) Finally, the median time-to-early-intervention was 5 months. Arguably this was too long and could have impaired our ability to identify a potential benefit. However, this is the reality of most health care systems globally, although some health care systems may be able to deliver intervention more quickly.

CONCLUSIONS

Higher midwall fibrosis burden identifies asymptomatic patients with severe aortic stenosis at greater risk of adverse outcomes of all-cause death and unplanned aortic stenosis-related hospitalization. For the primary outcome and its components, there was no demonstrable heterogeneity by the degree of midwall fibrosis for the treatment effects of early surgical or transcatheter aortic valve replacement compared to clinical surveillance.

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Declaration of interests

We have no competing interests.

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Access to Data and Data Analysis: The Chief Investigator had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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363 **Table 1. Clinical Characteristics of the Study Population**

	Low Midwall Fibrosis Burden (n=112)	High Midwall Fibrosis Burden (n=112)	*P*-value
Demographics			
Age, median [IQR], years	74 [68 – 80]	75 [69 – 79]	0.3
Age ≥75 years, No. (%)	55 (49)	62 (55)	
Sex, No. (%)			0.1
Male	74 (66)	87 (78)	
Female	38 (34)	25 (22)	
Body-mass index, median (IQR), kg/m^2	26.9 [24.6 – 30.8]	28.2 [24.5 – 31.1]	0.3
Body-mass index ≥30 kg/m^2, No. (%)	30 (27)	38 (34)	
Smoking history (current or ex-smoker), No. (%)	44 (39)	62 (55)	0.02
Comorbidities, No. (%)			
Hypertension, No. (%)	67 (60)	79 (71)	0.1
Hyperlipidaemia, No. (%)	50 (45)	61 (54)	0.1
Diabetes mellitus, No. (%)	21 (19)	20 (18)	0.9
Cerebrovascular disease, No. (%)	10 (9)	12 (11)	0.7
History of angina, No. (%)	4 (4)	9 (8)	0.2
Peripheral vascular disease, No. (%)	5 (5)	8 (7)	0.4
Past Procedures, No. (%)			
Previous percutaneous coronary intervention, No. (%)	5 (5)	9 (8)	0.3
Previous coronary artery bypass graft surgery, No. (%)	1 (1)	5 (5)	0.2
Medication, No. (%)			
- Statin	65 (68)	78 (74)	0.4
- Beta-blocker	27 (28)	23 (22)	0.3
- Angiotensin-converting enzyme inhibitor	26 (27)	35 (33)	0.4
- Diuretic	24 (25)	21 (20)	0.3
- Angiotensin-receptor blocker	25 (26)	21 (20)	0.3
High-sensitivity cardiac troponin I concentration[a], median [IQR], ng/L	10 [7 - 15]	13 [8 - 21]	0.1
Presence of left ventricular hypertrophy on electrocardiogram, No (%).	90 (80)	85 (76)	0.6
Presence of strain pattern on electrocardiogram, No (%).	35 (31)	31 (28)	0.6

	Low Midwall Fibrosis Burden (n=112)	High Midwall Fibrosis Burden (n=112)	*P*-value
Echocardiography, median [IQR]			
- Aortic valve peak velocity, m/s	4.3 [4.1 – 4.5]	4.3 [4.1 – 4.6]	0.2
- Aortic valve area, cm^2	0.8 [0.7 – 0.9]	0.9 [0.7 -1.0]	0.4
- Mean transvalvular pressure gradient, mmHg	43 [39 to 51]	44 [39 to 50]	0.6
Cardiac magnetic resonance			
- Bicuspid aortic valve, No. (%)	30 (27)	34 (30)	0.6
- Indexed left ventricular mass, median [IQR], g/m^2	82 [70 – 94]	84 [71 – 95]	0.3
- Indexed left ventricular end diastolic volume, median [IQR], mL/m^2	71 [61 – 84]	73 [65 – 87]	0.4
- Indexed left ventricular stroke volume, median [IQR], mL/m^2	51 [43 – 58]	49 [43 – 57]	0.8
- Left ventricular ejection fraction, median [IQR], %	69 [63 – 74]	67 [60 – 72]	0.2
- Prior myocardial infarction, No. (%)	6 (5)	13 (12)	0.1
- Quantified absolute subendocardial late gadolinium enhancement, median [IQR], g	9.9 [6.2 – 21.9]	5.5 [4.3 – 8.2]	0.1
- Percent myocardial involvement of subendocardial late gadolinium enhancement, median [IQR], %	5.2 [3.3 – 13.0]	3.6 [3.1 – 4.4]	0.5
- Quantified absolute midwall late gadolinium enhancement, median [IQR], g	0.8 [0.4 – 1.2]	3.3 [2.2 – 5.2]	
- Percent myocardial involvement of midwall late gadolinium enhancement, median [IQR], %	0.5 [0.3 – 0.7]	2.0 [1.4 – 3.1]	
	n=83	n=89	
- Indexed extracellular volume (iECV), median [IQR], mL/m^2	19.4 [17.2 – 23.1]	21.0 [18.3 – 24.7]	**<0.05**

- Extracellular volume fraction (%ECV), median [IQR], mL/m^2	25.9 [24.1 – 27.4]	26.4 [24.4 – 28.4]	0.2

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

Figure 1: Cumulative Incidence of the Primary Composite Endpoint and its Components for all Randomized Participants Stratified by Midwall Fibrosis Burden

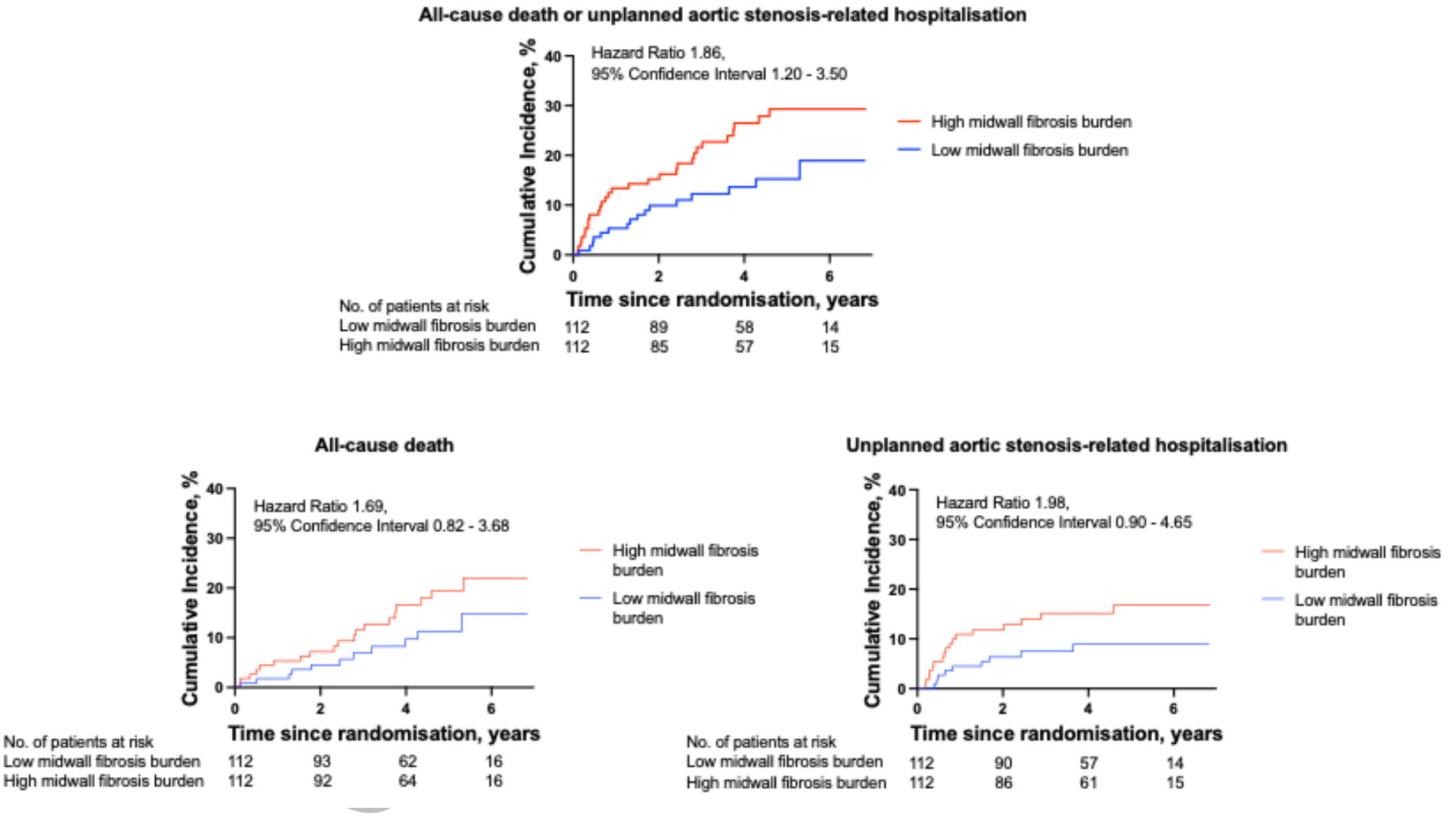

Figure 2: Cumulative Incidence of the Primary Composite Endpoint and its Components for Patients with High Midwall Fibrosis Burden by Trial Allocation