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Myocardial fibrosis in patients undergoing transcatheter aortic valve replacement: impact on left ventricular reverse remodeling and long-term outcome

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Abstract

Aims: We sought to investigate the relevance of myocardial fibrosis, assessed by mid-wall fibrosis risk (MFR) score, with respect to left ventricular (LV) reverse remodeling following transcatheter aortic valve replacement (TAVR).

Methods and Results: Between January 2010 and March 2015, we enrolled 207 patients in whom baseline MFR, which includes age, sex, high-sensitive cardiac troponin-I, presence of strain pattern on electrocardiograph, and peak-aortic valve velocity, as well one-year follow-up echocardiography were available. LV reverse remodeling was defined as a >10 % reduction in LV end-diastolic volume index (LVEDVi). A higher MFR score (≥ 52) was associated with increased LVEDVi and with decreased LV ejection fraction as well as higher baseline-NT-pro-BNP levels ($p < 0.05$ for all). One year after the TAVR procedure, a higher MFR score was associated with a decreased probability of LV reverse remodeling (OR 0.33; 95% CI, 0.23-0.87; $p = 0.03$), which was independent of baseline echocardiographic parameters and comorbidities. In contrast, there was no significant difference in five-year mortality between patients with lower and higher MFR score (57.9% vs. 60.5%, $p = 0.66$).

Conclusions: A higher MFR score is associated with reduced LV reverse remodeling at one-year follow-up, whereas the MFR score does not appear to interfere with long-term mortality after TAVR.

Classifications

Aortic stenosis; Imaging modalities; TAVI; Biochemical markers; Non-invasive imaging.

Condensed Abstract

Myocardial fibrosis is an important factor for poor prognosis in patients with aortic stenosis. The current observational study evaluates the impact of myocardial fibrosis, assessed by means of the mid-wall fibrosis risk (MFR) score, on left ventricular (LV) reverse remodeling and long-term prognosis after transcatheter aortic valve replacement (TAVR). A higher MFR score was associated with poor probability of LV reverse remodeling. In contrast, neither a correlation of the MFR score with an improvement of LV ejection fraction nor with five-year mortality was seen. Our findings suggest a limited impact of myocardial fibrosis on clinical outcome in patients undergoing TAVR.

Abbreviations:

AS = aortic stenosis

CMR = cardiovascular magnetic resonance

ECG = electrocardiography

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVM = left ventricular mass

MF = myocardial fibrosis

MFR score = mid-wall fibrosis risk score

NT-pro-BNP = N-terminal pro-B-type natriuretic peptide

ROC = receiver operating characteristic

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TTE = trans-thoracic echocardiography

Introduction

The increase in afterload imposed by aortic stenosis (AS) leads to adaptive left ventricular (LV) remodeling, resulting in LV hypertrophy and consecutively impaired systolic as well as diastolic LV function and poor prognosis^{1,2}. The histopathological causes of LV remodeling are the loss of viable myocardium and increased fibrosis, which have been found to correlate with increased adverse events in patients with AS³⁻⁵. Additionally, myocardial fibrosis (MF) appears to be associated with a lack of improvement in systolic and diastolic LV function after surgical aortic valve replacement (SAVR), suggesting an impact of MF on LV reverse remodeling^{6,7}. Recently, a clinical risk score has been introduced allowing for the estimation of myocardial fibrosis in patients with AS. The so-called mid-wall fibrosis risk (MFR) score has been found to predict adverse outcomes in moderate to severe asymptomatic AS⁸. In the context of TAVR, reduction of afterload has been shown to be linked to reverse remodeling, including a decrease of LV volume, a regression of LV mass, and an improvement of LV systolic function^{9,10}. Despite its clinical relevance, little is known about the impact of myocardial fibrosis following TAVR, especially on LV reverse remodeling.

In this study, we therefore sought to evaluate the impact of the MFR score on a) LV reverse remodeling, b) on improvement of LV systolic function, as well as c) on the long-term outcome in patients undergoing TAVR. Furthermore, we aimed to establish a correlation of potential biomarkers of MF with the MFR score in a subgroup of patients.

Methods

We performed a retrospective observational cohort study of patients with severe, symptomatic AS who underwent TAVR from May 2009 to March 2015 at the Heart Center of the University Hospital, Bonn, Germany. To evaluate the impact of LV remodeling, only those patients who underwent follow-up echocardiography one year after TAVR were included. Patients with incomplete baseline data, and those who were not available for assessment of LV function, were excluded. Also, patients in whom the MFR score could not be adequately calculated, that is, patients that were missing a baseline electrocardiograph (ECG) or had a pacemaker ECG were excluded. Likewise, patients with post-TAVR pacemaker dependency at follow-up were excluded to avoid an underestimation or misjudgment of LV

ejection fraction (LVEF). Clinical endpoints included all-cause mortality as well as complications (as defined by VARC 2), including minor and major vascular complications as well as paravalvular leakage¹¹.

This study was conducted retrospectively from patients enrolled in a local TAVR registry, which was approved by the institutional ethics committee of the University of Bonn and conducted in concordance with the Declaration of Helsinki. All patients provided written informed consent to a local TAVR registry.

Mid-wall fibrosis risk score

To assess the presence of MF, an MFR score was calculated using an app-based calculator (Calculate, QxMD Medical)⁴. As previously published, the MFR score includes the following parameters: age, sex, high-sensitive cardiac troponin I, the presence of strain pattern on the ECG, and peak aortic valve velocity. To evaluate the presence of an ECG strain pattern, a standard 12-lead ECG taken before TAVR was analyzed. The presence of ECG strain was defined as a concave down-sloping ST depression (>1 mm) with asymmetrical T-wave inversion in the lateral leads¹².

Echocardiographic measurement

Standard, two-dimensional echocardiographic assessments were performed at baseline as well as one year after the procedure, using the GE Vivid E9 system (GE Healthcare, Wisconsin) or Philips IE33 (Philips Healthcare, The Netherlands). Chamber volume, systolic function, and wall thickness were assessed according to the current guidelines of the American Society of Echocardiography and the European Society of Echocardiography^{13 14}. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass (LVM) were divided by body surface area to calculate the respective indices (i.e. LVEDVi, LVESVi, LVMi). Based on earlier studies investigating LV reverse remodeling, we defined LV reverse remodeling as a reduction of the LVEDVi by >10%^{9, 15}.

Biomarkers of fibrosis

We measured the levels of galectin-3, growth differentiation factor (GDF)-15, and soluble ST2. Galectin-3 has been shown to play a role in the development of MF, by stimulating macrophage migration and fibroblast proliferation. The levels of galectin-3 were assessed using an enzyme-linked immunosorbent assay (BG Medicine, USA) ¹⁶. GDF-15, measured by using an ELISA assay (R&D Systems, USA), has been found to be associated with a lack of reverse remodeling after TAVR ¹⁷. Soluble ST2, analyzed by using a high-sensitivity Presage® ST2 assay (Life Biomedical, UK), is a member of the interleukin-1 receptor family and is thought to be associated with cell proliferation and inflammatory states¹⁸.

Statistical analysis

The study population was divided into two groups according to a cut-off value for the MFR score by the receiver operating characteristic (ROC) curve for the reduction of LVEDVi by >10%. Continuous variables with a normal distribution are expressed as the means \pm standard deviation. Non-normally distributed variables are presented as median values with an interquartile range (IQR). Categorical variables are shown as frequencies and percentages.

Logistic regression analysis was used to examine associations between the MFR score and LV reverse remodeling. Diabetes, hypertension, atrial fibrillation, coronary artery disease, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) level, New York Heart Association (NYHA) functional class IV, LVEDVi, LVEF, LVMI, aortic valve area at baseline, para-valvular leakage $\geq 2+$, and the MFR score were introduced into the final multivariate model; this was based on clinical knowledge of LV remodeling in AS patients^{7, 9, 15}.

To estimate five-year mortality after TAVR, we performed a survival analysis using the Kaplan-Meier method. Based on previously published data demonstrating the prognostic relevance of the MFR score in patients with severe AS, we repeated the analysis with another cutoff of the MFR score (i.e. 57)⁸.

Two-tailed p values <0.05 were considered to denote statistical significance. All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Austria)¹⁹.

Results

Study population

For this study, data from 207 patients who underwent transfemoral TAVR were analyzed. Overall, the mean age was 81±6 years and 51% of patients were male. The mean STS score and logistic EuroSCORE were 6.9±5.2 % and 19.6±13.3 %, respectively.

The median MFR for the whole cohort was 53.3, IQR [26.8, 90.2]. With the use of an ROC analysis, an MFR score of 52 was determined as the cut-off value for predicting LV reverse remodeling. Using this calculation, 106/207 patients (51.2%) displayed an MFR score ≥52. These patients were more often male, had more frequently undergone percutaneous coronary intervention, and had higher surgical risk scores than those with an MFR score <52 (**Table 1**). Regarding procedural characteristics, patients with a higher MFR score had significantly larger implanted valve size (p<0.001). There were no significant differences between groups regarding the type of valve or in VARC-2 defined complications (**Supplemental Table 1**).

Association between MFR score and echocardiographic parameters

Overall, the patient cohort presented with a normal range of LVEDVi (68.2±25.0 ml/m²), a preserved LVEF (53.0±13.4 %), and an increased LVMi (131.3±44.5 g/m²) as well as a certain degree of diastolic dysfunction (E/A: 1.3±0.8; E/e': 24.2±12.9). Of note, compared to patients with a lower MFR score, patients with a higher MFR score had significantly greater LVEDVi (64.6±20.5 ml/m² vs. 71.6±28.4 ml/m², p=0.04) and lower LVEF (55.0±11.8 % vs. 51.0±14.6 % p=0.03), while there were no significant differences in LVMi or markers of diastolic dysfunction (i.e. E/A or E/e') (**Supplemental Table 2**).

At one-year follow-up, a significant reduction in LVEDVi, an increase in LVEF, and a regression of LVMi were observed in the overall cohort (**Supplemental Table 2**). Among the cohort,

101/207 (48.8%) patients showed LV reverse remodeling, defined as a reduction in LVEDVi > 10%. The relative change in LVEDVi (delta LVEDVi / baseline-LVEDVi) after one year was significantly lower in patients with a higher MFR score (median -20.3, IQR [-40.3, 4.3] % vs. median -14.4, IQR [36.1, 8.1] %, $p < 0.001$) than those with a lower MFR score. Additionally, the MFR score was significantly lower in patients in whom LV reverse remodeling was observed, compared to those without remodeling (median 50.2, IQR [26.1, 79.0] vs. median 54.7, IQR [29.5, 94.5], $p < 0.001$; **Supplemental Table 3**). After adjusting for baseline characteristics and echocardiographic parameters, a higher MFR score was associated with a decreased probability of LV reverse remodeling (OR 0.33; 95% CI, 0.23-0.87; $p = 0.03$; **Table 2**). The association remained significant in the sensitivity analysis with the MFR score as a continuous variable (**Supplemental Table 4**), which demonstrated that higher MFR scores were significantly associated with less reduction in LVEDVi ($p = 0.03$) and regression in LVMi ($p = 0.004$).

In contrast, no significant difference in the change in LVEF was seen in patients with a lower or higher MRF scores (2.9 ± 11.4 % vs. 5.7 ± 12.6 %, $p = 0.10$). In this context, also no significant correlation was seen between the MFR score and the change in LVEF ($p = 0.44$).

Long-term survival beyond one year after TAVR

At one year after TAVR, clinical symptoms as per the NYHA classification were similar between patients with a lower and higher MFR scores (NYHA III/IV: 13.8% vs. 19.0%, $p = 0.43$). The median duration of follow-up was 1550, IQR [1101, 2001] days with a yearly mortality rate (beyond one year after TAVR) of 9.3% per year. Regarding five-year mortality, there was no significant difference between the patients with a lower and higher MFR scores (57.9% vs. 60.5%, $p = 0.66$; **Figure 1**). Similarly, an additional analysis using another previously published prognostic cutoff of the MFR score (i.e. 57) revealed no significant differences in patients with a lower or higher MFR scores (56.0% vs. 63.1%, $p = 0.26$).

MFR and circulating markers of fibrosis

Several potential biomarkers of MF were available for analysis in a subgroup of 116 patients (56% of the cohort). There were no significant differences between patients with higher and lower MFR

score with regard to circulating markers of fibrosis (**Supplemental Table 5**). Furthermore, no significant correlation between the MFR score and potential biomarkers of fibrosis could be observed (soluble ST2: $r = -0.08$; $p=0.31$; GDF-15: $r = 0.06$; $p=0.52$; Galectin-3: $r = 0.03$; $p=0.71$). In contrast, the MFR score was positively associated with NT-pro-BNP ($r = 0.29$; $p<0.001$).

Discussion

In AS, MF is the result of histopathological myocyte death and LV scarring, leading to LV remodeling and consequently LV dysfunction^{4, 7}. The recently published MFR score allows for an estimation of MF in patients with aortic stenosis by integrating a number of clinical, echocardiographic and serological characteristics⁸. To the best of our knowledge, this study is the first report to evaluate the impact of MF (as determined by the MFR score) on LV reverse remodeling and on long-term outcome after TAVR.

Myocardial fibrosis and LV reverse remodeling

The role of MF is well described in the context of both AS and SAVR. In fact, several studies have reported an association of MF with LV remodeling in patients with AS^{1, 2}. Furthermore a negative impact of MF on LV reverse remodeling has been described in patients undergoing SAVR^{4, 5, 9}. However, little is known about the impact of MF on LV reverse remodeling following TAVR. In line with a prior study evaluating MF by means of the MFR score in patients with AS⁸, in the present study, there was a correlation of higher MFR scores with increased LVEDVi and LVMi at baseline, which indicates applicability of the MFR score in patients undergoing TAVR. Also, we found that a higher MFR score was associated with reduced LV reverse remodeling.

In contrast to prior studies on the impact of MF on the recovery of LV function after SAVR⁶, we did not observe a link between the MFR score and improvement of LVEF. A possible explanation could be related to paravalvular leakage after TAVR²⁰, interfering with LV recovery and the possible association of the MFR score and improvement of LVEF. A sub-analysis of the NOTION trial has found a less pronounced degree of LV remodeling in patients undergoing TAVR with a self-expanding prosthesis as compared to SAVR. Whereas the authors attributed this to the presence of relevant

paravalvular leakage and the need for permanent pacemakers²¹, in the present study, an adjustment to include paravalvular leakage ($\geq 2+$) did not statistically influence our findings. In any case, the lack of association of the MFR with an improvement of LVEF highlights the difficulty of predicting the course of LVEF after TAVR²².

Myocardial fibrosis and circulating biomarkers

Of interest, in the present study, no correlation between the previously reported biomarkers (i.e. Galectin-3, GDF-15, sST2) and the MFR score was observed. This observation stands in contrast to prior publications, which show a link between these biomarkers and MF. For example, sST2 has been shown to be a surrogate marker of LV remodeling as well as diastolic dysfunction in patients with aortic stenosis¹⁸. Furthermore, Kim et al. reported a correlation between levels of GDF-15 and the recovery of LV function, defined as an increase in global longitudinal strain, in patients undergoing TAVR¹⁷. Whereas a similar association was seen between the MFR score and LV reverse remodeling in our analysis, no direct correlation of the MFR score and these biomarkers could be established in our study.

One possible explanation could be the extensive degree of MF present in our cohort. In fact, our cohort exhibited an MFR score which was at the high end of the intermediate score range (7 to 57) in the original publication by Chin et al⁸. It is therefore conceivable, that the degree of MF and the already significantly elevated concentrations of above-mentioned biomarkers in our cohort have prevented the identification of a correlation.

Still, in line previous studies on MF in the context of AS^{4, 7}, we found a positive correlation between the MFR score and NT-pro-BNP levels.

Long-term survival after TAVR

Prior cohort studies have reported associations between MF and long-term adverse outcomes in patients with AS^{4, 5}. Although the original study by Chin et al demonstrated a predictive value of the MFR score on adverse outcomes in patients with AS⁴, in the present study, five-year mortality after TAVR was not influenced by the MFR score. In consequence, it may be speculated that the treatment of AS in patients undergoing TAVR which leads to reverse LV remodeling and improve LVEF^{7, 23}, may

have attenuated the impact of MF on clinical outcomes. Supporting this notion, a more recent cohort study of 31,199 patients undergoing TAVR reported that one-year mortality was not influenced by the type and extent of LV remodeling¹⁰. Alternatively, physiological and biological conditions (e.g. old age or frailty,) in patients undergoing TAVR may have contributed to the long-term clinical outcomes observed. As a matter of fact, the long-term prognosis after TAVR appears to be evenly depending on cardiovascular and non-cardiovascular determinants²⁴.

In addition, the fact that the mortality rates in both the lower and higher MFR score groups compared well to the long-term results from the PARTNER 1 study²⁵, which could prompt the conclusion that patients with severe symptomatic AS benefit from TAVR regardless of the extent of MF.

Limitations

First, the present study was conducted retrospectively, based on a single-center database and a relatively small cohort. Second, a major limitation of this study is the fact that MF was not detected by routine CMR imaging but was estimated by the MFR score. Therefore, we cannot directly confirm that the MFR score was similarly associated with MF. Nevertheless, the MFR score in the present study demonstrated the same associations with increased LVEDVi, LVMI, and decreased LVEF at baseline, as observed in the previous CMR studies. We are therefore confident that the MFR score acts as a specific marker for MF in the patients included in this study. Finally, we did not distinguish the cause of mortality (cardiovascular or non-cardiovascular).

Conclusion

While a higher MFR score is associated with decreased LV reverse remodeling at one year after TAVR, the score was not associated with a change in LVEF. Additionally, the MFR score did not seem to impact long-term mortality in patients in whom one-year follow-up echocardiography was available. Despite its impact on LV remodeling, our findings suggest that there is a limited impact of MF on the clinical outcome in patients undergoing TAVR.

Impact on daily practice

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MF, as assessed by MFR score, is associated with decreased LV reverse remodeling at one-year after TAVR. By contrast, the MFR score is neither associated with a change in LVEF nor five-year mortality. Our findings may suggest that patients with AS could potentially benefit on from TAVR regardless of their degree of MFR score.

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References

1. Dweck MR, Boon NA and Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol.* 2012;60:1854-63.
2. Vizzardi E, D'Aloia A, Fiorina C, Bugatti S, Parrinello G, De Carlo M, Giannini C, Di Bello V, Petronio AS, Curello S, Ettori F and Dei Cas L. Early regression of left ventricular mass associated with diastolic improvement after transcatheter aortic valve implantation. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2012;25:1091-8.
3. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn WP and Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation.* 2003;107:984-91.
4. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, Jenkins W, Koo M, Mirsadraee S, White AC, Japp AG, Prasad SK, Semple S, Newby DE and Dweck MR. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. *JACC Cardiovascular imaging.* 2017;10:1320-1333.
5. Park SJ, Cho SW, Kim SM, Ahn J, Carriere K, Jeong DS, Lee SC, Park SW, Choe YH, Park PW and Oh JK. Assessment of Myocardial Fibrosis Using Multimodality Imaging in Severe Aortic Stenosis: Comparison With Histologic Fibrosis. *JACC Cardiovascular imaging.* 2019;12:109-119.
6. Herrmann S, Fries B, Salinger T, Liu D, Hu K, Gensler D, Strotmann J, Christa M, Beer M, Gattenlohner S, Stork S, Voelker W, Bening C, Lorenz K, Leyh R, Frantz S, Ertl G, Weidemann F and Nordbeck P. Myocardial Fibrosis Predicts 10-Year Survival in Patients Undergoing Aortic Valve Replacement. *Circulation Cardiovascular imaging.* 2018;11:e007131.
7. Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuvana AN, Sheikh A, Lopez B, Gonzalez A, Manisty C, Lloyd G, Kellman P, Diez J and Moon JC. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. *J Am Coll Cardiol.* 2018;71:860-871.
8. Chin CW, Messika-Zeitoun D, Shah AS, Lefevre G, Bailleul S, Yeung EN, Koo M, Mirsadraee S, Mathieu T, Semple SI, Mills NL, Vahanian A, Newby DE and Dweck MR. A clinical risk score of myocardial fibrosis predicts adverse outcomes in aortic stenosis. *European heart journal.* 2016;37:713-

23.

9. Dobson LE, Musa TA, Uddin A, Fairbairn TA, Swoboda PP, Erhayiem B, Foley J, Garg P, Haaf P, Fent GJ, Malkin CJ, Blackman DJ, Plein S and Greenwood JP. Acute Reverse Remodelling After Transcatheter Aortic Valve Implantation: A Link Between Myocardial Fibrosis and Left Ventricular Mass Regression. *Can J Cardiol.* 2016;32:1411-1418.

10. Varshney AS, Manandhar P, Vemulapalli S, Kirtane AJ, Mathew V, Shah B, Lowenstern A, Kosinski AS, Kaneko T, Thourani VH and Bhatt DL. Left Ventricular Hypertrophy Does Not Affect 1-Year Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv.* 2019;12:373-382.

11. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2012;42:S45-60.

12. Shah AS, Chin CW, Vassiliou V, Cowell SJ, Doris M, Kwok TC, Semple S, Zamvar V, White AC, McKillop G, Boon NA, Prasad SK, Mills NL, Newby DE and Dweck MR. Left ventricular hypertrophy with strain and aortic stenosis. *Circulation.* 2014;130:1607-16.

13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, 3rd and Thompson A. 2017 AHA/ACC Focused Update of the 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 Clinical Practice Guidelines. *J Am Coll Cardiol.* 2017;70:252-89.

14. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL and Group ESCSD. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *European heart journal.* 2017;38:2739-2791.

15. Kortekaas KA, Hoogslag GE, de Boer RA, Dokter MM, Versteegh MI, Braun J, Marsan NA,

Verwey HF, Delgado V, Schalij MJ and Klautz RJ. Galectin-3 and left ventricular reverse remodelling after surgical mitral valve repair. *European journal of heart failure*. 2013;15:1011-8.

16. Baldenhofer G, Zhang K, Spethmann S, Laule M, Eilers B, Leonhardt F, Sanad W, Dreger H, Sander M, Grubitzsch H, Baumann G, Stangl K, Stangl V and Knebel F. Galectin-3 predicts short- and long-term outcome in patients undergoing transcatheter aortic valve implantation (TAVI). *Int J Cardiol*. 2014;177:912-7.

17. Kim JB, Kobayashi Y, Moneghetti KJ, Brenner DA, O'Malley R, Schnittger I, Wu JC, Murtagh G, Beshiri A, Fischbein M, Miller DC, Liang D, Yeung AC, Haddad F and Fearon WF. GDF-15 (Growth Differentiation Factor 15) Is Associated With Lack of Ventricular Recovery and Mortality After Transcatheter Aortic Valve Replacement. *Circulation Cardiovascular interventions*. 2017;10.

18. deFilippi C, Daniels LB and Bayes-Genis A. Structural heart disease and ST2: cross-sectional and longitudinal associations with echocardiography. *Am J Cardiol*. 2015;115:59b-63b.

19. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-8.

20. Kaneko H, Hoelschermann F, Schau T, Tambor G, Neuss M and Butter C. Different impact of aortic regurgitation assessed by aortic root angiography after transcatheter aortic valve implantation according to baseline left ventricular ejection fraction and N-terminal pro-B-type natriuretic peptide. *Cardiovascular intervention and therapeutics*. 2018;33:232-238.

21. Ngo A, Hassager C, Thyregod HGH, Sondergaard L, Olsen PS, Steinbruchel D, Hansen PB, Kjaergaard J, Winther-Jensen M and Ihlemann N. Differences in left ventricular remodelling in patients with aortic stenosis treated with transcatheter aortic valve replacement with corevalve prostheses compared to surgery with porcine or bovine biological prostheses. *European heart journal cardiovascular Imaging*. 2018;19:39-46.

22. Maes F, Lerakis S, Barbosa Ribeiro H, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, Windecker S, Enriquez-Sarano M, Cheema AN, Nombela-Franco L, Amat-Santos I, Munoz-Garcia AJ, Garcia Del Blanco B, Zajarias A, Lisko JC, Hayek S, Babaliaros V, Le Ven F, Gleason TG, Chakravarty T, Szeto W, Clavel MA, de Agustin A, Serra V, Schindler JT, Dahou A, Salah-Annabi M, Pelletier-Beaumont E, Cote M, Puri R, Pibarot P and Rodes-Cabau J. Outcomes From Transcatheter Aortic Valve

Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis and Left Ventricular Ejection Fraction Less Than 30%: A Substudy From the TOPAS-TAVI Registry. *JAMA cardiology*. 2019;4:64-70.

23. Alenezi F, Fudim M, Rymer J, Dunning A, Chiswell K, Swaminathan M, Bottiger B, Velagapudi P, Nicoara A, Kisslo J, Velazquez E, Vemulapalli S, Bloomfield GS and Samad Z. Predictors and Changes in Cardiac Hemodynamics and Geometry With Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2019;123:813-819.

24. Xiong TY, Liao YB, Zhao ZG, Xu YN, Wei X, Zuo ZL, Li YJ, Cao JY, Tang H, Jilaihawi H, Feng Y and Chen M. Causes of Death Following Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association*. 2015;4:e002096.

25. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ and Svensson LG. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-84.

Figure legends

Figure 1. Kaplan-Meier analysis for five-year survival in patients with higher or lower MFR score

At five-year follow-up, there was no significant difference in mortality between patients with lower (<52) and higher (≥ 52) MFR score (estimated survival rate: 57.9% vs. 60.5%; $p=0.66$).

Table legends

Table 1. Baseline characteristics

Compared with patients with higher MFR score, patients with higher MFR score were more likely to be male, had previous percutaneous coronary intervention, had higher surgical risk scores, and received significantly a larger size of TAVR device.

Table 2. Logistic regression analysis for LV reverse remodeling

In the multivariable logistic regression analysis, a MFR score ≥ 52 was associated with a poor LV reverse remodeling, independent of baseline echocardiographic parameters and comorbidities.

Table 1. Baseline characteristics

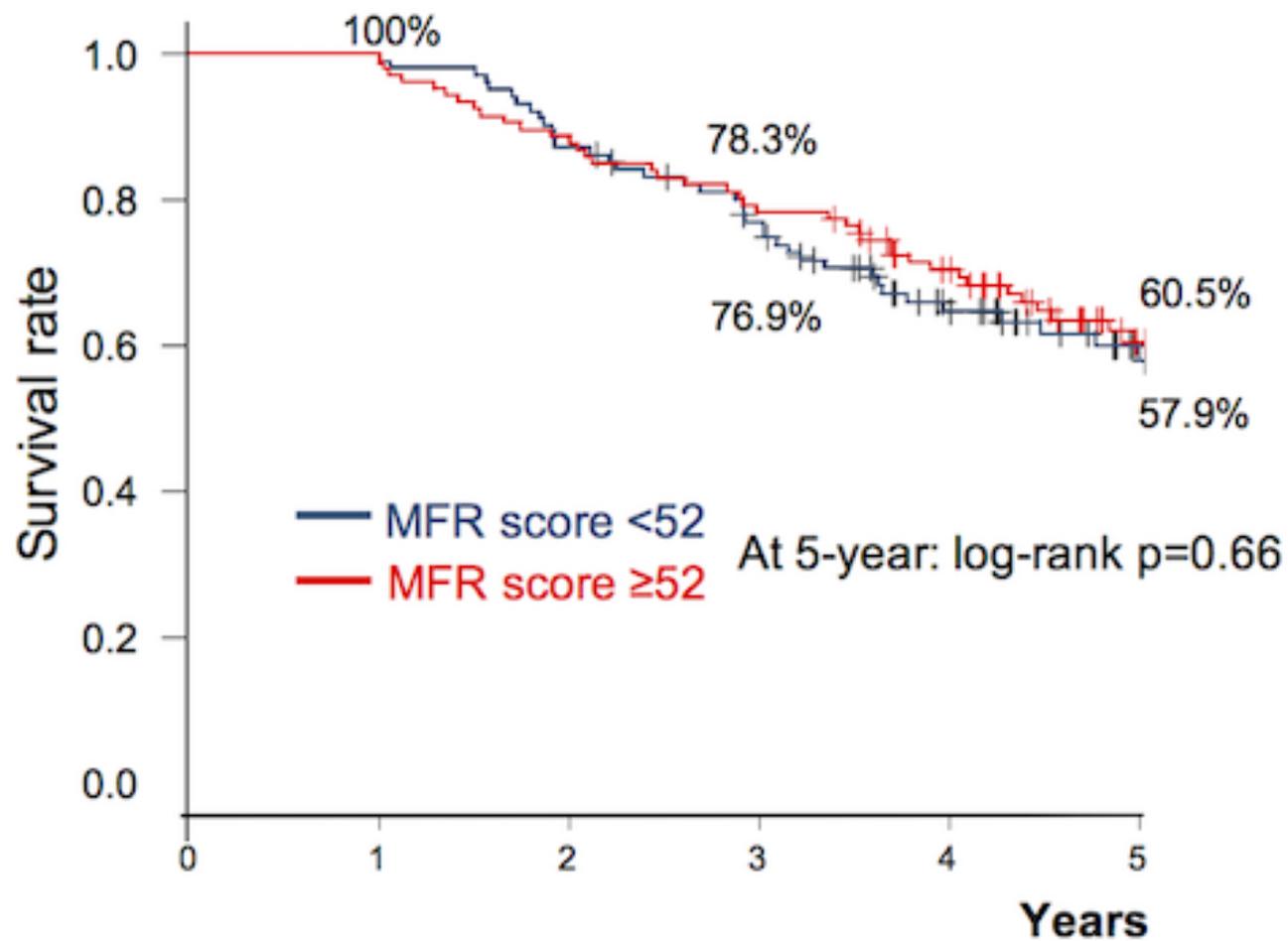
	MFR score <52 n = 101	MFR score ≥52 n = 106	p value
Age (year), mean ± SD	81 ± 6	81 ± 6	0.80
Sex male, n (%)	29 (28.7)	77 (72.6)	<0.001
Body mass index (kg/m ²), mean ± SD	27.2 ± 4.8	26.0 ± 4.9	0.08
Body surface area (m ²), mean ± SD	1.84 ± 0.22	1.86 ± 0.22	0.46
Comorbidities, n (%)			
Hypertension	85 (84.2)	94 (88.7)	0.45
Diabetes	28 (27.7)	29 (27.4)	0.99
Chronic kidney disease	49 (48.5)	59 (55.7)	0.37
Coronary artery disease	56 (55.4)	66 (62.3)	0.39
Previous myocardial infarction	14 (13.9)	12 (11.3)	0.73
Previous stroke	8 (7.9)	16 (15.1)	0.16
Peripheral artery disease	43 (42.6)	53 (50.0)	0.35
Atrial fibrillation	39 (38.6)	40 (37.7)	0.99
Chronic obstructive pulmonary disease	20 (19.8)	30 (28.3)	0.21
Previous percutaneous coronary intervention, n (%)	26 (25.7)	43 (40.6)	0.03
Prior cardiac surgery, n (%)	11 (10.9)	14 (13.2)	0.77
NYHA functional class, n (%)			0.34
Class III	80 (79.2)	76 (71.7)	
Class IV	11 (10.9)	19 (17.9)	
EuroSCORE, mean ± SD	17.0 ± 11.2	22.0 ± 14.6	0.006
STS-PROM score, mean ± SD	6.5 ± 4.8	7.3 ± 5.6	0.23
Laboratory parameters, mean ± SD or [IQR]			
eGFR (ml/min/1.73m ²)	55.9 ± 18.3	54.9 ± 18.7	0.80
High-sensitivity troponin I (ng/ml)	10.9 [6.3, 21.3]	26.3 [15.4, 54.8]	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; MFR, mid-wall fibrosis risk; NYHA, New York Heart Association; STS-PROM, the Society of Thoracic Surgeons-predicted risk of mortality.

Table 2. Logistic regression analysis for left ventricular reverse remodeling

	Multivariate		
	OR	95 % CI	p value
MFR score \geq 52	0.33	0.23-0.87	0.03
Hypertension	0.86	0.30-2.47	0.77
Diabetes	0.98	0.48-2.02	0.97
Atrial fibrillation	1.66	0.82-3.34	0.16
Coronary artery disease	1.05	0.54-2.06	0.88
LV ejection fraction	1.02	0.99-1.05	0.21
LV end-diastolic volume index	1.06	1.04-1.09	<0.001
LV mass index	0.99	0.98-0.99	0.001
Aortic valve area	0.17	0.02-1.23	0.08
Paravalvular leakage \geq 2+	0.49	0.13-1.77	0.28
NYHA functional class IV	1.35	0.49-3.78	0.56
NT-pro-BNP	1.02	0.98-1.07	0.36

Abbreviations: LV, left ventricular; MFR, mid-wall fibrosis risk; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.



	Number at risk			
	0	1	2	3
MFR score <52	101	99	79	49
MFR score ≥52	106	100	87	63

Table legends (Supplemental files)

Supplemental Table 1. Procedural characteristics

Compared with patients with a lower MFR score, patients with a higher MFR score had significantly larger implanted valve size. There were no significant differences between groups regarding the type of valve or in VARC-2 defined complications.

Supplemental Table 2. Echocardiographic parameters at baseline and changes after transcatheter aortic valve replacement

Changes in echocardiography parameters from baseline to one-year follow-up were assessed by using paired t-tests or a Wilcoxon signed-rank test as appropriate. At baseline, patients with higher MFR score had significantly greater LV volume and LVMi, and lower LVEF, compared to those with lower MFR score. At one-year follow-up, a significant reduction in LV volume, a regression of LVMi, and an improvement of LVEF were observed in the overall cohort. The relative change in LVEDVi was significantly lower in patients with higher MFR score compared with those with lower MFR score.

Supplemental Table 3. Baseline characteristics stratified by the presence of left ventricular reverse remodeling

Patients who showed LV reverse remodeling had significantly lower MFR score compared with those without.

Supplemental Table 4. Multivariable linear regression analyses for change in LV function at one-year after TAVR

To examine the consistency of the hypothesis, we performed a sensitivity analysis. The multiple linear regression analysis with the MFR score as a continuous variable was constructed for each change in LVEDVi, LVEF, and LVMi. In the multivariable linear regression analysis, higher MFR score was significantly associated with poor reduction in LVEDVi and regression in LVMi. In contrast, there was no significant association of MFR score with change in LVEF.

Supplemental Table 5. Circulating markers of fibrosis

There were no significant correlation between the MFR score and potential biomarkers of fibrosis. In contrast, the MFR score was positively associated with NT-pro-BNP.

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Supplemental Table 1. Procedural characteristics

	MFR score <52 n = 101	MFR score ≥52 n = 106	p value
Implanted TAVR devices, n (%)			0.58
Balloon-expandable devices	15 (14.9)	19 (17.9)	
Self-expandable devices	86 (85.1)	87 (82.1)	
Implanted valve size (mm), mean ± SD	26.3 ± 2.3	27.6 ± 2.5	<0.001
Paravalvular leakage ≥ 2+, n (%)	6 (5.9)	11 (10.4)	0.31
Complications at 30-day, n (%)			
Pacemaker implantation	22 (21.8)	13 (12.3)	0.32
Stroke	1 (1.0)	3 (2.8)	0.66
Myocardial infarction	0 (0)	1 (0.9)	0.99
Minor vascular complications	32 (31.7)	26 (24.5)	0.32
Major vascular complications	4 (4.0)	2 (1.9)	0.44
Major bleeding	2 (2.0)	6 (5.7)	0.28

Abbreviation: TAVR, transaortic valve replacement.

Supplemental Table 2. Echocardiographic parameters at baseline and changes after transcatheter aortic valve replacement

Characteristics	All			MFR score <52			MFR score ≥52			p value for the difference between groups at baseline	p value for the difference between groups at one-year
	Baseline	One year	P value	Baseline	One year	p value	Baseline	One year	p value		
Peak AV velocity (m/s)	4.2 ± 0.7	1.84 ± 0.60	<0.001	4.1 ± 0.7	1.9 ± 0.6	<0.001	4.4 ± 0.7	1.8 ± 0.6	<0.001	<0.001	0.47
Mean AV gradient (mmHg)	40.6 ± 17.0	7.4 ± 5.9	<0.001	37.7 ± 19.5	7.5 ± 5.2	<0.001	43.1 ± 14.2	7.3 ± 4.9	<0.001	0.07	0.71
LVEDVi (ml/m ²)	68.2 ± 25.0	55.7 ± 21.4	<0.001	64.6 ± 20.5	51.9 ± 21.7	<0.001	71.6 ± 28.4	59.3 ± 21.7	<0.001	0.04	0.01
Relative change in LVEDVi (%)	-	-17.0 [-37.8, 6.7]	-	-	-20.3 [-40.3, 4.3]	-	-	-14.4 [-36.1, 8.1]	-	-	<0.001
LVESVi (ml/m ²)	35.8 ± 19.2	24.5 ± 13.4	<0.001	33.5 ± 15.6	22.6 ± 12.9	<0.001	37.9 ± 22.0	26.2 ± 13.7	<0.001	0.09	0.049
LVEF (%)	53.0 ± 13.4	57.3 ± 10.3	<0.001	55.0 ± 11.8	58.0 ± 10.3	0.01	51.0 ± 14.6	56.7 ± 10.3	<0.001	0.03	0.39
Relative wall thickness	0.50 ± 0.13	0.50 ± 0.11	0.79	0.48 ± 0.14	0.50 ± 0.13	0.23	0.52 ± 0.12	0.51 ± 0.10	0.08	0.02	0.81
LVMi (g/m ²)	131.3 ± 44.5	116.3 ± 39.1	<0.001	127.0 ± 42.5	108.4 ± 33.0	<0.001	135.2 ± 46.1	123.5 ± 39.1	0.004	0.18	0.002
E/A	1.3 ± 0.8	1.3 ± 0.9	0.33	1.3 ± 0.8	1.3 ± 0.8	0.53	1.3 ± 0.7	1.3 ± 0.9	0.46	0.77	0.85
E/e'	24.2 ± 12.9	21.0 ± 10.5	0.03	24.4 ± 13.5	19.9 ± 9.6	0.006	24.0 ± 12.3	21.9 ± 11.2	0.14	0.86	0.25
DcT (ms)	186.9 ± 61.5	209.0 ± 66.2	<0.001	195.1 ± 59.7	200.7 ± 62.0	0.83	179.0 ± 62.6	216.9 ± 69.5	<0.001	0.07	0.13

Abbreviations: AV, aortic valve; DcT, deceleration time; LVEDVi, left ventricular end-diastolic volume index; LVEF; left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; MFR, mid-wall fibrosis risk.

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Supplemental Table 3. Baseline characteristics stratified by the presence of left ventricular reverse remodeling

Characteristics	LV reverse remodeling + n = 106	LV reverse remodeling - n = 101	p value
MFR score, median [IQR]	50.2 [26.1, 79.0]	54.7 [29.5, 94.5]	<0.001
Age (year), mean \pm SD	81 \pm 7	81 \pm 5	0.63
Sex male, n (%)	50 (47.2)	56 (55.4)	0.29
Body mass index (kg/m ²), mean \pm SD	26.1 \pm 4.9	27.1 \pm 4.8	0.14
Body surface area (m ²), mean \pm SD	1.82 \pm 0.24	1.88 \pm 0.20	0.04
Comorbidities, n (%)			
Hypertension	90 (84.9)	89 (88.1)	0.64
Diabetes	29 (27.4)	28 (27.7)	0.99
Chronic kidney disease	53 (50.0)	55 (54.5)	0.62
Coronary artery disease	63 (59.4)	59 (58.4)	0.99
Previous myocardial infarction	12 (11.3)	14 (13.9)	0.73
Previous stroke	10 (9.4)	14 (13.9)	0.44
Peripheral artery disease	52 (49.1)	44 (43.6)	0.51
Atrial fibrillation	41 (38.7)	38 (37.6)	0.99
Chronic obstructive pulmonary disease	22 (20.8)	28 (27.7)	0.31
Previous PCI, n (%)	48 (35.8)	31 (30.7)	0.52
Prior cardiac surgery, n (%)	10 (9.4)	15 (14.9)	0.33
NYHA functional class, n (%)			
Class III	82 (77.4)	74 (73.3)	
Class IV	17 (16.0)	13 (12.9)	
EuroSCORE, mean \pm SD	18.1 \pm 11.5	21.0 \pm 14.8	0.12
STS-PROM score, mean \pm SD	6.6 \pm 4.6	7.3 \pm 5.8	0.34

Laboratory parameters, mean \pm SD or [IQR]

eGFR (ml/min/1.73m ²)	55.9 \pm 15.0	54.7 \pm 20.2	0.65
High-sensitivity troponin I (ng/ml)	31.1 [8.0, 30.0]	101.5 [9.0, 38.3]	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; LV, left ventricular; MFR, mid-wall fibrosis risk; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS-PROM, the Society of Thoracic Surgeons-predicted risk of mortality; TAVR, transaortic valve replacement; TTE, trans-thoracic echocardiography.

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Supplemental Table 4. Multivariate linear regression analyses for change in LVDEVi, LVEF and LVMi function at one-year after TAVR

	Change in LVEDVi			Change in LVEF			Change in LVMi		
	β coefficient	95% CI	p value	β coefficient	95% CI	p value	β coefficient	95% CI	p value
MFR score	0.10	0.01 to 0.20	0.03	0.02	-0.03 to 0.06	0.44	0.24	0.08 to 0.40	0.004
Diabetes	3.70	-2.33 to 9.74	0.23	-2.24	-4.94 to 0.46	0.10	-0.29	-10.71 to 10.1	0.96
Hypertension	-3.48	-11.40 to 4.43	0.39	-3.56	-7.11 to -0.01	0.049	-1.11	-15.1 to 12.9	0.87
CAD	-3.30	-8.85 to 2.24	0.24	0.47	-2.01 to 2.96	0.71	1.04	-8.5 to 10.6	0.83
Atrial fibrillation	-5.82	-11.4 to -0.22	0.041	-2.29	-4.80 to 0.21	0.07	-3.73	-13.39 to 5.92	0.45
LVEF (%)	-0.19	-0.42 to 0.05	0.12	-0.63	-0.74 to -0.53	<0.001	-0.59	-1.00 to -0.19	0.004
LVEDVi (ml/m ²)	-0.80	-0.92 to -0.68	<0.001	-0.09	-0.15 to -0.04	<0.001	-0.10	-0.31 to 0.10	0.31
LVMi (g/m ²)	0.08	0.02 to 0.14	0.01	0.01	-0.02 to 0.04	0.41	-0.61	-0.73 to -0.50	<0.001
AVA (cm ²)	5.97	-9.78 to 21.72	0.46	-4.06	-11.11 to 3.00	0.26	18.48	-8.75 to 45.71	0.18
PVL \geq 2+	4.57	-5.62 to 14.76	0.38	-0.79	-5.37 to 3.78	0.73	2.68	-14.77 to 20.14	0.76
NYHA class IV	-7.04	-15.3 to 1.19	0.09	3.00	-0.69 to 6.69	0.11	-2.07	-16.31 to 12.14	-0.77
NT-pro-BNP (pg/L)	0.02	-0.25 to 0.30	0.85	0.01	-0.12 to 0.13	0.94	0.09	-0.39 to 0.57	0.73

Abbreviations: AVA, aortic valve area; CAD, coronary artery disease; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; MFR, mid-wall fibrosis risk; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PVL, para-valvular leakage.

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Supplemental Table 5. Circulating markers of fibrosis

	All n = 207	MFR score <52 n = 101	MFR score ≥52 n = 106	p value
Galectin-3 (ng/ml)	21.9 ± 9.6	21.7 ± 9.9	22.0 ± 9.4	0.82
GDF-15 (pg/ml)	3779 ± 2530	3607 ± 2654	3970 ± 2392	0.41
sST2 (ng/ml)	22.3 ± 12.8	23.3 ± 14.0	21.0 ± 11.0	0.20
NT-pro-BNP (pg/ml)	2147 [753, 5749]	1537 [596, 3562]	3623 [1112, 7559]	0.001

Abbreviations: GDF, growth differentiation factor, MFR, mid-wall fibrosis risk; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.