Determinants and prognostic implications of left ventricular mechanical dispersion in aortic stenosis

Edgard A. Prihadi, E. Mara Vollema, Arnold C.T. Ng, Nina Ajmone Marsan, Jeroen J. Bax, and Victoria Delgado*

1Department of Cardiology, Leiden University Medical Centre, Heart Lung Center, Albinusdreef 2, 2300RC Leiden, The Netherlands; 2Antwerp Cardiovascular Center, ZNA Middelheim, Lindendreef 1, 2020 Antwerp, Belgium; and 3Department of Cardiology, Princess Alexandra Hospital, The University of Queensland, 199 Ipswich Rd, Woolloongabba QLD 4102, Australia

Aims

The present study aimed at investigating the association between left ventricular (LV) mechanical dispersion measured with speckle tracking echocardiography and severity of aortic stenosis (AS) and its impact on prognosis.

Methods and results

This retrospective study included 630 patients [age 72 (62–78) years, 61.4% men] with various grades of AS (mild AS, 19.8%; moderate AS, 37.0%; severe AS, 43.2%). LV mechanical dispersion (defined as standard deviation of time from Q/R on electrocardiogram to peak longitudinal strain in 17 LV segments) was assessed by speckle tracking echocardiography. Clinical, electrocardiographic, and echocardiographic determinants of increased LV mechanical dispersion were evaluated. During a follow-up of 107 (43–133) months, the independent association between LV mechanical dispersion and all-cause mortality (n = 302, 48%) was evaluated including aortic valve replacement as time-dependent co-variate. LV mechanical dispersion increased significantly with increasing severity of AS (mild AS, 54.5 ± 17.2 ms; moderate AS, 56.7 ± 19.3 ms; severe AS, 70.9 ± 24.3 ms; P < 0.001). Independent determinants of increased mechanical dispersion included older age (β = 0.28; P = 0.003), lower LV ejection fraction (β = -0.24; P = 0.020), smaller aortic valve area (β = -8.55; P = 0.001), larger LV mass index (β = 0.20; P < 0.001), and longer QRS duration (β = 1.12 per each 10 ms increase; P = 0.012). LV mechanical dispersion showed incremental prognostic value for all-cause mortality (hazard ratio 1.10 per each 10 ms increase, 95% confidence interval 1.04–1.15; P < 0.001).

Conclusion

LV mechanical dispersion assessed by speckle tracking echocardiography increases significantly with severity of AS and is significantly associated with all-cause mortality.

Keywords

left ventricular • mechanical dispersion • aortic stenosis • prognosis

Introduction

Calcific aortic stenosis (AS) is one of the most prevalent valvular heart disease in the Western world.1,2 The increased afterload imposed by the narrow aortic valve area on the left ventricle induces a remodelling process, which is initially characterized by adaptive left ventricular (LV) hypertrophy. Long-standing AS further induces myocardial fibrosis, heart failure, and poor outcome.3,4 Therefore, alongside presence of symptoms and severity of AS, timely assessment of LV systolic dysfunction plays a pivotal role in the decision for referral to aortic valve replacement (AVR).3,5 Left ventricular ejection fraction (LVEF) is the benchmark parameter to define LV systolic function and is included in current guideline recommendations.3,5 However, LVEF may not recover after AVR and patients may remain symptomatic. Speckle tracking echocardiographic parameters of LV shortening and mechanical dispersion have been proposed to detect...
LV systolic dysfunction at an earlier stage than LVEF and are related to the presence of myocardial fibrosis on cardiac magnetic resonance. The increase in myocardial fibrosis may lead to slow conduction and heterogeneous activation of the left ventricle which can be quantified by measuring the LV mechanical dispersion on speckle tracking echocardiography. Prolonged LV mechanical dispersion has been associated with worse outcome in various cardiomyopathies, after myocardial infarction, and (as shown more recently) in patients with severe AS. However, the underlying mechanisms and relationship between LV mechanical dispersion, LV hypertrophy and QRS duration in various grades of AS are currently lacking. We hypothesize that LV mechanical dispersion increases with the severity of AS and may impact outcome.

Therefore, we aimed at evaluating the correlates and prognostic value of LV mechanical dispersion across various grades of AS.

**Methods**

**Patients**

Patients with any grade (mild, moderate, and severe) of native AS identified from the departmental echocardiographic database of the Leiden University Medical Center (Leiden, the Netherlands) were included consecutively. Patients with prosthetic aortic valves, subvalvular or supravalvular AS, dynamic subaortic obstruction, more than moderate aortic or mitral regurgitation and any grade of mitral stenosis, ventricular pacing, and active endocarditis were excluded.

Clinical parameters including medical history, cardiovascular risk factors, cardiac symptoms, and physical examination were collected from patients’ medical records. The first two-dimensional (2D) transthoracic echocardiography showing diagnosis of AS was considered the baseline reference and the resting 12-lead electrocardiogram (ECG) obtained at the moment of the baseline echocardiography was evaluated. Patients were followed for the occurrence of AVR and all-cause mortality.

Data entered in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Centre, Leiden, the Netherlands) was retrospectively collected and analysed. The institutional ethical committee approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

**Echocardiography**

Transthoracic echocardiography was performed at rest in all patients using commercially available ultrasound systems (Vivid 7 and E9 systems; GE-Vingmed, Horten, Norway). Data were stored digitally and analysed offline (EchoPAC version 113.0.3; GE-Vingmed, Horten, Norway). From parasternal, apical, subcostal and suprasternal views, 2D, colour, pulsed, and continuous-wave Doppler data were recorded according to current recommendations.

Using the Simpson’s biplane method of discs, LVEF was calculated from the LV end-diastolic and end-systolic volumes and acquired data and waived the need for patient written informed consent. LV systolic dysfunction was defined as peak velocity >4.0 m/s, mean gradient >40 mmHg, or aortic valve area <1.0 cm²; moderate AS was defined as peak velocity 3.0–4.0 m/s, mean gradient 30–40 mmHg, or aortic valve area 1.0–1.5 cm²; and mild AS was defined as peak velocity 2.6–2.9 m/s, mean gradient <20 mmHg, or aortic valve area >1.5 cm². Diastolic function was assessed according to current guidelines. LV mechanical dispersion according to speckle tracking echocardiography was calculated as the standard deviation of time from Q/R on the ECG, to peak longitudinal strain in 17 LV segments and expressed in milliseconds (ms).

**Electrocardiography**

Standard resting 12-lead ECGs performed within a time window of 12 months prior to or after the date of the baseline echocardiogram were included in the analysis and retrospectively assessed. Calibration of the ECG was set at 0.1 mV/mm and the paper speed was 25 mm/s. Sinus rhythm and atrial fibrillation were defined as recommended by current guidelines. QRS duration was measured in ms in the ECG lead with the greatest QRS width and the QRS morphology (left bundle branch block, right bundle branch block, and intraventricular conduction disorder) was defined according to current recommendations.

**Follow-up**

Patients were followed-up for the occurrence of all-cause mortality. Survival data were complete for all subjects and collected from the departmental cardiology information system, which is linked to the governmental death registry database. In addition, the occurrence and timing of AVR during follow-up was noted.

**Statistical analysis**

Continuous variables were presented as mean ± standard deviation if the distribution was Gaussian, whereas non-Gaussian distributed continuous variables were presented as median and interquartile range (IQR). Comparisons of continuous variables across patient groups were performed using the one-way ANOVA-test, with post hoc Bonferroni analysis when appropriate. All categorical variables were presented as percentages and compared with the χ² test. Univariable and multivariable linear regression analyses were performed to identify clinical, electrocardiographic, and echocardiographic correlates of LV mechanical dispersion. The level of significance for univariable analysis was set at P < 0.10.

The cumulative event rates for the clinical endpoint of all-cause mortality were estimated with the Kaplan–Meier curves and the log-rank test was used to compare two groups dichotomized according to the mean value of LV mechanical dispersion in the entire population. To investigate the independent associates of all-cause mortality, a multivariable Cox proportional hazards regression analysis was performed. Clinical and echocardiographic parameters known to influence mortality in patients with AS were included in the univariable analysis on a priori manner based on previous studies. The level of significance for univariable analysis was set at P < 0.10. Subsequent AVR was included in the model as a time-dependent co-variates. Additionally, the potential incremental value of LV mechanical dispersion for the association with all-cause mortality was evaluated by the change in χ² and the likelihood ratio. Furthermore, an IDI (integrated discrimination improvement) and NRI (net reclassification improvement) was performed. A tolerance level of >0.5 was set to avoid multicollinearity between the univariable determinants. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A two-tailed P-value of <0.05 was considered significant. Inter-observer and intra-observer variability of mechanical dispersion was tested by reanalysing 45 random studies (15 cases of mild, moderate, and severe AS) by two
cardiologists (E.A.P. and E.M.V.) who were blinded for the results of the first analysis. All statistical analyses were performed using SPSS for Windows version 23 (SPSS Inc.; Armonk, NY, USA: IBM Corp).

Results

Baseline characteristics
A total of 630 patients (61.4% men) with a median age of 72 (IQR 62–78) years were included in this study. Table 1 summarizes the clinical characteristics of the study population. Mild, moderate, and severe AS was noted in 125 (19.8%), 233 (37.0%), and 272 (43.2%) patients, respectively. Patients with severe AS were more likely to be older (P < 0.001) and present with worse New York Heart Association functional class (P < 0.001), compared with their counterparts. No significant differences in the usage of cardiovascular medications between the three groups were found. On the ECG, the QRS duration increased (from 99 ms in mild AS to 107 ms in severe AS, P < 0.001) and QRS conduction disturbances became more prevalent with increasing AS severity. Furthermore, atrial fibrillation was more frequently observed among patients with severe AS. Table 2 shows the echocardiographic characteristics according to the different AS groups. Patients with severe AS had significantly larger LV volumes, higher LV mass index, and higher percentage of reduced LVEF. Speckle tracking echocardiographic analysis showed a mean LV mechanical dispersion of 62.4 ± 22.5 ms in the total population. LV mechanical dispersion increased along worsening severity in AS (54.5 ± 17.2 ms in mild AS, 56.7 ± 19.3 ms in moderate AS, and 70.9 ± 24.3 ms in severe AS, P < 0.001) (Figure 1). Table 3 shows the characteristics of the population dichotomized according to the mean value of LV mechanical dispersion [<62 ms: indicating less mechanical dispersion (homogeneous LV contraction), >_62 ms: indicating more pronounced mechanical dispersion (heterogeneous LV contraction)]. Compared with patients with LV mechanical dispersion <62 ms (n = 352), patients with LV mechanical dispersion >_62 ms (n = 278) had more frequently a history of myocardial infarction, were older and had more prolonged QRS duration on the ECG. Furthermore, patients with LV mechanical dispersion >_62 ms showed larger LV volumes and mass index, worse LVEF and more severe AS on echocardiography.
Table 2  Echocardiographic characteristics according to the severity of aortic stenosis

| Variables                      | Mild AS (n = 125) | Moderate AS (n = 233) | Severe AS (n = 272) | P-value |
|--------------------------------|-------------------|-----------------------|---------------------|---------|
| Echocardiography               |                   |                       |                     |         |
| Heart rate (bpm)               | 72 ± 15           | 73 ± 13               | 74 ± 14             | 0.231   |
| LV mass index (g/m^2)          | 113.1 ± 25.5      | 114.0 ± 30.0          | 137.5 ± 39.8*†      | <0.001  |
| LV EDVI (mL/m^2)               | 50.8 ± 14.9       | 51.6 ± 14.8           | 60.0 ± 25.3*†       | <0.001  |
| LV ESVI (mL/m^2)               | 20.6 ± 8.0        | 21.3 ± 8.9            | 29.6 ± 21.6*†       | <0.001  |
| LVEF (%)                       | 60.0 ± 6.0        | 59.4 ± 7.8            | 54.5 ± 12.7*†       | <0.001  |
| LVEF <55% (%)                  |                   |                       |                     |         |
| Stroke volume index (mL/m^2)   | 47.0 ± 13.0 ‡     | 46.0 ± 11.0 ‡         | 38.7 ± 10.2*†       | <0.001  |
| Transmortal E/A ratio          | 0.90 ± 0.43       | 0.89 ± 0.32           | 1.04 ± 0.74         | 0.007   |
| Pulmonary S/D ratio            | 1.45 ± 0.42       | 1.46 ± 0.42           | 1.36 ± 0.48         | 0.038   |
| E/E'                           | 12.0 (9.7–16.6)   | 13.0 (10.4–17.1)      | 17.4 (12.4–24.7)    | <0.001  |
| Peak aortic valve jet velocity (m/s) | 2.3 ± 0.4±±       | 3.1 ± 0.7±±           | 4.0 ± 0.8±±         | <0.001  |
| Mean aortic valve gradient (mmHg) | 12.8 ± 5.3±±      | 24.4 ± 11.6±±         | 42.0 ± 17.2±±       | <0.001  |
| Aortic valve area (cm^2)       | 1.69 ± 0.23±±     | 1.18 ± 0.16±±         | 0.72 ± 0.16±±       | <0.001  |
| Mechanical dispersion (ms)     | 54.5 ± 17.2±±     | 56.7 ± 19.3±±         | 70.9 ± 24.3±±       | <0.001  |

Values are presented as mean ± standard deviation, median (interquartile range) or percentages.
P-value by ANOVA with Bonferroni-correction (*P < 0.05 vs. mild AS, †P < 0.05 vs. moderate AS, ‡P < 0.05 vs. severe AS).

AS, aortic stenosis; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; LV, left ventricular.

Figure 1  Evaluation of mechanical dispersion in patients with various degrees of aortic stenosis. Speckle tracking echocardiography of the left ventricle from the apical four-chamber view (A), long-axis view and two-chamber view is performed. The time durations (in ms) from Q/R on the ECG (B, yellow line) to peak longitudinal strain (B, white arrows) in 17 LV segments are automatically generated by the software (C) and LV mechanical dispersion is defined as the standard deviation of these 17 time durations. (D) Different examples of increasing AS severity where mechanical dispersion becomes more increased is shown. AVA, aortic valve area; ECG, electrocardiogram; LV, left ventricle.
### Table 3  Population characteristics according to LV mechanical dispersion

| Variables                              | LV mechanical dispersion <62 ms | LV mechanical dispersion ≥62 ms | P-value |
|----------------------------------------|---------------------------------|---------------------------------|---------|
|                                        | (n = 352)                       | (n = 278)                       |         |
| Clinical                               |                                 |                                 |         |
| Age (years)                            | 66.6 ± 13.4                     | 73.4 ± 10.6                     | <0.001  |
| Male sex (%)                           | 60.8                             | 62.2                             | 0.742   |
| Body mass index (kg/m²)                | 26.2 ± 4.1                       | 25.6 ± 4.1                      | 0.048   |
| Hypertension (%)                       | 48.9                             | 54.8                             | 0.163   |
| Diabetes mellitus (%)                  | 15.5                             | 21.4                             | 0.071   |
| Previous myocardial infarction (%)     | 9.1                              | 18.7                             | 0.001   |
| Dyslipidaemia (%)                      | 28.9                             | 30.0                             | 0.784   |
| NYHA functional class (%)              | 19.0                             | 25.6                             | 0.076   |
| Electrocardiography                    |                                 |                                 |         |
| QRS duration (ms)                      | 99 ± 17                          | 107 ± 23                         | <0.001  |
| Atrial fibrillation (%)                | 2.0                              | 5.0                              | 0.030   |
| Echocardiography                       |                                 |                                 |         |
| Heart rate (bpm)                       | 74 ± 14                          | 72 ± 13                          | 0.177   |
| LV mass index (g/m²)                   | 115.4 ± 31.4                     | 134.9 ± 38.1                     | <0.001  |
| LV EDVI (mL/m²)                        | 52.8 ± 16.3                      | 57.9 ± 24.5                      | 0.002   |
| LV ESVI (mL/m²)                        | 21.8 ± 10.3                      | 28.5 ± 20.8                      | <0.001  |
| LVEF (%)                               | 59.7 ± 7.9                       | 54.1 ± 12.0                      | <0.001  |
| Stroke volume index (mL/m²)            | 44.8 ± 11.3                      | 40.8 ± 11.9                      | <0.001  |
| Peak aortic valve jet velocity (m/s)   | 3.3 ± 0.9                        | 3.4 ± 1.0                        | 0.020   |
| Mean aortic valve gradient (mmHg)      | 28.1 ± 17.1                      | 31.7 ± 18.4                      | 0.013   |
| Aortic valve area (cm²)                | 1.17 ± 0.38                      | 0.96 ± 0.41                      | <0.001  |
| Mechanical dispersion (ms)             | 47.0 ± 9.5                       | 81.9 ± 18.7                      | <0.001  |

Values are presented as mean ± standard deviation or percentages.  
P-value by independent sample t-test or χ².  
EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; LV, left ventricular; NYHA, New York Heart Association.

### Table 4  Univariable and multivariable correlates of mechanical dispersion in aortic stenosis

| Variables                              | Univariable analysis |          |          |          | Multivariable analysis |          |          |
|----------------------------------------|----------------------|----------|----------|----------|------------------------|----------|----------|
|                                        | β                    | 95% CI   | P-value  | β        | 95% CI     | P-value  |          |
| Age (years)                            | 0.47                 | 0.34 to 0.61 | <0.001 | 0.28      | 0.15 to 0.42 | 0.003   |          |
| Sex (female)                           | -0.70                | -4.32 to 2.92 | 0.704 |          |            |          |          |
| Diabetes mellitus (%)                  | 3.16                 | -1.58 to 7.90 | 0.191 |          |            |          |          |
| Arterial hypertension                  | 2.50                 | -1.15 to 6.15 | 0.179 |          |            |          |          |
| Previous myocardial infarction (%)     | 9.87                 | 4.59 to 15.15 | <0.001 | 4.36      | -0.63 to 9.34 | 0.087   |          |
| Dyslipidaemia                          | -0.36                | -4.46 to 3.75 | 0.865 |          |            |          |          |
| History of atrial fibrillation         | 2.05                 | -3.78 to 7.88 | 0.490 |          |            |          |          |
| Beta-blockers                          | 2.15                 | -1.63 to 5.93 | 0.265 |          |            |          |          |
| RAAS-inhibitors                        | 2.08                 | -1.66 to 5.82 | 0.275 |          |            |          |          |
| Calcium blockers                       | 2.93                 | -1.50 to 7.36 | 0.195 |          |            |          |          |
| Diuretics                              | 6.26                 | 2.27 to 10.24 | 0.002 | 3.65      | -0.03 to 7.262 | 0.058   |          |
| Statins                                | 4.12                 | 0.39 to 7.85 | 0.031 | 2.42      | -0.96 to 5.80 | 0.160   |          |
| LVEF (%)                               | -0.77                | -0.93 to -0.61 | <0.001 | -0.24     | -0.44 to -0.04 | 0.020   |          |
| LV mass index (g/m²)                   | 0.25                 | 0.20 to 0.29 | <0.001 | 0.20      | 0.15 to 0.26 | <0.001  |          |
| Aortic valve area (cm²)                | -19.12               | -23.20 to -15.04 | <0.001 | -8.55     | -13.39 to -3.72 | 0.001   |          |
| Stroke volume index (mL/m²)            | -0.35                | -0.49 to -0.19 | <0.001 | -0.03     | -0.19 to 0.13 | 0.734   |          |
| QRS-duration (per 10 ms)               | 3.24                 | 2.35 to 4.14 | <0.001 | 1.12      | 0.25 to 1.99 | 0.012   |          |

Bold are those with a P<0.05 (significant).  
CI, confidence interval; EF, ejection fraction; LV, left ventricular; RAAS, renin-angiotensin-aldosterone system.
Analysis of LV mechanical dispersion showed a low inter-observer variability (intraclass correlation coefficient = 0.776) and intra-observer variability (intraclass correlation coefficient = 0.847).

**Independent correlates of mechanical dispersion**

To investigate the independent factors associated with an increase in LV mechanical dispersion, a multivariable linear regression analysis model was constructed including clinical, electrocardiographic, and echocardiographic variables (Table 4). Univariable clinical associates of LV mechanical dispersion included older age, previous myocardial infarction, and the use of diuretics and statins. Furthermore, lower LVEF, higher LV mass index, lower aortic valve area, and lower stroke volume index, and QRS prolongation were significant echocardiographic and electrocardiographic associates of LV mechanical dispersion. On multivariable analysis, older age ($\beta = 0.28$; (95% CI 0.15–0.42), $P = 0.003$), lower LVEF ($\beta = -0.24$; (95% CI -0.44 to -0.04), $P = 0.020$), smaller aortic valve area ($\beta = -8.55$; (95% CI -13.39 to -3.72), $P = 0.001$), larger LV mass index ($\beta = 0.20$; (95% CI 0.15–0.26), $P < 0.001$), and longer QRS duration ($\beta = 1.12$ per each 10 ms increase; (95% CI 0.25–1.99), $P = 0.012$) were independently associated with an increase in LV mechanical dispersion (Table 4).

**Long-term follow-up**

During a median follow-up of 107 (IQR 43–133) months, 246 patients received AVR and 302 died. Of those who died, 48.7% had severe AS, 33.1% had moderate AS, and 18.2% had mild AS at baseline. The cumulative event-free survival was significantly worse among patients with LV mechanical dispersion $\geq$62 ms, compared with patients with LV mechanical dispersion $<$62 ms (log rank $P < 0.001$) (Figure 2A). Similar results were observed when dividing the population into quartiles of LV mechanical dispersion ($<46$, 46–56, 56–70,
On univariable analysis, older age, previous myocardial infarction, diabetes mellitus, and QRS duration were associated with worse outcome, whereas AVR (as a time-dependent covariate) was related with improved outcome (Table 6). Furthermore, smaller aortic valve area, lower LVEF and stroke volume index, and larger LV mass index and LV mechanical dispersion were the echocardiographic parameters associated with worse outcome on univariable analysis. On multivariable analysis, older age (HR 1.05, 95% CI 1.04–1.06), smaller aortic valve area (HR 0.37, 95% CI 0.26–0.53), and lower LVEF (HR 0.98, 95% CI 0.97–0.99) were independently associated with worse outcome, whereas AVR as a time-dependent co-variate was associated with better survival (HR 0.42, 95% CI 0.32–0.56) (Table 5). The addition of LV mechanical dispersion to the baseline clinical model increased by 10% the risk of all-cause mortality (HR 1.10 per each 10 ms increase, 95% CI 1.04–1.15; P < 0.001). When performing IDI and NRI analyses, the addition of LV mechanical dispersion to a model containing age, LVEF, aortic valve area, and AVR as time dependent covariate did not result in significant change.

### Discussion

In a large unselected group of patients with various grades of AS, LV mechanical dispersion by speckle tracking echocardiography increased significantly with the severity of AS. Older age, lower LVEF, larger LV mass index, smaller aortic valve area, and more prolonged QRS duration were independently associated with increasing LV mechanical dispersion. Furthermore, LV mechanical dispersion was independently associated with increased all-cause mortality.

### Determinants of LV mechanical dispersion in AS

LV mechanical dispersion reflects regional heterogeneity in myocardial contraction throughout the cardiac cycle. Among several factors, one of the underlying substrates of increased LV mechanical dispersion is the abnormally increased amount of myocardial fibrosis. After myocardial infarction, the amount of dispersion in myocardial contraction and ventricular dyssynchrony is related to the presence and size of myocardial scar. In patients with hypertrophic cardiomyopathy, an increase in mechanical dispersion has been correlated with the presence of fibrosis on cardiac magnetic resonance. In AS, there is progressive LV hypertrophy to reduce the wall stress and maintain the LV systolic function in response to the increased pressure afterload. If left untreated, severe AS is characterized by myocyte apoptosis and myocardial fibrosis. The increased fibrosis leads to slow conduction and heterogeneous myocardial activation which may be detected by speckle tracking echocardiography. An earlier study by Klaeboe et al. on the use of speckle tracking echocardiography in AS patients, was not powered enough to identify the independent correlates of increased LV mechanical dispersion. The current study, which includes a larger population with various grades of AS allowed us to investigate the independent determinants of increased LV mechanical dispersion. Non-modifiable factors associated with myocardial fibrosis, such as older age,

### Table 5  Univariable and multivariable Cox proportional hazard models for the total population

| Variables                        | Univariables | Baseline model | Baseline model + mechanical dispersion |
|----------------------------------|--------------|----------------|----------------------------------------|
|                                  | HR  95% CI   | P-value        | HR  95% CI                             | P-value        |
| Age (years)                      | 1.06         | 1.05–1.07      | 1.05                                   | 1.04–1.06      | <0.001              |
| Male sex                         | 0.94         | 0.75–1.19      | 0.612                                  |                |
| Previous myocardial infarction   | 2.03         | 1.52–2.72      | <0.001                                 |
| Diabetes mellitus                | 1.48         | 1.12–1.96      | 0.005                                  |
| Hypertension                     | 1.19         | 0.95–1.50      | 0.131                                  |
| QRS duration per 10 ms           | 1.10         | 1.00–1.02      | 0.001                                  |
| AVR 0.40                         | 0.28–0.56    | <0.001         |
| Aortic valve area (cm^2)         | 0.39         | 0.29–0.53      | <0.001                                 |
| LVEF (%)                         | 0.98         | 0.97–0.99      | <0.001                                 |
| LV mass index per g/m^2          | 1.01         | 1.00–1.01      | <0.001                                 |
| LV stroke volume index (mL/m^2)  | 0.98         | 0.97–0.99      | 0.001                                  |
| LV mechanical dispersion         | 1.20         | 1.15–1.26      | <0.001                                 |
| Model discrimination Statistics  |             |                |                                        |
| χ^2                              | 160.9        |                | 181.4^b                                |
| -2 Log likelihood                | 3478         |                | 3466^b                                 |

AVR, aortic valve replacement; EF, ejection fraction; LV, left ventricular.
^aTime-dependent co-variate.
^bDifference with baseline model P < 0.001.
parameters reflecting increased myocardial fibrosis such as low LVEF, and prolonged QRS duration, or associated with increased myocardial fibrosis such as severe AS and increased LV mass index were independent correlates of prolonged LV mechanical dispersion. These factors have also been associated with increased myocardial fibrosis assessed on histology or with late gadolinium contrast enhanced cardiac magnetic resonance. Accordingly, LV mechanical dispersion could potentially be used as a surrogate of myocardial fibrosis in patients with AS, however, this needs further prospective validation with cardiac magnetic resonance-derived fibrosis data.

### Prognostic relevance of increased LV mechanical dispersion in AS

Current guidelines still advocate the use of LVEF as the main LV functional parameter to decide on AVR in severe AS. However, accumulating evidence has shown that other indirect markers (such as LV global longitudinal strain) or direct markers (late gadolinium enhancement on cardiac magnetic resonance) of myocardial fibrosis provide incremental prognostic value over LVEF. Those studies suggest that timely detection of myocardial fibrosis rather than deterioration of LV mechanical dispersion may be preferred to determine the optimal timing of AVR. The prognostic implications of LV mechanical dispersion in patients with AS have not been evaluated extensively.

In 162 patients with severe AS, Klaeboe et al. identified increased LV mechanical dispersion as an independent predictor of worse prognosis, which provided incremental prognostic value over LVEF. Our study provides more evidence in a much larger population with various grades of AS. LV mechanical dispersion had incremental prognostic value over LVEF, when corrected for age and AS severity at baseline and timing and occurrence of AVR during follow-up. The inclusion of patients with less than severe AS is clinically relevant, as concomitant LV systolic dysfunction in moderate AS is not infrequent and is associated with worse prognosis. It has been suggested that patients with moderate AS and reduced LVEF may also benefit from AVR. Whether prolonged LV mechanical dispersion can be used to justify AVR in this subset of patients, or, perhaps, as an indication for cardiac resynchronization therapy to try to correct it, needs to be investigated in randomized prospective studies. Furthermore, in a watchful waiting strategy in patients with significant AS, progressive increase of mechanical dispersion over time may be a more sensitive parameter for referral to AVR than decline in LVEF.

### Limitations

The present retrospective evaluation has limitations inherent to its observational design. A potential selection bias cannot be excluded as these patients were referred to a tertiary referral centre. Furthermore, this study included unselected patients with AS presenting with any grade of LV dysfunction at baseline. Although LVEF <55% was more prevalent with increasing severity of AS, this could also be attributed to a more frequent history of myocardial infarction in patients with more severe AS. However, on multivariable analysis, prior myocardial infarction was not significantly associated with an increase in LV mechanical dispersion. Also, after exclusion of these patients with prior myocardial infarction, the results of the multivariable analysis remained unchanged. Furthermore, all-cause mortality was chosen as the primary endpoint as these data were readily available. More specific causes of death, such as ventricular arrhythmias or sudden cardiac death, were not available for all patients and could have strengthened the results of the current study.

### Conclusions

LV mechanical dispersion by speckle tracking echocardiography increases significantly along with the severity of AS and is associated with well-known reflectors of increased myocardial fibrosis. Furthermore, LV mechanical dispersion was independently associated with increased all-cause mortality.

### Conflict of interest

The Department of Cardiology of the Leiden University Medical Center received research grants from Medtronic, Biotronik, Boston Scientific, GE Healthcare and Edwards Lifesciences. J.B. and V.D. received speaking fees from Abbott Vascular. All other authors declared no conflict of interest.

### References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart disease: a population-based study. Lancet 2006;368:1005–11.
2. d’Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people. The OxVALVE Population Cohort Study. Eur Heart J 2016;37:3515–22.
