Prevalence and Prognostic Relevance of Ventricular Conduction Disturbances in Patients With Aortic Stenosis

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The prevalence and prognostic implications of ventricular conduction disturbances in aortic stenosis (AS) have not been extensively evaluated. The present retrospective study investigated the prevalence and prognostic implications of ventricular conduction abnormalities (including the QRS morphology and duration) in AS. A total of 1,245 patients (mean age 66 ± 14 years, 62.8% men) with varying AS severity (aortic sclerosis 33.9%, mild AS 11.5%, moderate AS 29.9%, and severe AS 24.7%) were evaluated. Demographic, clinical variables, and presence of ventricular conduction abnormalities on the electrocardiogram (based on QRS morphology and duration) were related to occurrence of all-cause mortality, correcting for occurrence of aortic valve replacement. The prevalence of ventricular conduction disorders increased in parallel with AS severity, which was particularly significant for left bundle branch block (4.3% in aortic sclerosis, 2.1% in mild AS, 4.6% in moderate AS, and 8.1% in severe AS; $p = 0.042$). The QRS duration showed a slight prolongation with increasing AS severity (102 ± 21 ms in aortic valve sclerosis, 99 ± 18 ms in mild AS, 104 ± 22 ms in moderate AS, and 105 ± 22 ms in severe AS; $p = 0.044$). During a mean follow-up of 8.1 ± 4.8 years, 40.9% of patients died. Right bundle branch block morphology (hazard ratio 1.59, 95% confidence interval 1.18 to 2.13, $p = 0.002$) and increase of QRS duration (hazard ratio 1.06, 95% confidence interval 1.02 to 1.11; $p = 0.006$) were independently associated with all-cause mortality. In conclusion, ventricular conduction disorders became more prevalent with increasing severity of AS and have an impact on survival. © 2017 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (Am J Cardiol 2017;120:2226–2232)

Aortic valve stenosis (AS), one of the most common valvular diseases in developed countries, is a progressive process of valve calcification and inflammation, which can affect the conduction system directly through calcification and indirectly through increased pressure afterload on the left ventricle (LV).[1] In patients with severe AS, ventricular conduction disorders (left [LBBB] and right [RBBB] bundle branch block or nonspecific intraventricular conduction delay [IVCD]) are reported to be more prevalent than in the general population.[2] However, the factors influencing the increased prevalence of ventricular conduction disorders (QRS morphology and duration) are poorly understood and have not been evaluated in a large cohort of patients with varying grades of AS. Furthermore, the prognostic value of ventricular conduction disturbances have been studied only in specific subpopulations

of patients with AS.[3,4] Therefore, the present study aimed at investigating the prevalence of ventricular conduction disorders in a large registry of patients with AS and the prognostic relevance of QRS morphology and duration in this population.

Methods

Patients with native AS were identified from the departmental echocardiographic database at the Leiden University Medical Center (Leiden, The Netherlands) from December 1993 to August 2015.[5] Patients with prosthetic aortic valves, subvalvular or supravalvular AS, dynamic subaortic obstruction, coexisting (moderate or severe) aortic regurgitation, coexisting (moderate or severe) mitral regurgitation, and active endocarditis were excluded. In addition, patients with pacemaker rhythm were excluded.

Clinical history, physical examination, transthoracic echocardiography, and resting 12-lead electrocardiogram (ECG) were evaluated at time of first diagnosis of AS. Baseline clinical variables included cardiovascular risk factors, total cholesterol levels, hemoglobin level, and glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula.[6] All patients were followed up for the occurrence of all-cause mortality. The association between QRS duration and morphology across the AS grade groups and all-cause mortality at follow-up was investigated in this analysis.

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Patient data were collected in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Centre, Leiden, the Netherlands) and analyzed retrospectively. This retrospective analysis of clinically acquired data was approved by the institutional review board of the Leiden University Medical Center, and the need for patient written informed consent was waived.

Standard resting 12-lead ECGs performed within 12 months before or after the date of the index 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.[7] The QRS morphology was analyzed, and patients were divided based on the presence of LBBB, RBBB, and IVCD.[8] In addition, QRS duration was measured in milliseconds in the ECG lead with the greatest QRS width. The study population was divided into 2 groups according to the presence of a QRS duration ≥130 ms or <130 ms, as previously described.[4]

Transthoracic echocardiography was performed in all patients at rest using commercially available ultrasound systems (Vivid 7 and E9 systems; GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 113.0.3; GE Vingmed). Two-dimensional, color, pulsed, and continuous-wave Doppler data were acquired according to standard techniques. LV end-diastolic and end-systolic volumes were calculated using the Simpson's biplane method of discs and indexed to body surface area.[9] The LV ejection fraction was calculated and expressed as a percentage. The LV mass was calculated from the two-dimensional LV linear measurements obtained on the parasternal LV long-axis view as recommended,[9] and indexed to body surface area. From the apical LV long-axis or 5-chamber views, continuous-wave Doppler spectral recordings through the aortic valve were obtained, and the mean pressure gradient was estimated with the modified Bernoulli equation. The aortic valve area (AVA) was calculated with the continuity equation. The severity of AS was determined by the peak jet velocity, mean gradient, and calculated AVA, and classified into different categories (sclerosis, mild, moderate, and severe), as currently recommended.[10]

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 or the Social Security Death Index.

All continuous variables were tested for Gaussian distribution and were presented as mean ± standard deviation unless otherwise stated. All categorical variables were presented as frequencies and percentages. The cumulative event rates for the clinical end point of all-cause mortality were estimated with the Kaplan-Meier survival curves, and log-rank testing was used to compare the groups (QRS morphology [narrow QRS, LBBB, RBBB, IVCD] and QRS duration ≥130 ms vs <130 ms). Multivariable Cox proportional hazards regression analysis was performed to investigate the independent association between QRS morphology and duration with the clinical end point of all-cause mortality. Clinical and echocardiographic parameters known to influence mortality in patients with AS were chosen a priori based on published studies and incorporated as covariates in the model.[4,11] In addition, subsequent aortic valve replacement (AVR) during follow-up was treated as a time-dependent covariate in the model. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A 2-tailed p value of <0.05 was considered significant. All statistical analyses were performed using SPSS Statistics 23 (SPSS Inc; Armonk, NY: IBM Corp) and STATA version 12 (STATA Corporation, College Station, TX).

Results

The final population comprised 1,245 patients with AS (Figure 1). The mean age at first AS diagnosis was 66 ± 14 years, and 62.8% were men. The mean AVA, mean gradient, and peak jet velocity were 1.47 ± 0.68 cm², 22.4 ± 17.0 mm Hg, and 2.8 ± 1.0 m/s, respectively. A total of 422 (33.9%) patients had aortic sclerosis, 143 (11.4%) had mild AS, 372 (29.9%) had moderate AS, and 308 (24.8%) had severe AS. The majority of patients showed narrow QRS complex (n = 942, 76%), whereas the prevalence of LBBB, RBBB, and IVCD was 5%, 7%, and 12%, respectively. The number of patients with QRS duration ≥130 ms was 154 (12.4%). Table 1 shows the different patient characteristics according to the different QRS morphologies.

Figure 2 summarizes the distribution of different QRS morphologies and QRS duration across the various grades of AS. The prevalence of ventricular conduction disorders increased along the severity of AS, which was particularly significant for LBBB morphology (4.3% in aortic valve sclerosis, 2.1% in mild AS, 4.6% in moderate AS, and 8.1% in severe AS; p = 0.042). The QRS duration showed a slight prolongation with increasing severity of AS (102 ± 21 ms in aortic valve sclerosis, 99 ± 18 ms in mild AS, 104 ± 22 ms in moderate AS, and 105 ± 22 ms in severe AS; p = 0.044).

During a mean follow-up of 8.1 ± 4.8 years, 533 (42.8%) patients underwent AVR (75 had transcatheter aortic valve implantation), and 509 (40.9%) patients died. Figure 3 shows that the cumulative event-free survival was significantly worse in patients with RBBB morphology than in patients with narrow QRS (HR 1.72, CI 1.28 to 2.30, p <0.001). There was no difference in survival between patients with narrow QRS versus patients with LBBB (HR 1.247, CI 0.832 to 1.870, p = 0.286) and patients with IVCD (HR 1.23, CI 0.95 to 1.60, p = 0.122). When analyzing the prognostic effect of QRS duration, we found that patients with QRS duration ≥130 ms showed significantly worse survival than did patients with QRS duration <130 ms (HR 1.63, CI 1.28 to 2.07, p <0.001; Figure 3).

To determine the independent prognostic value of different QRS morphologies and QRS duration in all grades of AS, a multivariable Cox proportional hazards model was constructed with significant univariate determinants entered as covariates (Table 2). Age, AVA, LV ejection fraction, and subsequent AVR were significantly associated with all-cause mortality in the univariate analysis. Two different models were then constructed to evaluate the additional prognostic significance of QRS morphology and QRS duration on top of the clinical baseline model (Table 3). Both QRS morphology and QRS duration were significantly associated with all-cause mortality. The presence of RBBB was significantly associated with worse prognosis than narrow QRS, whereas LBBB and IVCD morphologies were not independently associated with increased all-cause mortality. In addition, each
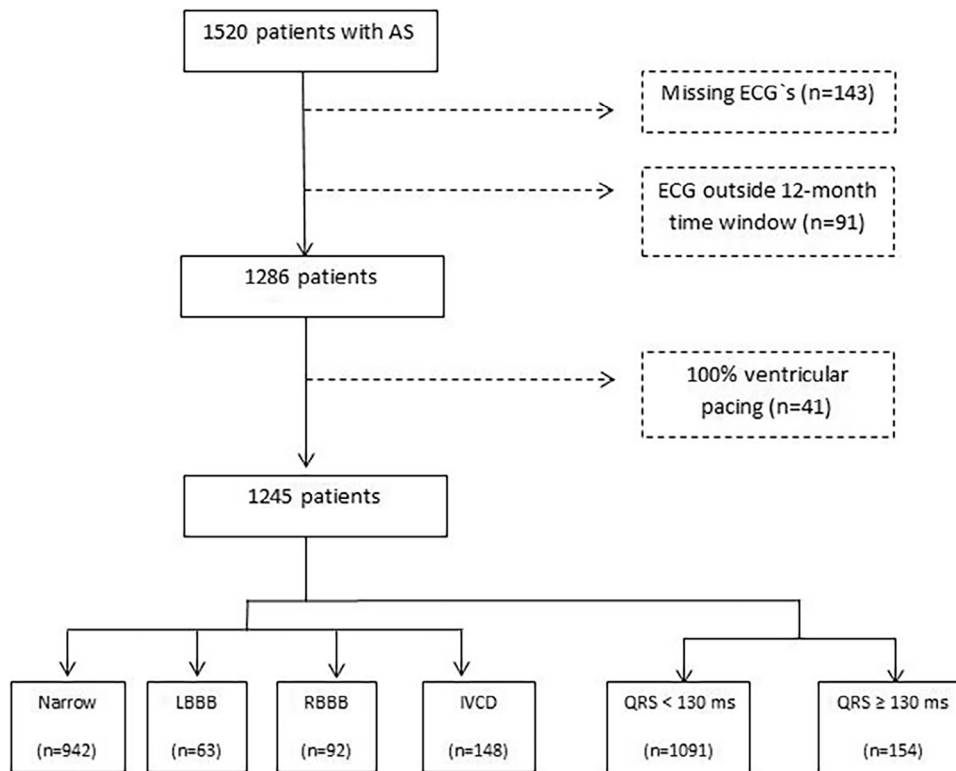
Figure 1. Flowchart of inclusion of patients with aortic stenosis. AS = aortic stenosis; ECG = electrocardiogram; IVCD = nonspecific ventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block.

10-ms increase in QRS duration was independently associated with 6% increase in the risk of all-cause mortality.

Figure 4 shows that addition of QRS morphology and QRS duration to the baseline model resulted in an equivalent and significant increase in the chi-square (baseline model chi-square = 54.7; baseline + QRS morphology model chi-square = 65.2, p = 0.027; baseline + QRS duration model chi-square = 63.7, p = 0.007), indicating an incremental value of QRS morphology (RBBB) and QRS duration in risk stratification of patients with AS.

Discussion

The prevalence of ventricular conduction disorders, particularly LBBB QRS morphology, increased along with the severity of AS. Both QRS duration and morphology were independently associated with all-cause mortality in patients with AS. Specifically, patients with RBBB morphology showed worse prognosis than did patients without RBBB. Whether these patients need careful follow-up and perhaps earlier valve replacement needs to be elucidated in prospective randomized studies.

An increased prevalence of ventricular conduction disorders in severe AS has been demonstrated in several studies.[12–15] In a large meta-analysis including 5,258 patients with severe AS undergoing transcatheter aortic valve implantation, a high percentage of preprocedural ventricular conduction disorders (LBBB 13%, RBBB 11%) was reported.[2] In the present study (involving an unselected cohort of patients with AS) we confirm and extend this relation by showing a significant increase of ventricular conduction disorders (LBBB, RBBB, and IVCD) and a significant increase in mean QRS duration with increasing severity of AS. More importantly, this progressive increase in conduction disorders is mainly determined by a significant increase in LBBB morphology (4-fold more frequent in severe versus mild AS, p = 0.042).

Several anatomic and hemodynamic mechanisms underlying the occurrence of ventricular conduction disorders in AS have been described. The close proximity of the aorta-mitral fibrous continuity to the His bundle and the origin of the left bundle branch can be affected by progressive calcification of the aortic valve.[16] In addition, the increased pressure afterload imposed by the stenotic valve leads to compensatory LV hypertrophy, increased wall stress, relative ischemia, and subsequent deterioration of LV function and development of fibrosis, which can further lead to slow ventricular conduction.[1] The association between longer QRS duration and myocardial fibrosis has been demonstrated in a previous histologic study, including mainly individuals with ischemic heart disease.[17]

To date, only 2 studies have focused on the prognostic implications of QRS duration and morphology in patients with AS.[3,4] A sub-study of the Simvastatin and Ezetimibe in Aortic Stenosis study,[3] including 1,542 asymptomatic patients with mild to moderate AS, demonstrated that prolonged QRS duration and LBBB or combined RBBB and left anterior fascicular block QRS morphologies were associated with poor prognosis. Noteworthy, in the Simvastatin and Ezetimibe in Aortic Stenosis study, the number of patients with QRS duration ≥120 ms was relatively low (6.5% of the total

Table 1
Characteristics of the patient population according to QRS morphology (n = 1,245)

Variable	Narrow (n = 942)	Left bundle branch block (n = 63)	Right bundle branch block (n = 92)	Intraventricular conduction disorder (n = 148)	P-value*
Age (years)	66 ± 14	72 ± 11	70 ± 13	67 ± 12	<0.001
Men	59.4%	58.7%	78.3%	76.4%	<0.001
Body mass index (kg/m^2)	25.4 ± 5.9	24.5 ± 7.1	25.2 ± 6.3	25.9 ± 6.4	0.333
Hypertension	51.4%	53.7%	61.9%	56.8%	0.335
Diabetes mellitus	19.4%	21.4%	15.9%	21.9%	0.806
Previous myocardial infarction	15.7%	25.6%	30.2%	21.9%	0.009
New York Heart Association functional class					0.718
III/IV	19.5%	27.5%	17.5%	14.5%	
Chronic obstructive pulmonary disease	10.8%	7.1%	12.7%	10.4%	0.842
Previous malignancy	14.2%	7.1%	9.5%	10.4%	0.345
Symptoms	67.3%	68.3%	74.6%	72.6%	0.517
Laboratory					
Haemoglobin (g/dL)	13.3 ± 1.9	13.3 ± 1.9	13.5 ± 2.1	13.8 ± 1.8	0.184
Estimated glomerular filtration rate (mL/min/1.73 m^2)	72.2 ± 25.9	65.3 ± 27.3	70.8 ± 23.7	65.3 ± 23.1	0.054
Total cholesterol (mg/dL)	197.5 ± 50.8	209.7 ± 79.8	202.2 ± 46.9	191.6 ± 39.9	0.573
Echocardiography					
Heart rate (beats/min)	73 ± 14	75 ± 14	71 ± 15	71 ± 15	0.175
Peak aortic valve jet velocity (m/s)	2.8 ± 1.0	2.9 ± 1.0	2.9 ± 1.0	2.9 ± 1.0	0.567
Mean aortic valve gradient (mmHg)	23.1 ± 14.9	23.1 ± 14.9	22.6 ± 16.8	23.7 ± 16.8	0.734
Aortic valve area (cm^2)	1.50 ± 0.69	1.18 ± 0.49	1.45 ± 0.68	1.41 ± 0.66	0.005
Bicuspid aortic valve	10.7%	5.4%	6.3%	12.9%	0.344
Left ventricular mass index (g/m^2)	113.7 ± 31.9	141.6 ± 43.0	122.5 ± 37.3	137.6 ± 37.8	<0.001
Left ventricular end-diastolic volume index (mL/m^2)	50.1 ± 16.8	69.9 ± 26.2	59.4 ± 29.2	63.4 ± 22.2	<0.001
Left ventricular end-systolic volume index (mL/m^2)	21.6 ± 11.7	41.2 ± 23.3	29.1 ± 25.9	31.3 ± 7.7	<0.001
Left ventricular ejection fraction (%)	58.2 ± 9.7	43.5 ± 14.4	55.3 ± 11.8	53.0 ± 12.2	<0.001
Electrocardiography					
QRS duration (ms)	93 ± 8	147 ± 21	144 ± 17	120 ± 11	<0.001
Atrial fibrillation	6.5%	17.5%	8.7%	8.8%	0.012
Medication					
Antiplatelet/anticoagulant	42.3%	68.3%	54.0%	46.9%	0.004
Beta-blockers	39.8%	46.3%	42.9%	38.5%	0.807
Calcium channel blockers	21.7%	26.8%	25.4%	31.3%	0.186
Renin-angiotensin-aldosterone inhibitors	41.8%	63.4%	42.9%	50.0%	0.029
Statins	39.5%	63.4%	50.8%	34.4%	0.004
Diuretics	27.9%	56.1%	30.2%	39.6%	<0.001

Values are mean ± SD or percentages.
* p Value by 1-way ANOVA, and chi-square test for continuous and categorical variables, respectively.

population), and the number of events at follow-up was also low, precluding the assessment of independent associates of outcome. In addition, in 88 patients with low flow, low gradient severe AS, wide QRS complex (≥130 ms) was significantly associated with all-cause mortality.[4] The current study is the first to demonstrate that QRS duration and morphology are significantly associated with all-cause mortality in a large group of patients with AS with a broad spectrum of AS severity. The risk of all-cause mortality increased progressively with longer QRS duration, and this association was modulated by QRS morphology.

The present retrospective evaluation has some limitations. Because of the retrospective design of the present study, including patients referred to a tertiary center, there may be a potential selection bias. The primary end point was all-cause mortality because these data are uniformly available, whereas cardiovascular death or other specific causes of death were not systematically available. Furthermore, the presence of atrioventricular block or concomitant fascicular block was not collected. Although the ECG and echocardiographic data were restricted for inclusion if they coincided within a 12-month time frame, we cannot exclude any confounding
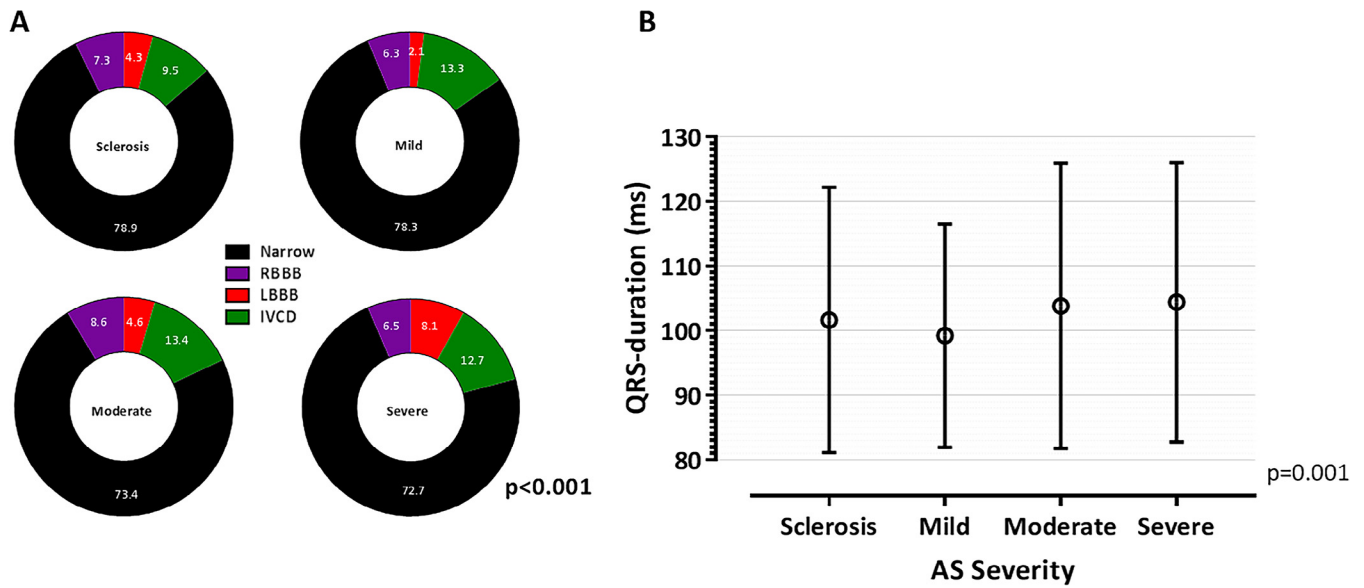
Figure 2. Distribution of *(A)* QRS morphology and *(B)* QRS duration in various grades of aortic stenosis. With increasing severity of aortic stenosis, there was a significant increase in prevalence of QRS conduction disorders (narrow vs IVCD, RBBB, and LBBB) and a significant increase in mean QRS duration. AS = aortic stenosis; IVCD = interventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block.
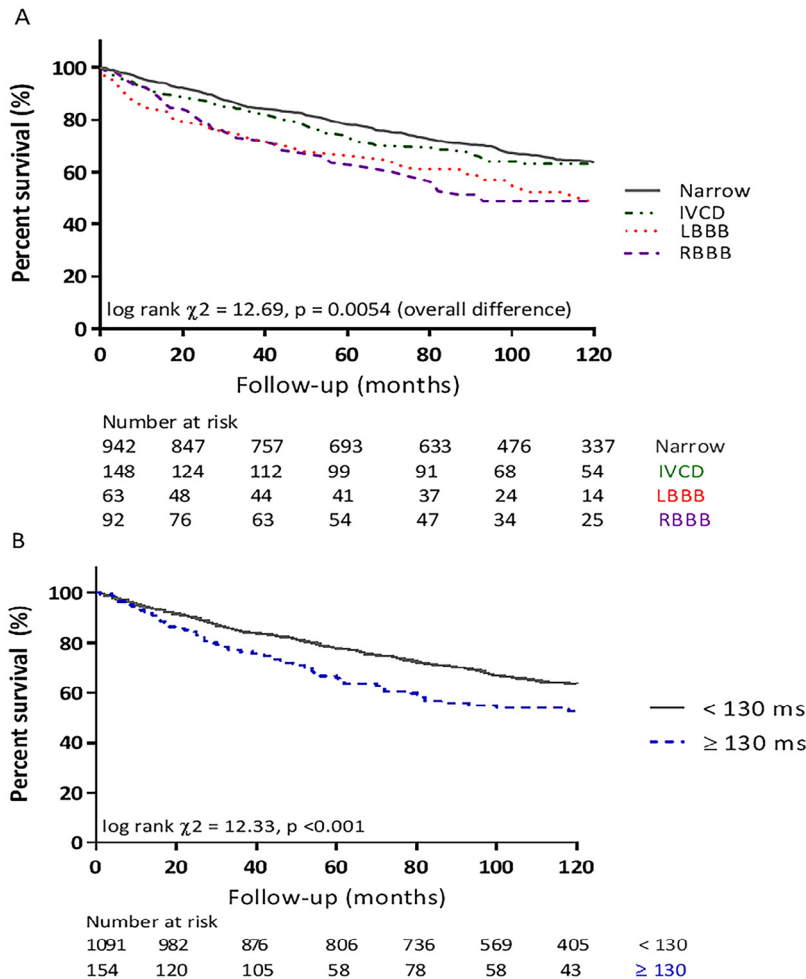

Figure 3. Kaplan-Meier survival curves in patients divided according to QRS morphology *(A)* and QRS duration *(B)*. IVCD = nonspecific ventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block.

Table 2

Uni-and multivariable Cox regression analyses for all-cause mortality

Variable	Univariable			Baseline Multivariable Model		
	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Age (years)	1.01	1.01–1.02	<0.001	1.02	1.01–1.02	<0.001
Body mass index (kg/m^2)	0.99	0.97–1.00	0.051	–	–	–
Men	1.09	0.91–1.31	0.332	–	–	–
Diabetes mellitus	1.44	1.14–1.84	0.003	–	–	–
Previous myocardial infarction	1.80	1.42–2.28	<0.001	–	–	–
Left ventricular ejection fraction (%)	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
Aortic valve area (cm^2)	0.77	0.67–0.89	<0.001	0.80	0.68–0.93	0.005
Hypertension	1.35	1.10–1.67	0.005	–	–	–
Aortic valve replacement	0.78	0.64–0.95	0.016	0.62	0.45–0.86	0.005
Atrial fibrillation	1.57	1.26–1.96	<0.001	–	–	–

Table 3

Multivariable Cox regression analysis for all-cause mortality

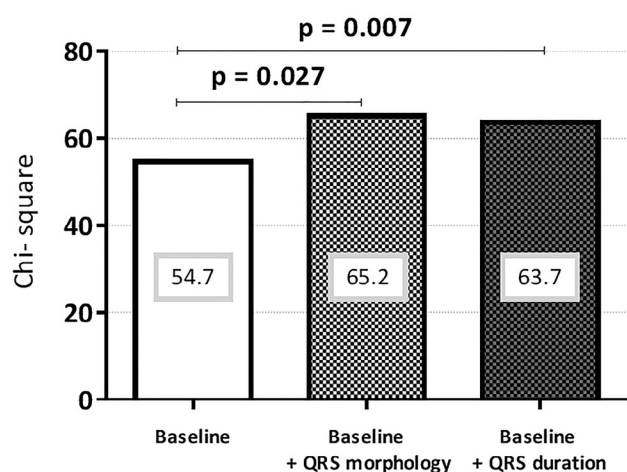| Variable	Baseline Model			Baseline Model + QRS morphology			Baseline Model + QRS duration		
	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Age (years)	1.02	1.01–1.02	<0.001	1.01	1.01–1.02	<0.001	1.01	1.01–1.02	<0.001
Left ventricular ejection fraction (%)	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001	0.99	0.98–0.99	<0.001
Aortic valve area (cm^2)	0.80	0.68–0.93	0.005	0.79	0.68–0.93	0.004	0.80	0.68–0.93	0.005
Aortic valve replacement	0.62	0.45–0.86	0.005	0.63	0.45–0.87	0.005	0.62	0.44–0.86	0.004
QRS morphology	–	–	–			0.017	–	–	–
Left bundle branch vs Narrow	–	–	–	0.89	0.58–1.39	0.614	–	–	–
Right bundle branch vs Narrow	–	–	–	1.59	1.18–2.13	0.002	–	–	–
Non-specific intraventricular conduction delay vs Narrow	–	–	–	1.11	0.84–1.46	0.475	–	–	–
QRS duration per 10 milliseconds	–	–	–	–	–	–	1.06	1.02–1.11	0.006
χ^2		**54.69**			**65.17**			**63.67**	

Figure 4. Incremental prognostic value of QRS morphology and QRS duration over baseline clinical model. Both QRS morphology and duration added comparable and significant prognostic value to the baseline model as reflected by similar increment in the chi-square of the model.

influence attributable to this timeframe. However, all patients were in stable conditions without AVR in this period.

In conclusion, the prevalence of ventricular conduction disorders increased in parallel with increasing AS severity. Longer QRS duration and RBBB morphology were independently associated with all-cause mortality in AS.

Disclosures

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