Journal of the American Heart Association

ORIGINAL RESEARCH

Relationship Between the Ratio of Acceleration Time/Ejection Time and Mortality in Patients With High-Gradient Severe Aortic Stenosis

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BACKGROUND: The ratio of acceleration time/ejection time (AT/ET) is a simple and reproducible echocardiographic parameter that integrates aortic stenosis severity and its consequences on the left ventricle. No study has specifically assessed the prognostic impact of AT/ET on outcome in patients with high-gradient severe aortic stenosis (SAS) and no or mild symptoms. We sought to evaluate the relationship between AT/ET and mortality and determine the best predictive AT/ET cutoff value in these patients.

METHODS AND RESULTS: A total of 353 patients (median age, 79 years; 46% women) with high-gradient (mean pressure gradient ≥40 mm Hg and/or aortic peak jet velocity ≥4 m/s) SAS, left ventricular ejection fraction ≥50%, and no or mild symptoms were studied. The impact of AT/ET ≤0.35 or >0.35 on all-cause mortality was retrospectively studied. During a median follow-up of 39 (25th–75th percentile, 23–62) months, 70 patients died. AT/ET >0.35 was associated with a considerable increased mortality risk after adjustment for established prognostic factors in SAS under medical and/or surgical management (adjusted hazard ratio [HR], 2.54; 95% CI, 1.47–4.37; *P*<0.001) or conservative management (adjusted HR, 3.29; 95% CI, 1.70–6.39; *P*<0.001). Moreover, AT/ET >0.35 improved the predictive performance of models including established risk factors in SAS with better global model fit, reclassification, and discrimination. After propensity matching, increased mortality risk persisted when AT/ET >0.35 (adjusted HR, 2.10; 95% CI, 1.12–3.90; *P*<0.001).

CONCLUSIONS: AT/ET >0.35 is a strong predictor of outcome in patients with SAS and no or only mild symptoms and identifies a subgroup of patients at higher risk of death who may derive benefit from earlier aortic valve replacement.

Key Words: aortic stenosis ■ echocardiography ■ ejection dynamic parameters ■ outcome

The sole optimal treatment for patients with severe aortic stenosis (SAS) is aortic valve replacement (AVR). Although symptomatic SAS is a class I indication for AVR, the optimal timing of intervention in patients with asymptomatic SAS is a matter of paramount importance.[1] Hence, several echocardiographic indexes have been proposed to refine the prognostic assessment of patients with SAS, including the severity of valve narrowing (aortic peak jet velocity [Vmax] >5 or 5.5 m/s, according to either European Society of Cardiology or American College of Cardiology/American Heart Association guidelines) and/or left ventricular (LV) systolic function impairment (LV ejection fraction ≤50%, low flow status, and impairment of global longitudinal strain [GLS] <15%).[2–5] LV ejection dynamic parameters have received in the past few years renewed attention in

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021873

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a cohort of patients with high-gradient severe aortic stenosis, preserved left ventricular ejection fraction, and no or only mild symptoms managed in routine clinical practice, the ratio of acceleration time/ejection time obtained on the waveform of the aortic flow by continuous wave Doppler was associated with a considerable increased risk of mortality.
- The present data suggest that a cutoff value of ratio of acceleration time/ejection time >0.35 may provide incremental prognostic value beyond established prognostic factors in severe aortic stenosis.

What Are the Clinical Implications?

- Our findings suggest that assessment of ratio of acceleration time/ejection time by Doppler echocardiography should be systematically performed in routine daily practice in asymptomatic or minimally symptomatic patients with severe aortic stenosis and preserved left ventricular ejection fraction.
- Future studies should be conducted to determine whether assessment of ratio of acceleration time/ejection time should be integrated in the decision-making process in patients with severe aortic stenosis and preserved left ventricular ejection fraction.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AT/ET	ratio of acceleration time/ejection time
AVA	aortic valve area
AVR	aortic valve replacement
GLS	global longitudinal strain
MPG	mean aortic pressure gradient
SAS	severe aortic stenosis
SBP	systolic blood pressure
SV	stroke volume
SVi	stroke volume index
Vmax	aortic peak jet velocity

the assessment of native aortic stenosis (AS).[6] Indeed, the ratio of acceleration time/ejection time (AT/ET) is a simple and reproducible echocardiographic parameter that integrates AS severity and its consequences on the LV.[7,8] Previous reports have suggested that increased AT/ET may be associated with adverse outcome in patients with moderate AS or SAS or with discordant grading, that is those with low-gradient SAS, and preserved LVEF, with divergent cutoff values among studies and regardless of symptomatic status.[9–12] Notwithstanding, no study has specifically assessed the relationship between AT/ET and mortality in the population of patients with "classic" (ie, high-gradient) SAS and no or only mild symptoms. Hence, the objectives of this bicenter study were (1) to evaluate the prognostic impact of AT/ET on mortality in a cohort of patients with high-gradient SAS with preserved LVEF and no or mild symptoms; (2) to establish a prognostic cutoff value of AT/ET associated with mortality risk; and (3) to assess the incremental prognostic value of AT/ET over established risk factors in SAS.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patient Population

Between 2012 and 2019, patients of at least 18 years of age, diagnosed with high-gradient (defined as mean aortic pressure gradient [MPG] ≥40 mm Hg and/or Vmax ≥4 m/s) SAS (defined as aortic valve area [AVA] ≤1 cm^2 and/or AVA normalized to body surface area ≤0.6 cm^2/m^2) and no or only mild AS related symptoms who attended the heart valve clinics of 2 tertiary hospitals in France (Lille and Amiens), were prospectively enrolled in the present ancillary study from a larger registry.[9] The following patients were excluded: (1) patients with more than mild aortic and/or mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supravalvular or subvalvular AS, or dynamic LV outflow tract obstruction; (3) those with past or current symptoms of New York Heart Association class III to IV heart failure; (4) those with angina or syncope; and (5) patients who refused to participate in the study. Clinical and demographic characteristics were collected at baseline. The Charlson comorbidity index, summating the patient's individual comorbidities, was calculated.[13] Patients were deemed as having coronary artery disease if they had a documented history of acute coronary syndrome, coronary artery disease previously documented by coronary angiography, or a history of coronary revascularization. Institutional review board approval was obtained. The study was approved by our institutional review committee, and the subjects gave informed consent.

Echocardiography

All patients underwent a comprehensive Doppler-echocardiography study, using commercially available

ultrasound systems by experienced echocardiographers. Echocardiograms were stored in Digital Imaging and Communications in Medicine format to allow subsequent offline analysis. Aortic flow was recorded using continuous-wave Doppler, by imaging and nonimaging transducers, systematically in several acoustic windows (apical 5-chamber, right parasternal, suprasternal, and epigastric). The view identifying the highest velocities was used to determine Vmax and MPG. Pressure gradients were calculated using the simplified Bernoulli equation. Pulsed Doppler LV outflow tract velocity was recorded in the apical 5-chamber view with the sample volume at 5 mm proximal from the plane of the aortic valve. Alignment of both pulsed and continuous-wave Doppler was optimized to be parallel with flow. Doppler recordings were performed at a sweep speed of 100 mm/s. AT was defined as time from the start to the peak of flow through the valve by continuous-wave Doppler. ET was defined from aortic valve opening to aortic valve closure. The AT/ET ratio was then calculated (Figure 1). The interobserver reproducibility of AT/ET was good in a previous report from our group, with an intraclass correlation coefficient of 0.90 (95% CI, 0.78–0.96) and a coefficient of variation of 7.3%.[9] Similarly, Einarsen et al reported an excellent intraobserver reproducibility for AT/ET, with an intraclass coefficient at 0.98 (95% CI, 0.98–0.99).[12] LV stroke volume (SV) was calculated by multiplying the LV outflow tract area with the LV outflow tract time-velocity integral. The LV outflow tract diameter was measured in zoomed parasternal long-axis views in early systole at the level of aortic cusp insertion (inner-to-inner edge). Flow rate (mL/s) was defined by the ratio of LV-SV/ET.[14] AVA was calculated using the continuity equation. AVA and LV-SV were indexed to body surface area. Low flow was defined as LV SV index (SVi) <30 mL/m^2.[5,15] LV mass was estimated using M-mode echocardiography, according to the American Society of Echocardiography formula. LV hypertrophy was defined as LV mass index >95 g/m^2 in women and >115 g/m^2 in men. Global longitudinal strain was obtained in a subset of the study population using either EchoPAC PC (GE Healthcare) (Amiens) or Tomtec LV Autostrain (Philips) (Lille). In a random subset of 20 patients from the present study in whom GLS measurement was possible on stored video loops, a good agreement was found between the 2 software platforms (intraclass correlation coefficient, 0.88; 95% CI, 0.76–0.94; bias, −0.8%). Conventional echocardiographic measurements were performed according to current European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines. When patients were in sinus rhythm, 3 cardiac cycles were averaged for all measures. For patients in atrial fibrillation (AF), 5 cardiac cycles were averaged.

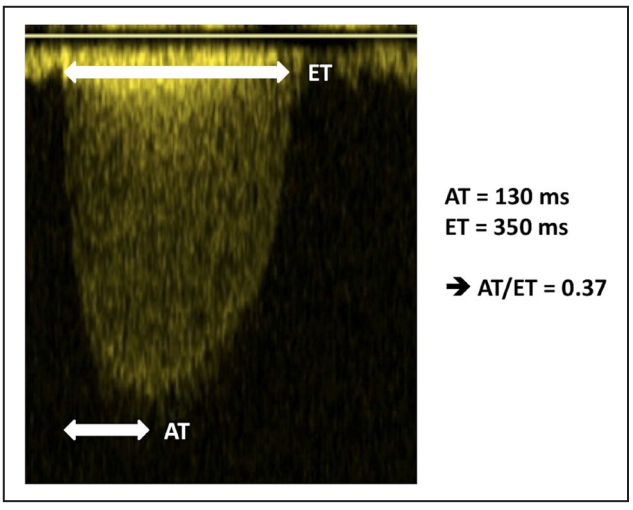

Figure 1. Measurement of ratio of acceleration time/ejection time (AT/ET) on a continuous-wave Doppler recording of transaortic flow.

Treatment Decision and Follow-Up

After the initial medical management, treatment was conservative or surgical, as deemed appropriate by the patient's personal physician. Most patients were followed up by clinical consultation and echocardiography in the outpatient clinics of the 2 tertiary centres. The others were followed up in public hospitals or private practices by referring cardiologists working together with the tertiary centres. Information on follow-up was retrospectively obtained. Events were ascertained by direct patient interview and clinical examination and/or by repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. Medical reports and death certificates were consulted for attribution of causes of death. The main outcome measure of interest was overall mortality after diagnosis, starting at baseline echocardiography, regardless whether there was AVR. Overall mortality was also analyzed in the subgroup of patients not undergoing AVR during the first 3 months after baseline echocardiography (conservatively managed group). In this case, the follow-up time during which events were collected for this end point was between diagnosis and either AVR (if performed) or last follow-up. Clinical decisions on medical management and referral for surgery were made by the heart team with the approval of the patient's cardiologist, in accordance with practice guidelines.

Statistical Analysis

Quantitative data are presented as mean±SD or median (25th–75th percentile). Qualitative data are presented as absolute numbers and percentages. Pearson coefficient correlations were used to evaluate the relationship between AT, ET, AT/ET, and heart rate. Patients

were stratified by AT/ET >0.35 or ≤0.35, according to the threshold identified with the use of maximally selected rank statistics. Maximally selected rank statistics allow the estimation or evaluation of a simple cut point that provides the classification of observations into 2 groups (ie, distinction of a low- and a high-risk group in survival studies) by a continuous or ordinal predictor variable (herein, AT/ET). To this effect, the maxstat.test() function from the maxstat R package 0.7-25 was used (pmethod="HL", smethod="LogRank").[16] The Pearson χ^2 statistic or Fisher exact test was used to examine the associations between the 2 groups and baseline categorical variables. Individual differences for continuous variables were compared using Mann-Whitney *U* tests. The intraclass correlation was used to express GLS variability between the 2 software platforms used, with the same observer performing the analysis with at least a 6-month delay between the 2 analyses (GE EchoPac and Tomtec LV Autostrain). The intraclass correlation coefficient estimates and their 95% CIs were calculated on the basis of a single rater/measurement, absolute-agreement, 2-way fixed-effects model. Event rates of the overall population and of the 2 groups were estimated according to the Kaplan-Meier method and compared with 2-sided log-rank tests. Median follow-up time was obtained using the reverse Kaplan-Meier method. Univariate and multivariable analyses of time to events were performed using Cox proportional-hazards models. Models were fit using the coxph() function from the survival R package 3.2-13.[17] Penalized smoothing splines were used to illustrate the association of AT/ET and the risk for mortality during follow-up. We did not use model building techniques; covariates were entered in the models that were considered of potential prognostic impact on an epidemiologic basis. Models were adjusted for age, sex, Charlson comorbidity index (not including age), systolic blood pressure (SBP), history of AF, LVEF, Vmax, LV-SVi, and AVR. No multiple imputation was performed for multivariable model building process because of the low number of missing data for these covariates (<2.5%). The effect of AVR on outcome was analyzed as a time-dependent covariate using the entire follow-up.[18] The proportional hazards assumption was confirmed using statistics and graphs based on the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. To verify the stability of the results, and any biases generated by overfitting, the Harrell C-statistics evaluating the adequacy of risk prediction for the multivariable models and the hazard ratio (HR) coefficients with their 95% CIs for AT/ET >0.35 were estimated by the bootstrapping technique with 1000 samples (boot package 1.3-28 in R).[19] The Harrell C-statistics were also calculated for the multivariable models using the k-fold cross-validation technique (k=5, 100 iterations), which lead to an estimate less sensitive to overfitting. To assess the incremental prognostic value of AT/ET over clinical and echocardiographic parameters known of prognostic importance in asymptomatic SAS, nested regression models were constructed and changes in χ^2 value were calculated. Integrated discrimination improvement and net reclassification improvement were determined to further describe the added utility of AT/ET when added to the multivariable models. Integrated discrimination improvement measures the new model's ability to improve integrated sensitivity without compromising integrated specificity. Net reclassification improvement measures the appropriateness of patient reclassification on the basis of the probability of death at selected time points. Net reclassification improvement and integrated discrimination improvement were computed at 36 months using the R package survIDINRI 1.1-1.[20]

We aimed also at identifying if there was a difference in the prognostic value of AT/ET ≤0.35 or >0.35 in prespecified subgroups of patients (aged >80 or ≤80 years, sex status, body surface area >1.80 m^2 or ≤1.80 m^2, New York Heart Association functional class I versus II, history of AF versus no history of AF, documented coronary artery disease versus no documented coronary artery disease, Vmax ≥5 m/s versus <5 m/s, MPG ≥50 mm Hg versus <50 mm Hg, AVA ≥0.75 cm^2 versus <0.75 cm^2, LVEF >60% versus ≤60%, LV-SVi >35 mL/m^2 versus ≤35 mL/m^2, and LV hypertrophy versus no LV hypertrophy). Hence, a first-order interaction term (between AT/ET ≤0.35 or >0.35 and categories of subgroups, corresponding to the product of these 2 variables) was systematically included in a Cox multivariable model including AT/ET ≤0.35 or >0.35 and the categories of each subgroup of patients in the whole cohort of patients. A significant interaction was considered in case of a *P* value for the interaction variable <0.05. Univariable Cox models testing the impact of AT/ET ≤0.35 or >0.35 on mortality were obtained thereafter in each category of the subgroups of patients. Sensitivity analysis was also conducted in a propensity-matched sample to compare the occurrence of mortality during follow-up between patients with AT/ET >0.35 and ≤0.35. Propensity matching was performed on the basis of 1-to-1 nearest neighbor matching with a greedy matching algorithm and a caliper width of 0.2 (Matchit package 4.2.0 in R).[21] The following covariates were used to assign the propensity score: age, sex, Charlson comorbidity index (not including age), SBP, history of AF, New York Heart Association functional class, LVEF, Vmax, LV-SVi, AVA, and LV mass index. Standardized mean differences before and after matching were estimated to assess the quality of the propensity score matching procedure. Standardized mean differences <0.2

after matching were considered as indicators of adequate balance and thus sufficient bias reduction. The quality of the matching was visually assessed by the distribution of propensity scores (jitter plot of the distance measure, QQ plots, and histograms of propensity score density for observations before and after matching). To account for the matching, we used a Cox model with a random effect for the matched pairs (shared frailty model, using a γ distribution). All *P* values are the results of 2-tailed tests. For all analyses, $P<0.05$ was considered statistically significant. Data were analyzed with R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), GraphPad Prism (GraphPad Software, La Jolla, CA), and SPSS version 20.0 (IBM, Armonk, NY).

RESULTS

Study Population

A total of 353 patients (women, 46%; median age, 79 years) were included in the present study. Their baseline characteristics are depicted in Table 1. Median AT/ET was 0.35 (25th–75th percentile, 0.32–0.39). A total of 139 (39%) patients used β blockers at time of examination. No differences were observed for use of β blockers between patients with AT/ET >0.35 versus ≤0.35 ($P=0.453$). ET was longer for patients using β blockers (320 [288–345] versus 300 [281–323] ms; $P=0.001$). However, AT (110 [96–123] versus 104 [93–120] ms; $P=0.108$) and AT/ET (0.35 [0.31–0.39] versus 0.35 [0.32–0.39]; $P=0.586$) were similar for patients under β blockers or not. An inverse linear relationship was observed between AT or ET and heart rate ($r=-0.19$ [$P<0.001$] and $r=-0.32$ [$P<0.001$], respectively). In contrast, no relationship was found between AT/ET and heart rate ($r=0.06$; $P=0.284$). AT/ET was slightly higher in women, but this difference did not reach statistical significance (0.36 [0.32–0.39] versus 0.35 [0.31–0.38]; $P=0.072$). Patients with low flow exhibit lower ET than those with normal flow (290 [262–302] ms versus 309 [285–334] ms; $P=0.001$). Patients were stratified by AT/ET ≤0.35 or >0.35. The differences in AT/ET between these 2 groups were driven by AT ($P<0.001$), whereas distribution of ET was similar ($P=0.647$; Figure S1). Briefly, patients with AT/ET >0.35 had similar demographic and clinical characteristics than patients with AT/ET ≤0.35, except for a lower SBP. For echocardiographic parameters, patients with AT/ET >0.35 shared features of more severe AS compared with other patients, with lower AVA, AVA indexed to body surface area, and dimensionless index and higher MPG and Vmax. Significant, but weak, positive linear relationships were observed between AT/ET and transaortic mean gradient or Vmax ($r=0.30$ [$P<0.001$] and $r=0.22$ [$P<0.001$], respectively). Last, patients with AT/ET >0.35 had higher LV mass and lower LV ejection fraction and GLS magnitude.

Clinical Management and Follow-Up

Median follow-up time was 39 (25th–75th percentile, 23–62) months. Overall mortality at 36 months was 19%. Among the 238 patients (67%) who underwent AVR, 31 had at least one associated coronary artery bypass graft at the time of surgery. A total of 154 (65%) patients underwent surgical AVR and 84 (35%) patients underwent transcatheter AVR (Table S1). Seventy patients (20%) died during the entire follow-up, 52 (74%) before AVR and 18 (26%) after AVR.

Outcome With Conservative and/or Surgical Management

On univariate analysis, AT/ET as a continuous variable (per increment of 0.01) was associated with increased risk of mortality (HR, 1.06; 95% CI, 1.06–1.11; $P=0.018$). In contrast, no relationship was found between AT or ET (per increment of 10 ms) taken aside and mortality risk (HR, 1.08; 95% CI, 0.97–1.21; $P=0.158$; and HR, 1.01; 95% CI, 0.96–1.07; $P=0.698$). The shape of the relationship between AT/ET as a continuous variable and risk for mortality during follow-up was estimated using spline functions for AT/ET (Figure 2). Optimal cut point of AT/ET for predicting mortality was obtained by the use of maximally selected rank statistics method (Figure 3). By statistical coincidence, the optimal threshold was observed at 0.35, which corresponded to the median value of AT/ET in this study population. The primary end point occurred during the entire follow-up in 26 patients (14%) with AT/ET ≤0.35 and 44 patients (26%) with AT/ET >0.35. Twenty-six percent of deaths (n=18) occurred during follow-up of patients who had undergone AVR. Among the 52 patients who died before AVR, 33 (63%) had AT/ET >0.35. The 1-, 2-, and 3-year overall mortality rates under medical and/or surgical management were 6%, 11%, and 12% for patients with AT/ET ≤0.35 and 11%, 17%, and 25% when AT/ET >0.35, respectively ($P=0.009$; Figure 4A). On multivariable analysis, AT/ET >0.35 was strongly associated with an increased risk of mortality compared with ≤0.35 (adjusted HR, 2.34; 95% CI, 1.36–4.03; $P=0.002$). After adjustment for AVR treated as a time-dependent covariate, patients with AT/ET >0.35 were at increased risk of death compared with those with AT/ET ≤0.35 (adjusted HR, 2.54; 95% CI, 1.47–4.37; $P<0.001$; Figure 4B and Table 2). The performance of the multivariable models was verified by bootstrap resampling and 5-fold cross-validation (Table S2). When Vmax was replaced by MPG in the fully adjusted multivariable model, AT/ET >0.35 was still associated with increased mortality risk (adjusted HR, 2.58; 95% CI, 1.49–4.46; $P<0.001$). When LV-SVi was replaced by

Table 1. Demographic, Clinical, and Echocardiographic Parameters, Overall and According to AT/ET ≤0.35 and >0.35

Variable	All (N=353)	AT/ET ≤0.35 (n=183)	AT/ET >0.35 (n=170)	Overall *P* value
Demographic and clinical characteristics				
Age, y	79 (71 to 85)	77 (68 to 84)	78 (70 to 84)	0.665
Female sex, n (%)	163 (46)	80 (44)	83 (49)	0.393
Body surface area, m^2	1.86 (1.72 to 2.00)	1.87 (1.69 to 2.00)	1.86 (1.73 to 2.00)	0.628
BMI, kg/m^2	27.1 (23.9 to 31.2)	27.0 (23.9 to 30.8)	27.3 (23.9 to 32.1)	0.274
SBP, mm Hg	140 (126 to 151)	140 (130 to 156)	138 (120 to 150)	0.002
DBP, mm Hg	73 (65 to 80)	72 (64 to 80)	75 (67 to 80)	0.536
Heart rate, bpm	75 (66 to 84)	75 (66 to 84)	74 (66 to 84)	0.965
Hypertension, n (%)	263 (74.5)	149 (81)	114 (67)	0.003
Diabetes, n (%)	107 (30)	59 (32)	48 (28)	0.483
Documented CAD, n (%)	124 (35)	69 (38)	55 (32)	0.347
History of AF, n (%)	86 (24)	50 (27)	36 (21)	0.222
Use of β blockers, n (%)	139 (39)	76 (41)	63 (37)	0.453
Charlson comorbidity index	1 (0 to 3)	1 (0 to 3)	1 (0 to 3)	0.573
NYHA functional class I, n (%)	147 (42)	84 (46)	63 (37)	0.115
Echocardiographic parameters				
Aortic valve				
AVA, cm^2	0.76 (0.63 to 0.87)	0.77 (0.67 to 0.90)	0.74 (0.58 to 0.85)	0.005
AVAi, cm^2/m^2	0.41 (0.34 to 0.47)	0.43 (0.37 to 0.48)	0.39 (0.32 to 0.45)	<0.001
Peak aortic jet velocity, m/s	4.40 (4.18 to 4.80)	4.35 (4.11 to 4.60)	4.50 (4.20 to 5.00)	0.001
Mean pressure gradient, mm Hg	49 (44 to 58)	46 (42 to 52)	53 (45 to 64)	<0.001
Dimensionless index	0.20 (0.17 to 0.24)	0.22 (0.19 to 0.24)	0.19 (0.16 to 0.22)	<0.001
Acceleration time, ms	107 (93 to 122)	96 (83 to 108)	120 (109 to 130)	<0.001
Ejection time, ms	305 (283 to 332)	304 (277 to 332)	306 (287 to 333)	0.647
AT/ET	0.35 (0.32 to 0.39)	0.32 (0.30 to 0.34)	0.39 (0.37 to 0.42)	By design
Other parameters				
AF during TTE, n (%)	31 (9)	19 (10)	12 (7)	0.361
LVEDD, mm	48 (43 to 52)	47 (43 to 52)	48 (43 to 54)	0.361
LVESD, mm	29 (26 to 34)	29 (25.5 to 33)	30 (26 to 35)	0.114
LV-SV, mL	80 (66 to 93)	80 (68 to 91)	79 (65 to 95)	0.508
LV-SVi, mL/m^2	43 (37 to 50)	44 (39 to 50)	42 (35 to 49)	0.082
LV ejection fraction, %	63 (60 to 68)	64 (60 to 68.5)	63 (59 to 66)	0.020
Flow rate, mL/s	260 (221 to 311)	262 (226 to 312)	256 (212 to 302)	0.182
GLS, % (N=244)	–14.9 (–17.2 to –12)	–15.5 (–18 to –12.9)	–14.5 (–16.6 to –11)	0.007
RWT	0.51 (0.43 to 0.61)	0.50 (0.42 to 0.59)	0.52 (0.44 to 0.63)	0.062
LVMi, g/m^2	120 (99.2 to 146)	117 (95.4 to 138)	128 (104 to 153)	0.004
LAVi, mL/m^2	41 (33 to 52)	41 (32 to 51)	43 (34 to 54)	0.140
E/A ratio	0.77 (0.63 to 1.01)	0.77 (0.65 to 1.01)	0.77 (0.63 to 1.01)	0.662
E/e' ratio	8.94 (6.50 to 12.9)	9.00 (7.00 to 12.4)	8.50 (5.92 to 13.1)	0.237
PAPs, mm Hg (N=266)	35 (29 to 42)	35 (29 to 41)	34.5 (30 to 42)	0.940
TAPSE	22 (19 to 25)	22 (19 to 26)	21 (18 to 25)	0.129

Continuous variables are presented as median (25th to 75th percentile). Categorical variables are presented as absolute numbers and frequency. A indicates mitral A wave velocity; AF, atrial fibrillation; AT/ET, ratio of acceleration time/ejection time; AVA, aortic valve area; AVAi, AVA indexed to body surface area; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; DBP, diastolic blood pressure; E, mitral E wave velocity; e', early diastolic mitral annular velocity; GLS, global longitudinal strain; LAVi, left atrial volume indexed to body surface area; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; LVMi, LV mass indexed to body surface area; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; SVi, SV indexed to body surface area; TAPSE, tricuspid annular plane systolic excursion; and TTE, transthoracic echocardiography.

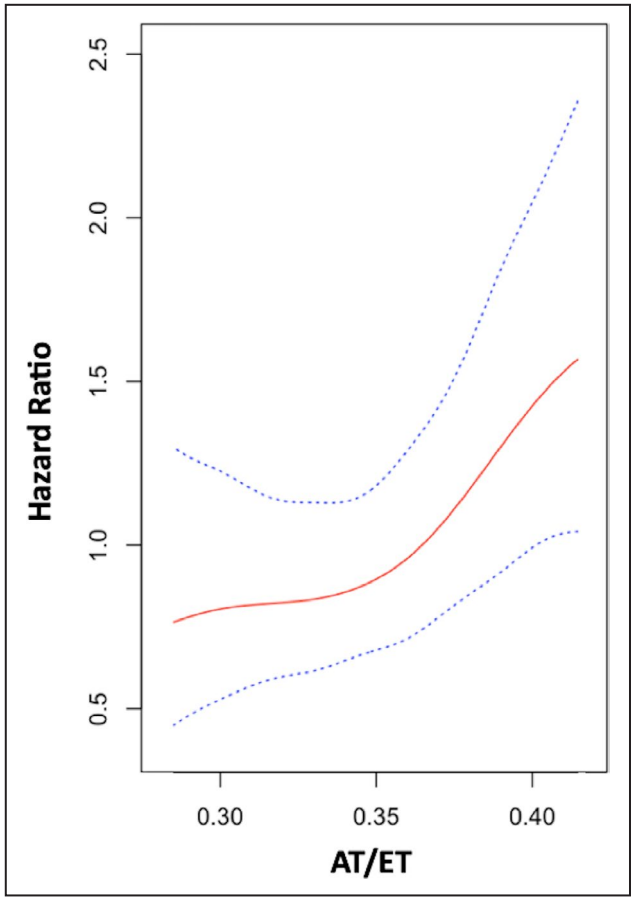

Figure 2. Relationship between ratio of acceleration time/ejection time (AT/ET) and overall mortality during follow-up. Hazard ratios and 95% CIs are estimated in Cox models with AT/ET represented as a spline function.

transaortic flow rate in the fully adjusted multivariable model, patients with AT/ET >0.35 still displayed an increased mortality risk compared with those with AT/ET ≤0.35 (adjusted HR, 2.55; 95% CI, 1.48–4.47; *P*<0.001). After further adjustment for GLS when available, AT/ET >0.35 was associated with increased risk of mortality (adjusted HR, 3.54; 95% CI, 1.67–7.49; *P*<0.001). When analysis was restricted to patients in sinus rhythm at time of examination (n=322), those with AT/ET >0.35 still displayed an increased mortality risk compared with those with AT/ET ≤0.35 (adjusted HR, 2.33; 95% CI, 1.31–4.15; *P*=0.004).

Outcome With Conservative Management

Median follow-up time under conservative management was 17 (25th–75th percentile, 7–37) months. Cumulative 1-, 2-, and 3-year overall mortality rates were 10%, 15%, and 20% for patients with AT/ET ≤0.35 and 16%, 31%, and 53% for patients with AT/ET >0.35, respectively (*P*=0.001; Figure 5A). On multivariable analysis, after adjustment for age, sex, Charlson comorbidity index, SBP, history of AF, LVEF, Vmax, and LV-SVi, patients with AT/ET >0.35 exhibited a significantly greater risk of death compared with patients with AT/ET ≤0.35 (adjusted HR, 3.29; 95% CI, 1.70–6.39; *P*<0.001; Figure 5B and Table 2). After further adjustment for GLS when available, AT/ET >0.35 remained strongly associated with an increased risk of mortality (adjusted HR, 4.30; 95% CI, 1.79–10.32; *P*=0.001).

Incremental Prognostic Value of AT/ET

As shown in Table 3, at 36 months, the addition of AT/ET >0.35 in contrast with AT/ET as a continuous variable (per increment of 0.01) to the multivariable models resulted in significant systematic improvement of 2 log-likelihood χ^2, continuous net reclassification improvement, and integrated discrimination index when survival was considered either on medical or medical and/or surgical management, thereby demonstrating the incremental prognostic value of AT/ET >0.35 in this study population over established predictors of outcome in SAS.

Subgroup Analyses

Overall, the increased risk of mortality in patients with AT/ET >0.35 was consistent in subgroups of patients with high-gradient SAS and no or mild symptoms (Figure 6). No significant interaction was found between AT/ET >0.35 and any of the subgroups.

Outcome Impact of AT/ET in the Propensity-Matched Cohort

The baseline characteristics of covariates used for propensity matching before and after matching are shown in Table 4. Between-group balance was obtained for all matched covariates. A total of 117 patients with AT/ET >0.35 were matched to 117 patients with AT/ET ≤0.35. Median (25th–75th percentile) AT/ET was 0.32 (0.30–0.34) in patients with AT/ET ≤0.35 and 0.39 (0.37–0.40) in patients with AT/ET >0.35. Patients with AT/ET >0.35 displayed an increased mortality risk compared with those with AT/ET ≤0.35 (HR, 2.21; 95% CI, 1.16–4.20; *P*=0.016). After adjustment for AVR as a time-dependent covariate in this propensity-matched sample, AT/ET >0.35 still was associated with increased risk of mortality (adjusted HR, 2.10; 95% CI, 1.12–3.90; *P*<0.001).

DISCUSSION

The present study, based on a cohort of patients with high-gradient SAS, preserved LVEF, and no or only mild symptoms, provides strong evidence of the relationship between overall mortality and baseline AT/ET assessed by Doppler-echocardiography. Our results show that the effect of AT/ET on mortality is powerful

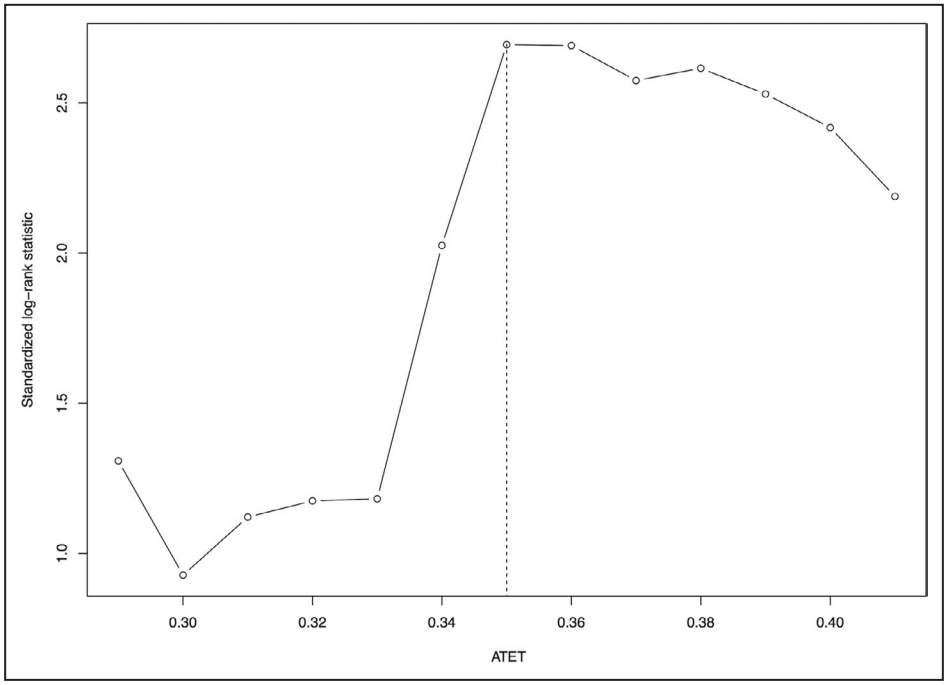

Figure 3. Determination of the optimal ratio of acceleration time/ejection time (AT/ET) threshold for mortality using the maximally selected rank statistics.
The dashed line demarcates the optimal AT/ET threshold: 0.35.

and remains valid after adjustment for factors known as major determinants of outcome, such as age, comorbidity, SBP, LV ejection fraction, flow assessed by LV-SVi, Vmax, and AVR, during follow-up. We observed that AT/ET above the 0.35 cutoff is associated with a 2.5-fold increase in the risk of death during the entire follow-up (medical and/or surgical management) and with a 3.29-fold increased risk of death when survival under medical management was specifically considered. More important, AT/ET provided incremental prognostic information over established predictors of outcome in SAS, thereby suggesting that in clinical

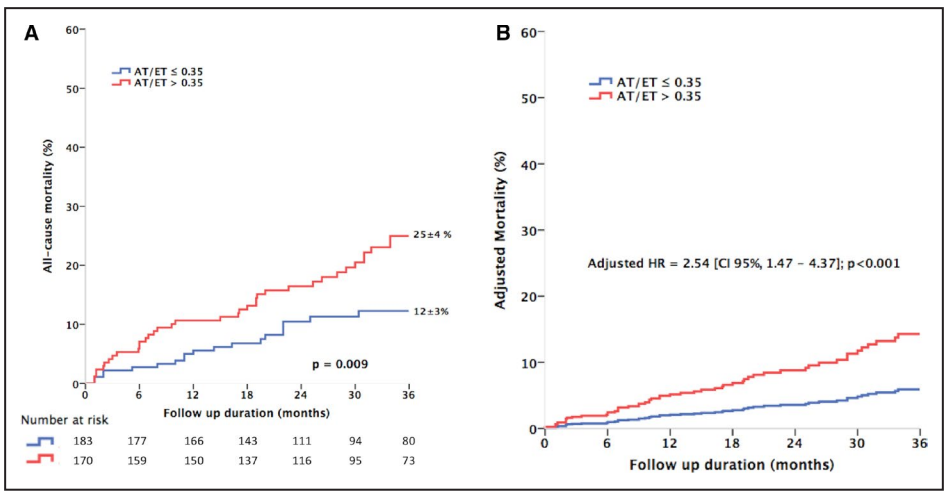

Figure 4. Survival analysis according to ratio of acceleration time/ejection time (AT/ET) ≤0.35 or >0.35 in patients with high-gradient severe aortic stenosis and no or mild symptoms under medical or surgical management (n=353).
A, Kaplan-Meier estimates of overall mortality. **B**, Adjusted mortality. Survival Cox curves are adjusted for age, sex, Charlson comorbidity index (not including age), systolic blood pressure, history of atrial fibrillation, left ventricular ejection fraction, aortic peak jet velocity, left ventricular stroke volume index, and aortic valve replacement as a time-dependent covariate. HR indicates hazard ratio.

Table 2. Relative Risk of All-Cause Mortality, According to AT/ET

Variable	All-cause mortality		
Outcome under conservative management		HR (95% CI)	*P* value
	Univariate analysis		
	AT/ET per increment of 0.01	1.09 (1.04–1.16)	<0.001
	AT/ET ≤0.35	Reference	
	AT/ET >0.35	2.44 (1.39–4.29)	<0.001
	Multivariable model (n=230)*		
	AT/ET per increment of 0.01	1.11 (1.04–1.18)	0.002
	AT/ET ≤0.35	Reference	
	AT/ET >0.35	3.29 (1.70–6.39)	<0.001
Outcome under medical and/or surgical management		Adjusted HR (95% CI)	*P* value
	Univariate analysis		
	AT/ET per increment of 0.01	1.06 (1.01–1.11)	0.018
	AT/ET ≤0.35	Reference	
	AT/ET >0.35	1.89 (1.16–3.08)	0.010
	Multivariable model without AVR (n=347)*		
	AT/ET per increment of 0.01	1.08 (1.02–1.14)	0.009
	AT/ET ≤0.35	Reference	
	AT/ET >0.35	2.34 (1.36–4.03)	0.002
	Multivariable model with AVR (n=347)†		
	AT/ET per increment of 0.01	1.09 (1.03–1.15)	0.004
	AT/ET ≤0.35	Reference	
	AT/ET >0.35	2.54 (1.47–4.37)	<0.001

AT/ET indicates ratio of acceleration time/ejection time; AVR, aortic valve replacement; and HR, hazard ratio.

*Multivariable model is adjusted for age, sex, systolic blood pressure, Charlson comorbidity index (without including age), history of atrial fibrillation, peak aortic jet velocity, left ventricular stroke volume index, and left ventricular ejection fraction.

†Model is adjusted for covariates included in the model without AVR and AVR as time-dependent covariate.

daily practice, assessment of AT/ET should be systematically performed in patients with asymptomatic or minimally symptomatic SAS with preserved LVEF and taken into consideration for decision purposes (Figure 7).[22–27]

The concept of delayed aortic AT associated with worsening AS severity is not new.[28,29] Indeed, previous landmark reports have observed a good correlation between AT/ET and invasive measurement of transaortic pressure gradients.[30,31] Rapid early-systolic opening of the normal aortic valve on Doppler spectrograms is replaced by a slow end-systolic opening of the stenotic aortic valve.[32] Alongside with this, although LV ET usually increases when AS is present, it may normalize in patients presenting with LV dysfunction or low flow.[33–36] Accordingly, guidelines already suggest that the aortic waveform shape could be useful to assess severity of native AS.[37] Calculation of AT/ET ratio provides reproducible quantification of this well-known phenomenon. Moreover, the AT/ET ratio, in contrast to AT or ET taken aside, is not influenced by heart rate. We previously reported an association between AT/ET ratio >0.34 and SAS in a large multicenter cohort of patients with mild to severe AS.[7] However, the reported correlations between AT/ET and parameters of AS severity, such as transvalvular gradient or AVA, obtained by Doppler echocardiography were only moderate. Accordingly, weak positive correlations were observed between AT/ET and transaortic mean gradient or Vmax in the present study. Indeed, the AT/ET ratio is not only associated with AS severity but also with its consequences on the LV. In a multicenter study involving 1107 patients with AS, decreased LVEF, decreased LV-SVi, increased LV mass index and relative wall thickness were independently associated with an increased AT/ET ratio.[7] On the basis of data from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, Einarsen et al similarly reported an independent relationship between higher AT/ET ratio and determinants of LV morphology and function, as mentioned above.[12] In the present study population, patients with greater AT/ET actually displayed lower LV ejection fraction or GLS magnitude. In a similar way, an inverse relationship between SBP and AT/ET has been previously reported.[7] In the presence of arterial stiffness, reflected waves display greater magnitude and higher propagation speed, thereby arriving earlier at the LV outflow tract than those with compliant aorta. This may lead to shorten AT because of early aortic flow deceleration. Furthermore, the increase in afterload associated with higher SBP is likely to induce compensatory lengthening of systolic ET, thereby reducing the AT/ET ratio. These potential confounding factors may explain why, for a given transaortic mean gradient, the AT/ET ratio can significantly differ from one patient to another. Herein, a wide range for AT/ET values was actually observed, despite the relatively similar phenotype of the patients from the present report with high-gradient SAS. In other words, a large number of patients diagnosed with high-gradient SAS can anyway present with short AT/ET. Thus, the question of whether patients with longer AT/ET ratios could share worse outcome compared with those with shorter ones may be raised.

To date, the clinical implications of AT/ET in the setting of native AS have been investigated only in patients presenting with discordant grading (ie, with low-gradient AS despite a narrow stenotic orifice)[10,12] or in heterogeneous study populations mixing moderate and severe AS regardless of their symptomatic status.[9,12] The present study builds on previous literature by focusing on the specific population of high-gradient

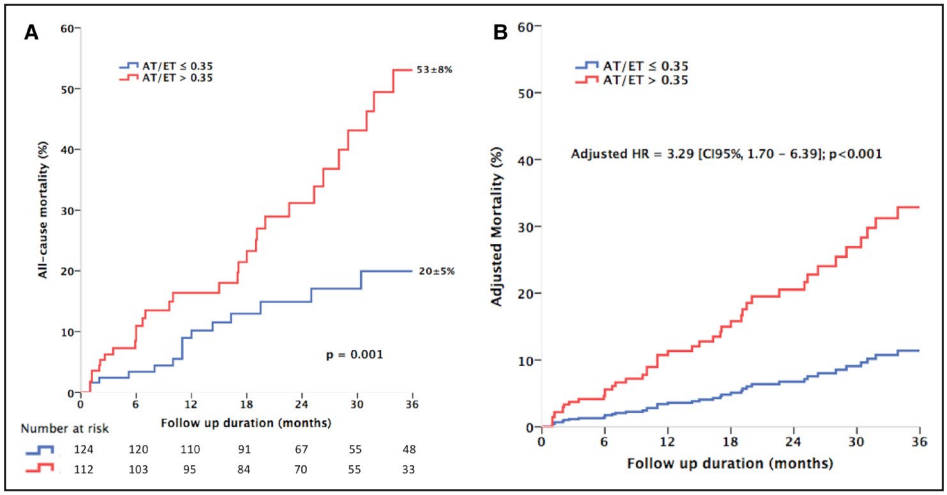

Figure 5. Survival analysis according to ratio of acceleration time/ejection time (AT/ET) ≤0.35 or >0.35 in patients with high-gradient severe aortic stenosis and no or mild symptoms under conservative management (n=236).
A, Kaplan-Meier estimates of overall mortality. **B**, Adjusted mortality. Survival Cox curves are adjusted for age, sex, Charlson comorbidity index (not including age), systolic blood pressure, history of atrial fibrillation, left ventricular ejection fraction, aortic peak jet velocity, and left ventricular stroke volume index. HR indicates hazard ratio.

SAS with no or only mild symptoms.[12] The results of this report expand previous findings by demonstrating, in these challenging high-risk patients, an incremental prognostic value of AT/ET over known features strongly linked with adverse outcome in SAS in both multivariable and propensity-matched analyses. More important, the relationship between increased AT/ET and mortality remained significant even after adjustment for LV ejection fraction, flow, SBP, or GLS, all previously suggested as potential confounders for AT/ET, thereby strengthening the clinical significance of this parameter. The finding that baseline AT/ET predicts mortality independently from AVR if LV function is preserved may be questioning. Multiple intricate factors account for AT/ET values in patients with preserved LVEF, including LV remodeling and function, AS severity, and SBP. Hence, increased AT/ET identifies patients with SAS and preserved LVEF at a more advanced stage of the disease, thereby explaining that an increased risk of mortality persists for increased AT/ET values, even after adjustment on AVR.

In addition, we did not purposefully use a combined end point associating mortality and valve intervention because the referral for AVR is potentially related to the

Table 3. Predictive Value, Discrimination, and Reclassification of the Cox Multivariable Models With and Without AT/ET on Overall Mortality

Overall mortality	Models	Log-likelihood χ^2	*P* value	Continuous NRI	*P* value	Integrated discrimination index	*P* value
Outcome under conservative management (n=230)	Multivariable model	49.25		Reference		Reference	
	+AT/ET >0.35	62.69	<0.001	0.35	0.033	0.09	0.013
	+AT/ET per increment of 0.01	59.31	0.001	0.30	0.106	0.07	0.033
Outcome under medical and/or surgical management (n=347)	Multivariable model without AVR*	90.7		Reference		Reference	
	+AT/ET >0.35	100.5	0.002	0.20	0.027	0.03	0.040
	+AT/ET per increment of 0.01	97.57	0.009	0.12	0.326	0.02	0.086
	Multivariable model with AVR†	108		Reference		Reference	
	+AT/ET >0.35	120	<0.001	0.23	<0.001	0.04	0.020
	+AT/ET per increment of 0.01	116.6	0.003	0.23	0.126	0.03	0.053

AT/ET indicates ratio of acceleration time/ejection time; AVR, aortic valve replacement; and NRI, net reclassification improvement.
*Multivariable model is adjusted for age, sex, systolic blood pressure, Charlson comorbidity index (without including age), history of atrial fibrillation, peak aortic jet velocity, left ventricular stroke volume index, and left ventricular ejection fraction.
†Model is adjusted for covariates included in the model without AVR and AVR as time-dependent covariate.

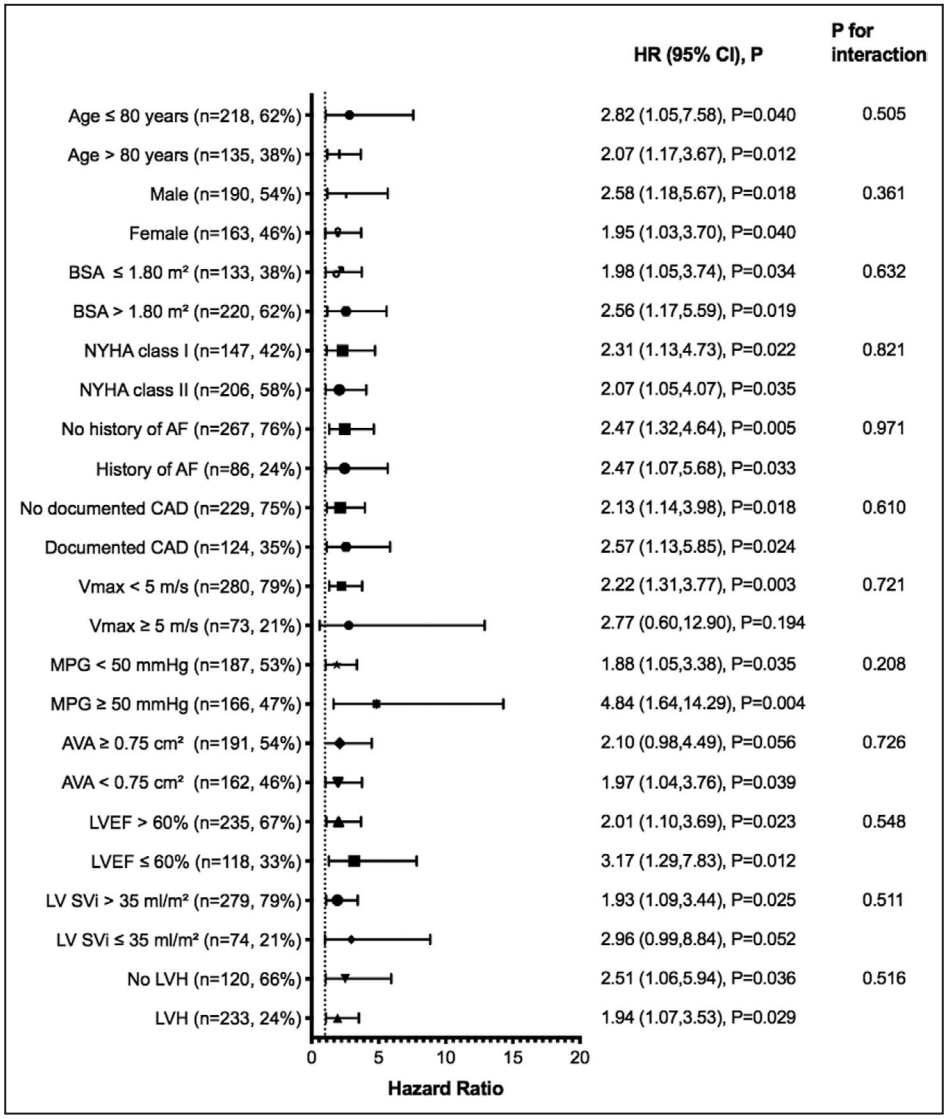

Figure 6. Hazard ratio (HR) and 95% CI for risk of overall mortality associated with ratio of acceleration time/ejection time ≤0.35 or >0.35 in subgroups of patients with high-gradient severe aortic stenosis and no or mild symptoms.

AF indicates atrial fibrillation; AVA, aortic valve area; BSA, body surface area; CAD, coronary artery disease; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; MPG, mean aortic pressure gradient; NYHA, New York Heart Association; SVi, stroke volume index; and Vmax, aortic peak jet velocity.

personal physician's assessment of disease severity and consequences. Thus, the present data provide a clear prognostic cutoff value for AT/ET (>0.35) associated with overall mortality. Indeed, previous reports have suggested different cutoffs for AT/ET (0.32–0.37) as these study populations involved displayed significant differences (inclusion of patients with mild, moderate, and/or discordant grading AS). Of note, an optimal cutoff for AT/ET of 0.35 was found to identify patients with SAS in a previous independent study.[11] Hence, we suggest herein that a unique 0.35 threshold may be useful in daily clinical cardiology practice in asymptomatic SAS.

This study has limitations. First, although echocardiograms were prospectively collected, follow-up was retrospectively obtained. The specific indications for AVR during follow-up were not recorded in our database. However, diagnosis and follow-up were performed by cardiologists with expertise in valvular heart disease, and surgical decisions were taken by the heart team with the approval of the patient's physician in accordance with current practice guidelines. Serum biomarkers were not routinely assessed in this patient population. The present study includes a "real-world" population of patients with SAS and no

Table 4. Baseline Characteristics, According to AT/ET >0.35 and ≤0.35, Before and After Propensity Score Matching

Covariates	Entire cohort			Matched cohort		
	AT/ET ≤0.35 (N=183)	AT/ET >0.35 (N=170)	SMD	AT/ET ≤0.35 (N=117)	AT/ET >0.35 (N=117)	SMD
Age, y	76±11	76±11	0.025	75±11	75±12	0.057
Women, n (%)	80 (44)	83 (49)	0.103	59 (50)	51 (44)	0.068
Charlson comorbidity index	1.6±1.9	1.7±1.6	0.014	1.8±2	1.7±1.6	0.047
History of AF	50 (27)	36 (21)	0.144	34 (29)	28 (24)	0.051
Systolic blood pressure, mm Hg	143±21	136±19	0.360	140±19	140±17	0.054
NYHA class I	84 (46)	63 (37)	0.180	50 (43)	50 (43)	<0.001
Peak aortic jet velocity, m/s	4.46±0.44	4.64±0.52	0.375	4.52±0.48	4.55±0.46	0.049
Aortic valve area, cm^2	0.78±0.17	0.73±0.19	0.289	0.76±0.17	0.76±0.20	0.024
LV ejection fraction, %	64±7	63±6	0.260	63±6	63±6	0.028
LV SVi, ml/m^2	45±10	43±10	0.140	44±10	44±12	0.031
LV mass index, g/m^2	118±36	131±40	0.327	123±37	130±38	0.17

SMDs are reported for the entire cohort and the matched cohort. SMDs <0.2 after matching were considered as indicators of adequate balance and thus sufficient bias reduction. Continuous variables are presented as mean±SD. Categorical variables are presented as absolute numbers and frequency. AF indicates atrial fibrillation; AT/ET, ratio of acceleration time/ejection time; LV, left ventricular; NYHA, New York Heart Association; SMD, standardized mean difference; and SVi, stroke volume indexed to body surface area.

or mild symptoms, in whom exercise testing was not systematically performed. Hence, we cannot assess if baseline AT/ET correlated with exercise tolerance. However, patients with SAS, especially those with older ages, often present with comorbidities, impaired physical mobility, or self-restrictions in their

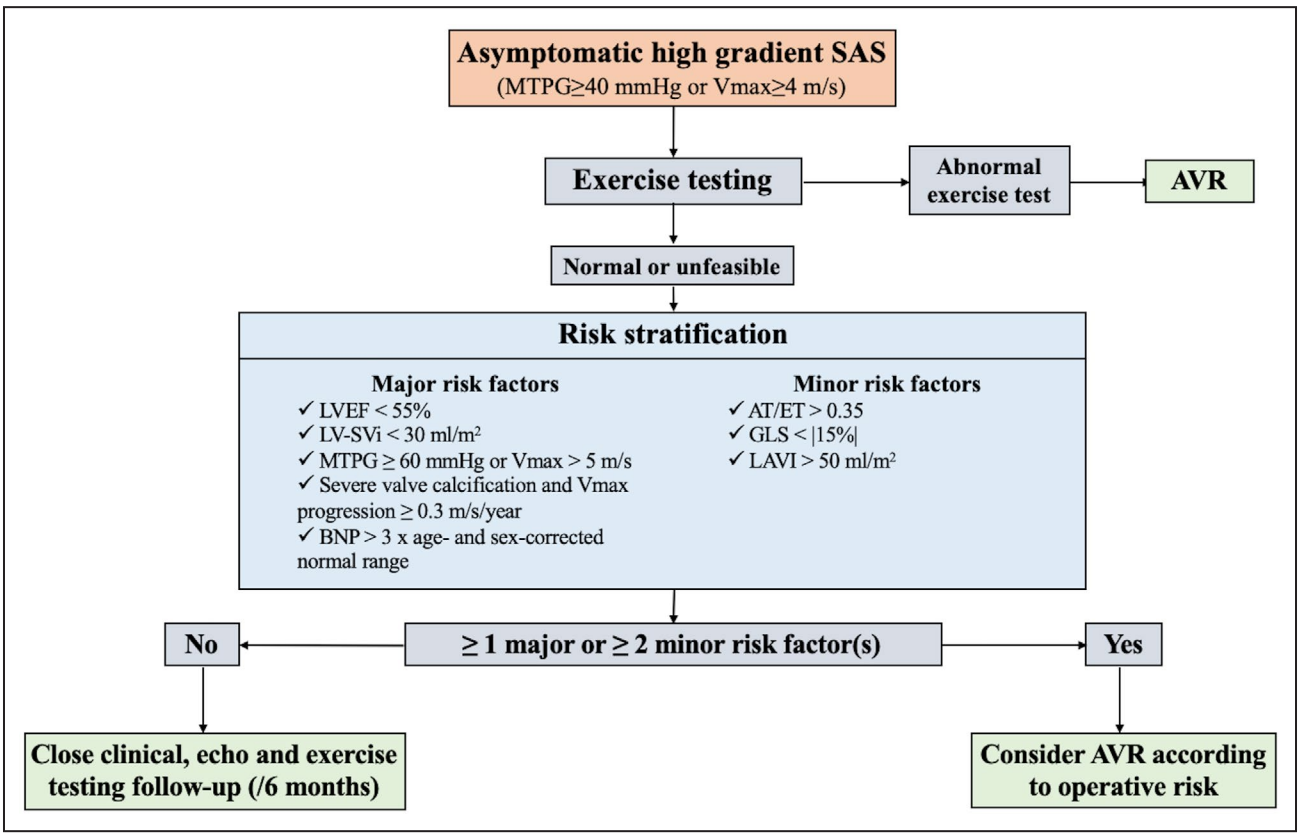

Figure 7. Proposed algorithm for the management of patients with high-gradient asymptomatic severe aortic stenosis (SAS). AT/ET indicates ratio of acceleration time/ejection time; AVR, aortic valve replacement; BNP, brain natriuretic peptide[22]; echo, echocardiographic; GLS, global longitudinal strain[4]; LAVI, left atrial volume index[26]; LV-SVi, left ventricular stroke volume index[5]; LVEF, left ventricular ejection fraction[23]; MTPG, mean transaortic pressure gradient[25]; severe valve calcification and aortic peak jet velocity (Vmax) progression, >0.3 m/s per year[24]; and Vmax, aortic peak jet velocity.[27]

daily activities. In such patients, exercise testing may not be feasible or may lack specificity.[38,39] Cardiac magnetic resonance imaging was not available in the vast majority of the study population. Hence, we cannot provide data on LV myocardial fibrosis. The results of this study cannot apply in patients with AF at time of echocardiography because of the small sample size of this subset of patients (n=31). We used propensity-matching analysis to strengthen the results of the present report. This analysis allows finding the similarity between patients on every observable characteristic included in the propensity score, given they were presenting with AT/ET >0.35 or ≤0.35. Therefore, propensity scoring ensures that the distribution of characteristics constituting the score, known as both predictors of outcome in SAS and possible modifying factors of AT/ET, was equivalent for the 2 groups of patients. However, propensity-matching analysis only accounts for identified covariates (those included in the score).[40] Hence, some imbalances may have remained between the 2 groups because of some unreported confounders associated with AT/ET >0.35 or ≤0.35. Then, the use of 1:1 nearest-neighbor matching algorithm allowed us to reduce selection bias by taking the most similar patient from one group compared with one from the other but leading to a reduced sample size. Even so, a 2.5-fold increased mortality risk for AT/ET >0.35 was observed in the propensity-matched sample, similar to the results in the whole study population, thereby strengthening the validity of this analysis. The data on AT/ET after AVR were not available in our database. The results of the present study cannot apply for patients with LV dysfunction (LVEF <50%) or those with significant valve regurgitation. Whether assessment of AT/ET may be associated with adverse outcome in patients with low-gradient AS and low LVEF needs further research. Finally, future studies should be conducted to externally validate the impact of AT/ET with a threshold value of 0.35 on adverse outcome and determine whether assessment of AT/ET should be integrated in the decision-making process in patients with SAS and preserved LVEF.

CONCLUSIONS

This study, based on a registry of patients with high-gradient SAS, preserved LV ejection fraction, and no or only mild symptoms managed in routine clinical practice, shows that AT/ET is a reliable parameter to predict mortality, with a threshold value of 0.35, beyond established prognostic factors in SAS. Our findings suggest that assessment of AT/ET should be integrated in the decision-making process in patients with SAS and preserved LVEF.

ARTICLE INFORMATION

Received April 1, 2021; accepted October 5, 2021.

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Sources of Funding

None.

Disclosures

None.

Supplementary Material

Tables S1–S2
Figure S1

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Supplemental Material

Table S1. Demographic, clinical and echocardiographic parameters in the subpopulation of patients who underwent aortic valve replacement (SAVR versus TAVR).

Variable	All N = 238	SAVR n = 154	TAVR n = 84	Overall p-value
Demographic and clinical characteristics				
Age, years	75 [67;82]	71 [63;77]	83 [79;87]	**<0.001**
Female sex, n (%)	103 (43)	63 (41)	40 (48)	0.389
Body surface area, m²	1.89 [1.73;2.03]	1.94 [1.81;2.08]	1.81 [1.68;1.92]	**<0.001**
BMI, kg/m²	27.8 [24.4;32]	28.9 [24.9;32.3]	26.9 [23.9;30.1]	**0.012**
SBP, mmHg	140 [128;151]	140 [124;150]	140 [130;151]	0.367
DBP, mmHg	73 [64;80]	75 [63;80]	70 [65;80]	**0.049**
Heart rate, bpm	73 [65;83]	75 [67;84]	70 [61;80]	**0.023**
Hypertension, n (%)	177 (74)	106 (69)	71 (84)	**0.013**
Diabetes mellitus, n (%)	69 (29)	49 (32)	20 (24)	0.249
Documented CAD, n (%)	99 (42)	62 (40)	37 (44)	0.668
History of AF, n (%)	55 (23)	31 (20)	24 (29)	0.188
Use of beta-blockers, n (%)	104 (44)	61 (40)	43 (51)	0.113
Charlson comorbidity index	1 [0;2]	1 [0;2]	2 [0;3]	**0.002**
NYHA functional class I, n (%)	86 (36)	65 (42)	21 (25)	**0.012**
Echocardiographic parameters				
Aortic valve				
AVA, cm²	0.76 [0.65;0.87]	0.76 [0.65;0.90]	0.76 [0.65;0.86]	0.640
AVAi, cm²/m²	0.41 [0.34;0.47]	0.40 [0.34;0.46]	0.43 [0.36;0.47]	0.101
Peak aortic jet velocity, m/sec	4.50 [4.20;4.95]	4.45 [4.20;4.95]	4.50 [4.20;4.93]	0.406
Mean pressure gradient, mm Hg	51 [44;62]	49.5 [43;62]	52 [45;64]	0.456
Dimensionless index	0.20 [0.17;0.24]	0.21 [0.17;0.24]	0.20 [0.18;0.23]	0.592
Acceleration time, ms	110 [95;124]	108 [93;121]	116 [101;130]	**0.016**
Ejection time, ms	309 [286;335]	300 [277;329]	325 [300;350]	**<0.001**
AT/ET	0.35 [0.33;0.39]	0.35 [0.32;0.39]	0.36 [0.33;0.39]	0.548
Other parameters				
AF during TTE	21 (9)	8 (5)	13 (15)	**0.015**
LVEDD, mm	49 [43;54]	48 [43;54]	50 [44;54]	0.406
LVESD, mm	30 [26;34]	29 [26;33]	31 [26;35]	0.158
LV-SV, ml	81 [69;100]	81 [68;95]	83.5 [70;101]	0.294
LV-SVi, ml/m²	44 [37;52]	42 [36;49]	46 [41;55]	**0.002**
LV ejection fraction, %	64 [60;68]	64.5 [60;69]	63 [60;66]	0.139
Flow rate (ml/s)	266 [229;319]	268 [230;329]	261 [229;314]	0.394
GLS, % (N=194)	-15.2 [-17.3;-12.8]	-15.5 [-18;-13.5]	-14.3 [-15.9;-11.1]	**0.013**
RWT	0.48 [0.42;0.59]	0.50 [0.42;0.59]	0.47 [0.40;0.55]	0.222
LVMi, g/m²	125 [104;152]	122 [98.0;148]	134 [112;161]	**0.042**
LAVi, ml/m²	40 [33;51]	39 [30;50]	45 [38;55]	**0.001**
E/A ratio	0.77 [0.64;0.98]	0.78 [0.65;1.00]	0.75 [0.61;0.88]	0.160
E/e' ratio	9 [6.50;13]	8.57 [6.25;11.6]	11.5 [7.65;16.1]	**<0.001**
PAPs, mmHg (N=266)	33 [29;42]	33 [29;38]	36 [30;46]	**0.021**
TAPSE	22 [19;26]	23 [19;26]	21 [18;24.5]	**0.031**

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as absolutes numbers and frequency. AF = atrial fibrillation; AT/ET = ratio of acceleration time to ejection time; AVA = aortic valve area; AVAi = aortic valve area indexed to body surface area; BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; EDD = end diastolic diameter; ESD = end systolic diameter, GLS = global

longitudinal strain; LAVi = left atrial volume indexed to body surface area; LV = left ventricular; PAPs = systolic pulmonary artery pressure; SVi: stroke volume indexed to body surface area; Mi = mass indexed to body surface area; RWT = relative wall thickness; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement, SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography

Table S2. Performance of the multivariable models in the original sample, after bootstrap re-sampling (1000 times) and after cross-validation.

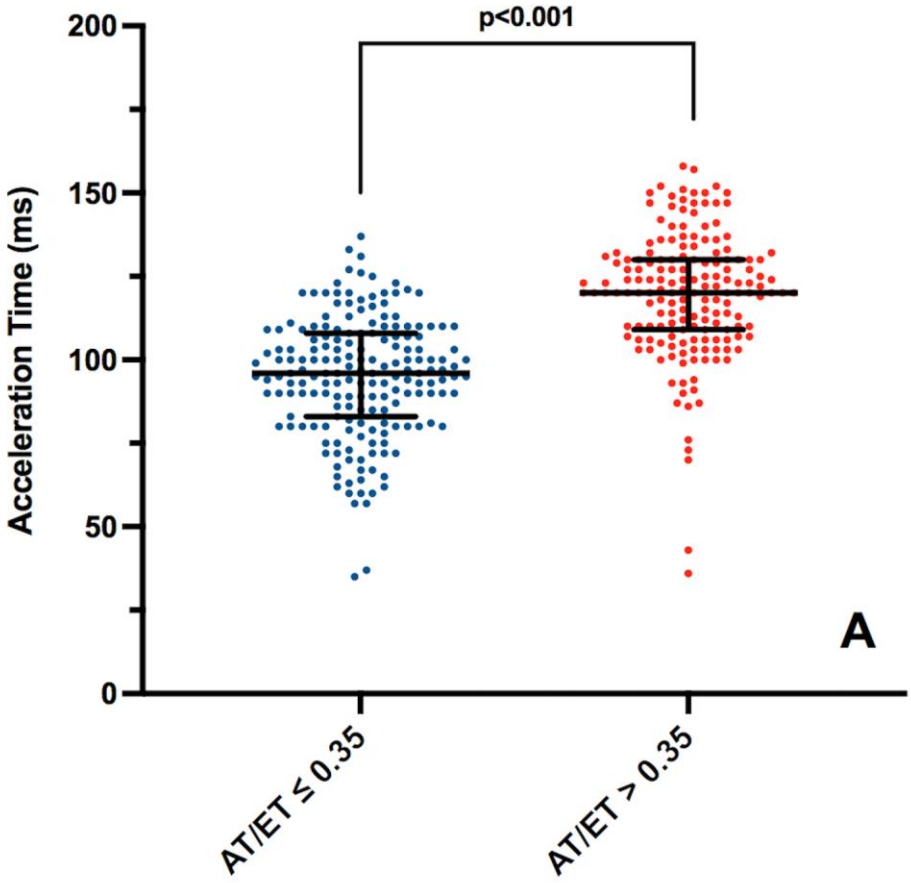
		Multivariable model under medical management* (n=230)	Multivariable model under medical and/or surgical management without AVR* (n=347)	Multivariable model under medical and/or surgical management with AVR† (n=347)
Harrell's C-statistic	**Original sample**	0.81	0.82	0.82
	After bootstrap re-sampling	0.83	0.83	0.84
	After cross-validation	0.77	0.80	0.80
Adjusted HR (CI 95%) for AT/ET > 0.35	**Original sample**	3.29 (1.70,6.39)	2.34 (1.36,4.03)	2.54 (1.47,4.37)
	After bootstrap re-sampling	3.38 (1.55-8.32)	2.32 (1.26-4.28)	2.58 (1.47-4.79)

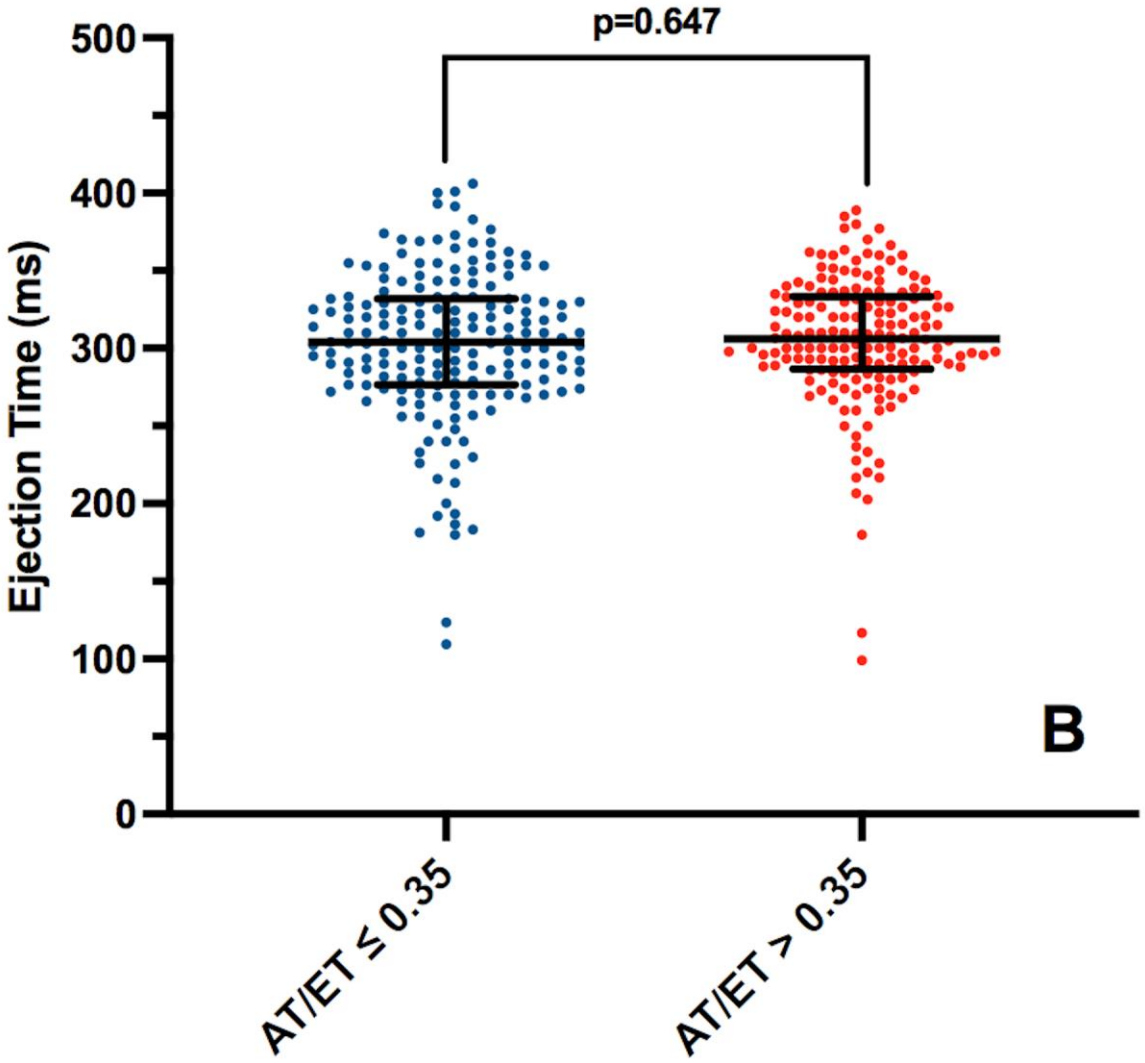
AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; AT/ET: ratio of acceleration time to ejection time

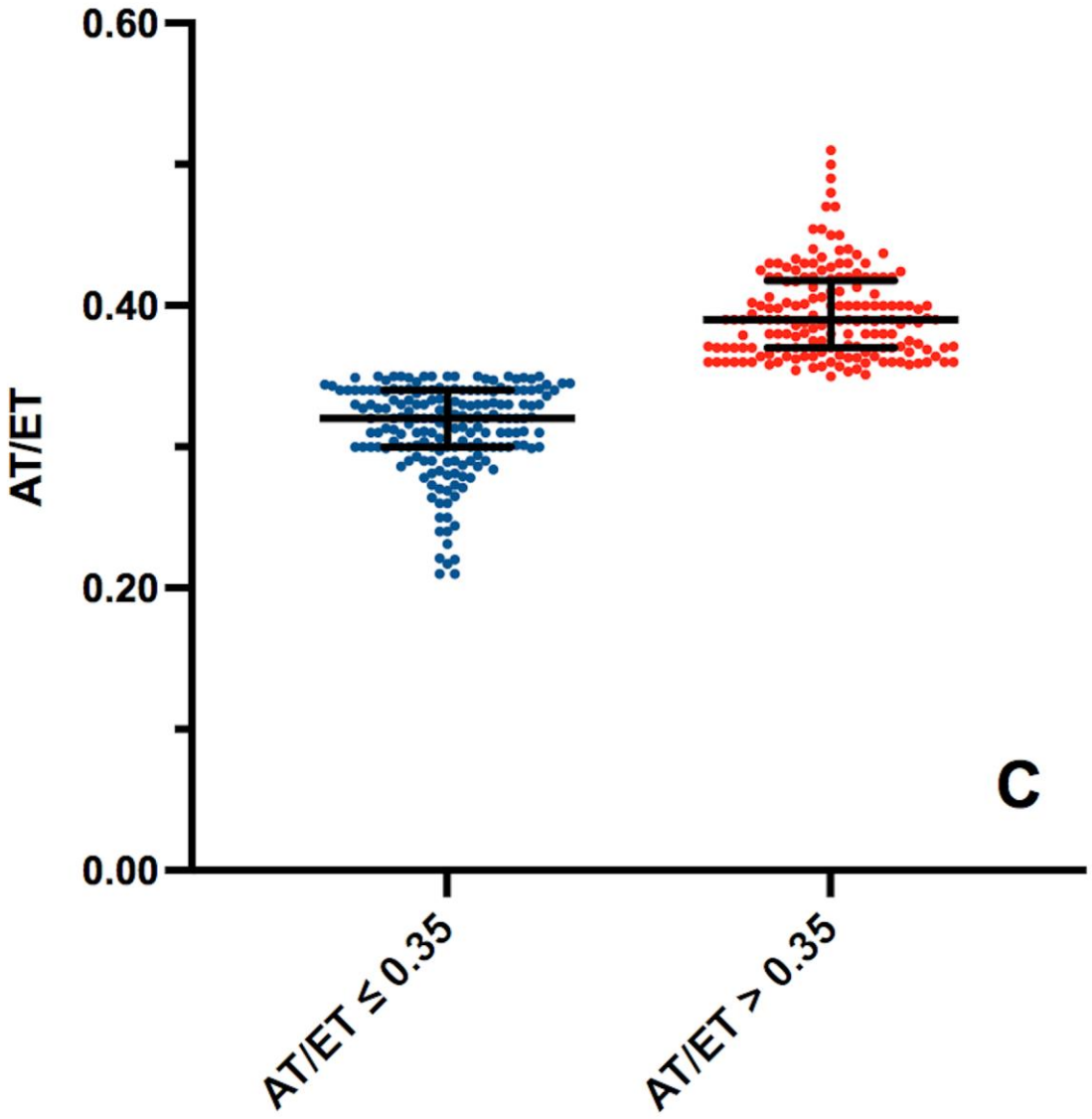
*Multivariable model is adjusted for age, sex, systolic blood pressure, Charlson comorbidity index (without including age), history of atrial fibrillation, peak aortic jet velocity, left ventricular stroke volume index and left ventricular ejection fraction

†Model is adjusted for covariates included in the model without AVR and AVR as time-dependent covariate

Figure S1. Distribution of AT (A), ET (B) and AT/ET (C) measurements according to AT/ET ≤ or > 0.35




p=0.647
500
400
300
200
100
0
Ejection Time (ms)
B
AT/ET ≤ 0.35
AT/ET > 0.35


0.60
0.40
0.20
0.00
AT/ET
C
AT/ET ≤ 0.35
AT/ET > 0.35