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Predictors of Progression in Patients With Stage B Aortic Regurgitation

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ABSTRACT

BACKGROUND The natural history of stage B aortic regurgitation (AR) is unknown.

OBJECTIVES This study sought to examine determinants, rate, and consequences of progression of AR.

METHODS Consecutive patients with ≤moderate chronic AR quantified by effective regurgitant orifice area (EROA) and regurgitant volume (RVol) from 2004 to 2017 who had ≥1 subsequent echocardiogram with quantitation were included.

RESULTS Of 1,077 patients (66 ± 15 years of age), baseline trivial/mild AR was noted in 196 (18%), mild-to-moderate AR in 465 (43%), and moderate AR in 416 (39%); 10-year incidence of progression to ≥moderate-severe AR (stage C/D; progressors) was 12%, 30%, and 53%, respectively. At 4.1-year follow-up (interquartile range: 2.1 to 7.2 years), there were 228 progressors (21%), whose annualized progression rates within 3 years before diagnosis of ≥moderate-severe AR were 4.2 mm^2/year for EROA and 9.9 ml/year for RVol. Baseline AR severity and dimensions of sinotubular junction and annulus were associated with progression (all $p \leq 0.007$); hypertension and systolic blood pressure were not. Progressors had faster chamber remodeling, functional class decline, and more aortic valve/aortic surgery. At medium-term follow-up, 242 patients (22%) died; poor survival was linked to age, comorbidities, functional class, resting heart rate, and left ventricular (LV) ejection fraction ($p \leq 0.003$), not LV end-systolic dimension index. Survival after progression to stage C/D AR was associated with LV end-systolic dimension index (adjusted $p = 0.02$).

CONCLUSIONS Progression from stage B to stage C/D AR was observed in 21% patients. Repeat echocardiography for trivial/mild, mild-to-moderate, and moderate AR at every 5, 3, and 1 years, respectively, was reasonable. EROA, RVol, annulus, and sinotubular junction should be routinely measured to estimate progression rates and identify patients at high risk of progression, which was associated with adverse consequences. (J Am Coll Cardiol 2019;74:2480–92)
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Aortic regurgitation (AR) is a common left-sided valvular heart disease (1). Severe AR has been shown to be associated with excess mortality (2) and heart failure. The current American College of Cardiology/American Heart Association guidelines on the management of patients with valve disease classify valve disease according to stage A (at risk of developing valve disease), stage B (progressive valve disease), stage C (asymptomatic severe valve disease), and stage D (symptomatic severe aortic valve [AV] disease) (3). Previous studies on the natural history of AR focused mainly on development of symptoms or left ventricular (LV) dysfunction in stage C AR. As for stage B AR, relevant studies are scarce; the anatomic and clinical features favoring progression from stage B to C/D have not been examined. Further, unlike aortic stenosis (AS) and mitral regurgitation (MR) (3,4), little information has been published regarding the progression rate of AR (i.e., effective regurgitant orifice area [EROA],

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regurgitant volume [RVol]) and its predictors. In addition, data on LV remodeling in stage B AR and the incidence of AR progression to stage C/D are lacking. Although current guidelines (3) recommend repeat transthoracic echocardiograms (TTEs) at 3 to 5 years in mild AR and 1 to 2 years in moderate AR, little supportive data exist (Level of Evidence: C).

Current unavailability of studies on predictors and rates of AR progression is not surprising, because large cohorts of patients with repeated echocardiograms, AR quantification, and long follow-up are required. To fill these gaps of knowledge and to further the understanding of stage B AR, we sought to examine the incidence, rates, and predictors of progression to stage C/D AR. We also reported adverse consequences of AR progression and determinants of survival in this population.

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METHODS

STUDY POPULATION AND CLINICAL DATA. Study flow is shown in Online Figure 1. Between January 2004 and July 2017, we identified consecutive patients with stage B AR (trivial, mild, mild-to-moderate, or moderate degree) at baseline who fulfilled the following criteria: 1) baseline TTE had quantitative measurements of AR, which included EROA or RVol derived from proximal isovelocity surface area (PISA) or quantitative pulsed Doppler method (based on aortic and mitral stroke volume measurements) if the PISA method was not feasible (5); and 2) at least 1 additional TTE performed at ≥3 months with available EROA and RVol. We excluded patients ≤18 years, those who denied research authorization, or those with any of the following at baseline: ≥moderate MR/mitral stenosis; ≥moderate AS; previous surgery on ascending aorta, aortic valve, and mitral valve; complex congenital heart disease; hypertrophic, restrictive, or constrictive cardiomyopathies; carcinoid heart disease; cardiac transplantation; acute aortic dissection; and active endocarditis. We also excluded patients who developed ≥moderate AS, MR, or mitral stenosis at the last available TTE to avoid uncertainty regarding confounding etiologies of chamber remodeling, as well as to prevent significant AS interfering with AR quantification or its progression. We extracted the comorbid conditions (prospectively recorded during clinic visit) and calculated the Charlson score (6) from electronic medical records.

ECHOCARDIOGRAPHY. Chamber quantification was performed according to guidelines (7). Annulus and aortic measurements were made from the parasternal long-axis window. Annulus was measured at mid-systole at leaflet insertions (inner-edge to inner-edge); sinus of Valsalva (SoV), sinotubular junction (STJ), and mid-ascending aorta were measured at end-diastole using the leading-edge to leading-edge method (8). Systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), rhythm, and body height/weight were recorded at the time of TTE.

ASSESSMENT OF AR AND DEFINITION OF PROGRESSION. In our echo lab, quantification of AR is routinely performed whenever feasible (5,9). The severity of AR was graded as trivial, mild (vena contracta width [VCW] <0.3 cm, pressure-half time [PHT] >500 ms, EROA <0.10 cm^2, RVol <30 ml/beat), mild-to-moderate (EROA or RVol were at the lower end of "moderate AR"), moderate (VCW 0.3 to 0.6 cm, PHT 200 to 500 ms, EROA 0.10 to 0.19 cm^2, RVol 30 to 44 ml), moderately severe (EROA 0.20 to 0.29 cm^2, RVol 45 to 59 ml/beat), and severe (VCW >0.6 cm, PHT <200 ms, EROA ≥0.3 cm^2, RVol ≥60 ml/beat) (4,10), using an integrated, comprehensive approach, including the aforementioned parameters and diastolic flow reversal in the descending aorta. PISA quantification of eccentric AR and measurement of VCW are demonstrated in **Figure 1**.

Although valve guidelines do not include moderately severe AR (3), 2017 American Society of Echocardiography guidelines (8) subclassify moderately severe AR as grade III AR, not uncommon in real-world practice (2,10), we defined stage C/D AR as ≥moderately severe AR. Patients whose AR progressed to ≥moderately severe AR were defined as progressors; the remainder whose AR severity remained at stage B were defined as nonprogressors.

RATE OF PROGRESSION AND PROGRESSION-RELATED CHAMBER CHANGE. For analysis of progression rates and LV remodeling, all available follow-up TTE measurements of EROA, RVol, LV ejection fraction (LVEF), LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), indexed LVESD (LVESDi), SBP, and DBP were considered. To compare effects of AR progression (i.e., chamber remodeling, changes in New York Heart Association [NYHA] functional class) between baseline and index follow-up TTE (index TEE), we defined index TTE as: 1) the TTE showing progression to stage C/D

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
AS = aortic stenosis
AV = aortic valve
AVR = aortic valve replacement
BAV = bicuspid aortic valve
CI = confidence interval
DBP = diastolic blood pressure
EROA = effective regurgitant orifice area
HR = hazard ratio
HTN = hypertension
IQR = interquartile range
LV = left ventricular
LVEDD = left ventricular end-diastolic dimension
LVEF = left ventricular ejection fraction
LVESD = left ventricular end-systolic dimension
LVESDi = left ventricular end-systolic dimension index
MR = mitral regurgitation
NYHA = New York Heart Association
PHT = pressure-half time
PISA = proximal isovelocity surface area
RHR = resting heart rate
RVol = regurgitant volume
SBP = systolic blood pressure
SoV = sinus of Valsalva
STJ = sinotubular junction
TTE = transthoracic echocardiogram
VCW = vena contracta width

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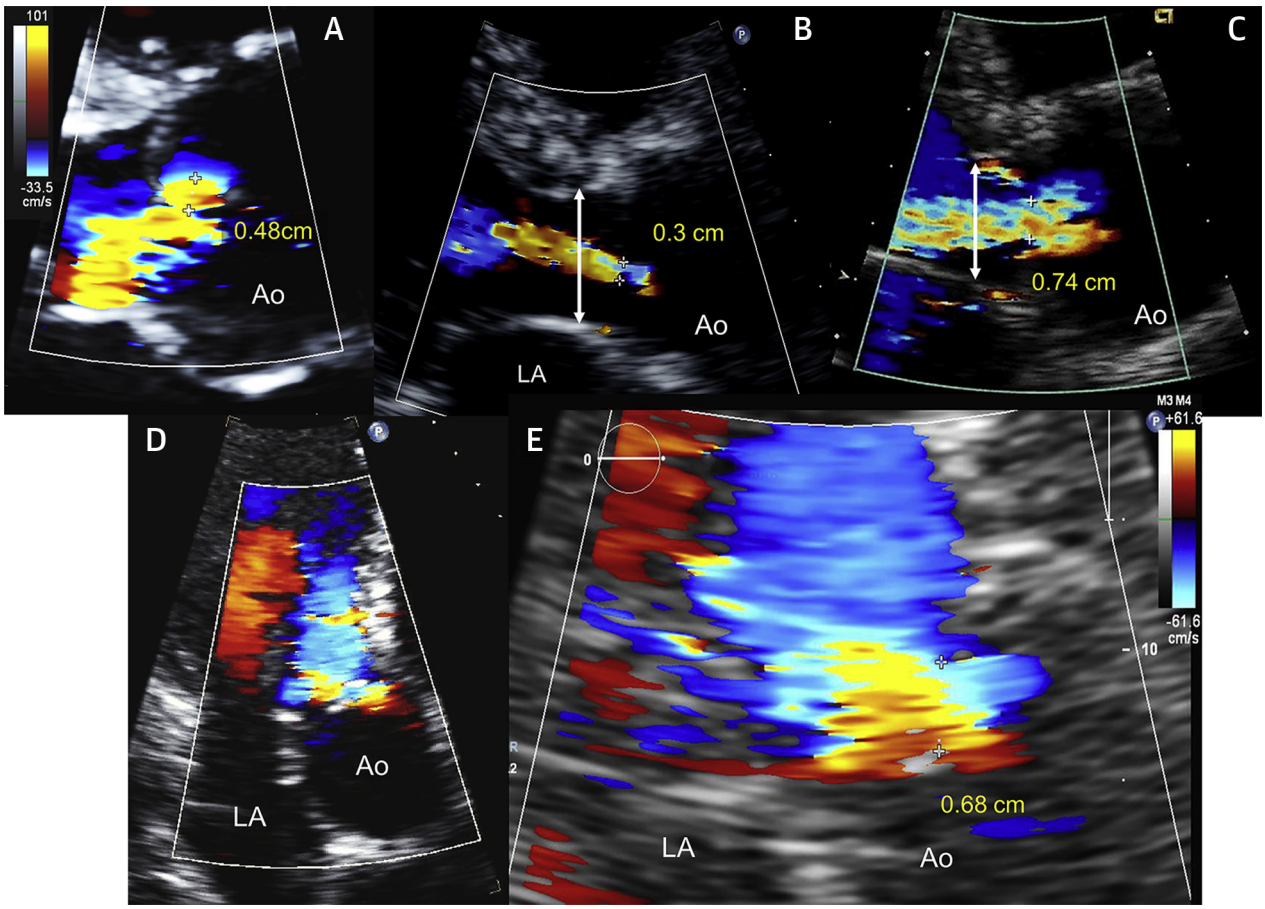
FIGURE 1 Measurements of EROA and VCW



Parasternal long-axis view can be used for EROA measurement (0.48 cm) for eccentric AR **(A)**. VCW can differentiate mild **(B)** and severe **(C)** AR. For eccentric jets, VCW can sometimes be measured via apical 3 chamber view **(D and E)** in which VCW is parallel to the insonation beam. **Double-headed arrow** = left ventricular outflow tract. Ao = ascending aorta; AR = aortic regurgitation; EROA = effective regurgitant orifice area; LA = left atrium; VCW = vena contracta width.

AR in progressors (second TTE in 31%); and 2) the second TTE in nonprogressors.

AV/AORTA SURGERY AND OUTCOME ANALYSIS. Surgical indications based on current guidelines (3) and procedures were extracted from our electronic medical records. The main outcome was all-cause mortality, instead of cardiac mortality, because of the limitations of death certificates in accurately specifying cause of death (11). The observation time for survival analyses in stage B AR was between the baseline TTE and death or last follow-up. To analyze survival after progression to ≥moderate-severe AR, the observation was between date of first TTE documenting progression (index TTE) and death/last follow-up. The survival status was retrieved using Accurint (LexisNexis, RELX Group, New York, New York), a proprietary resource combining multiple national sources (queried January 2019, Accurint).

STATISTICAL ANALYSIS. Continuous variables, expressed as mean ± SD or median (interquartile range [IQR]), were compared using the Student's *t*-test or Wilcoxon rank sum test as appropriate. Categorical data, presented as percentages, were compared using chi-square test. Linear and logistic regression models were used to compare groups with adjustment for covariates. Independent predictors for AR progression were analyzed using Cox proportional hazard regression models censoring patients at index TTE in progressors, and last available TTE or time of AV/aortic surgery in nonprogressors. Results presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Variables were removed stepwise from the model when the p value exceeded

TABLE 1 Clinical and Echocardiographic Characteristics of Patients With Stage B AR

	Total (N = 1,077)	Trivial/Mild (n = 196)	Mild-Moderate (n = 465)	Moderate (n = 416)	p Value	Progressors (n = 228)	Nonprogressors (n = 849)	p Value
Age, yrs	66 ± 15	69 ± 13	68 ± 14	65 ± 16	0.003	63 ± 15	68 ± 14	<0.0001
Women	527 (49)	117 (59)	262 (57)	148 (36)	<0.0001	61 (27)	465 (55)	<0.0001
Systolic blood pressure, mm Hg	128 ± 20	129 ± 18	129 ± 21	128 ± 20	0.97	128 ± 18	129 ± 20	0.59
Diastolic blood pressure, mm Hg	70 ± 11	70 ± 10	70 ± 10	68 ± 11	0.01	69 ± 11	70 ± 11	0.59
Heart rate, beats/min	64 ± 12	66 ± 12	64 ± 12	63 ± 11	0.01	64 ± 11	64 ± 12	0.57
Body mass index, m^2/kg	26.6 ± 4.6	26.5 ± 4.6	26.5 ± 4.6	26.6 ± 4.7	0.95	26.6 ± 3.8	26.5 ± 4.8	0.78
Body surface area, m^2	1.87 ± 0.24	1.83 ± 0.23	1.84 ± 0.24	1.92 ± 0.25	<0.0001	1.95 ± 0.24	1.84 ± 0.24	<0.0001
NYHA functional class III/IV, n = 1,000	37 (4)	8 (4)	19 (4)	10 (3)	0.39	5 (2)	32 (4)	0.20
Hypertension, n = 1,045	603 (58)	114 (61)	260 (58)	229 (55)	0.38	118 (53)	485 (59)	0.12
Diabetes mellitus, n = 1,045	216 (21)	47 (25)	81 (18)	88 (21)	0.12	36 (16)	180 (22)	0.05
Hyperlipidemia, n = 1,045	560 (54)	110 (59)	242 (54)	208 (50)	0.12	112 (50)	448 (54)	0.29
CAD/IHD, n = 1,045*	172 (16)	37 (20)	74 (17)	61 (15)	0.30	31 (14)	141 (17)	0.25
CKD ≥stage 3, n = 1,045	56 (5)	7 (4)	25 (6)	24 (6)	0.53	8 (4)	48 (6)	0.17
Endocarditis, n = 1,045	36 (3)	5 (3)	14 (3)	17 (4)	0.60	9 (4)	27 (3)	0.58
Connective tissue disease, n = 1,045	92 (9)	17 (9)	42 (9)	33 (8)	0.74	14 (6)	78 (9)	0.12
Atrial fibrillation at baseline TTE	62 (6)	13 (7)	25 (5)	24 (6)	0.82	8 (4)	54 (6)	0.08
Current/ever smoker	379 (35)	56 (29)	137 (29)	186 (45)	<0.0001	86 (38)	293 (35)	0.36
Charlson score, n = 1,034†	1.6 ± 1.5	1.79 ± 1.6	1.4 ± 1.4	1.7 ± 1.7	0.002	1.5 ± 1.3	1.6 ± 1.6	0.22
Antiplatelet agents, n = 865	275 (32)	54 (35)	119 (33)	102 (29)	0.39	54 (30)	221 (32)	0.52
Beta-blocker, n = 865	348 (40)	76 (49)	139 (38)	133 (38)	0.04	64 (35)	284 (42)	0.13
Diuretic agents, n = 865	293 (34)	58 (37)	122 (34)	113 (32)	0.55	58 (32)	235 (34)	0.55
Calcium-channel blocker, n = 865	196 (23)	32 (21)	83 (23)	81 (23)	0.79	36 (20)	160 (23)	0.31
ACE inhibitor/ARB, n = 865	343 (40)	58 (37)	134 (37)	151 (43)	0.18	71 (39)	272 (40)	0.89
Statin, n = 865	315 (36)	61 (39)	136 (38)	118 (34)	0.42	62 (34)	253 (37)	0.49
Echocardiographic parameters								
Bicuspid aortic valve	156 (14)	20 (10)	54 (12)	82 (20)	0.0008	50 (22)	107 (13)	0.0007
LVEF, %	60 ± 10	61 ± 10	60 ± 9	60 ± 10	0.38	59 ± 10	60 ± 10	0.19
LVEDD, mm	51 ± 6	49 ± 6	50 ± 6	54 ± 6	<0.0001	55 ± 6	50 ± 6	<0.0001
LVESD, mm	33 ± 6	32 ± 7	33 ± 6	35 ± 7	<0.0001	36 ± 6	33 ± 6	<0.0001
LVESDi, mm/m^2	18.0 ± 3.5	17.5 ± 3.8	17.9 ± 3.2	18.4 ± 3.7	0.007	18.6 ± 3.7	17.9 ± 3.4	0.010
AR regurgitant volume, ml	34 ± 13	22 ± 9	31 ± 11	42 ± 13	<0.0001	39 ± 14	32 ± 13	<0.0001
AR EROA, cm^2	0.14 ± 0.05	0.09 ± 0.03	0.13 ± 0.04	0.17 ± 0.05	<0.0001	0.16 ± 0.06	0.14 ± 0.05	<0.0001
Vena contracta, mm, n = 457	4.1 ± 1.3	3.7 ± 1.2	3.9 ± 1.2	4.5 ± 1.2	<0.0001	4.6 ± 1.3	3.9 ± 1.2	0.0001
Pressure-half time, ms, n = 718	520 ± 156	537 ± 148	526 ± 165	503 ± 147	0.06	488 ± 149	527 ± 156	0.009
Advanced diastolic dysfunction†	361 (34)	73 (37)	148 (32)	140 (34)	0.43	65 (29)	296 (35)	0.06
LA volume index, ml/m^2, n = 1,042	37 ± 13	36 ± 11	36 ± 12	39 ± 13	0.001	37 ± 12	37 ± 13	0.53
Annulus, mm	23.0 ± 2.7	22.2 ± 2.4	22.6 ± 2.4	23.8 ± 2.8	<0.0001	24.5 ± 2.8	22.6 ± 2.5	<0.0001
Sinus of Valsalva, mm, n = 1,054	36.9 ± 5.9	35.4 ± 6.0	36.1 ± 5.7	38.5 ± 5.7	<0.0001	39.4 ± 5.5	36.2 ± 5.7	<0.0001
Sinotubular junction, mm, n = 985	32.1 ± 6.4	30.9 ± 5.3	31.9 ± 5.2	33.1 ± 5.3	<0.0001	34.5 ± 5.3	31.5 ± 5.1	<0.0001
Mid-ascending aorta, mm, n = 916	38.3 ± 5.6	37.3 ± 5.7	37.9 ± 5.6	39.2 ± 5.5	0.0003	39.9 ± 5.4	37.8 ± 5.6	<0.0001

Values are mean ± SD or n (%). *Includes diagnosis of coronary artery disease (CAD), ischemic heart disease (IHD), previous coronary artery bypass grafting, or prior myocardial infarction. †Pseudo-normalization or restrictive pattern (Nagueh et al. J Am Soc Echocardiogr 2016;29:277–314).

ACE = angiotensin-converting enzyme; AR = aortic regurgitation; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; EROA = effective regurgitant orifice area; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESDi = left ventricular end-systolic dimension index; NYHA = New York Heart Association; TTE = transthoracic echocardiography.

0.1. Changes of echo parameters from baseline TTE were plotted over time using a LOESS (locally estimated scatterplot smoothing) smoother to understand patterns of change. Mixed linear regression models including a random time component and accounting for repeated measurements within the same patient over time were used to determine annualized progression rates of EROA/RVol in progressors. In these models, time of diagnosis of moderate-severe/severe AR was designated as time 0, and earlier measurements as negative (−) time duration. A time period variable and interaction was included in the model to account for different rates over the observation period. The incidence of progression and surgery were illustrated using Kaplan-Meier curves (patients were censored at time of progression, surgery, or last TTE) and compared using the log-rank statistic. Mortality was analyzed using the Cox proportional hazards

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TABLE 2 Predictors for Progression to ≥Moderately Severe AR in Patients With Baseline ≤Moderate AR

	OR (95% CI)	p Value
Model 1. AR severity by ERO*		
Age, yrs	0.97 (0.86–1.10)	0.61
Male	1.20 (0.80–1.82)	0.38
Bicuspid aortic valve	0.77 (0.49–1.21)	0.26
Annulus/5 mm	1.97 (1.38–2.82)	0.0002
STJ/5 mm	1.26 (1.08–1.48)	0.003
EROA/10 mm^2 increase	1.32 (1.18–1.48)	<0.0001
Model 2. AR severity by integrated qualitative assessment†		
Age, yrs	0.95 (0.85–1.07)	0.42
Male	1.13 (0.75–1.69)	0.56
Bicuspid aortic valve	0.70 (0.45–1.09)	0.12
Annulus/5 mm	1.94 (1.37–2.74)	0.0002
STJ/5 mm	1.30 (1.12–1.51)	0.0004
Mild-to-moderate AR vs. trivial/mild AR	2.25 (1.24–4.08)	0.007
Moderate AR vs. trivial/mild AR	4.71 (2.65–8.37)	<0.0001

Patients with ≥moderately severe AR, n = 228; patients with baseline ≤moderate AR, n = 1,077. Beta-blockers, warfarin, antiplatelet agents, direct oral anticoagulants, calcium-channel blockers, diuretic agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, and digoxin were not univariate predictors. *In a model adjusted for age, sex, bicuspid aortic valve, and hypertension or baseline systolic blood pressure, annulus, STJ, and EROA remained significant (p ≤ 0.008). †In a model adjusted for age, sex, bicuspid aortic valve, and hypertension or baseline systolic blood pressure, annulus, STJ, mild-to-moderate AR (vs. trivial/mild AR) and moderate AR (vs. trivial/mild AR) remained significant (p ≤ 0.022).

CI = confidence interval; OR = odds ratio; STJ = sinotubular junction; other abbreviations as in Table 1.

model using the left-truncation method by not placing patients at risk until the second TTE, to match the study design. On the basis of our findings that the incidence of progression to ≥moderate-severe AR at 5 years was 19.2%, we decided that the observation in nonprogressors whose last follow-up was >5 years from last TTE ended at 5 years after last TTE. To avoid potential bias, this same method was applied to all patients regardless of progression status. AV and/or aortic surgery and progression to ≥moderate-severe AR were analyzed as time-dependent covariates within the left-truncated proportional-hazard model. All statistical analyses were performed using commercially available software (JMP 11 and SAS 9.4; SAS Institute, Cary, North Carolina). A p value <0.05 was considered statistically significant.

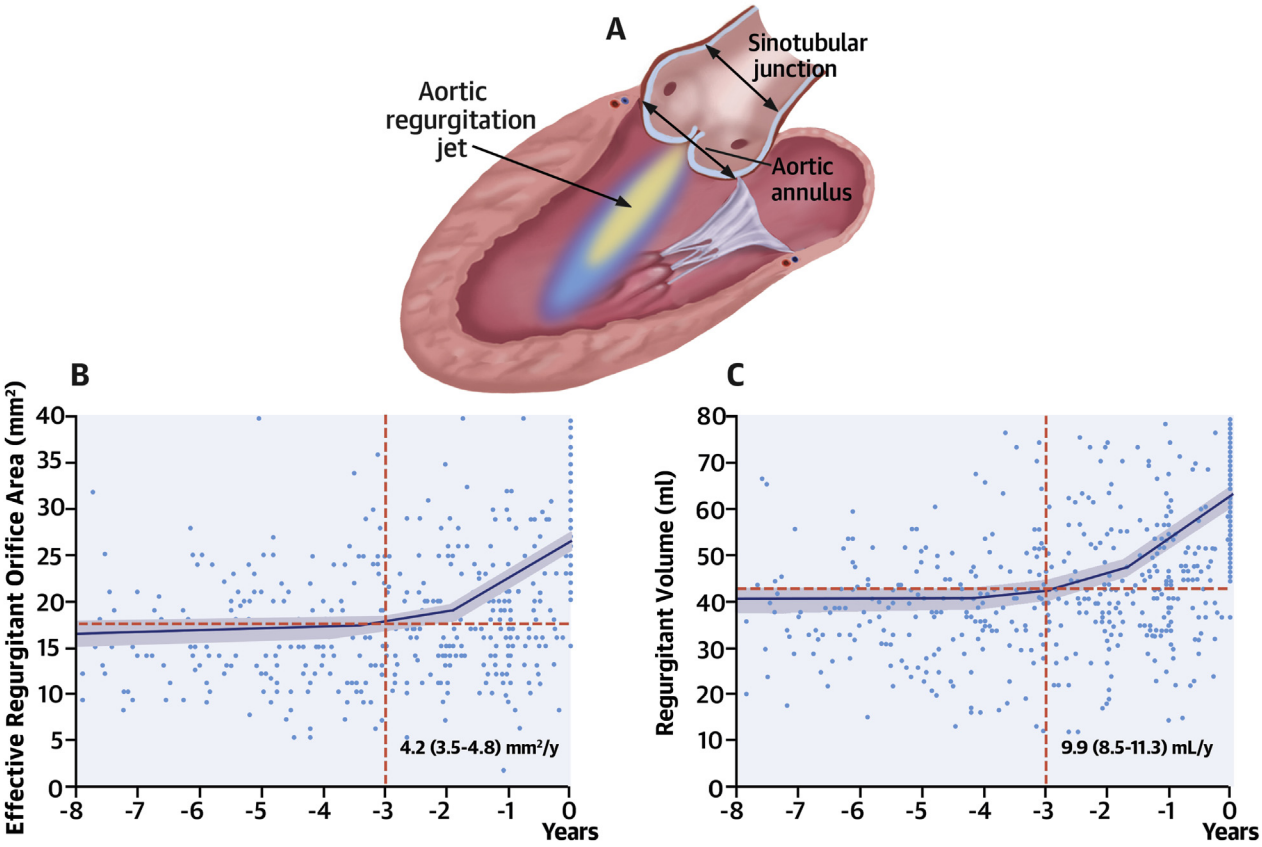
RESULTS

PATIENT CHARACTERISTICS. After applying exclusion criteria (Online Figure 1), our final cohort consisted of 1,077 patients (age 66 ± 15 years), with baseline trivial/mild AR in 196 patients (18%; 3 had baseline trivial AR), mild-to-moderate AR in 465 (43%), and moderate AR in 416 (39%); all had ≥1 additional TTE with EROA/RVol at a median interval of 19.5 (IQR: 12.2 to 35.7) months. At a median time of 4.1 (IQR: 2.1 to 7.2) years, 228 patients (21%) had progressed to ≥moderately severe (stage C/D) AR at a median of 3.3 (IQR: 1.7 to 5.9) years (Online Figure 1). Time of progression to stage C/D AR was significantly shorter in those having baseline moderate AR (n = 140; 2.96 [IQR: 1.2 to 5.4] years) versus baseline trivial/mild (n = 14; 4.2 [IQR: 2.8 to 5.7] years) and baseline mild-to-moderate AR (n = 74; 4.4 [IQR: 2.4 to 6.4] years) (p = 0.013). Of 228 progressors, the AR etiologies (determined by imaging) included bicuspid AV (BAV) in 50 (22%), functional AR (i.e., root complex dilatation) in 102 (45%), prolapsed cusp in 13 (6%), cusp restriction in 9 (4%), mixed mechanisms in 24 (11%), fenestration in 1 (<1%), quadricuspid AV in 1 (<1%), and undetermined in 28 (12%; 16 had hypertension [HTN]).

Regarding baseline characteristics (Table 1), patients at stage B AR had a high prevalence of hyperlipidemia and HTN. Those with baseline moderate AR compared with less-than-moderate AR were younger, more often male, had more BAV, lower DBP, larger aortic root, and larger LV chamber dimensions (p ≤ 0.01) (Table 1). Of note, moderate AR patients also had slower RHR but less β-blocker use. In a linear regression model adjusted for age, sex, Charlson score, β-blocker, and LVEF, patients with moderate AR had 3.9 beats/min lower RHR than those with mild AR (p = 0.001). Compared with nonprogressors (n = 849, 79%), progressors (n = 228, 21%) were younger, more likely male, had more BAV, larger aortic root, larger EROA/RVol, and larger LV (p ≤ 0.01) owing to having more baseline moderate AR (33% vs. 61%; p < 0.0001); nonetheless, progressors had similar hemodynamic parameters (SBP, DBP, and RHR) as compared with nonprogressors. The indications for TTE are shown in Online Result 1.

PREDICTORS OF AR PROGRESSION. In the Cox proportional hazard regression model, younger age, male sex, the presence of BAV, and larger EROA/RVol, annulus, STJ, SoV, and mid-ascending aorta were univariately associated with AR progression (p ≤ 0.029); baseline SBP, DBP, RHR, history of HTN, heart failure, chronic kidney disease ≥stage 3, endocarditis, smoking, connective tissue disease, body mass index, or medications were not (p ≥ 0.11) (Table 2). In multivariate analyses, annulus, STJ, and larger EROA (Table 2), but not SoV or mid-ascending aorta, were strongly associated with progression to significant AR (p ≤ 0.003). When EROA was replaced by integrated qualitative AR assessment (baseline trivial/mild AR as a reference), baseline mild-to-moderate AR (HR: 2.25), and moderate AR (HR: 4.71)

CENTRAL ILLUSTRATION Predictors and Progression Rates of Aortic Regurgitation



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Dilatation of annulus and sinotubular junction and baseline severity of aortic regurgitation (AR) were predictive of AR progression **(A)**. In progressors (n = 228), the rate of progression became more obvious at approximately 3 years before the diagnosis of ≥moderate-severe AR and at a rate of 4.2 mm^2/year for EROA **(B)**, and 9.9 ml/year for RVol **(C)**.

were positively associated with AR progression (**Table 2, Central Illustration**). After adjusting for baseline HTN or SBP, results were similar.

Figure 2 shows the incidence of AR progression to ≥moderately severe, which was 36.1% overall, and 11.7%, 30.2%, and 53.4% at 10 years in baseline trivial/mild, mild-to-moderate, and moderate AR, respectively ($p < 0.0001$).

ANNUALIZED GROWTH RATE OF LV PARAMETERS, EROA, AND RVol. The total number of measurements for each of the parameters EROA, RVol, LVEF, LVEDD, LVESD, LVESDi, SBP, and DBP ranged from 3,306 to 4,444 (average 4,036 ± 450; 0.6 to 0.8 measurement per person per year). As an entire cohort, there was an incremental change over time for EROA, RVol, LVEDD, LVESD, LVESDi, but decremental change for LVEF albeit slow annualized change ($p < 0.0001$) (**Figure 3**, Online Figure 2). Change over time was significant for SBP (annualized rate 0.53 mm Hg; 95% confidence interval [CI]: 0.28 to 0.78 mm Hg) ($p < 0.0001$), but not for DBP ($p = 0.10$). Compared with nonprogressors, progressors had significantly faster change of EROA, RVol, LVEDD, and LVESD over time (all $p \leq 0.04$) (**Figure 3**, Online Figure 2).

On the basis of the progression curves of EROA/RVol in progressors (**Central Illustration**), we calculated annualized progression rates within 3 years before progression, which were 4.2 (95% CI: 3.5 to 4.8) mm^2/year for EROA and 9.9 (95% CI: 8.5 to 11.3) ml/year for RVol.

CONSEQUENCES OF AR PROGRESSION: CHAMBER REMODELING AND FUNCTIONAL CLASS DECLINE. **Figure 4** shows the change of DBP, RHR, AR-remodeling, and chamber-remodeling parameters at

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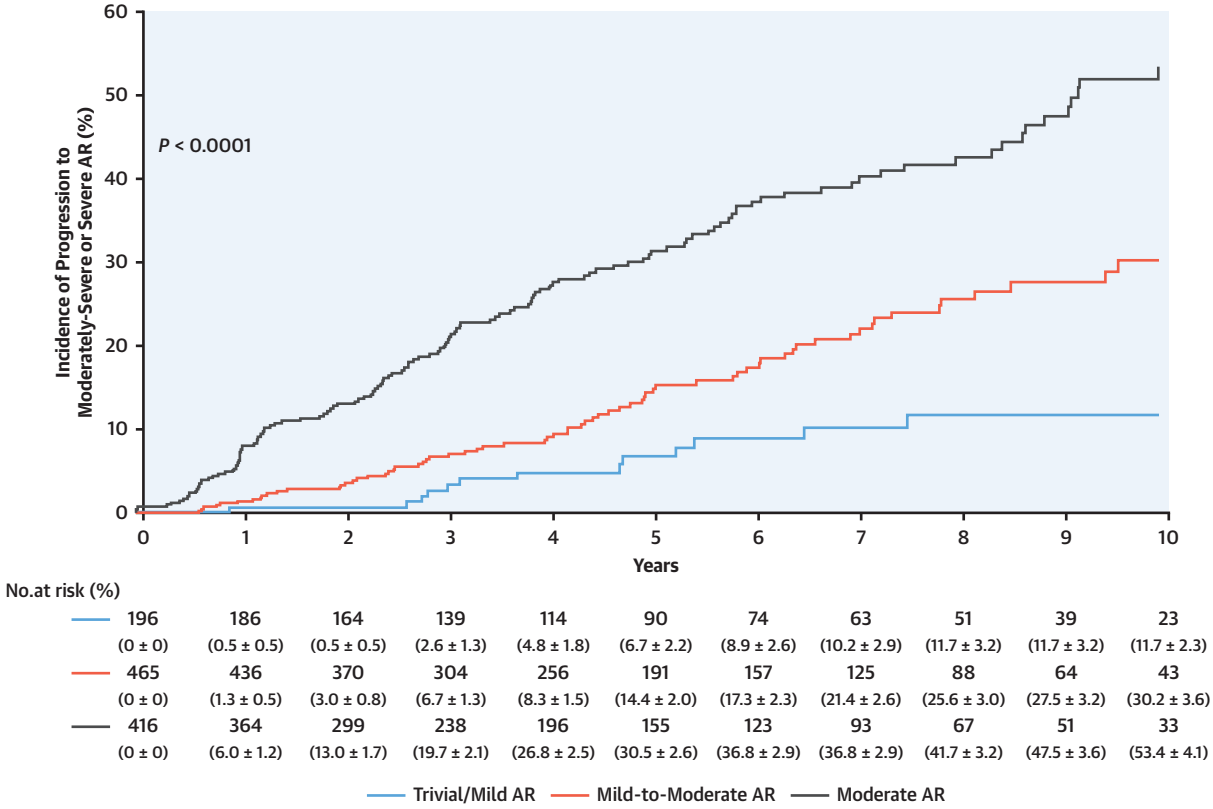
FIGURE 2 Incidence of Moderate-Severe or Severe AR by Different Baseline Severity

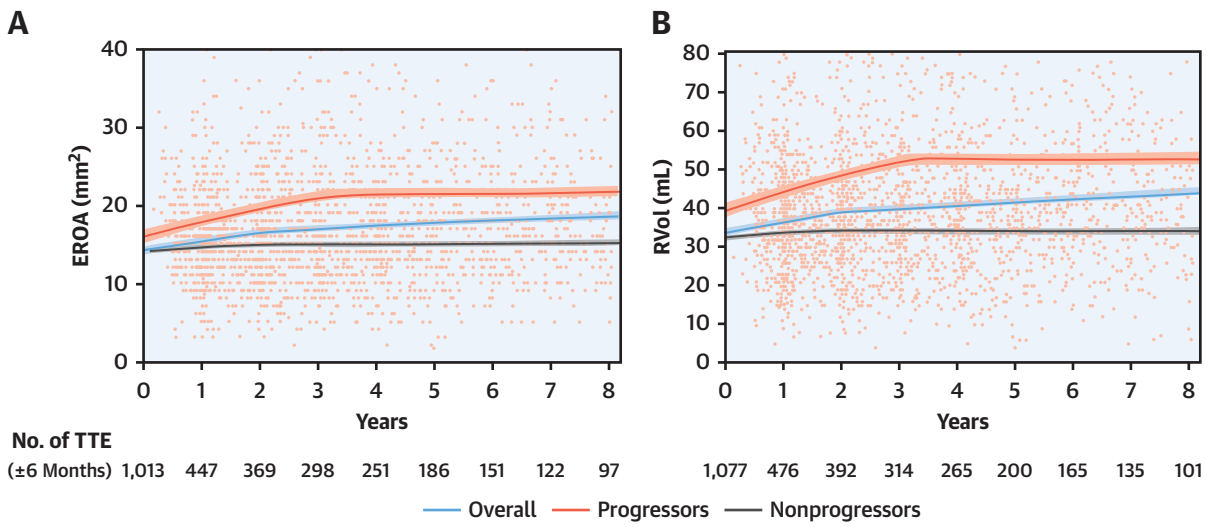


Progressors were censored at the time of progression to moderately severe/severe AR, whereas nonprogressors were censored at last available echocardiogram or aortic valve/aorta surgery. AR = aortic regurgitation.

baseline and index TTE (interval 3.3 [IQR: 1.7 to 5.9] years in progressors and 1.7 [IQR: 1.1 to 3.0] years in nonprogressors; $p < 0.0001$). At index TTE, progressors had lower RHR, DBP, and LVEF but larger LV dimensions and left atrial volume index compared with nonprogressors. Enlargement of mid-ascending aorta ($p = 0.0003$) and change of NYHA functional class ≥1 class were significant in progressors ($p = 0.008$). When we chose another set of follow-up TTEs in nonprogressors at a median of 3 years from baseline, nonprogressors had a negligible change of LV remodeling over time, and results were similar (Online Table 1). The dimensional change of annulus, STJ, and mid-ascending aorta of subgroups of progressors and those having surgeries for pure aortic aneurysms showed negligible increase over time and the largest change for the mid-ascending aorta (Online Table 2, Online Result 2). Finally, from the last available TTE (before AV/aorta surgery if applicable), there was stepwise increase in LV size, AR quantitative parameters, and decremental change for DBP in different AR-severity subgroups (Table 3).

AVR/REPAIR OR AORTIC SURGERY. The cumulative incidence of surgery and surgical procedures are shown in Figure 5 and Online Figure 1. Overall, 87 patients had aortic or AV surgery (88% had AVR), of whom 70 (80%) were progressors. Indications for surgery in progressors (n = 70), included: 1) Class I indications in 57 (pure symptoms in 43, pure LVEF <50% in 4, pure aortic aneurysms in 3, symptoms plus LVEF <50% in 6, and symptoms plus aneurysm in 1); 2) Class II indications in 7 (LVESD >50 mm or LVESDi >25 mm/m^2 in 3, LVEDD >65 mm in 4); and 3) the remainder (n = 6) opted for early surgery. Indications for surgery in nonprogressors (n = 17) included aortic aneurysms in 11 (64%), coronary artery bypass grafting in 4 (24%), dyspnea on exertion in 1 (6%), and unknown in 1 (6%; surgery performed elsewhere). In 70 progressors having surgery, the percentage of NYHA functional class III/IV at

FIGURE 3 2 Patterns of Clinical Course: Indolent Versus Progressive



The changes over time from baseline to last available TTE for EROA **(A)** and RVol **(B)** were significant in the entire group **(blue)**, in progressors **(orange)** (both $p < 0.0001$), and in nonprogressors **(gray)** ($p < 0.0001$ for EROA and $p = 0.03$ for RVol); progressors had significantly faster change (progressors vs. nonprogressors $p < 0.0001$ for both EROA and RVol). Although it is impossible to predict progression, this graph serves as a reference to compare serial EROA and RVol in order to estimate the potential clinical course. EROA = effective regurgitant orifice area; RVol = regurgitant volume; TTE = transthoracic echocardiography.

baseline, time of progression to ≥moderate-severe AR, and time of AV and/or aortic surgery were 0%, 5.8%, and 28.6%, respectively ($p < 0.0001$), aligned with the predominant surgical indication being "symptoms." The 10-year incidence from baseline TTE to having a surgery was 13.5 ± 1.7%.

OVERALL SURVIVAL. Median follow-up after second echocardiogram was 5.0 (IQR: 2.7 to 7.8) years, and maximal follow-up was 14.1 years. The follow-up rate was 100% as of January 2019. Death occurred in 242 patients (22%) (Online Figure 1). Overall survival at 5 and 10 years was 82.5 ± 1% and 66.5 ± 2%, respectively, similar to expected survival (Online Figure 3).

Table 4 shows multivariate models. LVEDD was not a univariate predictor of death; low DBP, high SBP, pulse pressure, larger LVESD, advanced diastolic dysfunction, and non-BAV were univariate, but not multivariate, predictors of survival. Besides age, comorbidities, and advanced functional class, RHR and LVEF, but not LVESDi, were independently predictive of survival in stage B AR (**Table 4**). Survival in progressors was associated with age, comorbidities, time-dependent AV and/or aortic surgery, lower LVEF, and increased LVESDi, but not the interval between baseline TTE and index TTE (**Table 4**). LVESDi was a more powerful survival determinant following progression as compared with the entire group of stage B AR.

DISCUSSION

This study, to the best of our knowledge, is the first to report characteristics, predictors/rates of AR progression, and outcomes in a large cohort of patients at stage B having long-term follow-up. The principle findings are: 1) patients with stage B AR had a high prevalence of systemic HTN, hyperlipidemia, and preserved LVEF; 2) in the majority, the course of AR was indolent, but 21% of our cohort progressed to ≥moderate-severe AR; 3) annulus and STJ dimensions, and AR severity were associated with progression to significant AR, but HTN or SBP was not; 4) annualized progression rates of EROA and RVol from −3 years to time 0 were 4.2 mm^2/year for EROA and 9.9 ml/year for RVol; 5) progression to stage C/D AR was associated with NYHA functional class decline, chamber remodeling, and surgery (mainly valve replacement); and 6) LVESDi was more useful in prognostication following progression as compared with the entire group of stage B AR.

Anatomic risk factors for AR development are ambiguously addressed as "dilated aortic sinuses or ascending aorta" in current guidelines (3). We found

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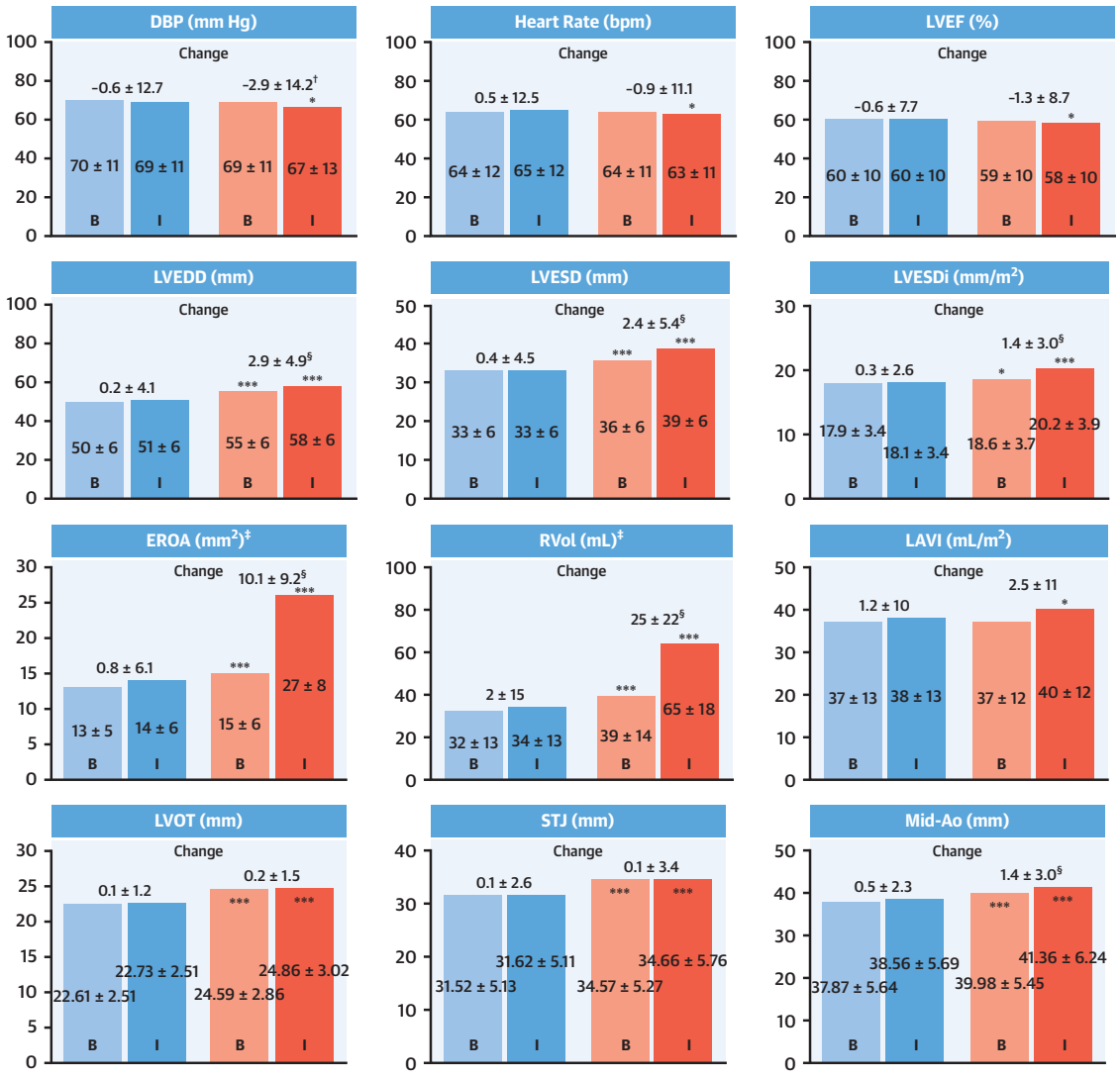
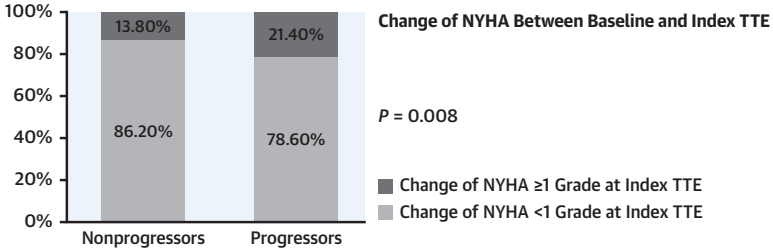
FIGURE 4 Influence of AR Progression



***$P < 0.001$; **$0.001 \leq P < 0.01$, *$0.01 \leq P < 0.05$: comparison between progressors and nonprogressors.
†, $0.01 \leq P < 0.05$; §, $P < 0.001$: comparison between change of progressors and nonprogressors.
Systolic blood pressure at baseline or index TTE were similar between 2 groups.
‡, At TTE_{index}, the EROA, RVol and vena contracta in moderately-severe and severe AR are 23 ± 6 vs. 33±8 mm^2, 58 ± 12 vs. 78 ± 21 ml, and 5.2 ± 1.4 vs. 6.2±2.5 mm, respectively (all $P \leq 0.02$).



At TTE_{index}, progressors had lower DBP, RHR, and LVEF, but larger LVEDD, LVESDi, and LAVI as compared with nonprogressors. Also, change of NYHA functional class ≥1 class was significant in progressors. B = baseline TTE; bpm = beats/min; DBP = diastolic blood pressure; I = TTE_{index}; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVESDi = left ventricular end-systolic dimension index; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; RHR = resting heart rate; STJ = sinotubular junction; other abbreviations as in Figures 1 and 3.

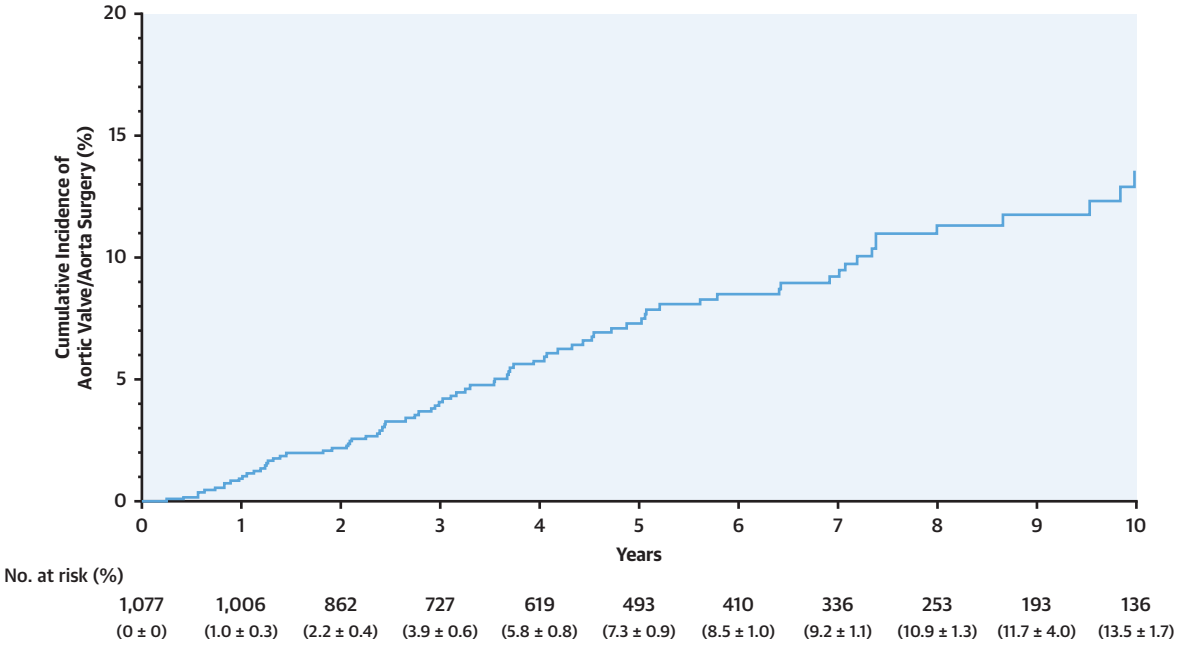
TABLE 3 Comparison of LV Size and AR Quantification According to AR Severity at Last Available TTE

	Mild (n = 55)	Mild-to-Moderate (n = 311)	Moderate (n = 482)	Moderately Severe (n = 148)	Severe (n = 81)	p Value
LVEDD, mm	48 ± 1	49 ± 6	52 ± 6	56 ± 6	60 ± 6	<0.0001
LVESD, mm	31 ± 6	32 ± 6	34 ± 6	37 ± 6	41 ± 7	<0.0001
LVESDi, mm/m^2	18 ± 4	18 ± 4	19 ± 3	20 ± 4	21 ± 4	<0.0001
AR EROA, cm^2, n = 806	0.09 ± 0.05	0.12 ± 0.04	0.17 ± 0.05	0.23 ± 0.06	0.31 ± 0.08	<0.0001
AR RVol, ml, n = 832	20 ± 9	29 ± 10	40 ± 13	53 ± 13	71 ± 19	<0.0001
Vena contracta, mm, n = 454	3.1 ± 1.0	3.9 ± 0.9	4.3 ± 1.2	5.1 ± 1.5	6.1 ± 1.8	<0.0001
Pressure-half time, ms, n = 646	517 ± 173	510 ± 165	503 ± 145	464 ± 135	399 ± 133	<0.0001
Diastolic blood pressure, mm Hg	71 ± 11	70 ± 12	67 ± 11	66 ± 12	63 ± 12	<0.0001

Values are mean ± SD.
Abbreviations as in Table 1.

that the aortic annulus and STJ, but not SoV, were important determinants of AR progression. This is likely because these 2 anatomic structures serve as 2 native stents that protect the integrity of AV function (12). The importance of annulus and STJ was also reflected in the techniques used for AV repair (i.e., subvalvular and supravalvular annuloplasty) (13), highlighting the concept of "root complex" akin to the concept of mitral valve apparatus. In other words, mere dilatation of SoV less likely leads to significant AR. These findings emphasize that routine measurements of annulus and STJ are essential. Also important to note is that in progressors, change of annulus and STJ over time was negligible (14). The correlation of blood pressure and AR is debatable (15); neither SBP nor baseline HTN was predictive of AR progression, likely because HTN was a prevalent comorbidity in both progressors and nonprogressors. Nonetheless, our result cannot be interpreted as blood pressure control in AR is not important. Analogous to MR (16), baseline AR severity was powerful in predicting AR progression, supporting different intervals for follow-up according to baseline AR severity (i.e., moderate AR requires shorter follow-up) (3). In addition to guideline recommendations (i.e., that mild and moderate AR be followed every 3 to 5 years and 1 to 2

FIGURE 5 Incidence of AV or Aortic Surgery



The 10-year risk from baseline transthoracic echocardiography to surgery was 13.5%.

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TABLE 4 Cox Proportional Model for Predictors of All-Cause Mortality

	HR (95% CI)	p Value
Survival in entire cohort (n = 1,077, 242 deaths)		
LVEF model*		
Age, yrs	1.07 (1.06–1.09)	<0.0001
Resting heart rate/10 beats/min	1.17 (1.06–1.29)	0.001
Charlson score	1.24 (1.16–1.32)	<0.0001
NYHA functional class III/IV	2.57 (1.60–4.12)	<0.0001
LVEF/10%	0.84 (0.75–0.94)	0.003
LVESDi model*		
Age, yrs	1.07 (1.05–1.09)	<0.0001
Resting heart rate/10 beats/min	1.17 (1.06–1.29)	0.002
Charlson score	1.23 (1.14–1.32)	<0.0001
NYHA functional class III/IV	2.85 (1.78–4.58)	<0.0001
LVESDi/1 mm/m^2	1.03 (1.00–1.07)	0.10
Survival in progressors (n = 228, 47 deaths)†		
LVEF model		
Age, yrs	1.06 (1.03–1.10)	0.0003
NYHA functional class III/IV	1.63 (0.76–3.48)	0.21
Charlson score	1.47 (1.23–1.77)	<0.0001
Time-dependent aortic valve/aortic surgery	0.34 (0.16–0.76)	0.008
LVEF/10%	0.73 (0.57–0.94)	0.01
LVESDi model		
Age, yrs	1.07 (1.03–1.10)	0.0004
NYHA functional class III/IV	1.67 (0.76–3.67)	0.20
Charlson score	1.45 (1.21–1.75)	<0.0001
Time-dependent aortic valve/aortic surgery	0.32 (0.14–0.72)	0.006
LVESDi/1 mm/m^2	1.10 (1.02–1.18)	0.02

*Models adjusted for sex, time-dependent progression (≥moderate-severe AR), and time-dependent aortic valve/aortic surgery. †After progression to ≥moderately severe AR. Variables at time of progression to ≥moderate-severe AR were used.

HR = hazard ratio; other abbreviations as in Tables 1 and 3.

years, respectively), which did not address patients with mild-to-moderate AR, we propose that those with baseline trivial/mild, mild-to-moderate, and moderate AR be followed whenever symptoms change, or every 5, 3, and 1 years, respectively. This strategy would allow identification of 1 case of moderately severe AR by screening an average of 15 to 17 patients (Figure 2).

Herein, we showed that the annualized progression rate was 4.2 mm^2/year for EROA and 9.9 ml/year for RVol at 3 years before transitioning to stage C/D AR, and the majority of patients (79%) remained at stage B AR. Unlike AS, which is assumed to be progressive in every patient, AR did not necessarily progress, akin to MR (5). This is likely because AS was mainly caused by calcific AV disease with an active ongoing process of inflammation, atherosclerosis, and ossification, whereas the mechanisms for AR were anatomic and related to root disease or abnormal valve structure (17).

The adverse consequences in progressors included faster chamber remodeling, confirming the effect of progressive AR on LV/left atrial enlargement, faster functional class decline, and the increased need for surgery. Of note, AVR rather than repair was performed in most patients; this implies patients had 1 disease (significant AR) traded for another (prosthesis and its inherent complications). These adverse consequences highlight the importance of recognizing aforementioned predictors of AR progression. It is also worth noting that the overall rate of LV remodeling was slow (Online Figure 2), and that LVEF is well-preserved in patients with stage B AR (Figure 4), when volume and pressure overload have not yet become hemodynamically prominent. Also, educating patients to be aware of new symptoms, which do not always coincide with LV dysfunction, is important (2).

Unlike stage B AS (18), determinants for survival in stage B AR have not been previously examined. Besides age, comorbidities, functional class, and LVEF, increased RHR was associated with mortality. Activation of sympathetic tone, increased oxygen demand, and LV burden may explain the association between higher RHR and mortality (19). Interestingly, the present study showed that patients with moderate AR had slower RHR and were less likely to be on beta-blockers compared with those having mild AR (Table 1). Activation of the parasympathetic system due to larger total stroke volume may emanate from more severe AR (moderate vs. mild AR). As for LVESDi, it seems to be more useful as a determinant for survival in stage C/D AR, not stage B AR in the present study. Last, although a shorter time to progression was predictive of outcome in tricuspid regurgitation (20), time to progression was not associated with survival in the present study.

CLINICAL IMPLICATIONS. Our study has several clinical implications for patients with stage B AR. First, the results provide supporting evidence to the TTE surveillance strategy endorsed by current guidelines and additionally provide recommendations for those having mild-to-moderate AR. Second, prediction of AR progression is challenging yet important for early intervention to improve outcomes (21). Potentially helpful strategies include identifying factors that place patients at high risk of progression (Table 2), and calculating the change of EROA and RVol during follow-up. If the change over time was negligible (Figure 3) and well below the annualized change we reported in progressors (Central Illustration), the patient is likely a nonprogressor. Third, patients need to know potential adverse effects of progression, including chamber remodeling, functional class decline, and the need for surgery.

Lastly, patients in stage B AR were not necessarily followed by cardiologists; our results may help other providers determine timing for referral.

STUDY LIMITATIONS. This retrospective study included only patients with quantitation of AR and at least 2 echocardiograms, and thus does not represent all patients with stage B AR. It is possible that those who received at least 2 TTE examinations tended to have more comorbidities. The interval between baseline and index TTE differed in progressors and nonprogressors because the interval of a follow-up TTE was not uniform, limiting the TTEs to choose from for comparison. Yet, we demonstrated that the progression rates of AR/chamber remodeling were negligible in nonprogressors, thus whichever follow-up TTE we selected for comparison should yield similar results. AV sclerosis/calcification and prolapse were not used for analysis; the former could be affected by the gain and harmonic settings (22), and the latter could be missed by a TTE. For definition of AR severity, the "mild-to-moderate" AR category could be subjective; however, we also showed consistent measurements on EROA/RVol and LV size (i.e., between those having mild and moderate AR) (**Table 1**). When analyzing rates of progression, we did not take mechanisms/etiologies of AR into account, which often require transesophageal echocardiography or surgical/pathological examination. Finally, we excluded patients who evolved to AS greater than mild degree at the end (mixed AV disease), whose outcome was not addressed in the present study.

CONCLUSIONS

Overall, patients with stage B AR had 36.1% 10-year risk of progression to hemodynamically significant AR. Our data provide evidence for current guidelines (3) on the interval of TTE follow-up. Two different progression patterns were observed; the majority of patients had an indolent natural course. Baseline annulus, STJ, and AR severity were predictive of progression to ≥moderate-severe AR. The progression rates for EROA and RVol were 4.2 mm^2/year for EROA and 9.9 ml/year for RVol in progressors, who had faster chamber remodeling, functional class decline, and the need for surgery. LVESDi was a more useful parameter for survival correlation after progression. Our results in stage B AR should help identify patients at increased risk of progression and patients with excess risks of mortality for tailored therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with stage B aortic regurgitation (AR), progression to stage C or D occurred in 21% during a median follow-up of 4.1 years. Baseline AR severity and the dimensions of the aortic valve annulus and sinotubular junction are associated with progression, whereas systolic blood pressure is not.

TRANSLATIONAL OUTLOOK: Future research should explore rates of progression according to the mechanism and etiology of AR.

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KEY WORDS aortic regurgitation, echocardiography, prognosis, progression

APPENDIX For supplemental results, figures, and tables, please see the online version of this paper.