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# Diastolic Blood Pressure and Heart Rate Are Independently Associated With Mortality in Chronic Aortic Regurgitation

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## ABSTRACT

**BACKGROUND** The prognostic significance of diastolic blood pressure (DBP) and resting heart rate (RHR) in patients with hemodynamically significant aortic regurgitation (AR) is unknown.

**OBJECTIVES** This study sought to investigate the association of DBP and RHR with all-cause mortality in patients with AR.

**METHODS** Consecutive patients with ≥ moderate to severe AR were retrospectively identified from 2006 to 2017. The association between all-cause mortality and routinely measured DBP and RHR was examined.

**RESULTS** Of 820 patients (age 59 ± 17 years; 82% men) followed for 5.5 ± 3.5 years, 104 died under medical management, and 400 underwent aortic valve surgery (AVS). Age, symptoms, left ventricular ejection fraction (LVEF), LV end-systolic diameter-index (LVESDi), DBP, and RHR were univariable predictors of all-cause mortality (all $p \leq 0.002$). When adjusted for demographics, comorbidities, and surgical triggers (symptoms, LVEF, and LVESDi), baseline DBP (adjusted-hazard ratio [HR]: 0.79 [95% confidence interval: 0.66 to 0.94] per 10 mm Hg increase, $p = 0.009$) and baseline RHR (adjusted HR: 1.23 [95% confidence interval: 1.03 to 1.45] per 10 beat per min [bpm] increase, $p = 0.01$) were independently associated with all-cause mortality. These associations persisted after adjustment for presence of hypertension, medications, time-dependent AVS, and using average DBP and RHR (all $p \leq 0.02$). Compared with the general population, patients with AR exhibited excess mortality (relative risk of death >1), which rose steeply in inverse proportion (p nonlinearity = 0.002) to DBP starting at 70 mm Hg and peaking at 55 mm Hg and in direct proportion to RHR starting at 60 bpm.

**CONCLUSIONS** In patients with chronic hemodynamically significant AR, routinely measured DBP and RHR demonstrate a robust association with all-cause death, independent of demographics, comorbidities, guideline-based surgical triggers, presence of hypertension, and use of medications. Therefore, DBP and RHR should be integrated into comprehensive clinical decision-making for these patients. (J Am Coll Cardiol 2020;75:29–39)


Chronic hemodynamically significant aortic regurgitation (AR) often exhibits a dramatic physical examination, ranging from vital signs (i.e., wide pulse pressure) to physical findings (1). This florid physical examination is in direct relation to the underlying AR pathophysiology in which a large total stroke volume is ejected in systole generating "bounding" peripheral pulses and then regurgitates into the left ventricle in diastole, resulting in decreased diastolic blood pressure (DBP) (1). This pathophysiology results in both increased preload and afterload (2); hence, patients with AR exhibit a wide pulse pressure and may develop systolic hypertension, which should be medically treated (3,4). Current valvular (4) and hypertension guidelines (3) hypothetically caution against the use of medications that could worsen volume overload by causing bradycardia and also hypothetically caution about marked

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**ABBREVIATIONS AND ACRONYMS**

**AR** = hemodynamically significant chronic aortic regurgitation

**AVS** = aortic valve surgery

**CCI** = Charlson comorbidity index

**DBP** = diastolic blood pressure

**EROA** = effective regurgitant orifice area

**LVEF** = LV ejection fraction

**LVESDi** = LV end-systolic diameter index

**RHR** = resting heart rate

**TTE** = transthoracic echocardiogram

DBP reduction (3) that could impair coronary perfusion. However, these concerns are only conjectural because the clinical significance of DBP and resting heart rate (RHR) in patients with AR is unknown. It is possible, however, that patients with AR and low DBP could display increased mortality as nonvalvular-disease populations with decreased DBP (J-phenomenon) (5,6). RHR is more puzzling, as well-compensated asymptomatic patients with AR tend to exhibit bradycardia at rest (7), yet it is an elevated RHR that has been associated with excess mortality in nonvalvular disease populations (8).

Therefore, our main objective was to investigate the prognostic significance of DBP and RHR in patients with AR, and whether these routinely measured parameters could predict outcomes independently of guideline-recommended surgical triggers, including symptoms, LV ejection fraction (LVEF), and LV end-systolic diameter index (LVESDi).

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## METHODS

**STUDY POPULATION AND CLINICAL DATA.** From January 2006, to October 2017, all consecutive patients with moderately severe or severe chronic AR by transthoracic echocardiogram (TTE) were retrospectively identified. Exclusion criteria included patients <18 years of age, patients with denied research authorization, or any of the following: > mild mitral regurgitation or stenosis; > mild aortic stenosis; any previous valvular surgery; congenital heart disease; hypertrophic, restrictive, or constrictive cardiomyopathies; carcinoid heart disease; acute aortic dissection; acute traumatic AR, and active endocarditis (Online Figure 1). Bicuspid, unicuspid and quadricuspid aortic valves, and tricuspid valve regurgitation were not excluded. Non-U.S. residents were excluded because of incomplete follow-up. After exclusions, 820 patients constituted the study cohort (748 patients belong to our previous cohort) (9). All patients had comprehensive cardiology and/or cardiovascular surgery evaluations within 30 days of TTE. At each visit, the physicians independently recorded baseline subjective symptoms and intensity of diastolic murmur (I to VI). These were meticulously abstracted from each patient's electronic medical record. Comorbid conditions recorded during AR consultation were electronically extracted by ICD-9,-10 codes, including systemic hypertension. Charlson comorbidity index (CCI) was calculated for each patient.

In our echocardiography laboratory, the measurements of blood pressure and RHR were routinely obtained and recorded in a quiet room after the patient was settled down for a few minutes, right before TTE was performed, by manual sphygmomanometry in approximately 75% of patients and automated cuff in the rest. The RHR was recorded directly from the echo machine in all patients as part of cardiac output/index determination. This study was approved by the institutional review board.

**ECHOCARDIOGRAPHY.** In patients with multiple TTEs, the first study with at least moderate to severe AR was used as baseline for analysis. TTE was performed by trained sonographers and reviewed by cardiologists with level III echocardiography training, using commercially available echo systems. Chamber quantification was performed according to guidelines (10). A comprehensive approach for diagnosis of severity of AR was used, including a combination of quantitative (proximal isovelocity surface area or quantitative pulsed Doppler-derived effective regurgitant orifice [EROA] and regurgitant volume), semi-quantitative measurements (vena contracta width [VCW], time-velocity integral of the reversed flow in the descending aorta), and qualitative observations (11). The severity of AR was graded as moderately severe (EROA 0.20 to 0.29 $cm^2$, RVol 45 to 59 ml/beat), and severe (VCW >0.6 cm, pressure half time [PHT] <200 ms, EROA ≥0.3 $cm^2$, RVol ≥ 60 ml/beat), using an integrated, comprehensive approach, including aforementioned parameters and diastolic flow reversal in the descending and abdominal aorta (11).

**OUTCOMES.** Our primary endpoint was all-cause death. Because of the known survival benefit associated with aortic valve surgery (AVS) (4), and to study the natural course of AR before surgical intervention, we assessed all-cause mortality under medical management. Therefore, follow-up began at baseline TTE and ended at AVS, death, or last follow-up. We also assessed all-cause mortality during the entire follow-up (observation ended at death or last follow-up) to verify our results. Secondary endpoints were AVS and the composite endpoint of AVS plus all-cause death. Mortality status and dates of death and last follow-up were retrieved using electronic medical records. For subjects not known to be deceased, linkage to mortality was done using Accurint (LexisNexis Risk Solutions, LexiNexis, New York, New York), a proprietary resource gathering multiple national sources,

**TABLE 1 Clinical and Echocardiographic Parameters at Baseline**

| | Total | DBP | | | RHR | |
|---|---|---|---|---|---|---|
| | (N = 820) | <55 mm Hg (n = 204) | 55–70 mm Hg (n = 339) | ≥70 mm Hg (n = 277) | <60 bpm (n = 319) | ≥60 bpm (n = 501) |
| Age, yrs | 59 ± 17 | 60 ± 19 | 60 ± 17 | 57 ± 16* | 61 ± 16 | 58 ± 18† |
| Women | 148 (18) | 40 (20) | 63 (19) | 45 (16) | 47 (15) | 101 (20)* |
| SBP, mm Hg | 130 ± 20 | 123 ± 19 | 129 ± 20 | 136 ± 19‡ | 130 ± 21 | 130 ± 20 |
| DBP, mm Hg | 64 ± 13 | 47 ± 5 | 62 ± 3 | 77 ± 7‡ | 64 ± 12 | 63 ± 13 |
| Resting heart rate, bpm | 64 ± 12 | 65 ± 13 | 63 ± 11 | 64 ± 11 | 53 ± 5 | 71 ± 10‡ |
| Body mass index, $m^2$/kg | 27.6 ± 5.3 | 27 ± 5 | 28 ± 5 | 28 ± 6 | 27 ± 4 | 28 ± 6* |
| Body surface area, $m^2$ | 2.01 ± 0.24 | 1.95 ± 0.23 | 2.01 ± 0.24 | 2.05 ± 0.24‡ | 2.01 ± 0.23 | 2.01 ± 0.24 |
| Baseline symptoms | 372 (46) | 107 (530 | 168 (50) | 97 (36)‡ | 112 (36) | 260 (53)‡ |
| NYHA functional class Class I+II | 687 (84) | 171 (84) | 282 (83) | 234 (84) | 290 (91) | 397 (79)‡ |
| Class III+IV | 101 (12) | 28 (14) | 46 (14) | 27 (10) | 20 (6) | 81 (16) |
| Indeterminate | 32 (4) | 5 (2) | 11 (3) | 16 (6) | 9 (3) | 23 (5) |
| Aortic valve surgery | 400 (49) | 121 (59) | 169 (50) | 110 (40)‡ | 133 (42) | 267 (53)† |
| Medical history | | | | | | |
| Hypertension (n = 820) | 420 (51) | 112 (55) | 178 (53) | 130 (47) | 167 (52) | 253 (50) |
| Diabetes mellitus (n = 752) | 32 (4) | 6 (3) | 13 (4) | 13 (5) | 10 (3) | 22 (5) |
| Hyperlipidemia (n = 752) | 288 (38) | 70 (38) | 125 (41) | 93 (36) | 130 (44) | 158 (35)* |
| Coronary artery disease§ (n = 820) | 74 (9) | 17 (8) | 25 (7) | 32 (12) | 35 (11) | 39 (8) |
| Atrial fibrillation at time of echo (n = 820) | 39 (5) | 7 (3) | 17 (5) | 15 (5) | 11 (3) | 28 (6) |
| Current/ever smoker (n = 803) | 344 (43) | 98 (49) | 138 (41) | 108 (40) | 135 (43) | 209 (43) |
| Chronic kidney disease > stage 3b (n = 736) | 50 (7) | 14 (8) | 25 (8) | 11 (4) | 13 (4) | 37 (8)* |
| Charlson comorbidity index (n = 801) | 1.66 ± 2.21 | 1.57 ± 2.15 | 1.53 ± 2.04 | 1.88 ± 2.42 | 1.79 ± 2.3 | 1.57 ± 2.09 |
| Hemoglobin (n = 759) | 13.6 ± 1.6 | 13.4 ± 1.5 | 13.4 ± 1.7 | 14.0 ± 1.3‡ | 13.8 ± 1.3 | 13.5 ± 1.7* |
| Medications | | | | | | |
| Beta-blockers (n = 685) | 365 (53) | 108 (62) | 150 (52) | 107 (48)* | 126 (48) | 239 (57)* |
| Diuretics (n = 685) | 385 (56) | 122 (70) | 162 (57) | 101 (45)‡ | 125 (48) | 260 (61)‡ |
| Calcium channel blockers (n = 685) | 197 (29) | 59 (34) | 94 (33) | 44 (20)‡ | 72 (27) | 125 (30) |
| ACE inhibitor or ARB (n = 685) | 311 (45) | 93 (53) | 127 (44) | 91 (40)* | 116 (44) | 195 (46) |
| Echo parameters | | | | | | |
| Bicuspid aortic valve | 296 (36) | 65 (32) | 110 (32) | 121 (44)* | 119 (37) | 177 (35) |
| LVEF, % | 59 ± 9 | 58 ± 10 | 59 ± 8 | 59 ± 9 | 60 ± 7 | 58 ± 10‡ |
| LVESD, mm | 40 ± 7 | 42 ± 8 | 40 ± 7 | 39 ± 6‡ | 40 ± 6 | 40 ± 7 |
| LVESDi, $mm/m^2$ | 20.2 ± 3.7 | 21.6 ± 4.0 | 19.9 ± 3.5 | 19.5 ± 3.5‡ | 19.9 ± 3.3 | 20.3 ± 4.0 |
| LVEDD, mm | 60 ± 7 | 62 ± 8 | 60 ± 7 | 59 ± 6‡ | 61 ± 7 | 60 ± 7 |
| Diastolic dysfunction‖ (n = 774) | 27.1 | 28.9 | 30.6 | 21.6* | 26.3 | 27.7 |
| Left atrial volume index, $ml/m^2$ (n = 771) | 39 ± 14 | 41 ± 16 | 40 ± 14 | 38 ± 13 | 42 ± 14 | 38 ± 14‡ |
| RVSP, mm Hg (n = 611) | 32 ± 10 | 34 ± 13 | 31 ± 11 | 30 ± 7* | 31 ± 9 | 32 ± 11* |
| Annulus, mm | 25.8 ± 3.6 | 25.6 ± 3.5 | 25.7 ± 3.8 | 25.9 ± 3.5 | 26.0 ± 3.6 | 25.6 ± 3.6 |
| Sinus of Valsalva, mm (n = 782) | 40.2 ± 5.9 | 39.3 ± 6.6 | 40.3 ± 5.6 | 40.7 ± 5.5 | 40.8 ± 5.3 | 39.8 ± 6.2* |
| Mid-ascending aorta, mm (n = 750) | 40.8 ± 7.4 | 38.6 ± 7.8 | 41.1 ± 7.6 | 42.0 ± 6.6‡ | 41.3 ± 6.8 | 40.4 ± 7.9 |
| Aortic regurgitation quantification | | | | | | |
| Regurgitant volume, ml (n = 687) | 70.6 ± 25.7 | 74.6 ± 24.5 | 69.4 ± 24.8 | 69.5 ± 27.4 | 74.5 ± 28.9 | 67.8 ± 22.8‡ |
| EROA, $mm^2$ (n = 649) | 29.5 ± 11.6 | 35 ± 13 | 28 ± 10 | 28 ± 11‡ | 27 ± 10 | 32 ± 12‡ |
| Vena contracta, mm (n = 685) | 5.9 ± 1.5 | 6.2 ± 1.6 | 5.9 ± 1.5 | 5.9 ± 1.5 | 5.9 ± 1.4 | 6.0 ± 1.6 |
| Descending aorta flow reversal time-velocity integral, cm/s (n = 695) | 14.8 ± 5.1 | 16.6 ± 6.1 | 14.5 ± 4.8 | 13.9 ± 4.3‡ | 15.3 ± 5.7 | 14.5 ± 4.5* |
| TTE-AR severity (severe) | 505 (62) | 146 (72) | 206 (61) | 153 (55)† | 202 (63) | 303 (60) |

Values are mean ± SD or n (%). *0.01 ≤ p <0.05, †0.001 ≤ p <0.01, and ‡p <0.001 between subgroups of DBP and RHR. §Coronary artery disease included known ischemic heart disease, previous coronary intervention (percutaneous coronary intervention and coronary artery bypass grafting), and previous myocardial infarction. ‖Diastolic dysfunction was defined as pseudonormalization or restrictive left-ventricular filling pattern.

ACE = angiotensin-converting enzyme; AR = hemodynamically significant chronic aortic regurgitation; ARB = angiotensin II receptor blockers; DBP = diastolic blood pressure; EROA = effective regurgitant orifice area; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESDi = end-systolic dimension index; NYHA = New York Heart Association; RVSP = right ventricular systolic pressure; SBP = systolic blood pressure; TTE = transthoracic echocardiogram.

on June 30, 2018. Subjects who were linked to Accurint and not found to be deceased were censored on December 31, 2017.

**STATISTICAL ANALYSIS.** Continuous variables, expressed as mean ± SD or median (interquartile range [IQR]) according to data distribution, were compared using the Student's *t*-test or Wilcoxon rank sum test, whenever appropriate. Categorical data, presented as percentages, were compared using chi-square test. Generalized linear and logistic regression models, both binary and ordinal, were used to compare continuous and categorical variables, respectively, between groups when adjustment for covariates was needed. Survival was illustrated using Kaplan-Meier curves and compared using the log-rank statistic. The primary endpoint of mortality under medical management was analyzed using the Cox-proportional hazard model. The proportional hazard assumption was evaluated both visually by plotting residuals versus time and formally by testing for a correlation between residual and time. No violations of the proportional hazard assumption were observed.

The main analysis was performed using different depths of multivariable adjustment: first for age, sex, CCI; second, adjusted additionally for guideline-based surgical triggers (symptoms, LVEF, LVESDi); and third, adjusted additionally for AR severity (moderately severe or severe). In combined models, guideline-based surgical triggers, medications, and cardiovascular risk factors were adjusted separately because of limited mortality count to avoid overfitting. Differences in effects of RHR and DBP by AVR or surgical triggers were tested by inclusion of an interaction term in the proportional hazards regression. Survival C-statistics were computed for these various models and p values for C-statistics comparisons were based on bootstrap standard errors from 1,000 bootstrap samples. We also computed the integrated discrimination improvement (IDI) to further compare risk discrimination among models. Confidence limits and p values were also based on the bootstrap samples. The associations of mortality with DBP/RHR were plotted using restricted cubic splines in which the number of knots was chosen based on goodness of fit chi-square test. The hazard ratio (HR) was plotted by using RHR 60 bpm and DBP 70 mm Hg as the referents. Expected mortality was derived, based on the mortality of subjects in the general population of similar age and sex, and excess mortality curves for DBP and RHR were plotted using penalized smoothing splines. All statistical analyses were performed using commercially available software (JMP 11 and SAS 9.4, SAS Institute, Cary, North Carolina). A 2-sided p value $<0.05$ was considered statistically significant.

## RESULTS

**BASELINE CHARACTERISTICS.** Baseline characteristics are displayed in **Table 1**, overall and by DBP and RHR. Notably, when compared with patients with AR and DBP ≥ 70 mm Hg and RHR <60 bpm, those with lower DBP (<70 mm Hg) and increased RHR (≥60 bpm) had more baseline symptoms, underwent more AVS, had lower hemoglobin, more use of medications at baseline, and higher right ventricular systolic pressure. Also, patients with the lowest DBP (<55 mm Hg) had larger LV, more severe AR (vs. moderate to severe), higher EROA, and underwent more AVS. Although patients with RHR ≥60 bpm had smaller regurgitant volume, they had larger EROA and underwent more AVS. Compared with those without hypertension (Online Table 1), hypertensive patients were older, had higher SBP, worse diastolic function, larger left atria, higher right ventricular systolic pressure, more chronic kidney disease, and more symptoms. However, their AR severity and LV parameters were not different from those without hypertension. The use of medications was driven by the presence of hypertension, but, of note, DBP was identical among those with and without hypertension (Online Table 1). The mechanisms of AR (12) included single mechanisms in 411 (50%; dilatation of annulus/sinotubular junction in 212, cusp prolapse in 103, cusp restriction/retraction in 86, and cusp fenestration or perforation in 10), mixed mechanisms (i.e., a combination of the aforementioned) in 355 (43%), and indeterminate in 54 (7%) patients.

**PREDICTORS OF ALL-CAUSE MORTALITY UNDER MEDICAL MANAGEMENT.** Mean follow-up was 5.5 ± 3.5 years, during which 400 patients (49% of the entire cohort) underwent AVS, and 153 died (104 deaths under medical management [endpoint of our study] and 49 deaths after AVS). Survival under medical management was 94 ± 1% at 1 year, 79 ± 2% at 5 years, and 63 ± 4% at 10 years.

Guideline-based surgical triggers (symptoms, LVEF, and LVESDi) were univariate predictors of death ($p \leq 0.0002$). After adjustment for age, sex, comorbidities, and guideline-based surgical triggers, separate multivariable analysis models revealed that lower DBP and higher RHR were each independently associated with all-cause death (models 1 and 2, **Table 2**). After further adjusting for severity of AR (moderate to severe vs. severe), similar HRs were noted (model 3, **Table 2**). A combined multivariable

**TABLE 2 Association of DBP and RHR With All-Cause Death, Aortic Valve Surgery, and the Combined Endpoint**

| | Models for All-Cause Death | | | |
|---|---|---|---|---|
| | Baseline DBP | | Baseline RHR | |
| | HR (95% CI) | p Value | HR (95% CI) | p Value |
| **All-cause death; follow-up under medical management; N = 820, 104 deaths** | | | | |
| Separate models for baseline DBP and baseline RHR (per 10-unit increase) | | | | |
| Univariate Cox analysis | 0.71 (0.60–0.84) | <0.001 | 1.29 (1.09–1.50) | 0.0015 |
| **Model 1.** + age, sex, CCI | 0.77 (0.65–0.91) | 0.0022 | 1.32 (1.12–1.55) | 0.0013 |
| **Model 2.** Model 1 + symptoms, LVEF, LVESDi | 0.78 (0.65–0.93) | 0.0063 | 1.24 (1.05–1.47) | 0.011 |
| **Model 3.** Model 2 + AR severity | 0.78 (0.65–0.93) | 0.0068 | 1.23 (1.03–1.46) | 0.017 |
| Combined model adjusted for age, sex, CCI, symptoms, LVEF and LVESDi | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.79 (0.66–0.94) | 0.009 | | |
| Baseline RHR, per 10 bpm increase | 1.23 (1.03–1.45) | 0.018 | | |
| Combined model adjusted for age, sex, CCI, calcium channel blockers, beta-blockers, diuretics, ACE inhibitors/ARB | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.76 (0.63–0.92) | 0.003 | | |
| Baseline RHR, per 10 bpm increase | 1.34 (1.11–1.58) | 0.001 | | |
| Combined model adjusted for age, sex, HTN, CKD stage ≥ 3b, ischemic stroke, coronary artery disease* | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.72 (0.59–0.86) | 0.0005 | | |
| Baseline RHR, per 10 bpm increase | 1.32 (1.10–1.58) | 0.003 | | |
| **All-cause death; entire follow-up (includes medical management, AVS, and post-AVS); N = 820, 153 deaths** | | | | |
| Model adjusted for age, sex, CCI, symptoms, LVEF, and LVESDi | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.84 (0.73–0.96) | 0.01 | | |
| Baseline RHR, per 10 bpm increase | 1.28 (1.11–1.47) | 0.0005 | | |
| Time-dependent aortic valve surgery | 0.84 (0.73–0.96) | 0.01 | | |
| Model adjusted for age, sex, CCI, symptoms, LVEF, LVESDi, calcium channel blockers, beta-blockers, diuretics, and ACE inhibitors/ARB | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.83 (0.72–0.96) | 0.009 | | |
| Baseline RHR, per 10 bpm increase | 1.29 (1.12–1.48) | 0.0004 | | |
| Time-dependent aortic valve surgery | 0.40 (0.26–0.62) | <0.0001 | | |
| **All-cause death; entire follow-up (includes medical management, AVS, and post-AVS); N = 820, 153 deaths** | | | | |
| Models adjusted for age, sex, symptoms, Charlson index, LVEF and LVESDi | | | | |
| Average DBP, per 10 mm Hg increase | 0.81 (0.68–0.97) | 0.02 | | |
| Average RHR, per 10 bpm increase | 1.29 (1.10–1.50) | 0.001 | | |
| Time-dependent aortic valve surgery | 0.41 (0.28–0.61) | <0.0001 | | |
| **Predictors of aortic valve surgery; N = 820, 400 had AVS** | | | | |
| Models adjusted for age, sex, symptoms, Charlson index, LVEF, and LVESDi | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.87 (0.80–0.95) | 0.002 | | |
| Baseline RHR, per 10 bpm increase | 1.10 (1.02–1.19) | 0.014 | | |
| **Composite endpoint of All-cause death and aortic valve surgery; N = 820, 153 deaths** | | | | |
| Models adjusted for age, sex, symptoms, Charlson index, LVEF and LVESDi | | | | |
| Baseline DBP, per 10 mm Hg increase | 0.86 (0.79–0.92) | 0.0001 | | |
| Baseline RHR, per 10 bpm increase | 1.13 (1.05–1.21) | 0.0008 | | |

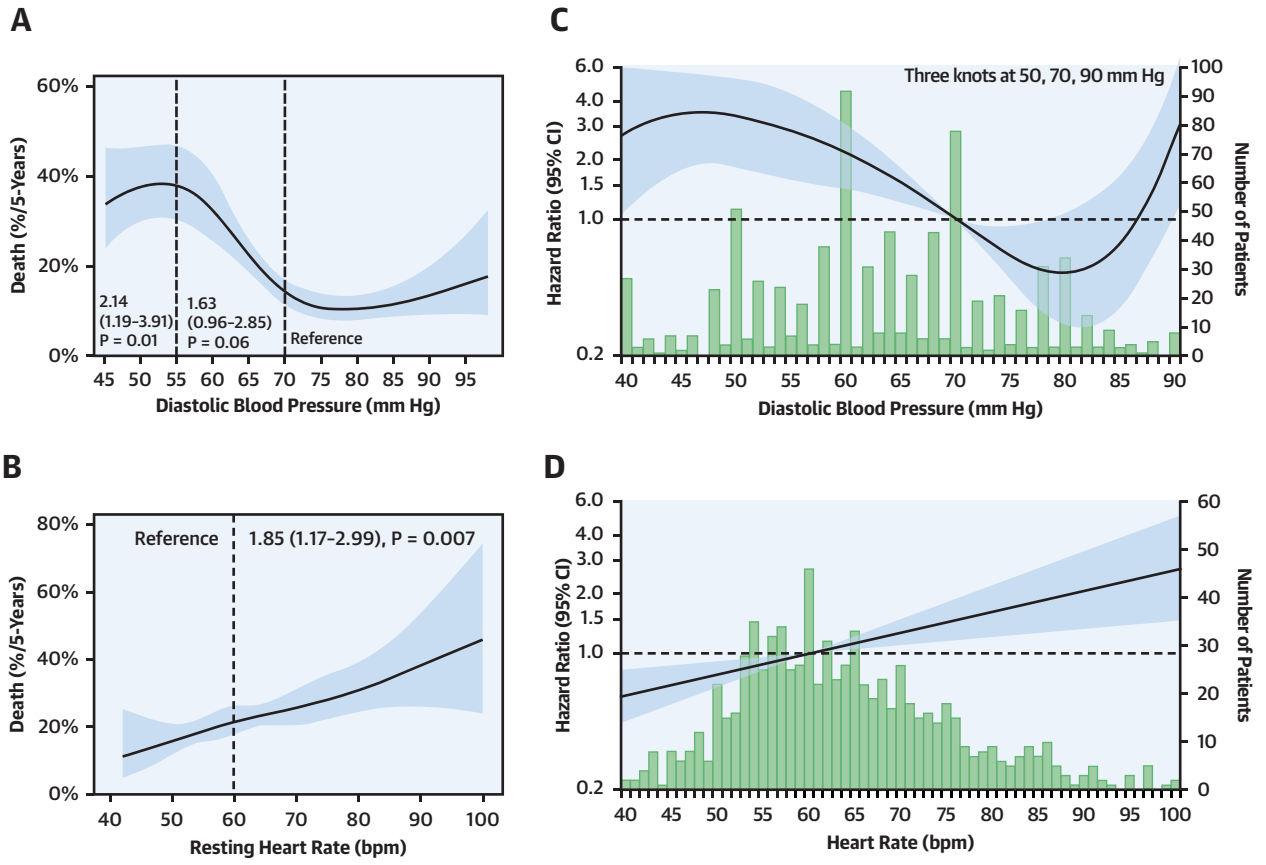
*See Table 1 for definition.

CCI = Charlson comorbidity index; CI = confidence interval; CKD = chronic kidney disease; DBP = diastolic blood pressure; HR = hazard ratio; RHR = resting heart rate; Other abbreviations as in Table 1.

model adjusting for baseline characteristics and guideline-derived surgical triggers demonstrated independent predictive power of DBP and RHR (Table 2). Adjustment for medications did not affect the mortality association for DBP and RHR (Table 2); except for diuretics, all medications were not univariately or multivariately associated with mortality. When we replaced CCI with hypertension, chronic kidney disease ≥3b, stroke, and coronary artery disease, the results were similar, confirming independent prognostic value of DBP and RHR (Table 2).

Systolic blood pressure and the intensity of AR diastolic murmur were not univariate predictors of mortality ($p \geq 0.1$), but the intensity of the murmur was associated with increased EROA and regurgitant volume (both $p < 0.001$). Although less prominent than DBP, there was an association between pulse

**FIGURE 1** Risk of Death by DBP and RHR in Patients Under Medical Management



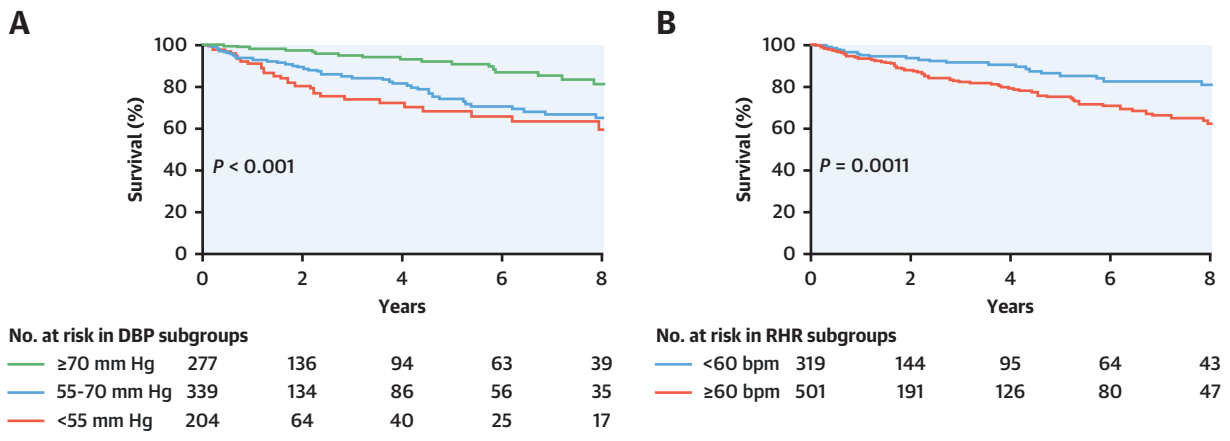

Spline models show that 5-year mortality starts to increase in patients with **(A)** DBP <70 mm Hg and **(B)** RHR ≥60 bpm. Patients with DBP ≤ 55 mm Hg and RHR ≥60 bpm had 2.1-fold (95% CI: 1.19 to 3.91; p = 0.01) and 1.8-fold (95% CI: 1.17 to 2.99; p = 0.007) excess risk of death, respectively, in models adjusted for age, sex, Charlson score, symptoms, LVEF, and LVESDi. Relative risk of mortality crosses 1.0 when **(C)** DBP <70 mm Hg and **(D)** RHR ≥60 bpm; **green bars** show the distribution of patients across different values of DBP and RHR. Nonlinearity test p = 0.002 and p = 0.89 for DBP and RHR, respectively. Note that the beginning of the tall portion of the J-curve for DBP is interrupted (right side of **A** and **C curves**) because there are few patients with AR who have higher DBP, yet the risk of mortality begins to rise after DBP >85 mm Hg. The risk ratio and 95% confidence interval are expressed by the **solid line** and **blue shaded area**, respectively.
AR = aortic regurgitation; bpm = beats per min; DBP = diastolic blood pressure; LVEF = left-ventricular ejection fraction; LVESDi = left-ventricular end-systolic diameter index; RHR = resting heart rate.

pressure and mortality (HR per 10 mm Hg increase, 1.1; 95% confidence interval [CI]: 1.01 to 1.24; p = 0.02) in a model adjusted for age, sex, CCI, symptoms, LVEF, LVESDi, and RHR.

**DBP/RHR CUTOFFS FOR PREDICTING ALL-CAUSE MORTALITY UNDER MEDICAL MANAGEMENT.** Using a spline fit, the association between 5-year mortality and DBP was mimicking the tail of a J-curve (nonlinearity p = 0.002): risk started to rise at DBP <70 mm Hg and peaked at 55 mm Hg (**Figures 1A and 1C**). Risk of death started to increase again at DBP >80 to 85 mm Hg but with very few patients with AR in this category (**Figure 1C**), the usually taller part (right portion) of the J-curve appears "interrupted." For RHR, 5-year mortality risk started to rise when RHR ≥60 bpm and continued to increase in a linear fashion (nonlinearity test p = 0.89) (**Figures 1B and 1D**). Kaplan-Meier curves showed survival differences according to subgroups of DBP and RHR (**Figure 2**; **Central Illustration, panel A**).

When compared with expected age- and sex-matched general population, patients with AR exhibited a continuous higher overall risk of death under medical management, which rose sharply in

**FIGURE 2** Kaplan-Meier Survival of Patients Under Medical Management, by Diastolic Blood Pressure (DBP) and Resting Heart Rate (RHR)




Patients with **(A)** DBP <70 mm Hg and **(B)** RHR ≥60 bpm had worse 8-year survival.

direct proportion to RHR and inverse proportion to DBP (Central Illustration, panel B).

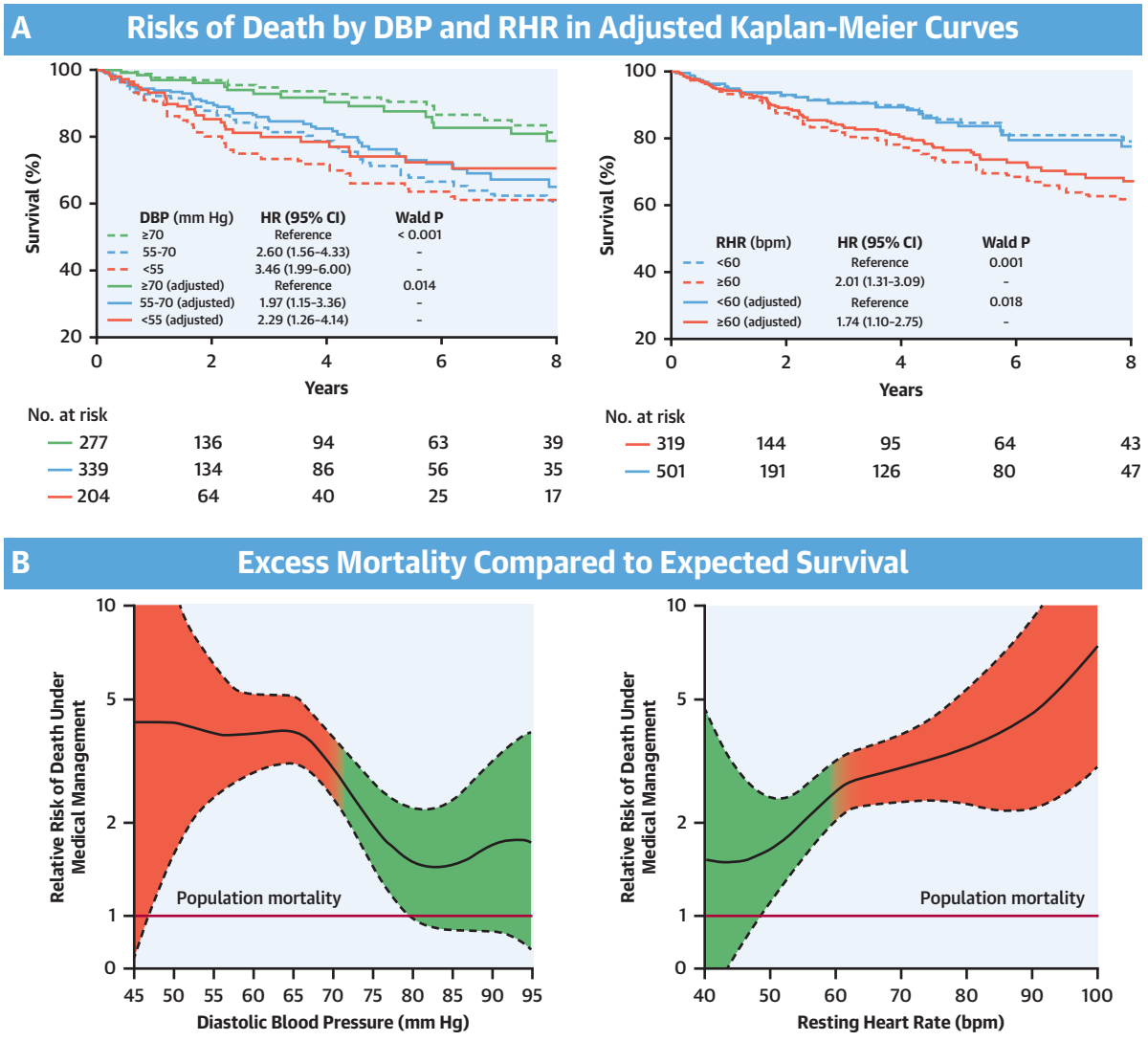
**MORTALITY RISK-DISCRIMINATING VALUE OF DBP AND RHR.** Adding guideline-based surgical triggers on top of baseline characteristics showed an increase of C-statistic from 0.74 to 0.79 (change in C-statistic = 0.05, p = 0.005) (Table 3, model 3). Further addition of DBP and RHR modestly increased C-statistic from 0.79 to 0.81 (change in C-statistic = 0.02, p = 0.03) (Table 3, model 4). Of note, the addition of DBP and RHR on top of baseline characteristics only provided similar risk discriminating value as surgical triggers by increasing C-statistic from 0.74 to 0.78 (Table 3, model 2). Improvement in risk discrimination was also supported by the IDI calculations for each model (Table 3).

**CONSISTENCY OF DBP AND RHR AS SURVIVAL PREDICTORS.** The aforementioned independent associations were from 1-time measurement of DBP and RHR at baseline, and their association with mortality was examined under medical management (i.e., censor at AVS). To assess the consistency/reliability of these findings, we performed the following analyses: 1) multivariable models for the entire follow-up, using baseline DBP/RHR and time-dependent AVS; and 2) multivariable models for the entire follow-up with averaged DBP and RHR measurements obtained within ± 2 weeks of baseline TTE. At least 1 additional office measurement was found in 90% and 83% of patients for DBP and RHR, respectively. The median of total office measurements within ± 2 weeks to baseline was 3 (IQR: 2 to 5) and 3 (IQR: 2 to 4) for DBP and RHR, respectively. The average DBP in patients with baseline DBP <55, 55 to 70, ≥70 mm Hg were 53 ± 8, 62 ± 7, and 73 ± 8 mm Hg, respectively (p < 0.0001). The average RHR in patients with baseline RHR <60 and ≥60 bpm were 58 ± 7 and 73 ± 10 bpm, respectively (p < 0.0001). Multivariable models for the entire follow-up, using baseline DBP and RHR (Table 2), and for the entire follow-up using averaged DBP and RHR (Table 2), revealed that lower DBP and higher RHR were still independently associated with all-cause mortality.

With regard to mortality association of DBP and RHR in patients without NYHA (New York Heart Association) functional class I or IIa triggers, we tested the interaction between NYHA functional class I/IIa surgical triggers and DBP (p = 0.08) or RHR (0.31), suggesting no strong association between NYHA functional class I/IIa triggers and DBP/RHR and RHR in particular. Despite limited statistical power (only 43 deaths in patients without triggers), RHR was associated with mortality in patients without class I/IIa triggers (Online Table 2, Section I), but not DBP. DBP and RHR were strongly correlated with mortality in those with triggers (Online Table 2, Section II).

**PREDICTORS OF SURGERY, COMPOSITE ENDPOINT, POST-AVS SURVIVAL AND REDUCED LV REVERSE REMODELING.** Lower DBP and higher RHR were independently associated with the need for AVS and the composite endpoint of AVS plus all-cause death

**CENTRAL ILLUSTRATION** **Risks of Death by Increasing Resting Heart Rate and Decreasing Diastolic Blood Pressure**




Yang, L.-T. et al. J Am Coll Cardiol. 2020;75(1):29-39.

**(A)** Kaplan-Meier curves adjusted for age, sex, Charlson index, symptoms, LVEF, and LVESDi showed increased risks of death when DBP dropped below 70 mm Hg and when RHR rose >60 bpm. **(B)** Spline curves representing the relative risk of excess mortality compared with expected survival in the general population. The **y-axis** represents the relative risk of excess mortality with risk of 1 as the referent mortality of the age- and sex-matched general population, where risk >1 indicates excess mortality. The salient point of this graph is that, compared with the general population, patients with hemodynamically significant AR under medical management exhibited a persistent excess risk of death, which increased steeply with low DBP (starting at DBP <70 mm Hg) and high RHR (starting at RHR >60 bpm).
AR = aortic regurgitation; bpm = beats per min; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; LVEF = left-ventricular ejection fraction; LVESDi = left-ventricular end-systolic diameter index; RHR = resting heart rate.

(Table 2). After surgery, higher RHR (adjusted HR: 1.30; 95% CI: 1.03 to 1.62; p = 0.024) continued to be associated with post-AVS survival but not DBP (p = 0.7), presumably because the pathophysiology underlying low DBP was corrected by AVS. These findings were supported by the interaction test of time-dependent AVS with DBP (p = 0.07) and RHR (p = 0.47). Of 400 patients having AVS, 238 (60%) had last available post-AVS TTE at a median of 2.6 (IQR: 1.1 to 6.5) years post-AVS and at a median of

**TABLE 3 Incremental Risk-Discriminating Value of DBP and RHR on Top of Guideline-Derived Surgical Triggers**

| Models | C-Statistic | 95% CI | Change in C-Statistic* | p Value | IDI (95% CI), p Value | Relative IDI% (95% CI) |
|---|---|---|---|---|---|---|
| **Model 1.** Age, sex, and CCI (Reference) | 0.748 | (0.700, 0.796) | – | – | – | – |
| **Model 2.** Model 1 + DBP + RHR | 0.783 | (0.738, 0.827) | 0.039 (0.010, 0.067) | 0.008† | 0.04 (0.01, 0.10) p < 0.001 | 27 (4, 69) |
| **Model 3.** Model 1 + symptoms, LVEF, and LVESDi | 0.796 | (0.754, 0.838) | 0.052 (0.016, 0.089) | 0.005† | 0.08 (0.03, 0.15) p < 0.001 | 49 (14, 106) |
| **Model 4.** Model 3 + DBP + RHR | 0.812 | (0.772, 0.853) | 0.017 (0.001, 0.033) | 0.03‡ | 0.04 (0.01, 0.10) p < 0.001 | 17 (3, 40) |

*Change in C-statistic, confidence interval, and p value calculated based on 1,000 bootstrap samples. †p value indicates changes in C-statistic in comparison to **model 1**. ‡p value indicates changes in C-statistic in comparison to **model 3**.

IDI = integrated discrimination improvement.

3.2 (IQR: 1.3 to 7.0) years from baseline TTE. Compared with baseline, LVEDD, LVESD, and LVESDi had decreased significantly at last available post-AVS TTE (all $p < 0.0001$), whereas LVEF remained similar (**Table 4**). Reduced reverse LV remodeling was defined as LVEDD >56 mm, LVESD >38 mm, and LVESDi >18 mm/m$^2$ at last-available post-AVS TTE; these cutoffs were derived from 75th percentile values at last-available TTE post-AVS. Baseline-higher RHR was predictive of reduced reverse LV remodeling in terms of LVESDi (**Table 4**), and baseline DBP was not.

## DISCUSSION

In this large contemporary cohort of consecutive patients with hemodynamically significant chronic AR, we report, to the best of our knowledge, for the first time the prognostic significance of DBP and RHR. The main results are as follows: 1) routinely-measured DBP and RHR were robust predictors of all-cause mortality, independent of guideline-recommended surgical triggers, medications, and hypertension; 2) there was a nonlinear, inverse relationship between DBP and mortality, whereas the relationship between RHR and mortality was directly proportional and linear; 3) for DBP, excess mortality began to rise at 70 mm Hg and peaked at 55 mm Hg, and for RHR it began to rise at 60 bpm; 4) compared with the general population, patients with AR incurred excess risk of death, which rose steeply with increased RHR and with lower DBP (**Central Illustration**); and 5) after AVS, DBP ceased to predict mortality, whereas RHR continued to predict post-AVS mortality and was also associated with post-AVS reduced LV reverse remodeling.

**TRADITIONAL CLINICAL PARADIGMS IN AR.** The clinical paradigms upon which management of AR has revolved include avoidance of bradycardia (4); avoidance of marked reduction of DBP (3); and use of symptoms and LV function/size as surgical triggers. Of these paradigms, only surgical triggers have been prospectively (13) and retrospectively (9) studied showing clear associations with adverse outcomes. Although bradycardia would theoretically worsen regurgitant volume, artificially induced bradycardia in patients with AR has resulted in inconclusive physiologic observations (14), but, more importantly, there were no outcomes studies addressing RHR in AR until now. In addition, low DBP has been a mere feature of severe AR that explains the wide pulse pressure; however, there were no outcome data supporting the theoretical concern of low DBP in AR until now.

**DBP AND RHR IN AR: A CLINICAL PARADIGM SHIFT.** Our study demonstrated that, akin to patients without AR (5,6,15), low DBP was associated with all-cause mortality in patients with AR in a similar J-curve fashion ("interrupted J-curve" in our study) (**Figure 1A to 1C**), independent of guideline-based surgical triggers, hypertension, and medications. Low DBP in AR, therefore, should not be regarded as an irrelevant finding but as an independent risk factor for death that should be integrated into comprehensive clinical decision making.

Patients with lower DBP had more severe AR (larger EROA and LV dimensions), required more surgery, and were older (**Table 1**). Hence, the cause of low DBP could be multifactorial, including severe AR and possibly coexistent aortic stiffness (16). The "interrupted" J-curve exposes an absence of DBP "reserve" in these patients (**Figure 1C**)—a particularly relevant concept in light of current hypertension guidelines recommending intensive reduction of BP (3,17)—with our study suggesting that awareness and possibly avoidance of very low DBP could be important in patients with AR treated for hypertension. Nonetheless, it is essential to recognize that low DBP was a robust marker of death independent of hypertension and medications in this study, DBP was similar between hypertensive and nonhypertensive patients (Online Table 1), and medications (except diuretics) were not even univariate predictors of mortality. Importantly, the 70 mm Hg cutoff for DBP mirrors findings from other nonvalvular

**TABLE 4 Association Between RHR* and Reduced Left-Ventricular Reverse Remodeling at Last Available Post-AVS TTE†**

| | 95% CI | p Value |
|---|---|---|
| Predictors for LVESD >38 mm at last available TTE (N = 53)‡ | | |
| Baseline RHR, per 10 bpm increase | 1.36 (1.13–1.62) | 0.001 |
| Baseline LVESD, mm | 1.04 (1.01–1.06) | 0.001 |
| Predictors for LVESDi >18 mm/m$^2$ at last available TTE (N = 70)‡ | | |
| Baseline RHR, per 10 bpm increase | 1.23 (1.03–1.45) | 0.017 |
| Baseline LVESDi, mm/m$^2$ | 1.10 (1.05–1.16) | <0.0001 |

*Baseline RHR was a univariable predictor of LVESD >38 mm and LVESDi >18 mm/m$^2$ but not a univariable predictor of LVEDD > 65 mm. †Compared with baseline TTE, LVEDD (62 ± 7 vs. 53 ± 8 mm), LVESD (42 ± 7 vs. 35 ± 8 mm) and LVESDi (20.5 ± 3.8 vs. 17.3 ± 3.6 mm/m$^2$) decreased significantly (all p < 0.0001), whereas LVEF (58 ± 9 vs. 57 ± 10%) was similar. ‡Models were adjusted for baseline age, sex, and symptoms.

Abbreviations as in Table 1.

studies (5,15,18), and the mean DBP of our cohort (i.e., 64 mm Hg) was similar to previous AR studies (19,20).

Contrary to current thinking, our study demonstrates that it is not bradycardia but an increasing RHR that exhibits a linear-risk association with all-cause death in patients with AR. In our study cohort, 45% of patients presented with RHR ≤60 bpm (**Figure 1D**), supporting the clinical observation of relative bradycardia in patients with hemodynamically significant AR (7). We hypothesize that increased total stroke volume in AR could activate parasympathetic tone, which slows RHR in patients with well-compensated AR. We further suggest that as the severity of AR overwhelms the LV, sympathetic tone activation occurs (8), resulting in higher RHR, increased myocardial oxygen consumption, and further LV burden, resulting in worse outcomes. Likewise, we hypothesize that very low DBP could result in coronary hypoperfusion of an already hypertrophied myocardium, leading to worse outcomes. These hypotheses, however, require physiologic studies for corroboration. Notwithstanding, clinically, the simple combination of lower DBP and higher RHR provided incremental risk-discrimination value to baseline characteristics and guideline-based surgical triggers (**Table 3**). Consequently, we propose that a patient with chronic, significant AR presenting with DBP in the low 60s or 50s mm Hg and RHR in the 70s or 80s should be referred to specialized care (i.e., valvular heart team), independently of other triggers, for close follow-up and further evaluation, given their heightened risk of death. In addition, we propose that during interval follow-up of these patients, a decreasing DBP and increasing RHR in subsequent visits should be red flags of a hemodynamic change linked to increased risk of death, prompting referral to specialized care to determine if surgical intervention is warranted. In patients with equivocal symptoms (i.e., patients in whom the link between symptoms and AR is unclear), additional information from hemodynamic markers of bad outcome (DBP and RHR) could also be helpful. Finally, it is important to note that the cutoffs of DBP (70 mm Hg) and RHR (60 bpm) represent points at which risk of death begins to rise and be noticeable within a continuum of cumulative risk, such that clinicians should pay attention to noticeable values (i.e., DBP <60 to 65 mm Hg, RHR 70 to 80 bpm) or gradual decreases in DBP and increases in RHR in subsequent visits, instead of rigid cutoffs.

**STUDY LIMITATIONS.** The observational nature of our study does not support inference of a causal relationship among DBP, RHR, and mortality. The retrospective nature of our study increases the potential for referral and selection bias within patients chosen for AVS versus medical management. Nonetheless, the independent association of DBP and RHR with all-cause mortality was observed in both medically managed patients and the entire cohort (medically managed plus AVS). We did not report cardiac death; however, we reported all-cause mortality, which is the most robust outcome. Retrospective analysis of cause-of-death data derived from death certificates is subject to inconsistencies and biases (21). The nature of our study precluded the assessment of differences in duration, dosage, compliance, and changes in the medications reported at baseline; therefore, conclusions regarding medication use in patients with AR cannot be made. In addition, the purpose of this study was to investigate the prognostic significance of DBP and RHR in patients with AR, and not the causes of low DBP. Yet, even after adjustment for medications, low DBP and high RHR remained robustly associated with all-cause mortality. Our findings are not applicable to younger patients with rheumatic heart disease, which is a rare cause for isolated AR. Finally, our study was composed of adult patients who were predominantly white.

## CONCLUSIONS

This large contemporary, real-world cohort demonstrated that in patients with chronic hemodynamically significant AR, routinely measured DBP and RHR are associated with all-cause mortality; lower DBP (<70 mm Hg) and higher RHR (>60 bpm) are robust predictors of mortality, independent of guideline-based surgical triggers, medications, and

hypertension. These low-cost clinical markers, which can be easily obtained by general practitioners and specialists, provide added value to current guidelines, serving as red-flag alerts for increased risk of death in these patients. These findings represent a clinical paradigm shift and should be integrated into comprehensive clinical decision making.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In patients with hemodynamically significant, chronic AR, resting DBP below 70 mm Hg and heart rate above 60 bpm are associated with higher all-cause mortality, independent of hypertension and medications or indications for valve surgery.

**TRANSLATIONAL OUTLOOK:** Future research should explore the physiological mechanisms underlying these associations of resting heart rate and DBP with mortality in patients with chronic AR.

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**KEY WORDS** aortic regurgitation, diastolic blood pressure, heart rate, mortality

**APPENDIX** For a supplemental figure and tables, please see the online version of this paper.