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Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease

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Citation

Butcher, S. C. (2023, September 7). *Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease*.

Version: Publisher's Version

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Prevalence and Prognostic Implications of Moderate or Severe Mitral Regurgitation in Patients with Bicuspid Aortic Valve

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J Am Soc Echocardiogr. 2022 Nov 1;S0894-7317(22)00568-5. doi: 10.1016/j.echo.2022.10.019.

ABSTRACT

Background

Significant ($\geq$ moderate) mitral regurgitation (MR) could augment the hemodynamic effects of aortic valvular disease in patients with bicuspid aortic valve (BAV), imposing a greater hemodynamic burden on the left ventricle and atrium, possibly culminating in a faster onset of left ventricular (LV) dilation and/or symptoms. The aim of this study was to determine the prevalence and prognostic implications of significant MR in patients with BAV.

Methods

In this large, multicenter, international registry, a total of 2,932 patients (48 ± 18 years, 71% male) with BAV were identified. All patients were evaluated for the presence of significant primary or secondary MR by transthoracic echocardiography and were followed-up for the endpoints of all-cause mortality and event-free survival.

Results

Overall, 147 patients (5.0%) had significant primary (1.5%) or secondary (3.5%) MR. Significant MR was associated with all-cause mortality (HR 2.80, 95% CI 1.91 to 4.11, $p < 0.001$) and reduced event-free survival (HR 1.97, 95% CI 1.58 to 2.46, $p < 0.001$) on univariable analysis. MR was not associated with all-cause mortality (adjusted HR 1.33, 95% CI 0.85 to 2.07, $p = 0.21$) or event-free survival (adjusted HR 1.10, 95% CI 0.85 to 1.42, $p = 0.49$) after multivariable adjustment. However, sensitivity analyses demonstrated that significant MR not due to aortic valve disease retained an independent association with mortality (adjusted HR 1.81, 95% CI 1.04 to 3.15, $P = 0.037$). Subgroup analyses demonstrated an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation (HR 2.037, 95% CI 1.025 to 4.049, $p = 0.042$), although this association was not observed for subgroups with significant aortic stenosis or without significant aortic valve dysfunction.

Conclusions

Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality.

INTRODUCTION

Bicuspid aortic valve (BAV) is frequently associated with other congenital cardiac abnormalities, such as aortic coarctation, hypoplastic left heart syndrome, Shone's syndrome or reversal of coronary artery dominance¹⁻⁵. In addition, several studies have suggested an association between BAV and primary mitral regurgitation (MR), although further research is required to confirm this relationship⁶⁻⁹. Severe aortic stenosis or regurgitation due to BAV may also be associated with left ventricular (LV) remodeling and dysfunction, which can lead to secondary MR.

In patients with BAV, significant ($\geq$ moderate) MR could augment the hemodynamic effects of coexistent aortic valvular disease^{10, 11}, imposing a greater hemodynamic burden on left ventricle and atrium, conceivably culminating in a faster onset of LV dilation or symptoms, or a poorer long-term outcome¹². Although previous studies have demonstrated that significant MR is independently associated with an adverse prognosis in the general population^{13, 14}, until now, the prognostic importance of significant MR in patients with BAV had not been investigated.

In this context, the aims of this study were i) to determine the prevalence of significant primary and secondary MR in patients with BAV, and ii) to investigate the association of significant MR with overall survival and event-free survival in individuals with BAV.

METHODS

Study population

From an international, multicenter registry of patients with BAV, patients with MR were identified¹⁵. Individuals with previous aortic or mitral valve surgery, endocarditis of the mitral valve or complex congenital heart disease were excluded. Demographic (including age, sex and body surface area calculated by the Mosteller method¹⁶), clinical data and cardiovascular risk factors (hypertension, dyslipidemia, diabetes and smoking history¹⁷⁻¹⁹) were collected from medical records at the time of the first diagnosis of BAV by transthoracic echocardiography. Coronary artery disease was defined as a history of previous myocardial infarction or revascularization, or coronary artery stenosis $\geq 50\%$ on coronary angiography. Data were collected according to the regulations approved by institutional review boards of each research center and retrospectively analysed. Due to the retrospective study design and anonymous handling of clinical data, the ethical committees of participating centers waived the need for written informed consent. This investigation conforms to the principles outlined in the *Declaration of Helsinki*. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Echocardiography

All echocardiograms were performed using commercially available equipment and were retrospectively analyzed by experienced investigators in each centre. The first transthoracic echocardiogram confirming a diagnosis of BAV was considered as the index study. The phenotype of BAV was defined according to the classification proposed by Sievers and Schmidtke²⁰: type 0, valve without raphe; type 1, valve with one raphe (which is further sub-classified according to the orientation of the raphe in relation to the coronary sinuses); and type 2, valves with two raphes. The presence of either aortic valve stenosis and/or regurgitation was assessed and graded as none, mild, moderate, and severe according to current guidelines, where moderate or severe grading was considered as significant^{21,22}. MR was assessed and classified according to the mechanism: primary (organic/structural intrinsic mitral valve disease) or secondary (without evident structural abnormality of the mitral valve). The severity of MR was graded as none, mild, moderate, and severe according to guideline recommendations, integrating qualitative, semiquantitative and quantitative parameters²³. Vena contracta (VC) width was measured from an apical four-chamber view at the narrowest portion of the regurgitant flow at the regurgitant orifice. The effective regurgitation orifice area (EROA) and regurgitant volume were calculated using the proximal isovelocity surface area method²³. Mitral valve prolapse was evaluated in the parasternal long-axis window and was defined as systolic displacement of the mitral leaflet/s into the left atrium of at least 2 mm from the mitral annular plane²³. A mixed aetiology of significant MR was defined as including components of both primary and secondary MR²³. The diameter of the aortic root and ascending aorta (4 to 5 cm distal to the sinotubular junction) were measured by two-dimensional (2D) echocardiography on the parasternal long-axis view using the leading edge-to-leading edge convention in an end-diastolic frame²⁴. The aortic dilatation configurations were reported following the classification by Fazel and colleagues: aortic root dilatation only, ascending aorta dilatation only and diffuse involvement of both aortic root and ascending aorta²⁵. LV end-diastolic diameter and LV end-systolic diameter were calculated using the linear 2D approach. LV ejection fraction (LVEF) and LV end-diastolic volume were calculated using the biplane Simpson method²⁴. All other standard measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines²⁴.

Follow-up

The primary endpoint of the study was all-cause mortality. Follow-up started at the time of the index echocardiogram confirming the diagnosis of BAV. The secondary endpoint was a composite of aortic valve repair/replacement and all-cause mortality (event-free survival). Indications for aortic valve surgery were based on contemporary guidelines^{26,27}. Data of all patients were included up to the last date of follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages and were compared using the Pearson χ^2 test. Adherence to a normal distribution was evaluated by comparing histograms to overlaid normal probability curves. Normally distributed continuous variables are presented as mean $\pm$ standard deviation and were compared using the Student *t*-test or one-way ANOVA, while non-normally distributed parameters are presented as median and interquartile range (IQR) and were compared with the Mann-Whitney *U* or Kruskal-Wallis test. Multiple comparisons were tested using Bonferroni's correction. The association between BAV morphology and significant primary MR with prolapse of the anterior mitral valve leaflet was evaluated with logistic regression.

Cumulative 1- and 5- year survival rates were estimated using the Kaplan Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was performed to investigate the association of significant MR with all-cause mortality and event-free survival. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. Prespecified clinical and echocardiographic variables known to be associated with all-cause mortality or event-free survival were entered into the respective multivariable models, with additional adjustment for aortic root/ascending aorta dilation in the model evaluating the combined endpoint. Aortic root/ascending aorta diameter ≥ 50 mm was defined as aortic root/ascending aorta dilation, to reflect current guideline indications for surgical intervention²⁸. Sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for each multivariable Cox regression model that evaluated all-cause mortality as the endpoint. In addition, further sensitivity analyses evaluating the prognostic implications of significant MR stratified according to etiology (due to aortic valve disease or not) were performed. The proportional-hazards assumption was verified with the evaluation of scaled Schoenfeld residuals.

In addition, subgroup analyses of BAV patients with significant aortic regurgitation, significant aortic stenosis and without significant aortic valvular disease were performed. The relationship of significant MR with all-cause mortality and event-free survival were examined for each subgroup in univariable and multivariable Cox regression models. Multivariable subgroup analyses were limited to adjustment of four pre-specified variables (age, diabetes mellitus, LV end-diastolic volume and LVEF) due to the risk of model overfitting²⁹. All tests were two-sided and *P* values < 0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient population

A total of 2932 patients with BAV (mean age 48±18 years, 71% male) met the study inclusion criteria (Figure 1). Significant MR was identified in 148 patients (5%), with primary MR observed in 44 (1.5%) patients and secondary MR in 104 (3.5%) patients. Individuals with significant MR were older and more likely to have diabetes mellitus. Overall, the most frequently encountered BAV morphology was type 1 with raphe fusion between the right and left coronary cusps (Table 1). Patients with significant primary MR were more likely to have a type 1 raphe with left and non-coronary cusp fusion compared to patients without significant primary MR (19.0% vs 4.6%, $p<0.001$) (Figure 2). Furthermore, the presence of a type 1 raphe with left and non-coronary cusp fusion was associated with a significantly higher prevalence of significant MR due to prolapse of the anterior mitral valve leaflet compared to patients with other BAV morphologies (OR 6.76, 95% CI 2.42 to 18.90, $p<0.001$). Etiologies of significant primary MR included mitral valve prolapse (57%), leaflet calcification (18%), rheumatic heart disease (5%), leaflet billowing (5%), mitral valve cleft (2%), parachute mitral valve (2%), and mixed (11%). Of those with secondary MR, the etiology was aortic valve disease in 76 (73%), non-ischemic cardiomyopathy in 11 (11%), ischemic cardiomyopathy in 8 (8%), hypertensive cardiomyopathy in 3 (3%), atrial functional MR in 2 (2%) and unclear aetiology in 4 (4%). The clinical and demographic characteristics of the total population are summarised in Table 1.

Table 1: Clinical and BAV characteristics of patients divided according to mitral regurgitation mechanism.

	Total population (n=2932)	No significant MR (n=2784)	Significant MR (n=148)	P value
Clinical characteristics				
Age (years)	47.9 (±17.7)	47.3 (±17.5)	59.0 (±17.5)	<0.001
Male (%)	2065 (70.5%)	1961 (70.5%)	104 (70.3%)	0.960
Prior CAD (%)	216 (8.0%)	198 (7.8%)	18 (12.6%)	0.040
BSA, m ²	1.90 (±0.26)	1.90 (±0.27)	1.87 (±0.22)	0.27
Hypertension (%)	950 (34.7%)	891 (34.4%)	59 (41.3%)	0.092
Dyslipidemia (%)	741 (26.2%)	695 (25.9%)	46 (31.1%)	0.162
Diabetes mellitus (%)	285 (10.5%)	262 (10.2%)	23 (15.9%)	0.032
Current smoker (%)	447 (16.5%)	421 (16.4%)	26 (17.9%)	0.638
BAV characteristics				
No raphe (%)	397 (14.6%)	386 (15.0%)	11 (7.5%)	<0.001
Type 1 raphe (L-R), (%)	1759 (64.6%)	1657 (64.3%)	102 (69.9%)	
Type 1 raphe (R-N), (%)	422 (15.5%)	405 (15.7%)	17 (11.6%)	
Type 1 raphe (L-N), (%)	132 (4.8%)	116 (4.5%)	16 (11.0%)	
Type 2 raphe, (%)	13 (0.5%)	13 (0.5%)	0 (0.0%)	

Values are mean ± SD and n (%). Percentages are calculated based on data availability.
AA = ascending aorta; CAD = coronary artery disease; LA = left atrium; LVEDd = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESd = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; SD = standard deviation.

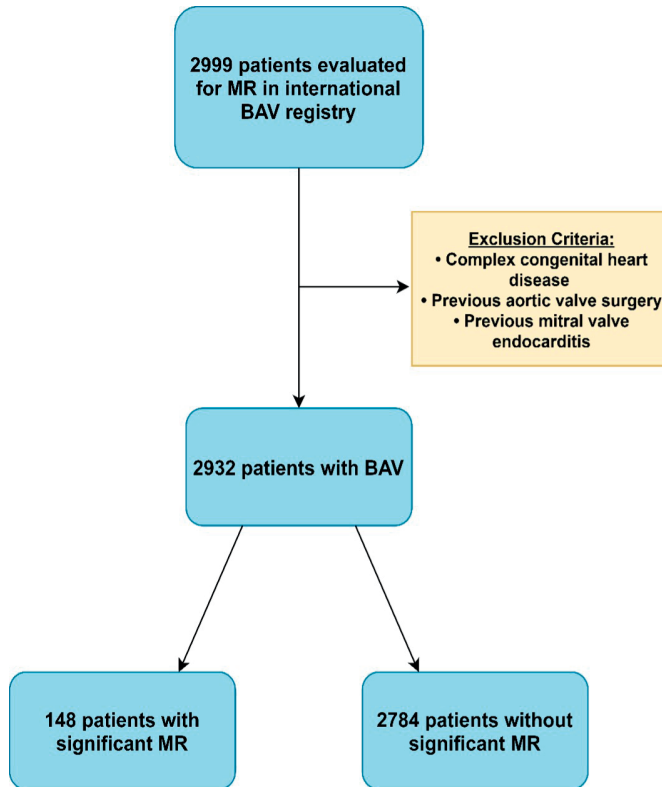


Figure 1: Study flow chart

BAV = bicuspid aortic valve; MR = mitral regurgitation.

Echocardiographic characteristics

The echocardiographic characteristics of the population are presented in Table 2. The mean LVEF for the total population was $60.8 \pm 11.8\%$ and the median LV end-diastolic volume was 122 (IQR 94 to 154) ml. Patients with significant secondary MR had lower LVEF and larger LV dimensions compared to those with significant primary MR and those without significant MR (Supplementary Table 1 and Supplementary Table 2). In addition, a higher proportion of patients with significant secondary MR had moderate or severe aortic regurgitation (45.2% vs 27.3%, $p < 0.001$) and aortic stenosis (54.8% vs 35.4%, $p < 0.001$) compared to those without significant MR. Individuals with significant secondary MR had larger ascending aorta (39.0 ± 8.0 vs 36.4 ± 7.3 mm, $p = 0.001$) and sinus of Valsalva diameters (37.2 ± 7.2 vs 34.6 ± 6.2 mm, $p < 0.001$) compared to those without significant MR, while aortic annulus and sinotubular junction diameters were similar between the two groups.

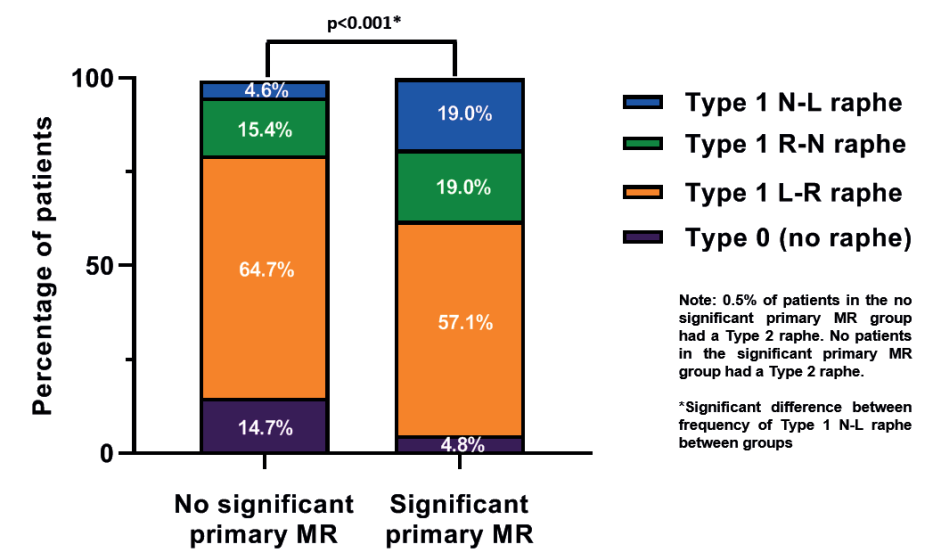


Figure 2: Distribution of BAV raphe phenotype according to the presence or absence of significant primary MR.
BAV = bicuspid aortic valve; MR = mitral regurgitation.

Table 2: Echocardiographic characteristics

Variable	Total population (n=2932)	No significant MR (n=2784)	Significant MR (n=148)	P value
Left ventricle				
LV EDD, mm	51.7 (±8.7)	51.3 (±8.3)	57.9 (±12.3)	<0.001
LV ESD, mm	34.4 (±9.1)	33.8 (±8.4)	43.6 (±14.1)	<0.001
LV EDV, ml	122 (94 to 154)	120 (93 to 153)	154 (110 to 211)	<0.001
LV EF, %	60.8 (±11.8)	61.5 (±11.0)	48.3 (±17.8)	<0.001
Mitral inflow E velocity, m/s	0.8 (±0.3)	0.8 (±0.3)	1.0 (0.4)	<0.001
Aortic Valve and Aortic Root				
Aortic annulus diameter, mm	23.0 (±3.2)	23.0 (±3.2)	23.5 (±3.1)	0.081
SOV diameter, mm	34.7 (±6.3)	34.6 (±6.2)	36.4 (±6.9)	0.001
STJ diameter, mm	30.5 (±6.5)	30.5 (±6.4)	31.0 (±7.4)	0.321
Ascending aorta diameter, mm	36.5 (±7.4)	36.4 (±7.3)	38.0 (±8.1)	0.014
Dilated aortic root or tubular aorta (≥ 40mm), %	1125 (39.1%)	1058 (38.8%)	67 (45.6%)	0.099
Dilated aortic root or tubular aorta (≥ 50mm), %	140 (4.9%)	130 (4.8%)	10 (6.8%)	0.255
Moderate or severe AS, %	1054 (36.0%)	984 (35.4%)	70 (47.3%)	0.003
Moderate or severe AR, %	822 (28.1%)	760 (27.3%)	62 (41.9%)	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).

AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricle; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction

Survival analysis

Over a median follow-up time of 51 months (IQR 18 to 95 months), 223 (7.6%) patients died. In total, 84 (38%) patients had a cardiovascular cause of death, 67 (30%) patients had a non-cardiovascular cause of death, while 72 (32%) patients had an unknown cause of death. One- and five- year cumulative survival rates were 97% and 93%, respectively. Analysis with the Kaplan-Meier method demonstrated a reduction in survival for patients with significant MR compared to their counterparts (91% and 81% vs 97% and 93%, at 1- and 5-years of follow-up, respectively, $\chi^2=29.95$, $p<0.001$). To further evaluate the association between significant MR and all-cause mortality, univariable and multivariable Cox regression analyses were performed (Table S3). In the unadjusted model, significant MR was associated with all-cause mortality (HR 2.80, 95% CI 1.91 to 4.11, $p<0.001$). However, following adjustment for age, smoking, hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, LV end-diastolic volume and LVEF, significant MR was not associated with the primary outcome (HR 1.33, 95% CI 0.85 to 2.07, $p=0.21$) (Figure 3). When stratified by etiology of MR, significant secondary MR due to aortic valve disease was not associated with all-cause mortality (adjusted HR 0.99, 95% CI 0.54 to 1.83, $P=0.98$), whereas significant MR not due to aortic valve disease was independently associated with worse survival (adjusted HR 1.81, 95% CI 1.04 to 3.15, $P=0.037$) (Table S4). For the analysis of the secondary endpoint of event-free survival, after a median follow-up of 23 months (IQR 3 to 67 months), 996 (34.0%) patients died ($n=161$, 5.5%) or underwent aortic valve surgery ($n=835$, 28.5%). Univariable analysis demonstrated that significant MR was associated with a reduction in event-free survival (Table S3), although this association was not observed following adjustment (adjusted HR 1.10, 95% CI 0.85 to 1.42, $p=0.49$).

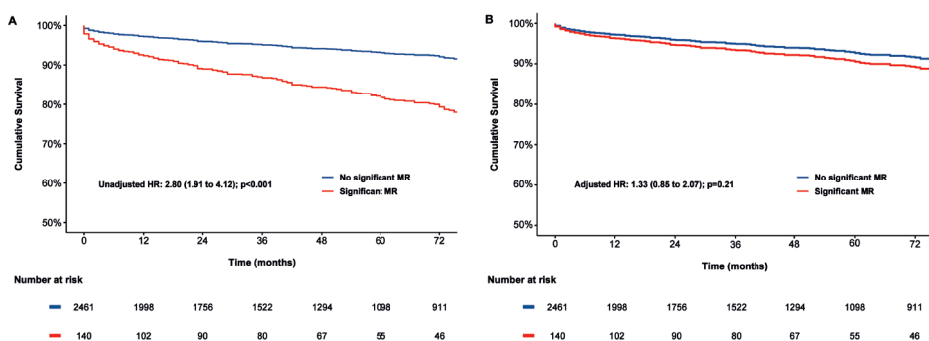


Figure 3: Cumulative survival estimates for all-cause mortality according to the presence or absence of significant MR in the overall population.

Panel A demonstrates that significant MR is associated with all-cause mortality in an unadjusted model in patients with BAV. However, panel B demonstrates that significant MR was not associated with all-cause mortality in a model adjusted for important confounding variables. The model in panel B is adjusted based on the average covariate values of the study population for age, diabetes mellitus, hypertension, smoking, dyslipidemia, coronary artery disease, LV ejection fraction and LV end-diastolic volume.

BAV = bicuspid aortic valve; LV = left ventricle; MR = mitral regurgitation

Subgroup analyses were performed to investigate the association between significant MR and outcomes for patients with significant aortic regurgitation, significant aortic stenosis and for those without significant aortic valvular disease (Figure 4). Significant MR was independently associated with all-cause mortality in the subgroup with moderate or severe aortic regurgitation (adjusted HR 2.037, 95% CI 1.025 to 4.049, $p=0.042$). However, no independent association with all-cause mortality was observed in patients with significant aortic stenosis or without significant aortic valvular disease. Moreover, there was no independent association between significant MR and the endpoint of event-free survival in any subgroup.

In addition, sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for all multivariable Cox regression models utilising all-cause mortality as the endpoint. The results of all sensitivity analyses were consistent with the main analysis (Table S5).

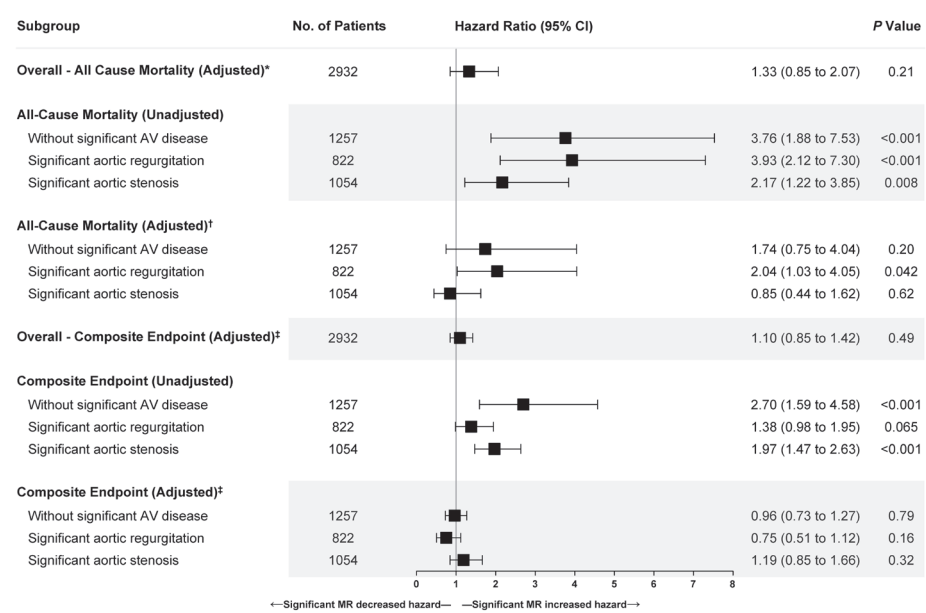


Figure 4: Forest plot of Cox regression models investigating the association between significant MR for the endpoints of all-cause mortality and event-free survival in patient subgroups

* Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

† Multivariable model adjusting for age, diabetes mellitus, LVEDV and LVEF.

‡ Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation ≥ 50 mm, LVEDV and LVEF.

AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

DISCUSSION

In this large, international BAV registry, significant primary and secondary MR were uncommon, with a prevalence of 1.5% and 3.5%, respectively. Significant MR was not independently associated with either all-cause mortality or event-free survival on multivariable analysis. However, when stratified by the etiology of MR, significant MR not due to aortic valve disease was independently associated with worse survival. Subgroup analyses suggested an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation, although not for subgroups with significant aortic stenosis or without significant aortic valve disease.

Prevalence of primary and secondary MR in BAV

The association between BAV and primary MR remains somewhat contentious^{6, 7, 9}. Previously, in a retrospective study of 1820 patients referred for surgery for significant BAV disease, Lad et al.⁶ demonstrated a prevalence of significant primary MR of 1.6%, similar to that observed in the present study. In another smaller study of 191 patients with BAV, the prevalence of significant primary MR was 2.0%⁷. In comparison, in a large community cohort study of the general adult population, the prevalence of significant primary MR was approximately 0.26%¹³. However, despite evidence suggesting a higher prevalence of primary MR in individuals with BAV compared to the general population, a large study of approximately 360,000 patients did not observe an increased prevalence of mitral valve prolapse in individuals with BAV⁹. However, the authors did not report on the frequency of significant MR due to mitral valve prolapse, which may explain this discrepancy. Interestingly, an association between mitral valve prolapse and BAV has previously been described by several authors, who reported an increased prevalence of a large and myxomatous anterior mitral valve leaflet in those with BAV⁶⁻⁹. In the present study, the prevalence of significant primary MR due to mitral valve prolapse was 0.9%. Although a prevalence of significant secondary MR of 3.5% was observed in the current study, this could be an overestimation and not representative of the general BAV population, due to referral center bias and the associated higher rate of significant aortic valve disease, which may influence LV remodeling that leads to secondary MR.

Association of MR with BAV morphology and aortic root dimensions

In the present study, an association between primary MR with prolapse of the anterior mitral valve leaflet and the type 1 left-non coronary cusp fusion BAV raphe phenotype was observed. In contrast to the findings of our study, Schaefer et al.⁷ observed an association between primary MR due to mitral valve prolapse and a type 1 raphe with right-non coronary cusp fusion, although in a limited number of patients. Several mechanisms may explain the association between primary MR and BAV. Individuals with

BAV may have an extension of the degenerative process that results in dilation of the aortic root to the anterior mitral valve leaflet, either mediated anatomically through the fibrous aortic-mitral continuity or because of a common embryological origin^{6,30,31}. This could potentially manifest as an enlarged, myxomatous anterior mitral valve leaflet, as described earlier.

In addition, we also observed an association between secondary MR and larger sinus of Valsalva and ascending aorta dimensions. This may be explained by the common relationship between significant aortic regurgitation, secondary MR and aortic root dilation in BAV disease, or alternatively, could represent altered motion of the anterior mitral valve leaflet, owing to changes in biomechanical forces transmitted through the aortic-mitral continuity in the presence of aortic root dilation.

Prognostic implications of MR in patients with BAV

In this large cohort of patients with BAV, no independent association between significant MR and all-cause mortality was observed. This contrasts with several large community studies of the general population that reported an independent association between significant MR and increased all-cause mortality^{13,14}. However, in those studies, limited adjustment for important confounding variables were performed, notably for LV end-diastolic volume and LV ejection fraction. Moreover, the patients with significant MR in those studies were nearly 20 years older, and it is likely that the etiology of secondary MR differed dramatically from the BAV population in our study. Indeed, a substantial proportion of secondary MR in the present study was due to significant aortic valve disease, which typically has a more favorable prognosis than secondary MR due to LV systolic dysfunction or ischemic heart disease, particularly in the context of timely aortic valve intervention. Following aortic valve surgery, approximately 55% of patients with aortic stenosis and 70% of those with aortic regurgitation will have improvement in the grade of secondary MR, likely due to a combination of reverse LV remodeling and alterations in mitral valve hemodynamics³²⁻³⁴. In accordance with this hypothesis, when stratifying by the etiology of MR, we observed an independent association between significant MR not due to aortic valve disease and all-cause mortality, findings consistent with prior literature. In contrast, no association between significant secondary MR due to aortic valve disease was observed. This suggests that consideration of the etiology of significant MR is essential in the setting of treatable AV disease.

In the present study, the absence of a relationship between the composite endpoint of aortic valve repair/replacement and all-cause mortality with significant MR was unexpected, given the greater hemodynamic burden on the left ventricle in multiple left-sided valvular disease¹⁰. The combination of significant MR and aortic stenosis and/or aortic regurgitation, may have been expected to culminate in additional LV and LA remodeling, an earlier onset of symptoms, and therefore, an earlier indication for aortic

valve surgery¹⁰. However, there are several explanations for these findings. Significant MR may mask reductions in LVEF³⁵, an important indication for intervention in aortic regurgitation and aortic stenosis, leading to a delay in referral. In addition, significant MR may lead to low-flow low-gradient aortic stenosis and an underestimation of the hemodynamic severity of disease³⁶, potentially delaying referral for surgery or intervention.

The subgroup analysis suggested an independent association between significant MR and all-cause mortality in patients with moderate to severe aortic regurgitation. This finding is consistent with a previous study of 756 patients with severe aortic regurgitation due to a variety of etiologies, which also demonstrated an independent association between all-cause mortality and significant MR¹². The relationship between mortality and significant MR in aortic regurgitation is probably mediated by increased LV dilation and eccentric hypertrophy, with poorer long-term LV functional recovery¹⁰. In addition, due to the absence of the premature mitral valve closure usually seen in severe aortic regurgitation, the combination of significant MR and aortic regurgitation may lead to elevated left atrial and pulmonary capillary wedge pressures and poor clinical tolerability¹⁰. In an additional subgroup analysis of patients with moderate or severe aortic stenosis, we did not observe an independent association between significant MR and all-cause mortality. Indeed, the association of significant MR with mortality in severe aortic stenosis remains contentious in the context of both surgical and transcatheter aortic valve interventions^{32, 37}. As discussed previously, the BAV population is typically much younger, with fewer comorbidities, and it is likely that the absence of an association with all-cause mortality in the aortic stenosis subgroup can be attributed to patients with BAV having etiologies of secondary MR with a more favorable prognosis. In addition, it is also conceivable that the concentric remodeling induced by severe pressure overload in aortic stenosis is fundamentally different and not additive to the severity of eccentric remodeling that is typically observed in significant MR (and vice-versa). In contrast, volume overload secondary to both aortic regurgitation and MR may be additive, causing a greater degree of eccentric remodeling and severe LV dilatation, which could induce an earlier onset of LV systolic dysfunction and ultimately, a poorer prognosis^{38, 39}.

Limitations

This study is subject to the inherent limitations of any observational, retrospective registry. Furthermore, due to the registry study design, clinical outcomes could be underreported if a patient left the registry or was lost to follow-up, and although all centers followed guideline recommendations, assessment and treatment criteria may vary across countries and centers. In addition, many of the participating international centers act as referral centers for their respective regions, resulting in increased complexity

in the interpretation of epidemiological data, due to a higher prevalence of clinically significant aortic valve disease than in the general BAV population. Furthermore, data pertaining to the specific indication for aortic valve surgery were not available.

CONCLUSION

Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality.

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SUPPLEMENTARY MATERIAL

Table S1: Echocardiographic characteristics divided according to mitral regurgitation mechanism.

Variable	No significant MR (n=2784)	Significant primary MR (n=44)	Significant secondary MR (n=104)	P value
Left ventricle				
LV EDD, mm	51.3 (±8.3)	54.0 (±10.2)	59.1 (±12.7) ^{††}	<0.001
LV ESD, mm	33.8 (±8.4)	36.5 (±8.7)	45.7 (±14.8) ^{††}	<0.001
LV EDV, ml	120 (93 to 153)	135 (98 to 186)	163 (121 to 232) [*]	<0.001
LV EF, %	61.5 (±11.0)	59.4 (±13.5)	44.3 (±17.5) ^{††}	<0.001
Mitral inflow E velocity, m/s	0.8 (±0.25)	1.1 (±0.4) [*]	0.95 (±0.3) ^{††}	<0.001
Aortic Valve and Aortic Root				
Aortic annulus diameter, mm	23.0 (±3.2)	23.3 (±2.8)	23.7 (±3.3)	0.179
SOV diameter, mm	34.6 (±6.2)	34.5 (±5.7)	37.2 (±7.2) [*]	<0.001
STJ diameter, mm	30.5 (±6.4)	30.2 (±5.6)	31.4 (±8.1)	0.366
Ascending aorta diameter, mm	36.4 (±7.3)	35.4 (±7.8)	39.0 (±8.0) ^{††}	0.001
Dilated aortic root or tubular aorta (> 50mm), %	130 (4.8%)	3 (7.1%)	7 (6.7%)	0.520
Moderate or severe AS, %	984 (35.4%)	13 (29.5%)	57 (54.8%) ^{††}	<0.001
Moderate or severe AR, %	760 (27.3%)	15 (34.1%)	47 (45.2%) [*]	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricle; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction
^{*}p<0.05 vs Group I; [†]p<0.05 vs Group II

Table S2: Clinical and BAV characteristics divided according to mitral regurgitation mechanism.

	No significant MR (n=2784)	Significant primary MR (n=44)	Significant secondary MR (n=104)	P value
Clinical characteristics				
Age (years)	47.3 (± 17.5)	58.6 (± 20.1) [*]	59.1 (± 16.4) [*]	<0.001
Male (%)	1961 (70.5%)	29 (65.9%)	75 (72.1%)	0.750
Prior CAD (%)	198 (7.8%)	4 (9.3%)	14 (14.0%)	0.077
Hypertension (%)	891 (34.4%)	15 (34.9%)	44 (44.0%)	0.140
Dyslipidemia (%)	695 (25.9%)	13 (29.5%)	33 (31.7%)	0.362
Diabetes mellitus (%)	262 (10.2%)	4 (9.5%)	19 (18.4%) [*]	0.028
Current smoker (%)	421 (16.4%)	6 (14.3%)	20 (19.4%)	0.673
BAV characteristics				
No raphe (%)	386 (15.0%)	2 (4.8%)	9 (8.7%)	<0.001
Type 1 raphe (L-R), (%)	1657 (64.3%)	24 (57.1%)	78 (75.0%) ^{††}	
Type 1 raphe (R-N), (%)	405 (15.7%)	8 (19.0%)	9 (8.7%)	
Type 1 raphe (L-N), (%)	116 (4.5%)	8 (19.0%) [*]	8 (7.7%) [†]	
Type 2 raphe, (%)	13 (0.5%)	0 (0.0%)	0 (0.0%)	

Values are mean $\pm$ SD, median (interquartile range) and n (%). Percentages are calculated based on data availability. AA = ascending aorta; CAD = coronary artery disease; LA = left atrium; LVEDd = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESd = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; SD = standard deviation.

^{*}p<0.05 vs Group I; [†]p<0.05 vs Group II

Table S3: Cox regression models investigating the association between significant MR for the endpoints of all-cause mortality and a composite of aortic valve surgery and all-cause mortality

Total Population (n=2932)	All-cause mortality ^a		Composite endpoint of aortic valve surgery and all-cause mortality ^b	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariable analysis				
No significant MR	Reference		Reference	
Significant MR	2.801 (1.907 to 4.115)	<0.001	1.971 (1.581 to 2.459)	<0.001
Multivariable analysis				
No significant MR	Reference		Reference	
Significant MR	1.330 (0.854 to 2.071)	0.207	1.095 (0.847 to 1.417)	0.49

^a Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

^b Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, aortic root or ascending aorta dilation, LVEDV and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

Table S4: Cox regression models investigating the association between significant MR stratified according to MR etiology for the endpoints of all-cause mortality and a composite of aortic valve surgery and all-cause mortality

Total Population (n=2932)	All-cause mortality ^a		Composite endpoint of aortic valve surgery and all-cause mortality ^b	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariable analysis				
No significant MR (N=2784; 192 and 909 events)	Reference		Reference	
Secondary MR due to AV disease (N=76; 13 and 50 events)	2.32 (1.32 to 4.09)	0.004	2.91 (2.19 to 3.87)	<0.001
Significant MR not due to AV disease (N=72; 18 and 37 events)	3.30 (2.03 to 5.37)	<0.001	1.40 (1.01 to 1.95)	0.045
Multivariable analysis				
No significant MR	Reference		Reference	
Secondary MR due to AV disease	0.99 (0.54 to 1.83)	0.98	1.17 (0.85 to 1.62)	0.33
Significant MR not due to AV disease	1.81 (1.04 to 3.15)	0.037	0.85 (0.59 to 1.24)	0.41
Univariable analysis				
No significant MR	Reference		Reference	
Secondary MR due to AV disease	2.31 (1.31 to 4.08)	0.004	2.91 (2.19 to 3.87)	<0.001
Secondary MR not due to AV disease	5.17 (2.74 to 9.78)	<0.001	1.77 (1.09 to 2.86)	0.02
Primary MR	2.25 (1.10 to 4.60)	0.026	1.19 (0.76 to 1.86)	0.45
Multivariable analysis				
No significant MR	Reference		Reference	
Secondary MR due to AV disease	1.00 (0.54 to 1.84)	1.00	1.16 (0.84 to 1.60)	0.38
Secondary MR not due to AV disease	2.04 (0.98 to 4.25)	0.055	0.67 (0.39 to 1.17)	0.16
Primary MR	1.57 (0.69 to 3.59)	0.29	1.06 (0.66 to 1.70)	0.82

^a Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

^b Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, aortic root or ascending aorta dilation, ≥moderate AS, ≥moderate AR, LVEDV and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

Table S5: Cox regression models investigating the association between significant MR and all-cause mortality adjusted for aortic valve surgery as a time-dependent covariate

	Total population ^a (n=2932, 223 events)		Individuals without significant AV disease ^b (n=1257, 83 events)		Individuals with significant AR ^b (n=822, 54 events)		Individuals with significant AS ^b (n=1054, 106 events)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Multivariable analysis								
No significant MR	Reference		Reference		Reference		Reference	
Significant MR	1.278 (0.818 to 2.00)	0.281	1.691 (0.727 to 3.931)	0.223	2.015 (1.012 to 4.015)	0.046	0.814 (0.420 to 1.578)	0.541

^a Multivariable model adjusting for aortic valve surgery (as a time dependent covariate), age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

^b Multivariable model adjusting for aortic valve surgery (as a time dependent covariate), age, diabetes mellitus, LVEDV and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation