Survival Benefit of Aortic Valve Replacement in Older Patients With Asymptomatic Chronic Severe Aortic Regurgitation

Rami Turk, MD, Padmini Varadarajan, MD, Ashvin Kamath, BA, Unnati Sampat, MD, Sumit Khandhar, DO, Reena Patel, MD, and Ramdas G. Pai, MD

Division of Cardiology, Loma Linda University Medical Center, Loma Linda, California

Background. According to American College of Cardiology/American Heart Association guidelines, isolated aortic valve replacement (AVR) is a class III indication for patients with asymptomatic chronic severe aortic regurgitation (AR), left ventricular (LV) ejection fraction (EF) greater than 50%, LV end-diastolic dimension less than 70 mm, and LV end-systolic dimension less than 50 mm.

Methods. We screened our echocardiographic database for all chronic severe AR patients between 1993 and 2007. Chart reviews were performed to collect clinical, demographic, and pharmacological data. Mortality was analyzed as a function of AVR.

Results. In all, 123 patients were found to have chronic severe asymptomatic AR; they had a mean age of 60 ± 17 years and mean LVEF of 60% ± 15%. A subgroup of 79 patients was found to have asymptomatic severe AR with an LVEF greater than 50%, LV end-diastolic dimension less than 70 mm, and LV end-systolic dimension less than 50 mm. By Kaplan-Meier analysis, patients not undergoing AVR had 1-, 5-, and 10-year survival rates of 86%, 71%, and 46%, respectively, compared with 100%, 94%, and 94%, respectively, for patients who underwent AVR ($p = 0.004$). Aortic valve replacement remained an independent predictor of increased survival after adjusting for group differences and univariate predictors of mortality. The benefit of AVR was further supported by propensity score analysis.

Conclusions. Despite serving as a class III indication, AVR is independently associated with increased survival among patients with severe asymptomatic AR, LVEF greater than 50%, LV end-diastolic dimension less than 70 mm, and LV end-systolic dimension less than 50 mm.

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It has been reported that patients with asymptomatic severe aortic regurgitation (AR) with a left ventricular (LV) ejection fraction (EF) greater than 50%, LV end-diastolic dimension (LVEDD) less than 70 mm, and LV end-systolic dimension (LVESD) less than 50 mm have a benign prognosis. The American College of Cardiology/American Heart Association (ACC/AHA) valvular disease guidelines do not recommend aortic valve replacement (AVR) for patients with isolated severe asymptomatic AR with an LVEF greater than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm in the absence of concomitant cardiac or aortic surgery [1].

The ACC/AHA guidelines on asymptomatic AR are based on 9 published series with 593 total patients (range, 27 to 104 per series) with a mean follow-up of 6.6 years [1]. Although these studies elegantly analyzed the natural history of asymptomatic severe AR, they did not study the effect of AVR on survival in the asymptomatic phase of the disease. Once the left ventricle is exposed to volume overload, deleterious neurohormonal and second messenger pathways are activated. These pathways cause myocyte hypertrophy and apoptosis as well as interstitial remodeling in an attempt to compensate for volume overload [2, 3]. These processes are similar to the heart failure state, in which neurohormonal activation causes progressive LV remodeling [4].

We hypothesized that AVR would reduce mortality in asymptomatic severe AR patients by eliminating the impetus for neurohormonal activation and LV remodeling. This hypothesis was tested using a large group of patients obtained from our echocardiographic database.

Patients and Methods

Patient Population

This is a retrospective cohort study from a large university medical center. The study was approved by our Institutional Review Board, which waived the need for patient consent because of the retrospective nature of the study. We queried our echocardiographic database from 1993 to 2007 for all patients with severe AR based on the attending cardiologist's final interpretation of the echocardiogram. This review yielded a total of 785 patients. Complete clinical, echocardiographic, and pharmacologic data were compiled on all these patients from comprehensive chart review. One hundred fifty-nine

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Address correspondence to Dr Pai, Division of Cardiology, Loma Linda University Medical Center, No. 4414, 11234 Anderson St, Loma Linda, CA 92354; e-mail: ramdaspai@yahoo.com.

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Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/ American Heart Association
AR	= aortic regurgitation
AVR	= aortic valve replacement
CAD	= coronary artery disease
COPD	= chronic obstructive pulmonary disease
LV	= left ventricular
LVEF	= left ventricular ejection fraction
LVEDD	= left ventricular end-diastolic diameter
LVESD	= left ventricular end-systolic diameter

patients were reported to have no cardiac symptoms (exertional chest pain, dyspnea on exertion, dyspnea at rest, paroxysmal nocturnal dyspnea, or orthopnea) at the initial encounter. That was confirmed with a thorough chart review. We also confirmed that the medications were not started for symptoms. After the exclusion of aortic dissection patients and infective endocarditis patients who underwent surgery within 3 months of their initial endocarditis diagnosis, the remaining 123 asymptomatic chronic severe AR patients formed the study cohort. A subgroup of this study cohort with an LVEF greater than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm was identified and analyzed as well.

Definition of Clinical Variables

Hypertension was defined as two or more blood pressure values greater than 139/89 mm Hg, a history of hypertension, or therapy with antihypertensive medications. Diabetes mellitus was defined as a fasting blood sugar greater than 125 mg/dL, a history of diabetes mellitus, or therapy with antidiabetic agents. Chronic kidney disease was defined as a baseline serum creatinine greater than greater than 2.0 mg/dl. Coronary artery disease (CAD) was deemed to be present if any of the following were present on clinical history: angina pectoris, myocardial infarction, a positive stress test, angiographic evidence of coronary artery disease, coronary intervention, coronary

Table 1. Baseline Characteristics of All Asymptomatic Severe Aortic Regurgitation Patients With and Without Aortic Valve Replacement (AVR)

Variables	AVR (n = 44)	No AVR (n = 79)	*p* Value
Clinical variables			
Age, years	54 ± 17	63 ± 16	0.003
Males	77%	56%	0.02
Hypertension	61%	57%	0.71
Diabetes mellitus	11%	8%	0.49
Coronary artery disease	46%	37%	0.35
Chronic kidney disease	9%	19%	0.15
Chronic obstructive pulmonary disease	2%	14%	0.04
Previous stroke	21%	20%	0.98
Atrial fibrillation	21%	22%	0.89
Coronary artery bypass graft surgery	18%	8%	0.08
Echocardiography			
Ejection fraction, %	57.3 ± 15.7	61.9 ± 14	0.10
LV end-diastolic dimension, mm	63.6 ± 10.4	53.3 ± 8.7	< 0.0001
LV end-systolic dimension, mm	43.8 ± 12.1	35.9 ± 9.3	0.0003
LV end-systolic dimension/BSA, mm/m^2	20.8	19.5	0.39
Ventricular septum thickness, mm	12.8 ± 1.8	12.4 ± 3.0	0.48
LV posterior wall thickness, mm	12.3 ± 2.2	12.0 ± 2.1	0.46
RV systolic pressure, mm Hg	42.3 ± 14.4	37.0 ± 9.3	0.053
Mitral regurgitation grade (1+ to 4+)	1.5 ± 1.3	1.3 ± 1.1	0.28
Drug therapy			
Aspirin	27%	33%	0.52
β-Blocker	59%	28%	0.0006
ACE inhibitor	48%	28%	0.03
Angiotensin receptor blocker	2%	6%	0.32
Statin	29.5%	19.0%	0.18
Dihydropyridine calcium-channel blocker	11%	19%	0.28
Hydralazine	0%	0.03%	0.30
Spironolactone	2%	6%	0.32

ACE = angiotensin-converting enzyme; LV = left ventricular; RV = right ventricular.

artery bypass surgery, or the presence of pathologic Q waves on the surface electrocardiogram.

Pharmacologic Data

Pharmacotherapy at the time of echocardiography was recorded in all patients. This was broadly categorized into β-blockers, dihydropyridine calcium-channel blockers, nondihydropyridine calcium-channel blockers, thiazide diuretics, loop diuretics, spironolactone, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, hydralazine, and statins. Patients were considered to be on a particular medication only if they were treated for at least 1 month.

Echocardiographic Data

All patients had complete two-dimensional and Doppler echocardiographic examinations. Left ventricular ejection fraction was assessed by a level 3 trained echocardiographer and entered into a database at the time of the examination. The determination of LVEF incorporated the reader's visual estimation of EF as well as all available quantitative data including fractional shortening, biplane Simpson's measurements of EF, and LV systolic and diastolic dimensions. Visual estimation has been shown to be reliable and has been validated against contrast and radionuclide left ventricular angiography [5, 6]. The AR gradings were performed according to the recommendations of the American Society of Echocardiography [7].

Mortality Data

The primary end point of the study was all-cause mortality. Mortality data were obtained from the National Death Index using Social Security numbers.

Statistical Analysis

The data were imported into the Stat View 5.01 program (SAS Institute, Cary, NC) for statistical analysis. Group comparisons were made using Student's *t* test for continuous variables and the χ^2 test for categorical variables. Survival analysis was performed using various statistical tools such as Kaplan-Meier analysis, Cox regression models, and propensity score analysis, as discussed later in the results section. A *p* value of 0.05 or less was considered statistically significant.

Table 2. Baseline Characteristics of Asymptomatic Severe Aortic Regurgitation Patients With Left Ventricular (LV) Ejection Fraction Greater Than 50%, LV End-Diastolic Dimension Less Than 70 mm, and LV End-Systolic Dimension Less Than 50 mm With and Without Aortic Valve Replacement (AVR)

Variables	AVR (n = 21)	No AVR (n = 58)	*p* Value
Clinical variables			
Age, years	52	63	0.01
Males	81%	59%	0.07
Hypertension	65%	55%	0.45
Diabetes mellitus	19%	5%	0.048
Coronary artery disease	38%	31%	0.56
Chronic kidney disease	5%	17%	0.16
Chronic obstructive pulmonary disease	0%	12%	0.1
Previous stroke	19%	21%	0.87
Atrial fibrillation	24%	26%	0.86
Coronary artery bypass grafting	14%	3%	0.08
Echocardiography			
Ejection fraction, %	66.7 ± 5.8	66.3 ± 6.3	0.81
LV end-diastolic dimension, mm	57.7 ± 6.0	52.0 ± 6.9	0.001
LV end-systolic dimension, mm	35.9 ± 6.3	33.4 ± 6.5	0.13
Ventricular septum thickness, mm	13.3 ± 1.7	12.7 ± 3.0	0.33
LV posterior wall thickness (mm	12.5 ± 2.1	12.1 ± 2.0	0.46
Right ventricular systolic pressure, mm Hg	37.1 ± 11.5	36.0 ± 8.6	0.72
Mitral regurgitation grade (1+ to 4+)	1.2 ± 0.9	1.2 ± 1.0	0.75
Drug therapy			
Aspirin	33%	33%	0.96
β-Blocker	81%	29%	< 0.0001
ACE inhibitor	48%	21%	0.02
Angiotensin receptor blocker	5%	7%	0.73
Statin	43%	22%	0.08
Dihydropyridine calcium-channel blocker	10%	17%	0.41
Hydralazine	0%	3%	0.4
Spironolactone	0%	7%	0.22

ACE = angiotensin-converting enzyme.

Results

Baseline Patient Characteristics

There were 123 patients from the severe AR group (n = 756) who were found to be asymptomatic. The mean age was 60 ± 17 years, and 64% were men. The mean LVEF was 60% ± 15%. The mean LVESD was 39 ± 11 mm, and the mean LVEDD was 57 ± 10 mm. Forty percent of the patients had been diagnosed with CAD, and 9% had diabetes mellitus. The etiology of AR was degenerative/calcific in 37 (30%) of the patients, bicuspid aortic valve in 24 (20%), rheumatic in 14 (11%), infective endocarditis in 10 (8%), and unknown in the remaining patients. Mean ascending aortic diameter was 3.7 cm, and no patients underwent surgery for aortic aneurysm. Forty-four patients had AVR during follow-up, and 44 patients died over a mean follow-up of 4.8 years.

As shown in Table 1, patients not undergoing AVR were older ($p < 0.003$), and consisted of more female patients ($p = 0.02$). The patients who did not undergo AVR had smaller LVEDD and LVESD ($p < 0.0001$ and $p = 0.0003$, respectively). The nonsurgical group had a higher prevalence of chronic obstructive pulmonary disease (COPD), and was less likely to receive cardiac medications such as angiotensin-converting enzyme inhibitors and β-blockers. The prevalence of diabetes, hypertension, CAD, and prior stroke was similar in both groups. Both groups also had similar degrees of mitral regurgitation and no significant difference in aortic valve area or LVEF.

In the subgroup of 79 asymptomatic patients with an LVEF greater than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm, patients not undergoing AVR were older and less likely to receive β-blockers and angiotensin-converting enzyme inhibitors (Table 2). The nonsurgical group had a lower prevalence of diabetes and smaller LVEDDs. The prevalence of hypertension, CAD, and prior stroke was similar in both groups. Both groups also had similar degrees of mitral regurgitation and no significant difference in aortic valve area or LVEF. The etiology of AR was degenerative/calcific in 24 (30%) of patients, bicuspid aortic valve in 19 (24%), rheumatic in 8 (10%), and unknown in the remaining patients. Mean ascending aortic diameter was 3.7 cm, and no patients underwent surgery for aortic aneurysm.

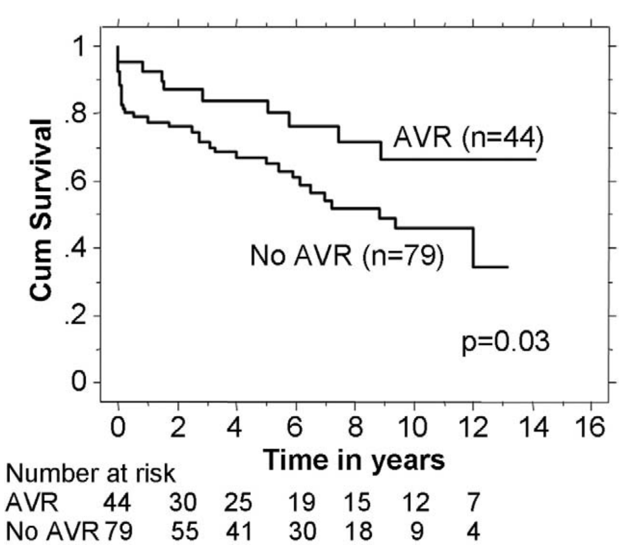

Fig 1. Kaplan-Meier survival curve with and without aortic valve replacement (AVR) in all asymptomatic severe aortic regurgitation (AR) patients.

Table 3. Cox Regression Analysis Adjusting for Significant Group Differences Among All Asymptomatic Severe Aortic Regurgitation Patients

Variable	Relative Risk	95% Confidence Interval	*p* Value
AVR	0.174	0.045–0.682	0.01
Age, years	1.045	1.016–1.075	0.002
Female	0.797	0.363–1.751	0.57
COPD	3.486	1.347–9.026	0.01
LV internal dimension (diastole)	0.822	0.289–2.339	0.71
LV internal dimension (systole)	1.712	0.706–4.153	0.23
ACE inhibitor use	1.022	0.43–2.431	0.96
β-Blocker use	0.638	0.265–1.534	0.32

ACE = angiotensin-converting enzyme; AVR = aortic valve replacement; COPD = chronic obstructive pulmonary disease; LV = left ventricular.

Survival With AVR in the Whole Group

Over a mean follow-up period of 4.8 years, 44 patients underwent AVR and 44 patients died. By Kaplan-Meier analysis, patients not undergoing AVR had 1-, 5-, and 10-year survival rates of 78%, 68%, and 46%, respectively, compared with 92%, 83%, and 67%, respectively, for patients who underwent AVR ($p = 0.03$; Fig 1). Mortality over 4.8 years was 43% in the non-AVR group and 23% in the AVR group. Surgical mortality in the entire group (AVR = 44) was 4.5% (2 deaths).

Two types of Cox regression models were created to adjust for the effect of confounding variables on mortality. In the first model, the effect of AVR on survival was

Table 4. Cox Regression Analysis Adjusting for Significant Univariate Predictors of Mortality Among All Asymptomatic Severe Aortic Regurgitation Patients

Variable	Relative Risk	95% Confidence Interval	*p* Value
AVR	0.425	0.185–0.977	0.04
Age (per year)	1.03	1.0–1.05	0.04
Chronic kidney disease	2.6	1.3–5.2	0.005
COPD	4.3	1.9–9.4	0.0004
Mitral regurgitation (3 to 4+)	1.5	0.73–3.2	0.26
Diabetes mellitus	2.7	1.0–7.2	0.04
Coronary artery disease	1.4	0.69–2.9	0.35

AVR = aortic valve replacement; COPD = chronic obstructive pulmonary disease.

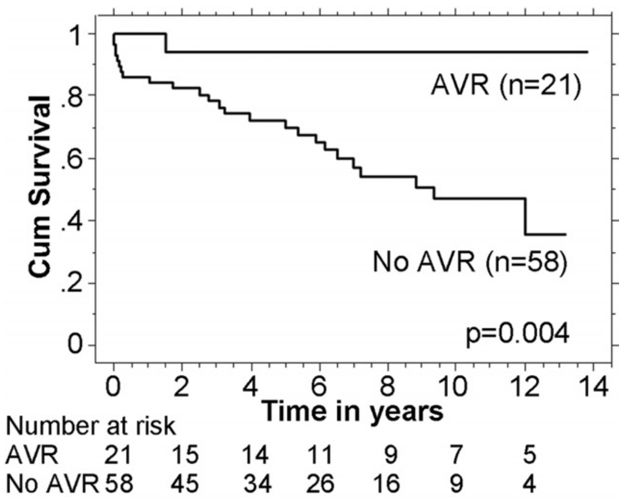

Fig 2. Kaplan-Meier survival curve with and without aortic valve replacement (AVR) in all asymptomatic severe aortic regurgitation (AR) patients with left ventricular (LV) ejection fraction greater than 50%, LV end-diastolic dimension (LVEDD) less than 70 mm, and LV end-systolic dimension (LVESD) less than 50 mm.

adjusted for significant group differences. Aortic valve replacement was a significant predictor of better survival with a hazard ratio for death of 0.17 (95% confidence interval [CI]: 0.05 to 0.68, $p = 0.01$; Table 3).

In the second multivariate model, the effect of AVR on survival was adjusted for statistically significant univariate predictors of mortality. These included age, chronic kidney disease, CAD, COPD, diabetes mellitus, and moderate or severe mitral regurgitation (Table 4). Aortic valve replacement had a large survival benefit, with a hazard ratio for death of 0.43, (95% CI: 0.19 to 0.98, $p = 0.04$). Independent predictors of decreased survival included greater age, chronic kidney disease, COPD, and diabetes mellitus.

Table 5. Cox Regression Analysis Adjusting for Significant Group Differences Among Asymptomatic Severe Aortic Regurgitation Patients With Left Ventricular (LV) Ejection Fraction Greater Than 50%, LV End-Diastolic Dimension Less Than 70 mm, and LV End-Systolic Dimension Less Than 50 mm

Variable	Relative Risk	95% Confidence Interval	p value
AVR	0.03	0.002–0.392	0.007
LV internal dimension (diastole)	1.48	0.76–2.9	0.25
Age (per year)	1.04	1.005–1.073	0.03
ACE inhibitor use	0.61	0.2–1.9	0.38
β-Blocker use	0.74	0.27–2.0	0.56
Diabetes mellitus	27.6	6.0–127.1	< 0.0001

ACE = angiotensin-converting enzyme; AVR = aortic valve replacement.

Table 6. Cox Regression Analysis Adjusting for Significant Univariate Predictors of Mortality Among Asymptomatic Severe Aortic Regurgitation Patients With Left Ventricular (LV) Ejection Fraction Greater Than 50%, LV End-Diastolic Dimension Less Than 70 mm, and LV End-Systolic Dimension Less Than 50 mm

Variable	Relative Risk	95% Confidence Interval	p value
AVR	0.068	0.007–0.673	0.02
Age (per year)	1.03	0.996–1.07	0.09
Chronic kidney disease	3.3	1.2–8.8	0.02
COPD	4.1	1.4–12.3	0.01
Diabetes mellitus	14.1	3.1–64.6	0.0007
Coronary artery disease	1.7	0.74–4.1	0.21

AVR = aortic valve replacement; COPD = chronic obstructive pulmonary disease.

Survival With AVR in Subgroup With LVEF Greater Than 50%, LVEDD Less Than 70 mm, and LVESD Less Than 50 mm

In the subgroup of 79 patients with LVEF more than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm, AVR was associated with increased survival. By Kaplan-Meier analysis, patients not undergoing AVR had 1-, 5-, and 10-year survival rates of 86%, 71%, and 46%, respectively, compared with 100%, 94%, and 94%, respectively, for patients who underwent AVR ($p = 0.004$; Fig 2). Mortality over 4.8 years was 43% in the non-AVR group and 5% in the AVR group. There was no surgical mortality in this group. Cox regression analysis adjusting for significant group differences between the surgical and nonsurgical patients demonstrated that AVR was a significant predictor of survival, with a hazard ratio of 0.03 (95% CI: 0.002 to 0.392, $p = 0.007$; Table 5). After adjusting for univariate predictors of mortality, AVR was associated with a significant survival benefit, with a hazard ratio for death of 0.07 (95% CI: 0.007 to 0.673, $p = 0.02$). Chronic kidney disease, COPD, and diabetes were independent predictors of decreased survival in this group (Table 6).

Propensity Score Analysis

The propensity score for an individual patient is the probability of receiving a treatment only on the basis of an individual patient's covariate values. Given the observational nature of this study, the intent of propensity score analysis is to balance the difference in pretreatment covariates to reduce the impact of treatment bias. A propensity score for receiving AVR was calculated using logistic regression analysis based on clinically relevant covariate imbalances. After adjusting for the propensity score using the Cox regression model, for the entire group of asymptomatic severe AR patients, AVR carried a hazard ratio of 0.46 (p value = 0.06). In the subgroup of patients with an EF greater than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm, AVR carried a hazard ratio of 0.11 ($p = 0.04$).

Cox Regression Analysis in Entire Cohort Adjusting for EF, LV Size, and Symptoms

Effect of AVR on survival adjusting for LVEF, LV size, and New York Heart Association (NYHA) functional class was also carried out in the entire cohort of 756 patients with severe AR. Cox regression analysis showed AVR to be a strong predictor of better survival ($p < 0.0001$) with a hazard ratio for death of 0.43 (95% CI: 0.32 to 0.59). The other significant predictors of better survival in this analysis included higher EF, smaller LVEDD, and lower NYHA class.

Comment

Benefit of AVR in Asymptomatic Severe AR

Aortic valve replacement was associated with a significant survival benefit for patients with asymptomatic severe AR. This difference remained significant after adjusting for group differences and univariate predictors of mortality. In the subgroup of patients who had an LVEF greater than 50%, LVEDD less than 70 mm, and LVESD less than 50 mm, AVR was also associated with a significant survival benefit. Aortic valve replacement without concomitant cardiac surgery is currently an ACC/AHA class III recommendation for this group of patients. The survival benefit in this group remained significant after propensity score analysis and adjustment for group differences and univariate predictors of mortality.

Comparison With Other Published Series

The patients in our study had higher baseline mortality rates than most prior published series. That is likely due to the older age of our patient group and the higher prevalence of significant comorbidities including CAD, chronic kidney disease, and diabetes mellitus.

Dujardin and colleagues [8] were one of the first groups that observed higher than expected mortality in AR patients. They followed 246 patients with moderately severe or severe AR and found that mortality rates with nonsurgical management were higher than expected based on prior studies. The difference in mortality was attributed primarily to selection bias. Prior observational studies showed higher mortality rates whereas prospective studies that enrolled volunteers demonstrated lower mortality rates [9–11]. The lower mortality rate in prospective studies was attributed to the healthy volunteer effect. The mean age in this study was 56 years, significantly older than in most prior studies. Exclusion criteria were far less rigorous than prior studies, making these results more applicable to severe AR patients encountered in clinical practice [8].

In 1998, Borer and colleagues [12] published a prospective study that evaluated 104 patients with asymptomatic or minimally symptomatic AR for an average duration of 7.3 years. The study population was young, with a mean age of 46 years, and patients with CAD or comorbid valve disease were excluded. These patients had isolated severe pure AR with no known CAD or significant comorbid valve disease. Nonetheless, 4 sudden deaths occurred in patients with asymptomatic severe AR and normal LVEF. Prior studies had reported few cardiac deaths among patients with asymptomatic severe AR who did not undergo AVR [13–16].

Bonow and colleagues [9] followed 104 patients with asymptomatic severe AR patients for an average duration of 8 years (range, 2 to 16) with serial echocardiographic and radionucleide imaging. The mean age in this study was 36 years. There was no significant comorbid valve disease and no prior history of myocardial infarction in any patient at the start of or during this study. Nonetheless, 2 cardiac deaths were observed, and no predictors of sudden death were identified [9].

Similar to the Bonow series, most other studies that found low mortality rates among patients with severe asymptomatic AR enrolled patients who were young and excluded patients with any significant cardiac or noncardiac comorbidities [13–17].

Our study population is older, with a mean age of 60 years, and only aortic dissection patients were excluded. Therefore, our study population has far more comorbidities than the populations examined in prior studies. However, this study population is representative of patients encountered in current clinical practice. Echocardiography was used for the diagnosis of AR in our study as opposed to aortic root cineangiography, which was used in the initial AR studies. Echocardiography is currently the most widely used test to evaluate AR. The older age of our patients, use of echocardiography for the diagnosis of AR, and lack of rigorous exclusion criteria makes our results more applicable to the average patient with severe AR encountered in clinical practice.

Study Limitations

One of the main limitations of this study is its retrospective, observational nature. Hence, the treatment assignment was not randomized but, rather, was at the discretion of the patient and physician. Other drawbacks of this study include the reliability of symptom assessment and the influence of unmeasurable and unmeasured prognostic variables. We employed propensity score analysis to reduce the impact of selection bias. Propensity score analysis has been estimated to eliminate 85% to 90% of the treatment bias that is associated with the observational studies [18–20].

It is not uncommon that patients with a chronic disease learn to live within their symptoms and claim asymptomatic status. Symptoms are subjective and depend upon patient expectations, lifestyle, and other comorbidities that may limit exercise tolerance. It is quite possible that some of the patients that were asymptomatic by chart review would experience symptoms if they underwent exercise treadmill testing.

We obtained the clinical, echocardiographic, and pharmacologic variables that were clearly measurable. Chart review did not allow us to clearly understand the thought processes employed in clinical decision making. However, there has not been a randomized study in this area, and there are none in progress to our knowledge. The results of this study will assist in clinical decision making until a randomized trial occurs.

In conclusion, our study shows that AVR may increase survival of patients with asymptomatic severe AR. This effect persisted after controlling for all the pertinent clinical, pharmacologic, and echocardiographic variables that were evaluated in this study. Our data are more comprehensive when compared with those of other published studies and include pharmacologic data that were not available in earlier studies. Moreover, our patients are older (mean age 60) and were only excluded if they had aortic dissection. That makes the results of our study applicable to the average severe AR patient encountered in clinical practice. The influence of unmeasured or unmeasurable variables on mortality cannot be fully excluded despite the application of propensity score analysis. Their influence can only be eliminated in a randomized study. We are not aware of any randomized study addressing this question either in progress or in planning. Hence, we believe our data will assist physicians in the clinical management of severe AR patients until the results from randomized studies become available. Our observational study supports a strategy of earlier aortic valve replacement in severe asymptomatic aortic regurgitation patients despite normal LVEF and size. Aortic valve replacement in these patients was associated with a better survival. These data are at variance with current ACC/AHA valve guidelines.

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