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Effect of Beta-Blocker Therapy on Survival in Patients With Severe Aortic Regurgitation

Results From a Cohort of 756 Patients

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

Loma Linda, California

Objectives We sought to investigate the effect of beta-blocker (BB) therapy on survival in patients with severe aortic regurgitation (AR).

Background Beta-blockers are thought to be contraindicated in patients with AR because a slower heart rate increases the duration of diastole during which AR occurs. But AR also causes neuroendocrine activation similar to a heart failure state for which BBs are potentially beneficial.

Methods This is an observational study. Our echocardiographic database was screened for patients with severe AR. Detailed chart reviews were performed for clinical, demographic, and therapeutic data. Mortality data were obtained from the Social Security Death Index and analyzed as a function of BB therapy.

Results Three hundred fifty-five (47%) of the 756 patients with severe AR were on a BB; mean age 61 ± 18 years and ejection fraction was 54 ± 19%. Over a mean follow-up of 4.5 years, BB therapy was associated with a higher survival rate (1- and 5-year survival rates of 90% and 70%, respectively) compared with those without (1- and 5-year survival rates of 75% and 55%, respectively) ($p = 0.0009$). The Cox regression model showed that BB therapy was an independent predictor of better survival after adjusting for age, sex, heart rate, hypertension, coronary artery disease, diabetes mellitus, heart failure, renal insufficiency, ejection fraction, and aortic valve replacement (hazard ratio: 0.74, 95% confidence interval: 0.58 to 0.93, $p = 0.01$). The survival benefit of BB therapy was further supported by propensity score analysis.

Conclusions This observational study strongly suggests that BB therapy is associated with a survival benefit in patients with severe AR. (J Am Coll Cardiol 2009;54:452–7) © 2009 by the American College of Cardiology Foundation

Aortic regurgitation (AR) represents a condition of combined volume and pressure overload (1). Volume overload imposed by aortic regurgitation (AR) results in neuroendocrine activation, including a heightened beta-adrenergic state, reduced myocyte protein synthesis, and extracellular matrix (ECM) degradation similar to a heart failure state (1–3). Beta-blockade in patients with heart failure decreases proinflammatory cytokines and is associated with increased survival (4–8). Animal studies of chronic AR have shown a protective effect of beta-blockers (BBs) against development of myocardial dysfunction (9,10) and for improved survival. We investigated the potential survival benefit of BB therapy in a large cohort of patients with severe AR.

From the Division of Cardiology, Loma Linda University Medical Center, Loma Linda, California.

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Methods

Patient selection. This was a retrospective observational study conducted in a large university medical center. The study was approved by the institutional review board, which waived the need for patient consent. The echocardiographic database was searched for patients with severe AR during the period from 1993 to 2007. Severe AR was diagnosed

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based on 1 or more criteria, including jet height to left ventricular (LV) outflow tract diameter of ≥60% or prominent holodiastolic flow reversal in the aortic arch or abdominal aorta as judged by a Level 3-trained echocardiographer (11). This yielded a total of 786 patients. Complete clinical, echocardiographic, and pharmacological data were compiled on these patients from comprehensive chart review. Thirty of the 786

patients, who did not have any follow-up, were excluded from the study. The remaining 756 patients formed the study cohort.

Clinical variables. Various clinical comorbidities were defined as follows: Hypertension was defined as a blood pressure >130/90 mm Hg, being on any antihypertensive medication, or a documented history of hypertension. Diabetes mellitus was defined as a fasting blood sugar of >126 mg/dl or being on treatment for diabetes. Renal insufficiency was defined as a creatinine value ≥2 mg/dl. Coronary artery disease (CAD) was defined as the presence of 1 of the following: a documented history of myocardial infarction or CAD, a positive stress test, angiographic evidence of CAD with lesions ≥50%, or a history of coronary intervention or coronary artery bypass grafting, or the presence of significant Q waves on the electrocardiogram.

Echocardiography. All patients had standard 2-dimensional echocardiographic examinations. The LV ejection fraction (EF) was assessed visually by a Level 3-trained echocardiographer and entered into a database at the time of the examination. This has been proven to be reliable and has been validated against contrast and radionuclide LV angiography (12,13). Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography (14).

Pharmacological data. Pharmacotherapy around the time of initial echo was recorded and placed into broad categories of BBs, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretic agents, antiarrhythmic agents, digoxin, aspirin, and statins. Patients were considered to be on a pharmacological agent only if they received it for at least 1 month's duration. However, most of the patients continued on the BB and other medications for the length of the recorded clinical observation.

Mortality data. The end point of the study was all-cause mortality. Mortality data were obtained from the National Death Index using social security numbers. Mortality was assessed and patient follow-up was censored in August 2007.

Statistical methods. Stat View version 5.01 (SAS Institute, Cary, North Carolina) program was used for statistical analysis. Kaplan-Meier survival curves were computed for patients with severe AR with and without BBs and were compared using the log-rank statistic. Characteristics of patients with and without BB therapy were compared using the Student *t* test for continuous variables and the chi-square test for categorical variables. Cox proportional hazards models and propensity score analysis were employed to adjust for comorbidities and covariate imbalances (15–17). A p value of ≤0.05 was considered significant.

Results

Patient characteristics. A total of 756 patients had severe AR. Baseline characteristics of these patients were: mean age 61 ± 18 years, 59% men, mean LVEF 54 ± 19%, and diabetes mellitus in 14%, hypertension in 65%, and CAD in 33%. Of the entire cohort, 47% were on a BB, and 38% underwent aortic valve replacement (AVR) during follow-up. The likely causes of AR based on echocardiographic appearance and chart review were as follows: bicuspid aortic valve in 78 (10%), dilated aortic root in 79 (10%), degenerative or calcific aortic valve disease in 220 (30%), and prior infective endocarditis in 78 (10%) patients. The rest of the patients had mixed or unclear mechanisms.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AR = aortic regurgitation
AVR = aortic valve replacement
BB = beta-blocker
CAD = coronary artery disease
EF = ejection fraction
LV = left ventricular

Comparison of patients with and without BB. Table 1 shows the comparison of patients with severe AR, with and without BB therapy. Patients on BBs were younger (60 ± 17 years vs. 63 ± 18 years, p = 0.01) and had a higher prevalence of CAD (38% vs. 29%, p = 0.007), hypertension (74% vs. 56%, p < 0.0001), AVR (49% vs. 28%, p < 0.0001), and concomitant ACE inhibitor therapy (52% vs. 40%, p = 0.0005).

Table 1 Characteristics of Aortic Regurgitation Patients With and Without Beta-Blockers

Variables	No Beta-Blocker (n = 401)	Beta-Blocker (n = 355)	p Value
Age, yrs	63 ± 18	60 ± 17	0.01
Men	56%	63%	0.06
Coronary artery disease	29%	38%	0.007
Hypertension	56%	74%	<0.0001
Diabetes mellitus	13%	15%	0.36
Renal insufficiency	20%	21%	0.67
Heart failure	68%	72%	0.19
Atrial fibrillation	27%	24%	0.27
Heart rate, beats/min	66 ± 38	76 ± 26	<0.0001
Ejection fraction, %	54 ± 19	54 ± 18	0.68
Left ventricular end-diastolic diameter, cm	5.6 ± 1.1	5.8 ± 1.0	0.05
Left ventricular end-systolic diameter, cm	3.9 ± 1.2	4.0 ± 1.2	0.07
Ventricular septum, cm	1.2 ± 0.26	1.3 ± 0.25	0.001
Posterior wall, cm	1.1 ± 0.24	1.2 ± 0.21	0.002
Pulmonary artery systolic pressure >60 mm Hg	18%	16%	0.54
Aspirin use	32%	47%	<0.0001
Angiotensin-converting enzyme inhibitor use	40%	53%	0.0005
Statin use	12%	30%	<0.0001
Dihydropyridine calcium-channel blocker use	16%	22%	0.03
Nondihydropyridine calcium-channel blocker use	14%	13%	0.67
Aortic valve replacement	29%	49%	<0.0001
Coronary artery bypass grafting	13%	20%	0.005

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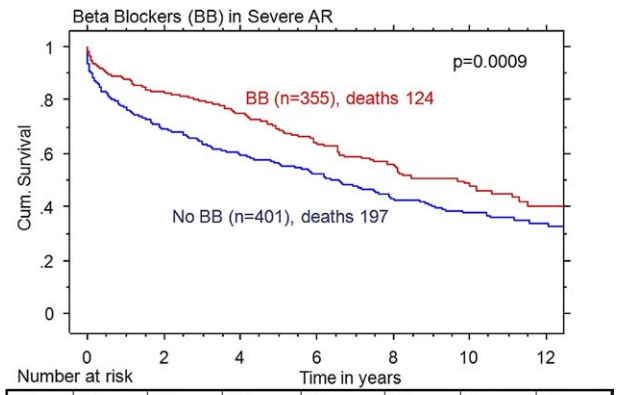

Figure 1 Kaplan-Meier Survival Curves of Patients With Severe AR With and Without BB Therapy

AR = aortic regurgitation; BB = beta-blocker.

Effect of BBs on survival. Over a period of 4.4 ± 4.1 years, there were a total of 321 deaths, 124 in the BB group and 197 in the no BB group. Figure 1 shows the effect of BB therapy on survival in patients with severe AR using Kaplan-Meier analysis and log rank statistic. Patients on BBs (n = 355) had a significantly higher survival of 90% and 70% at 1 and 5 years, respectively, compared with 75% and 55%, respectively, for patients without BB (n = 401) (p = 0.0009).

Stratification by CAD status. To investigate whether the BB effect was through its anti-ischemic effect, we evaluated BB effect stratified by CAD status. In the CAD group (n = 253), there were 141 deaths (81 in the BB group and 60 in the no BB groups); and in those without known CAD (n = 503), there were 180 deaths (63 in the BB group and 117 in the no BB group). Figure 2 shows the effect of BBs on survival by CAD status. In patients without CAD, the 1- and 5-year survival rates with BBs were 90% and 75%, respectively, compared to 75% and 62%, respectively, for those on no BB therapy (p = 0.02). The p value adjusted for age, sex, and EF was 0.03. In patients with CAD, 1- and 5-year survival rates with BB therapy were 85% and 65%, respectively, compared with 72% and 45%, respectively, for no BB therapy (p = 0.0002), showing a mortality benefit independent of CAD status. The adjusted p value of the CAD group was 0.002.

Stratification based on hypertension. To eliminate the possibility that the effect of BB therapy is through blood pressure reduction alone in hypertensive patients, we analyzed those with and without hypertension separately. Of the 487 patients with a history of hypertension, 263 were on a BB. There were 231 deaths (101 in those on BB therapy and 130 in those on no BB) in those with hypertension, and 90 (24 in those on a BB and 66 in those with no BB) in the 269 patients without hypertension. Use of BBs was associated with a significantly higher 1- and 5-year survival (88% and 68%, respectively) compared with 75% and 52% in those without BB therapy (n = 224) (p = 0.0007) (Fig. 3A). The p value adjusted for age, sex, and EF was 0.02. In patients without hypertension, 1- and 5-year survival rates with BBs (n = 94) were 90% and 81%, respectively, compared with 78% and 68%, respectively, in those without BB therapy (n = 175, p = 0.03) (Fig. 3B), indicating a survival benefit independent of hypertension status.

Stratification based on heart rate. Of the 756 patients with severe AR, 657 had heart rate data recorded. The effect of BBs on survival was analyzed in heart rate quartiles. Beta-blocker therapy was not associated with improved survival in the first and second quartiles (slower heart rates), but was associated with better survival in the third and fourth quartiles (p = 0.04 and p = 0.001, respectively). In other words, benefit was seen in those with higher heart rates.

Cox regression models. Two types of Cox regression models were created to adjust for confounders. In the first,

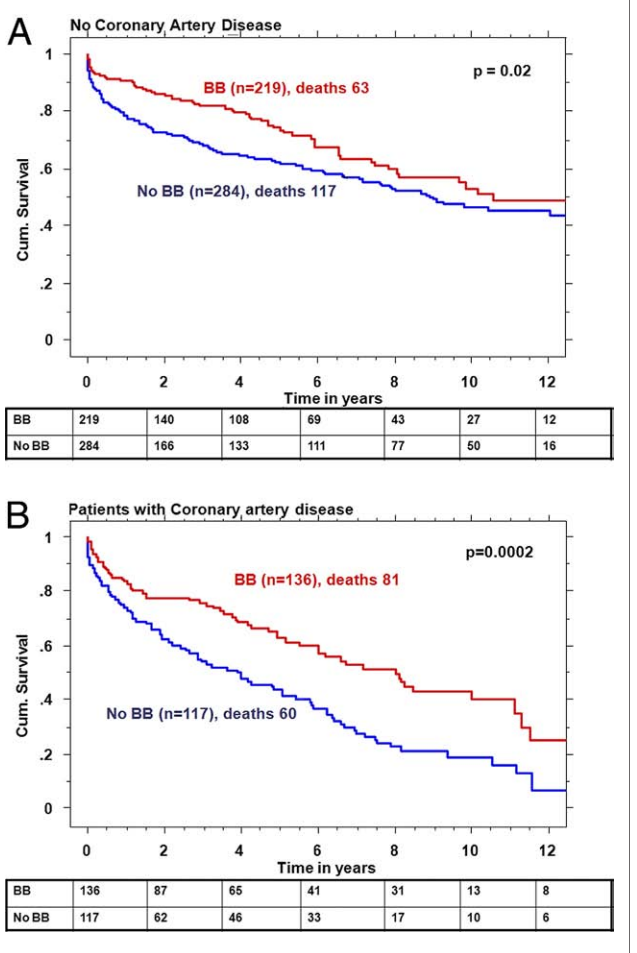

Figure 2 Effect of BBs on Survival Stratified by CAD Status

Survival was better with beta-blockers (BBs) in patients without **(A)** and with **(B)** coronary artery disease (CAD).

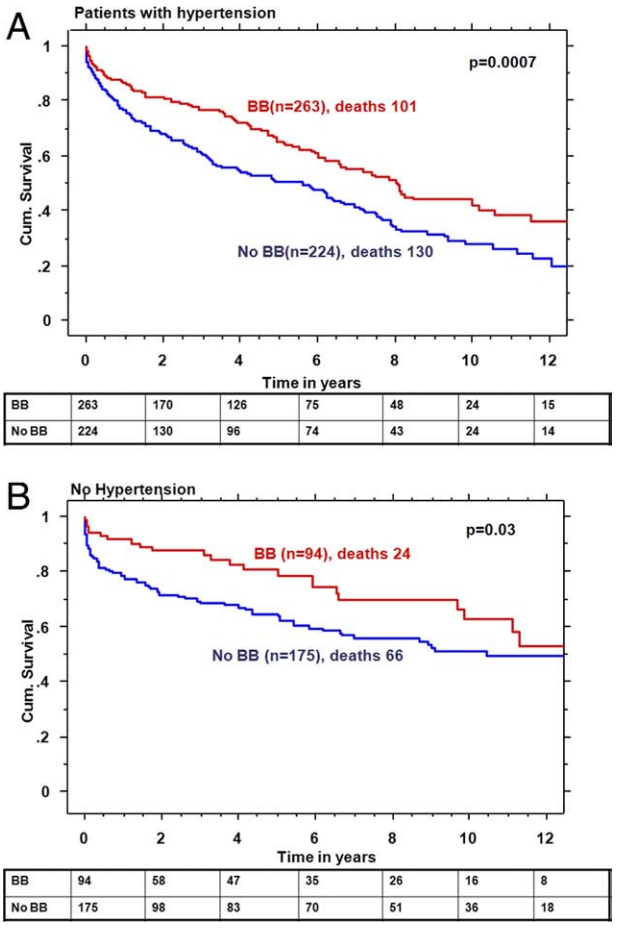

Figure 3 **Effect of BBs on Survival Stratified by Hypertension Status**

Survival was better with beta-blockers (BBs) in patients with **(A)** and without **(B)** hypertension.

the effect of BB therapy on survival was assessed by adjusting for all group differences with $p \leq 0.10$. Adjusted mortality risk with BB therapy was 0.74 (95% confidence interval [CI]: 0.57 to 0.97, $p = 0.03$). In the second model, adjustments were made for age, sex, heart rate, hypertension, CAD, diabetes, heart failure, renal insufficiency, LVEF, and aortic valve replacement. The mortality benefit associated with BB therapy was unchanged (relative risk: 0.74, 95% CI: 0.58 to 0.93, $p = 0.01$).

Propensity score analysis. Propensity score analysis was also carried out to address the effect of covariate imbalance between the BB group and comparison group. The probability of receiving BBs (propensity score) for each patient was modeled by using a logistic regression model conditioned on covariate values for that individual. This has been shown to reduce bias in observational studies (15–17). Beta-blocker therapy was an independent predictor of survival after adjusting for the propensity score using the Cox regression model ($p = 0.01$).

Analysis censoring at the time of AVR. To analyze the effect of BB therapy on AR mortality alone rather than its effect after AVR, a separate analysis was performed by censoring patients at the time of AVR. Kaplan-Meier analysis showed that patients on BB therapy had a higher survival rate as compared with those who were not on a BB ($p = 0.05$).

Discussion

This observational study indicates that BB therapy may benefit patients with severe AR irrespective of CAD and hypertension status. The benefit is also predominantly seen in those with faster heart rates, which may indicate higher adrenergic tone. Our observations are consistent with in vitro and animal data published by other investigators and support a hypothesis that elevated catecholamines are likely to be detrimental in patients with severe AR, and blocking their effects could be beneficial.

Myocardial changes produced by AR in humans. AR causes LV remodeling, myocyte hypertrophy, degeneration, and apoptosis, an increase in intercellular collagen, and an increased ECM. Volume overload from chronic AR leads to a series of compensatory mechanisms, including an increase in end-diastolic volume and eccentric hypertrophy, followed by an increase in LV afterload as evidenced by an increase in mean systolic stress leading to further hypertrophy (18–21). Eventually, LV systolic dysfunction sets in, which is initially reversible and later irreversible (19–21). Myocardial dysfunction can be detected in asymptomatic patients with severe AR and in patients with moderate to severe AR with normal LVEF using indices of LV contractile function adjusted for afterload (22). The LV long-axis function has been shown to be abnormal in severe AR despite normal EF (23). Analysis of endomyocardial biopsies has shown that degeneration of the cardiomyocytes is more prevalent in AR compared with aortic stenosis (24). As discussed later, many of these deleterious processes are prevented by BBs.

Possible mechanisms of BB benefit in AR. In animal model AR, there is an increase in the level of circulating catecholamines, myocardial fibrosis, and degeneration of cardiac myocytes (24–26). Gupta et al. (27) have shown an increase in fibronectin synthesis in cardiac fibroblast cultures subjected to simulated AR. Plante et al. (9) have studied the effectiveness of metoprolol in chronic AR in adult male Wistar rats. They found that metoprolol treatment increases the expression of $beta_1$ adrenoceptor mRNA, reduces G protein receptor kinase 2 levels, and reduces the cross-sectional area of cardiomyocytes, and it had a beneficial effect on ECM remodeling by inhibiting collagen and fibronectin expression. Subsequently, in a similar animal study, they found that metoprolol improved 1-year survival, minimized LV hypertrophy, improved LV filling pressures, decreased LV subendocardial fibrosis, and helped restore the beta-adrenergic receptor ratio (10). Animal studies in the context of heart failure have also shown that BBs

prevent myocardial fibrosis even at doses that do not reduce systemic blood pressure (28,29).

BBs after AVR. Matuyama et al. (30) studied the effects of BB therapy in patients with normal EF after AVR for chronic AR and found that the post-operative LV volume and LV mass index were significantly decreased in patients with BBs and concomitant ACE inhibitors compared with ACE inhibitors and no BBs. However, their sample size was too small, and the effects of BB treatment were studied only after AVR.

Severe AR and heart rate. It is generally believed that a faster heart rate is beneficial in severe AR as it potentially shortens the diastolic period during which AR occurs. But a faster heart rate would also reduce left atrial emptying and myocardial blood flow. A faster heart rate is also a reflection of a higher level of circulating catecholamines, which are potentially cardiotoxic. The ideal heart rate for hemodynamics is unknown in human AR. In our study, the benefit of BBs was seen in those with faster heart rates, perhaps reflecting the benefit of BBs in those with a higher sympathetic drive. It is also possible that the optimum target heart rate in these individuals is perhaps in the range of 70 to 80 beats/min because a benefit of BB therapy was not seen in those with heart rates <70 beats/min. But it is more likely that the cellular and biochemical effects, rather than hemodynamics, were more related to the survival benefit of BBs.

Potential therapeutic mechanisms of BBs. Our study is the first human study, to our knowledge, to show the potential survival benefit of BB therapy in patients with chronic severe AR. This was independent of the presence of CAD or hypertension, indicating that the benefit of BBs is likely due to mechanisms other than their antihypertensive and anti-ischemic properties. Selective benefit in those with faster heart rates perhaps indicates that the mechanism may be through blocking the actions of catecholamines resulting in up-regulation of myocardial beta receptors. In addition, BBs have an effect on metalloproteinases, which may result in reduced LV remodeling and LV diastolic stiffness (28,29). BBs also reduce myocardial apoptotic rates and reduce myocyte hypertrophy (31). In addition, BBs have antiarrhythmic properties with a potential reduction in atrial and ventricular arrhythmias.

Study limitations. This is a retrospective observational study, and hence, treatment assignment is not random. There were covariate imbalances between treatment and control groups. Adjustments for these were made using Cox regression models and propensity score analysis. The latter model is reported to eliminate up to 90% of treatment bias (15–17), but a cause–effect relationship can not be concluded. We do not have comprehensive data on type, dose, and duration of BB therapy because of multiple formulations and changing doses, making the intensity of exposure difficult to measure. However, we included only those patients who received BBs for at least 1 month's duration. Most of the patients continued on the BB for the length of the recorded clinical observation. Only a randomized controlled trial can remove the bias and reliably measure exposure to treatment.

Conclusions

This retrospective observational study indicates that BB therapy is associated with a better survival in patients with severe AR. Prospective randomized controlled trials are warranted to confirm these findings.

Reprint requests and correspondence: Dr. Ramdas G. Pai, Division of Cardiology, 11234 Anderson Street, Room 4414, Loma Linda University Medical Center, Loma Linda, California 92354. E-mail: ramdaspai@yahoo.com.

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Key Words: aortic regurgitation ■ beta-blocker ■ survival.