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EDITORIAL COMMENT

Beta-Blockers in the Treatment of Aortic Regurgitation

A New Opportunity?*

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Chronic aortic regurgitation (AR) is associated with left ventricular (LV) volume overload that can lead to LV dilation, increase in wall stress, LV hypertrophy, and eventually, to symptomatic heart failure and death (1,2). Aortic valve replacement (AVR) is the only proven beneficial treatment, but it is usually reserved for patients with advanced disease and performed after the development of symptoms and/or significant alteration in ventricular size or systolic function (2). For lack of adequate, large-scale, randomized clinical trials, there is no established medical treatment for patients with chronic severe AR prior to or after surgery (3).

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Because of the demonstrated favorable acute effect of vasodilators in reducing regurgitant volume and improving cardiac performance in AR (4–6), an attempt has been made to use these drugs in the treatment of chronic AR. A recent review by Mahajerin et al. (7) has provided an excellent summary of the available data on the effect of vasodilator therapy in a total of 544 patients included in 10 prospective, randomized clinical trials that evaluated this form of therapy in asymptomatic patients with chronic AR with at least moderate severity and normal LV function. The drugs included were nifedipine, hydralazine, and angiotensin-converting enzyme (ACE) inhibitors. Although most studies demonstrated a favorable effect on some hemodynamic and/or structural parameters, other studies did not. The effect on clinical outcome was reported in only 2 clinical trials, the first by Scognamiglio et al. (8), who compared the effects of the calcium antagonist nifedipine to that of digoxin in 143 asymptomatic patients with chromic, severe AR followed for an average of 6 years, and reported a significantly superior effect of nifedipine on delaying progression to AVR. In contrast, a second study by Evangelista et al. (9) failed to demonstrate a similar superior effect of nifedipine compared with enalapril or even placebo on the rate of progression to AVR in 130 similar patients who were followed for 7 years. These conflicting results and the relatively small number of patients included in these studies help to explain the considerable uncertainty regarding the long-term effect of vasodilator and ACE inhibitor therapy in patients with chronic AR (2,3).

The use of beta-blockers in patients with AR has been traditionally considered relatively contraindicated (2,10) because of their negative inotropic as well as chronotropic effects; the latter may lead to prolongation of diastole and thus to an increase in aortic regurgitant volume. Recent studies in animals with chronic AR have shown, however, a favorable effect of beta-blockers in the prevention of LV dilation and preservation of LV ejection fraction and filling parameters (11), as well as decreased LV subendocardial fibrosis and even prolongation of survival (12).

In this issue of the *Journal*, Sampat et al. (13) published a retrospective observational study that demonstrated a potential survival benefit of beta-blockers in patients with severe AR. The study included 756 patients that were identified from the investigators' institutional echocardiographic database between 1993 to 2007. The average age was 61 ± 18 years, 59% were men, and the mean LV ejection fraction was 54 ± 19%. Over a period of 4.4 ± 4.1 years, patients who were treated with beta-blockers for at least 1 month had a significantly better survival of 90% and 70% at 1 and 5 years, respectively, compared with patients not treated with beta-blockers (75% and 55%, respectively, $p = 0.0009$). The beneficial effect of beta-blockers was seen in patients with and without known coronary artery disease and with and without a history of hypertension. Analysis of the effect of beta-blockers in subgroups of the study population stratified by heart rate demonstrated that the effect of therapy was limited to patients with higher heart rates. What are the clinical implications of this study? Unfortunately, and similar to other retrospective studies, this analysis suffers from major limitations that include a heterogeneous patient population (patients with and without AVR, coronary artery disease, and hypertension, as well as patients with variable degrees of LV function). In addition, because of its retrospective design, the paper cannot provide information on the type and dose of the beta-blocking agents used, nor on concomitant therapy. Although propensity score analysis was appropriately performed in an attempt to adjust for comorbidities and covariate imbalances between the beta-blockers and the comparison groups, this method of analysis cannot completely rule out potential selection bias. Because it is not possible to identify and adjust for all possible factors, differences between those patients who

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were treated with beta-blockers and those who were not cannot be completely excluded. These differences include age, incidence of coronary artery disease and hypertension, heart rate, LV end-diastolic dimension, presence of LV hypertrophy, concomitant medications, rate of AVR, and coronary artery bypass grafting. In addition, treatment must have started at various times during the study period, leading to potential inception time bias.

Because of these limitations, the results of the study can only be considered as hypothesis generating rather than evidence that can change clinical practice. Despite these limitations, the relatively large number of patients with severe AR included in the analysis as well as the consistent benefits demonstrated with beta-blocker therapy, both in the entire group as well as in important subgroups, are impressive and may provide clinically important information. My own conclusions based on the results of the study are that the recommendations (which have not been based on clinical evidence) not to use beta-blockers in patients with AR should be removed. The use of beta-blockers in patients with AR for the treatment of other conditions such as hypertension, arrhythmias, and coronary artery disease seems reasonable and may be beneficial. The encouraging results of this study should provide a strong incentive for investigators to design, and for funding institutions to support, a large, prospective and randomized study aimed at evaluating the therapeutic effect of beta-blockers in the treatment of patients with clinically significant AR.

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