Metoprolol Reverses Left Ventricular Remodeling in Patients With Asymptomatic Systolic Dysfunction

The REversal of VEntricular Remodeling with Toprol-XL (REVERT) Trial

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Background—There are no randomized, controlled trial data to support the benefit of β-blockers in patients with asymptomatic left ventricular systolic dysfunction. We investigated whether β-blocker therapy ameliorates left ventricular remodeling in asymptomatic patients with left ventricular systolic dysfunction.

Method and Results—Patients with left ventricular ejection fraction <40%, mild left ventricular dilation, and no symptoms of heart failure (New York Heart Association class I) were randomly assigned to receive extended-release metoprolol succinate (Toprol-XL, AstraZeneca) 200 mg or 50 mg or placebo for 12 months. Echocardiographic assessments of left ventricular end-systolic volume, end-diastolic volume, mass, and ejection fraction were performed at baseline and at 6 and 12 months. The 149 patients randomized to the 3 treatment groups (200 mg, n=48; 50 mg, n=48; and placebo, n=53) were similar with regard to all baseline characteristics including age (mean, 66 years), gender (74% male), plasma brain natriuretic peptide (79 pg/mL), left ventricular end-diastolic volume index (110 mL/m²), and left ventricular ejection fraction index (27%). At 12 months in the 200-mg group, there was a 14 ± 3 mL/m² decrease (least square mean ± SE) in end-systolic volume index and a 6 ± 1% increase in left ventricular ejection fraction (P<0.05 versus baseline and placebo for both). The decrease in end-diastolic volume index (14 ± 3) was different from that seen at baseline (P<0.05) but not with placebo. In the 50-mg group, end-systolic and end-diastolic volume indexes decreased relative to baseline but were not different from what was seen with placebo, whereas ejection fraction increased by 4 ± 1% (P<0.05 versus baseline and placebo).

Conclusion—β-Blocker therapy can ameliorate left ventricular remodeling in asymptomatic patients with left ventricular systolic dysfunction. (Circulation. 2007;116:49-56.)

Key Words: heart failure □ receptors, adrenergic, beta □ remodeling □ ventricles

A symptomatic left ventricular (LV) systolic dysfunction is common in the general population, with a prevalence on the order of 3%, constituting a high percentage of all patients with LV dysfunction. For example, in the Olmstead County population, less than half of all patients with an LV ejection fraction (EF) <40% had been diagnosed with congestive heart failure (HF). Although asymptomatic, these patients are at high risk for developing clinical HF. In asymptomatic patients with a LVEF <40% in the Framingham Heart Study population, the annual incidence of symptomatic HF was ~6%, and the annual mortality rate was ~8%. Despite the important consequences of asymptomatic LV systolic dysfunction, very few clinical trials of therapeutic agents have been conducted in this population.

In patients with symptoms of HF due to systolic LV dysfunction, extensive clinical trial data have demonstrated that β-blockers improve survival, decrease hospitalizations related to HF, and alleviate symptoms. The improved
outcomes are associated with amelioration of LV remodeling characterized by decreases in end-diastolic and end-systolic volumes and an increase in EF. The studies that have demonstrated these beneficial effects on outcomes and remodeling have been performed almost exclusively in symptomatic patients in New York Heart Association (NYHA) functional classes II, III, or IV.

Although an exception would be the Australia/New Zealand Carvedilol Trial, in which approximately one third of subjects were asymptomatic, the survival benefits of carvedilol in that trial were not analyzed with regard to functional class. Likewise, although some patients in the Carvedilol Prospective Randomized Cumulative Survival (CAPRICORN) trial had asymptomatic LV dysfunction, the impact of therapy was not analyzed with regard to functional class and would not be directly applicable to patients with chronic LV dysfunction.

There have been no randomized controlled trials of the effects of β-blockers on clinical outcomes or remodeling in patients who have chronic LV systolic dysfunction but are free of symptoms. Theoretically, patients with asymptomatic LV dysfunction may be less responsive to β-blockers because the degree of sympathetic nervous system activation is less. Alternatively, there is reason to believe that β-blockers would be effective in such patients because some studies have shown clinical benefit in patients with mild (predominantly NYHA class II) symptoms of HF.

Because of the lack of direct evidence from randomized controlled trials, the current recommendation for the use of β-blockers in patients with a chronic reduction in LVEF but no HF symptoms is based only on expert opinion. Furthermore, it is unlikely that a placebo-controlled study can be performed to test the effects of β-blockade on clinical outcomes in this population.

There is evidence that the outcome benefits of β-blockers in patients with systolic LV dysfunction are related to the antiremodeling effect, which might therefore be used as a reasonable surrogate for clinical benefit. Accordingly, we designed a placebo-controlled, randomized trial, RE Versal of VEntricular Remodeling with Toprol-XL (REVERT), to test the hypothesis that β-blocker therapy would ameliorate LV remodeling in asymptomatic (NYHA functional class I) patients with LV systolic dysfunction.

**Methods**

**Entry Criteria**

To be eligible, patients must have had a LVEF <40% and mild LV dilatation [LV end-diastolic volume index (LVEDVI) >75 mL/m2] due to idiopathic, ischemic, or hypertensive cardiomyopathy and must have had no symptoms of HF for at least 2 months. The determination of LV systolic dysfunction and dilation was based on a screening echocardiogram that was performed within 14 days of randomization and interpreted by the core laboratory. Asymptomatic LV systolic dysfunction was defined as no limitation of ordinary physical activity because of fatigue or dyspnea (NYHA functional class I). Patients previously treated for symptomatic HF were allowed to participate if they met the inclusion and exclusion criteria for the study. The use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker for at least 3 months, as tolerated, was required before enrollment. Patients must have had no changes in the doses of their cardiovascular medications, including ACE inhibitors, angiotensin receptor blockers, diuretics, digoxin, and/or vasodilators for at least 3 months before randomization.

Patients were excluded if they had indications for or contraindications to β-blocker therapy or took β-blockers (including ophthalmic preparations) for >1 week during the 6 months preceding randomization. Also excluded were patients who, during the 6 months before randomization, had myocardial infarction, unstable angina, coronary intervention, or hospitalization for cardiovascular-related causes, as well as patients with heart rate <60 bpm, sitting blood pressure >140/90 mm Hg, heart block greater than first degree not treated with a permanent pacemaker, history of ventricular or atrial fibrillation, or serum creatinine >3 mg/dL. The institutional review boards of the participating institutions approved the protocol, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

**Echocardiographic Measurements**

Two-dimensional echocardiograms with Doppler were recorded at screening (baseline) and at 6 and 12 months, with the same scanner used for each patient. The videotapes were evaluated in a blinded fashion by the core echocardiography laboratory at the University of Michigan.

The echocardiograms were analyzed with the use of a dedicated offline echocardiography analysis system (TomTec Imaging Systems, Munich, Germany). LV end-systolic volume (LVESV), LVEDV, and LVEF were measured by Simpson’s method in the apical 4-chamber view, which was used for the main analyses, as well as the apical 2-chamber view when possible. LV mass was calculated from the 2-dimensional parasternal long-axis view with the use of the Penn cubic formula, LVESV index (LVESVI), LVEDVI and LV mass index (LVMI) were determined by dividing volume or mass by body surface area.

**Treatment Regimen**

Patients who met inclusion/exclusion criteria were randomized in a 1:1:1 ratio to a 52-week treatment with metoprolol succinate extended-release tablets (metoprolol succinate, TOPROL-XL, AstraZeneca, Wilmington, Del) or placebo as follows: (1) metoprolol succinate 200 mg/d (high-dose group); (2) metoprolol succinate 50 mg/d (low-dose group); or (3) placebo. The study drug was force-titrated to the assigned dose over the first 2 months on the basis of tolerability, and the achieved dose was maintained as tolerated until the end of the study. Drug blinding was achieved with the use of a double-blind, double-dummy technique. Treatment compliance was verified by pill count of returned study medication at each visit.

**Brain Natriuretic Peptide**

In a substudy that enrolled 82 patients, venous blood was collected at baseline and at 6 and 12 months for determination of plasma brain natriuretic peptide, which was measured by radioimmunounassay (Quest Diagnostics, Van Nuys, Calif).

**Statistical Analyses**

The change in LVESVI from baseline to 12 months was chosen as the prespecified primary end point because it reflects changes in both LV size and systolic function and has been shown to be a sensitive index of LV remodeling. The power calculation was based on a SD for LVESVI at 12 months of 15 mL/m2 and a dropout rate of 20%. With an α of 0.050 for a 2-sided test, 150 patients would provide 94% power to detect a change of 12 mL/m2 and 84% power to detect a change of 10 mL/m2. Prespecified key secondary end points included the change from baseline in LVESVI at month 6 and changes from baseline in LVEDVI, LVMI, and LVEF at months 6 and 12. Efficacy was analyzed by a modified intention-to-treat population (n=149 patients) who took at least 1 dose of study medication after randomization and had at least 1 follow-up echocardiogram. All available data were analyzed, and no substitutions were made for missing values. Pairwise comparisons were made between the high-dose group and placebo (primary comparison) and between the low-dose group and placebo (secondary comparison) for
all LV end points. Changes from baseline in LV dimensions were analyzed with a repeated-measures ANOVA, with terms for treatment group, time (6 and 12 months), and the interaction between treatment group and time. Least square means of the interaction term were used to estimate treatment group effects at each time, to make pairwise comparisons of the metoprolol groups versus placebo, and to test whether changes within each treatment group were different from zero (ie, different from baseline values). All tests were 2-sided and were performed at a significance level of 0.050. All values are reported as mean ± SD unless otherwise specified. All analyses were conducted with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Drug Exposure

Of the 164 patients randomized, 149 patients who had at least 1 dose of drug and 1 follow-up echocardiogram were used for the modified intention-to-treat analysis. Fifteen patients (placebo, n=4; low dose, n=6; high dose, n=5) were excluded from the intention-to-treat analysis because they did not have a follow-up echocardiogram. The median (range) duration of treatment was 357 (9 to 391), 358 (4 to 376), and 358 (15 to 383) days in the placebo, low-dose, and high-dose groups, respectively. Mean compliance during the 52-week double-blind treatment period ranged from 97% to 100% in the 3 treatment groups. In the low-dose group, 87% of patients achieved the 50-mg/d dose (mean dose, 47 ± 9 mg/d). In the high-dose group, 68% of patients achieved the 200-mg/d dose (mean dose, 155 ± 69 mg/d).

Baseline Characteristics

The 149 patients in the intention-to-treat efficacy analysis had a mean age of 66 ± 13 years; 74% were male, and 77% were white (Table 1). The cause of HF was attributed to ischemia (54%), idiopathic dilated cardiomyopathy (29%), hypertension (12%), or other causes (5%). Ninety-four percent of patients were receiving an ACE inhibitor and/or an angiotensin receptor blocker, 64% were receiving a diuretic, and 42% were receiving digoxin.

At baseline the mean heart rate was 77 ± 11 bpm, and the mean blood pressure was 125/73 mm Hg. Plasma brain natriuretic peptide averaged 79 ± 71 pg/mL. Baseline heart rate, blood pressure, and brain natriuretic peptide levels were similar among the 3 treatment groups.
Effects of Treatment on Heart Rate and Blood Pressure
Heart rate decreased by 3/100, 8/100, and 12/100 bpm in the placebo, low-dose, and high-dose groups at 12 months, respectively (Figure 1). There were no significant changes in systolic or diastolic blood pressure from baseline to 12 months in any group.

Effects of Treatment on LV Dimensions
At baseline, LV dimensions and EF were similar in the 3 groups (Table 2). At 12 months, LVESVI, the primary end point, was decreased by 4±3, 8±3, and 14±3 mL/m² (least square mean±SE) in the placebo, low-dose, and high-dose groups, respectively (Table 3, Figure 2A). The decrease with the high dose was significant versus both baseline and placebo, whereas the decrease with the low dose was significant only versus baseline. Similar effects were seen at 6 months. There was a similar directional pattern for changes in LVEDVI with regard to both dose and treatment duration, although the changes were not statistically different from placebo (Table 3, Figure 2B).

At 12 months, LVEF was unchanged in the placebo group and increased by 4±1% in the low-dose group and 6±1% in the high-dose group (Table 3, Figure 2C). There were similar directional changes at 6 months. LVMI tended to increase in the placebo group and to decrease in both the high-dose and low-dose groups at both 6 and 12 months, although none of these differences reached statistical significance (Table 3, Figure 2D).

Adverse Events and Tolerability
The most common adverse events were fatigue, dizziness, dyspnea, peripheral edema, and HF. The percentage of patients discontinuing the study because of adverse events was 18%, 13%, and 11% in the placebo, low-dose, and high-dose groups, respectively. There were 2 deaths in the placebo group, 2 in the low-dose group, and 4 in the high-dose group. The cause of death was cardiovascular in 7 patients.

Discussion
The REVERT trial shows that treatment with metoprolol succinate reduces LVESV and improves LVEF in patients with asymptomatic LV systolic dysfunction. These results suggest that metoprolol succinate therapy ameliorates and reverses pathological cardiac remodeling in asymptomatic patients with LV systolic dysfunction.

Although prior controlled studies have demonstrated that β-blockers can reverse LV remodeling in patients with HF, these studies have been conducted entirely or predominantly in symptomatic patients. Metoprolol succinate was shown to...
improve survival and decrease hospitalizations in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), a trial that studied predominantly NYHA class II and III patients and excluded patients in NYHA class I.4 In the magnetic resonance imaging substudy of MERIT-HF, treatment with metoprolol succinate for 6 months decreased LVEDVI by 24 mL/m², decreased LVESVI of MERIT-HF, treatment with metoprolol succinate for 6 months decreased LVEDVI by 24 mL/m², decreased LVFSVI of MERIT-HF, treatment with metoprolol succinate for 6 months decreased LVEDVI by 24 mL/m², decreased LVFSVI by 26 mL/m², and increased LVEF by 8%.9 Qualitatively and quantitatively similar effects of metoprolol succinate on LV volumes and EF were seen in the echocardiographic substudy of MERIT-HF10 and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study.20 Likewise, carvedilol has been shown to improve both survival and remodeling in patients with symptomatic HF. Although LV dimensions were not reported in the US Carvedilol Trials Program, treatment with carvedilol for a mean of 213 days increased LVEF from 22% to 32%.21 In the Australia/New Zealand Trial, carvedilol decreased LV end-diastolic and end-systolic dimensions and increased EF.7 Approximately 75% of patients in the Australia/New Zealand Trial were in class II or III, and the results of that study were not reported with regard to NYHA class.11

Although the determination of symptoms is subjective, several observations suggest that the patients in REVERT differed markedly from those with class II and III symptoms that are typical of prior β-blocker trials. Perhaps the most objective measure of clinical severity is the average plasma brain natriuretic peptide level of 75 pg/mL, which is below the cutoff of 100 pg/mL that has a high level of selectivity for excluding a diagnosis of HF.22 Another important indicator of disease severity is mortality rate, which was 5% per year in this study, a rate well below the rate of ~10% to 15% per year that is typical of symptomatic patients treated with an ACE inhibitor4,21,23 and similar to the rates observed in asymptomatic patients in the treatment arm of the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial24 or a general community population.1 An important indicator of milder LV dysfunction is the lesser extent of LV remodeling at baseline. For example, the baseline LVEDVI in REVERT (110±29 mL/m²) is substantially smaller than the LVEDVI of 153±64 mL/m² in the MERIT-HF substudy.9 Other indicators of mild disease in this study population are the relatively low pretreatment heart rate of 77 compared with 82 bpm in MERIT-HF, the relatively preserved systolic blood pressure of 126 mm Hg, and the need for diuretics of any type in only ~64% of patients. It should be noted that although the patients in REVERT had to be asymptomatic for at least 2 months before randomization, before that time they may have had symptoms that responded to therapy with diuretics and/or renin-angiotensin system blockade.

In REVERT, the effects of metoprolol on LVESVI and LVEF appear to be dose dependent. Although the study was not powered to detect a dose-effect relationship, in the high-dose group the decrease in LVESVI and the increase in LVEF were significantly different from those seen in the placebo group at both 6 and 12 months, whereas these changes in the low-dose group were intermediate in magnitude and, for the most part, not significantly different from those seen with placebo. Of note, the mean dose achieved in the high-dose group (155 mg/d) of REVERT is very similar to the mean dose achieved in MERIT-HF (159 mg/d), which, like REVERT, had a target dose of 200 mg/d. The vast majority (94%) of patients in REVERT were receiving an ACE inhibitor or an angiotensin receptor blocker before enrollment, indicating that the antiremodeling effect of β-blocker therapy in asymptomatic patients is in addition to

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LSM indicates least square mean.
the benefits afforded by blockade of the renin-angiotensin system.

A decrease in heart rate, as occurs with β-blocker therapy, may allow more complete LV filling, thereby leading to increases in stroke volume and EF. A limitation of this study is that LV dimensions were not repeated after withdrawal of therapy, which would have allowed the exclusion of a transient effect due to the decrease in heart rate. However, the decrease in LVESVI and the increase in LVEF observed with metoprolol at both 6 and 12 months were associated with a decrease in LVEDVI, indicating that the observed improvements cannot be attributed to the slowing of heart rate, per se.

In 2001, when REVERT began enrollment, the existing American College of Cardiology/American Heart Association guidelines, published in 1999, concluded that the benefit of β-blocker therapy beyond the first 3 months after acute myocardial infarction had not been established conclusively, and as a result the use of β-blockers in patients with moderate or severe LV failure received only a class IIb recommendation. In this setting, REVERT allowed the enrollment of patients who had a history of a remote myocardial infarction and LV dysfunction should be treated with β-blockers. The findings of REVERT support this recommendation.

REVERT was not designed to test the effect of β-blockade on morbidity or mortality rates. There are very few outcomes trials in patients with asymptomatic HF. The SOLVD Prevention Trial demonstrated an improvement in symptoms and a decrease in hospitalization for HF but did not achieve statistical significance with regard to survival. Of note, a post hoc analysis of the SOLVD Prevention Trial found that survival was improved significantly in patients who were randomized to enalapril and were also taking a β-blocker. It is unlikely that an outcomes trial of β-blockers in patients with asymptomatic LV systolic dysfunction could be conducted. However, it has been suggested that a beneficial effect on remodeling may allow use as a surrogate for clinical outcomes in patients with HF due to LV systolic dysfunction. It is reasonable to expect that, by ameliorating LV remodeling, β-blocker therapy will delay the emergence or reemergence of symptoms in asymptomatic patients. This premise is further supported by the established positive relationship between improvements in LV remodeling and survival with β-blocker therapy in symptomatic patients.
The results of REVERT suggest that the survival benefit observed in symptomatic patients treated with metoprolol succinate may extend to asymptomatic patients with LV systolic dysfunction as well.

Appendix

REVERT Study Group

REVERT Steering Committee
Wilson S. Colucci (Chairman), Kirkwood F. Adams, William F. Armstrong, Stephen S. Gottlieb, Barry Greenberg, Merrick L. Kukin.

Sources of Funding
The REVERT study was funded by AstraZeneca, which was responsible for data collection and analysis, which was conducted according to a prespecified analysis plan. Academic leadership was provided by the Steering Committee, which supervised the management of the study and was responsible for interpretation of the data, preparation, review, and approval of the manuscript.

Disclosures
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