

The Effect of β -Blockers on Morbidity and Mortality Associated with Heart Failure

Based on a presentation by Sidney Goldstein, MD

Presentation Summary

Recent studies of β -blockers for treatment of chronic heart failure have ushered in a new era in clinical management. The Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) was the largest trial to date of β -blocker therapy in heart failure. Terminated prematurely because of an overwhelmingly beneficial effect favoring metoprolol, the MERIT-HF study showed a 34% reduction in all-cause mortality, a 41% reduction in the risk of sudden death, and a 49% reduction in the risk of death from worsening heart

failure. An updated analysis that included a longer follow-up showed no degradation of the benefits. Moreover, the follow-up analysis showed that the beneficial effects of metoprolol therapy extended across a wide range of patient subgroups and baseline clinical characteristics. More patients in the placebo group discontinued treatment for any reason and specifically for worsening heart failure. The results of the MERIT-HF study confirmed and extended evidence that patients with stable class II or class III heart failure benefit from the addition of a β -blocker to standard therapy.

Although angiotensin-converting enzyme (ACE) inhibitors revolutionized treatment of heart failure, data from clinical trials of β -blockers in heart failure turned the world of heart failure therapy upside down during the 1990s.

Historically contraindicated in heart failure, β -blockers have dispelled myth and defied conventional clinical wisdom in proving their value as components of optimal heart failure therapy. Overcoming physician

misconceptions and misinformation remains the primary challenge to extending the benefits of β -blockade to the majority of heart failure patients.

Evidence of the beneficial effects of β -blockade in heart failure dates back to pioneering Swedish studies in the 1970s.¹ Those studies attracted scant attention until 2 decades later, when a series of landmark clinical studies forced the issue of β -blockers to the forefront of heart failure treatment.

Among notable early investigations, the Metoprolol in Dilated Cardiomyopathy (MDC) trial showed that β -blockade in heart failure could reduce the risk of mortality and progression to cardiac transplantation.² Most of the benefit related to cardiac transplantation, because the absolute number of deaths in the metoprol group was higher than in the placebo group.

Following the MDC trial, the US Carvedilol Heart Failure Study Group conducted 4 trials.³⁻⁶ The data from 1,094 patients were combined to evaluate the effect of carvedilol on the clinical progression of heart failure. Clinical progression was defined as worsening heart failure leading to death, hospitalization, or a sustained increase in background medication. Post hoc analysis showed an impressive survival benefit, although there were only 53 deaths in total.

Results of the carvedilol trials paved the way for 2 subsequent trials that have confirmed and added to the evidence of the beneficial effects of β -blockers in heart failure: the second Cardiac Insufficiency Bisoprolol Study (CIBIS II)⁷ and the Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF).⁸

The CIBIS-II compared the β -1 selective drug bisoprolol dosed once daily against placebo in heart failure patients who were already on optimal therapy, including ACE inhibitors. The trial was terminated early because of the emergence of a significant reduction in mortality in patients treated with bisoprolol.

The MERIT-HF investigation represents the largest study to date of β -blocker therapy in heart failure, involving almost 4000 patients. As in most previous investigations of β -blockers in heart failure, the MERIT-HF study patients were already receiving optimal therapy that included ACE inhibitors and diuretics. Aside from the size of the study, a distinguishing

feature of MERIT-HF was its use of a new once-daily, extended-release formulation of metoprolol.

The MERIT-HF study limited enrollment to patients who had class II through IV New York Heart Association (NYHA) heart function and a left ventricular ejection fraction of less than 40%. All patients were on optimal heart failure therapy, including ACE inhibitors in almost all cases, when randomized. The patients were randomized to placebo or to 12.5 mg/d (class III and IV) or 25 mg/d (class II) of metoprolol CR/XL, which was titrated to a maximum dose of 200 mg daily.

The dose escalation strategy employed in the MERIT-HF study essentially destroyed a long-standing myth: that heart failure patients cannot tolerate high doses of β -blockers. The metoprolol dose in the trial averaged 159 mg/d, and 87% of patients were taking at least 100 mg daily at the end of the study. Two thirds of the metoprolol cohort had achieved the target dose of 200 mg daily by the end of the study.

Similar to those in most previous trials of β -blocker therapy in heart failure, the vast majority of the MERIT-HF study patients had class II or III heart function. However, 4% had class IV function. The distribution of functional class in the trial emphasizes a key issue: investigations of β -blockers in heart failure have, by and large, involved stable patients. More data are needed to support the use of β -blockers in patients with class IV heart failure or who recently have had unstable symptoms.

The MERIT-HF study ended prematurely when clear evidence of a statistically significant clinical benefit emerged in the metoprolol cohort. At termination of the trial, follow-up averaged 1 year. There were 362 deaths in this study.

For the primary endpoint of all-cause mortality, patients treated with metoprolol had a 34% reduction in rel-

ative risk compared with those in the placebo group and a 38% reduction in risk of cardiovascular death.

The relative risk of sudden death was 41% lower, and the risk of death as a result of worsening heart failure was reduced by 49% in the metoprolol group.

The impact of β -blockade on the risk of sudden death cannot be overemphasized. In the MERIT-HF study, two thirds of the deaths were sudden. Although the disease is progressive, and many patients do succumb to progressive failure, the majority of heart failure patients die suddenly out of the hospital. The exception is class IV patients, who are more likely to die from progressive heart failure.

Not surprisingly, mortality increased across functional class, but the benefits of β -blockade were seen in each class. Mortality was 7% in placebo-treated class II patients, increasing to 13% in class III patients and to almost 25% in class IV patients. Metoprolol CR/XL reduced mortality among patients in each functional class: 5.3%, 8.1%, and 16.7% for classes II through IV, respectively. More data are needed on the effects of β -blockade in class IV heart failure patients because of the small number of class IV, patients enrolled but the data from the MERIT-HF trial and other clinical studies suggest that β -blockers represent no hazard in ambulatory class IV patients and might well confer a mortality benefit.

The follow-up analysis showed significant reductions in hospitalization rates in metoprolol CR/XL-treated patients. The benefits included a 16% reduction in the cardiovascular hospitalization rate, a 30% reduction in the rate of hospitalization for worsening heart failure, and an 11% reduction in hospitalization for any reason. Metoprolol CR/XL reduced the total number of hospital days by 2000 days or 17%.

Similarly, β -blockade favorably influenced the incidence of cause-specific

hospitalization events. The metoprolol CR/XL patients had an 18% lower rate of all clinical events, a 25% lower incidence of cardiovascular events, and a 35% lower incidence of heart failure-related events; all these differences were highly statistically significant.

The combined endpoint of total mortality and all-cause hospitalization was 19% lower in the metoprolol CR/XL patients. The risk of the combination of total mortality and heart failure hospitalization was reduced by 31% with the extended release formulation of metoprolol.

With respect to a change in functional class, significantly more metoprolol patients had improvement in NYHA class—29% versus 26% with placebo. Fewer patients in the metoprolol group also had a worsening of NYHA functional class during the course of the study.

Extensive subgroup analysis revealed a robust effect of metoprolol CR/XL across a wide clinical spectrum of patients. Men and women alike benefited from β -blockade, although the trial included relatively few women (about one third of the study population overall). Older and younger patients benefited from β -blockade, whether judged by a cut-off point of 69 years or less than 80 years of age. Metoprolol CR/XL had a beneficial effect in smokers and nonsmokers, diabetic and nondiabetic patients, those with heart disease of ischemic origin or nonischemic origin, and in patients with and without a history of myocardial infarction. Not all the differences achieved statistical significance, but the results of all subgroup analyses exhibited at least a trend in favor of metoprolol.

Additionally, metoprolol CR/XL benefited patients irrespective of their baseline ejection fraction. The magnitude of benefit was greater in patients with an ejection fraction of 25% or less, but patients with a higher ejection fraction also benefited. Notably, a beneficial effect was also observed in

patients who had an ejection fraction of less than 20%, a finding that should help dispel concerns about the use of β -blockers in patients with extremely compromised left ventricular function.

A similar beneficial pattern was observed when specific clinical endpoints were evaluated across patient subtypes. In general patients who had a higher baseline risk benefited the most from metoprolol CR/XL; for example, patients with the lowest baseline ejection fractions derived the most benefit in terms of mortality and hospitalization.

Data on safety and tolerability also favored metoprolol CR/XL. Overall, about 10% fewer patients in the metoprolol arm discontinued treatment—14% versus 15.5% in the placebo group. From a broad perspective, β -blockade clearly was tolerated at least as well as placebo.

The rate of discontinuation because of worsening heart failure was 6% in the placebo group and 4.1% with the extended release version of metoprolol. Discontinuation for worsening angina, myocardial infarction, and atrial fibrillation all occurred more often in the placebo group. Dizziness, fatigue, dyspnea, bradycardia, and hypotension were more common in the metoprolol CR/XL group.

The difference in discontinuation because of atrial fibrillation is noteworthy. Only one metoprolol CR/XL patient discontinued therapy because of new-onset atrial fibrillation compared with 14 in the placebo group. Overall, new-onset atrial fibrillation occurred in 45 patients in the placebo group, compared with 22 documented cases in the metoprolol CR/XL cohort. The findings suggest a new, previously unrecognized benefit of β -blocker therapy that deserves further investigation.

The results of the MERIT-HF study demonstrated that once-daily controlled-release/extended-release metoprolol, when added to standard heart failure therapy, improved survival and reduced the incidence of

all-cause hospitalization and hospitalization for worsening heart failure. The beneficial effects of extended release metoprolol remained consistent across a wide range of patient subgroups and baseline clinical characteristics. The

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results of this trial have served to confirm and extend previously reported evidence that patients with stable class II or III heart failure benefit from the addition of a β -blocker to standard therapy. Whether the findings are applicable to class IV or unstable patients has yet to be determined.

... QUESTION-AND-ANSWER SESSION ...

After delivering his presentation, Dr. Goldstein answered questions from the audience.

Question: How many patients were ineligible for the MERIT-HF [Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure] study because of contraindications to β -blockade? That is, how much physician judgment will be required when considering patients for treatment with metoprolol?

Dr. Goldstein: About two thirds of the patients screened were subsequently randomized in the MERIT-HF study. I'm not sure what that might mean in terms of physician judgment. A large number of the exclusions involved patients who had ejection fractions greater than 40%.

Question: Can you comment on the use of β -blockers in patients who have significant left ventricular dysfunction in the absence of heart failure?

Dr. Goldstein: Take the asymptomatic class I patient, for example. The only study that looked at that issue was the Australia-New Zealand carvedilol trial.⁹ The study was relatively small and had a relatively small number of events, but for the combination of death and rehospitalization, there was a benefit from treatment with carvedilol.

Question: Do you have any thoughts about the risk of depression in elderly patients who are treated with higher doses of metoprolol?

Dr. Goldstein: We surveyed patients for all types of side effects and saw no increase in depression in older patients. Clinical studies of depression have generally shown that patients do better with β -blockers than with placebo.

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