

Dispelling the Myth: Incorporating β -Blockers into Practice Guidelines

Based on a presentation by Milton Packer, MD

Presentation Summary

Compelling data from multiple clinical trials have revealed a significant reduction in mortality risk among heart failure patients who are treated with β -blockers. The magnitude of the benefit is 30% to 35%, and the data have indicated a reduction of at least 35% to 40% in the risk of death or hospitalization for worsening heart failure. The message contained in those data has yet to be heard by many physicians in

clinical practice. Underuse of β -blockers as heart failure therapy remains a major obstacle to improved treatment. The rationale for use of β -blockers in the treatment of heart failure is at least as sound as the justification for use of angiotensin-converting enzyme inhibitors. The weight of the clinical evidence has created a mandate for prescribing β -blockers for the vast majority of stable class II or III heart failure patients.

An overwhelming amount of clinical experience and data have documented the benefits of β -blocker therapy in heart failure patients. The weight of the evidence has provided a strong rationale for use of β -blockers in a broad-based group of patients.

More than 2 dozen placebo-controlled trials of β -blocker therapy have been conducted, involving more than 10,000 patients with heart failure; another 3000 patients have been evaluated in other types of clinical trials. Those figures compare with 9000 patients in controlled clinical trials of angiotensin-converting enzyme (ACE) inhibitors and 7000 patients in trials of digitalis.

The evidence favoring β -blockade in heart failure is consistent in

demonstrating improvement in cardiac function, symptoms, and clinical status. Collectively, the data from clinical trials of β -blockers in heart failure have shown a 30% to 35% relative reduction in all-cause mortality and a 35% to 40% relative reduction in the risk for the combined endpoint of death and hospitalization.

Examples of the substantial benefits conferred by β -blocker therapy in heart failure include the US carvedilol trial, which showed a 65% relative reduction in mortality risk in the carvedilol group¹; the second Cardiac Insufficiency Bisoprolol Study (CIBIS II), which showed a 34% relative reduction in mortality risk²; and the Metoprolol Controlled Release/ Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart

Failure (MERIT-HF), which also demonstrated a 34% relative reduction in all-cause mortality in heart failure patients who were treated with extended-release metoprolol.³ Each of the trials was terminated prematurely by ethics committees because of the emergence of a clear-cut reduction in mortality risk in patients who received a β -blocker.

The weight of the clinical evidence favoring β -blocker therapy in heart failure also received recognition and affirmation in recently promulgated clinical guidelines, representing the opinion of more than 150 physicians who are experienced in heart failure management.⁴ The panel of heart failure experts recommended that all patients with stable New York Heart Association (NYHA) class II or III heart failure resulting from left ventricular systolic dysfunction should receive a β -blocker in addition to an ACE inhibitor, unless a patient has a contraindication to the use of a β -blocker or cannot tolerate treatment.

Although the recommendation provides a strong clinical rationale for the use of β -blockers in the vast majority of heart failure patients, physicians continue to omit β -blockers from their treatment regimens for most heart failure patients.

A number of factors might cause physicians to hesitate to use β -blockers in heart failure patients. Etiology, ischemic versus nonischemic, is one such example. However, the data have clearly demonstrated, across a variety of clinical trials, that patients derive similar benefits from β -blocker therapy irrespective of disease etiology.

Some physicians still consider diabetes to be a contraindication to β -blockers; the data indicate such a fear is unfounded. Results of multiple clinical trials have shown that diabetic patients respond to β -blockers at least as well as nondiabetic patients, and some evidence suggests that diabetic patients may respond even better than nondiabetics.

Physicians might defer β -blocker use while they try to optimize patients' ACE-inhibitor dosage. Such a strategy assumes that a higher dose of an ACE inhibitor provides substantially better results than a lower dose; data from the Assessment of Lisinopril and Survival (ATLAS) trial suggest otherwise.⁵ Investigators randomized 3200 patients to a low dose of lisinopril (defined as 2.5 mg to 5 mg daily) or to a high dose (32.5 mg to 35 mg daily). Given the enormous difference in dosage, an equally large clinical effect might be expected; in fact, patients in the high-dose group had a nonsignificant 8% reduction in mortality risk and a 12% reduction in the combined endpoint of death and all-cause hospitalization. Those improvements assume that the dosage is increased from the lowest to the highest range. The benefits would be even less if a low dose of ACE inhibitor were increased to an intermediate dose or an intermediate dose to a high dose.

In the ATLAS trial high- and low-dose ACE inhibition had a similar effect on symptom improvement, as assessed by NYHA functional class. A 6 fold higher dose of the ACE inhibitor resulted in a miniscule difference in mortality, a very modest difference in the combination of death and hospitalization, and no difference in symptoms. The findings clearly call into question the wisdom of deferring β -blockade pending optimization of ACE inhibition.

On the other hand, adding a β -blocker to existing ACE-inhibitor therapy would lead to dramatic symptom improvement, a 30% to 35% reduction in mortality risk, and a decreased combined risk of morbidity and mortality of 40% or more. These data clearly support early initiation of β -blockade in heart failure, before optimizing ACE-inhibitor therapy.

Evidence also exists for a dose-dependent relationship between β -blocker therapy and clinical benefits. The

MERIT-HF study showed a greater reduction in mortality risk with a higher dose of metoprolol compared with the Metoprolol in Dilated Cardiomyopathy trial.^{3,5} Similarly, a higher dose of bisoprolol resulted in a 34% reduction in mortality risk in CIBIS II compared with 20% in CIBIS I.^{2,6}

However, the data must be interpreted cautiously, because not all the evidence suggests a dose-response relationship with β -blockers. For example, in one of the carvedilol trials patients were randomized to placebo or to 1 of 3 doses of carvedilol. All 3 β -blocker doses proved superior to placebo, but they were quite similar to each other with respect to their effects on fatal and nonfatal events.⁷ The data suggested that titration of carvedilol to the highest tolerated dose might not be necessary to achieve the desired effect, as is true with ACE inhibitors.

Many physicians might not use β -blockers because they are reluctant to titrate patients to high-target doses. Titration is time consuming, and some patients do not tolerate high β -blocker doses; in fact, the dose-response issue has not been resolved. A therapeutic range of doses might exist. The β -blocker dose might have to be titrated individually for each patient. Low β -blocker doses might be shown to work quite well in heart failure. This issue will acquire increasing clinical significance in the future, as new neurohormonal blockers emerge and are used in combination. Titration of each agent to a maximum tolerated dose might not be practical.

Fear of adverse events may also dissuade physicians from using β -blockers in the treatment of heart failure. Arguably, the most feared complication is fluid retention and worsening heart failure, because that is the adverse event physicians learned about in medical school, and it formed the basis for the contraindication of the use of β -blockers in heart failure.

Many physicians might believe that worsening of heart failure occurs because β -blockers are cardiodepressant. Although that might be true

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in some cases, the vast majority of patients whose condition worsens after initiation of β -blockade have a decrease in renal blood flow, accompanied by salt and water retention.

The worsening appears to be a delayed phenomenon that occurs 5 to 10 days after initiation of β -blockade. More than 90% of the cases are associated with a weight increase, which is an important signal and predictor of worsening heart failure. Patients require careful monitoring for evidence of salt and water retention, which can be effectively treated by increasing the dose of diuretic.

The key to making β -blockers safe is to ensure that patients are in a euvolic state before starting therapy and that they remain euvolic during therapy, a strategy that is most likely employed in many clinical trials, even though it might not have been written into the protocols. Keeping patients at a dry weight probably accounted for the safe use of β -blockers in clinical trials.

Monitoring for a weight gain indicative of sodium and water retention can provide physicians with considerable reassurance about their ability to identify patients who are at risk for worsening heart failure. Physicians also get reassurance that they can act to prevent progression and worsening of heart failure symptoms.

A significant new treatment algorithm has emerged for the manage-

ment of heart failure. Treatment should begin with a diuretic to control volume. Regardless of the patient's response to the diuretic, the physician should add an ACE inhibitor to the treatment regimen. Even if the patient responds well to ACE inhibition, a β -blocker should be added. The primary purpose of using both an ACE inhibitor and a β -blocker is not to improve symptoms but to affect the natural history of the disease process and to reduce heart failure morbidity and mortality.

The use of ACE inhibitors and β -blockers should no longer be considered optional in the treatment of heart failure. Data from multiple clinical trials have created a mandate for the use of these drugs. Physicians should be required to present justification for each heart failure patient who is not receiving both an ACE inhibitor and a β -blocker.

In contrast, digitalis does not have a clinical mandate, because it has not been demonstrated to affect mortality. Digitalis can be added at virtually any stage in the management process as a means of improving symptoms and helping patients feel better.

Clinical thinking about the use of β -blockers in the treatment of heart failure has evolved significantly. β -blockers were once viewed as dangerous drugs that were strictly contraindicated for heart failure; a line of thought that was so pervasive and definitive in medical education that it probably persists even today and contributes to the underuse of β -blockers for treatment of heart failure. In reality, physicians should look at the side effects of β -blockers in the same way they consider the potential side effects of ACE inhibitors.

β -blockers have evolved into mandated therapy for all heart failure patients, except for those with ad-

vanced decompensation. Limited experience with β -blockers in hospitalized class IV heart failure patients precludes extending the use of the drugs to that patient population.

Outpatients who are candidates for treatment with ACE inhibitors are just as likely to be good candidates for β -blocker therapy. The data supporting the use of β -blockers in heart failure is just as persuasive, if not more persuasive, than the data used to support the use of ACE inhibitors for the treatment of heart failure. Only by adherence to the data can the benefits observed in clinical trials be seen in clinical practice.

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