CME CREDIT

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients with severe heart failure be treated with beta-blockers?

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A: YES, beta-blocker therapy can be attempted cautiously in patients who have severe, advanced heart failure.

The results of the recently completed COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study, reported at the American Heart Association's scientific sessions November 12 to 15, 2000, indicated that beta-blocker therapy with carvedilol (Coreg) in patients with severe heart failure reduced the risk of death by 35%. The COPERNICUS study is particularly significant because its patients had the most advanced heart failure of any large-scale clinical trial of beta-blockade.

In previous beta-blocker trials, the proportion of patients with class IV heart failure (the most severe class in the New York Heart Association scale) was small, ranging from 3% to 16%. Taken together, the studies demonstrated conflicting results: therapy with carvedilol and metoprolol had favorable benefits on heart failure outcome, but therapy with bucindolol did not, suggesting that beta-blockers are not identical as a class.

THE COPERNICUS STUDY

The COPERNICUS study patients had heart failure caused by either ischemic or nonischemic cardiomyopathy; ischemic cardiomyopathy was twice as common as nonischemic. Symptoms were present at rest or with minimal exertion for at least 2 months, despite treatment with diuretics and an angiotensin-converting enzyme (ACE) inhibitor. Although the mean ejection fraction at baseline was less than 20%, patients entering the trial had no or minimal evidence of fluid retention on physical examination. Hospitalized patients were included only if they were not fluid-overloaded, not in the intensive care unit, and not receiving intravenous vasodilators or intravenous inotropic drugs.

Patients were randomized in a 1:1 ratio to receive either placebo (1,133 patients) or carvedilol (1,156 patients). Baseline characteristics of both groups were similar. The initial dose of carvedilol was 3.125 mg twice a day; the dose was doubled every 2 weeks until a target of 25 mg twice a day was reached.

The primary end point of the trial was all-cause mortality; secondary end points included all-cause mortality plus hospitalizations. The mean follow-up was 300 days.

Trial halted early due to marked survival benefit

The trial was terminated in March 2000, when its data safety and monitoring board noted a highly significant effect on mortality in patients receiving carvedilol, which exceeded predefined criteria for early termination.

The all-cause mortality rate was 18.5% in the placebo group vs 11.4% in the carvedilol group, a 35% difference (P = .00014). A survival benefit was noted as early as 4 months, and the difference in survival between the placebo and treatment groups became more evident during the next 2 years. The therapeutic benefit was consistent across all subgroups regardless of gender, age (> 65 years vs younger), ejection fraction (< 20% vs greater), cause of cardiomyopathy (ischemic vs nonischemic), or hospitalization within the previous year.

In this study, 13% of patients withdrew from carvedilol therapy vs 16% from placebo therapy. Serious adverse effects were more common in the placebo group.

It is important to remember that the COPERNICUS study did not include several patient groups: the very elderly, extremely sick

Beta-blockers are beneficial in severe heart failure, if used cautiously

patients on parenteral vasodilators or inotropes, and patients with fluid retention, severe hypotension, marked renal dysfunction, or recent onset of heart failure.

HOW TO USE BETA-BLOCKERS TO TREAT SEVERE HEART FAILURE

Most patients with severe heart failure should be treated with digoxin, a diuretic, an ACE inhibitor, and a beta-blocker, with the goal of improving symptoms, functional capacity, left ventricular function, and survival.

A beta-blocker can be started once the patient is already taking digoxin, a diuretic, and an ACE inhibitor. The patient should be euvolemic, with no evidence of fluid overload at the onset of therapy. Beta-blockers should be avoided or used with extreme caution in patients with hypotension. Patients with hyponatremia have a higher incidence of adverse effects, whereas those with resting sinus tachycardia appear to be good candidates for beta-blocker therapy.

Treatment can begin with either carvedilol or metoprolol. Metoprolol succinate may have some slight advantages over metoprolol tartrate, but as yet, neither form of metoprolol is listed by the Food and Drug Administration as indicated for heart failure. Carvedilol may be easier to use in patients with adequate blood pressure, in whom hypotension is not a likelihood, because it has concomitant vasodilating properties. Metoprolol succinate may be a better choice for patients with lower blood pressure, who are more likely to develop hypotension, because metoprolol does not have concomitant vasodilating properties (which can lead to hypotension in susceptible patients).

In giving beta-blockers, start low and increase slowly

The initial dose should be low (carvedilol 3.125 mg twice a day or metoprolol succinate 12.5 mg daily). As in the COPERNICUS trial, the dose of carvedilol can be doubled every 2 to 3 weeks as tolerated to a maximum of 25 mg twice a day. For metoprolol succinate, the target dose is 200 mg daily in a single dose or divided doses. Observe the patient for hypotension, light-headedness, or bradycardia during the first 1 to 2 hours after the first dose. Beta-blockers are given after meals to minimize light-headedness.

Patients are instructed to watch for fluid retention or weight gain and to report these signs to the physician. Side effects of beta-blockers include light-headedness, hypotension, fatigue, bradycardia, fluid retention, and worsening heart failure.[5–7] Most patients tolerate beta-blockers, although sluggishness may be a temporary problem.

Seventy-four percent of patients in the COPERNICUS study were able to achieve the target carvedilol dose of 25 mg twice a day. The ability to achieve the target dose of beta-blockers often depends on maintaining adequate blood pressure, as hypotension is the most frequent limiting factor in up-titration.

In some instances, the dose of the ACE inhibitor and the dose of beta-blocker require mutual adjustment to achieve a balanced effect from both agents.

Patients usually start to feel better subjectively between 3 and 12 weeks after starting therapy, but improvement may be preceded by fatigue. Some patients who depend on adrenergic tone for inotropic effect may experience clinical deterioration, however.

SUGGESTED READING

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