Are All β-Blockers for Heart Failure the Same?

To the Editor:

Kukin et al. suggest that little difference may exist between the benefits of metoprolol, a β₁-selective blocker, and carvedilol, an α- and nonselective β-blocker with antioxidant properties, on pathophysiological variables in patients with heart failure. The study was unblinded and randomized only 67 patients, with more older patients who had advanced symptoms and coronary disease allocated to receive carvedilol. Considerable evidence shows that patients with left ventricular systolic dysfunction due to coronary disease have a more heterogeneous improvement in ejection fraction than do patients with dilated cardiomyopathy. Moreover, a study that randomized many more (n=120) patients showed that when compared with metoprolol, carvedilol had greater effects on ejection fraction and filling pressures.

No widely accepted surrogates exist for morbidity or mortality in heart failure; therefore, physicians should not assume that a similar hemodynamic benefit leads to equal clinical benefit. The Carvedilol or Metoprolol European Trial (COMET) is currently comparing metoprolol and carvedilol in >3000 patients with chronic heart failure to determine whether the effects of these drugs on mortality and/or morbidity differ. This is the first adequately powered study to compare outcomes between β-blockers in any clinical setting.

The authors are appropriately and commendably cautious in the interpretation of their data; some commentators are less so. Currently, only carvedilol is approved for use in heart failure. Even if metoprolol is as effective as carvedilol, where is the clinician to get the doses required for initiating therapy? The manual preparation of small quantities of reconstituted low-dose metoprolol is likely to be expensive; the problems of quality control and erratic dosing also exist. It is also inappropriate to assume that substituting maintenance carvedilol with metoprolol is safe. Illicit, large-scale production of generic metoprolol in small doses may occur, but will this be endorsed without proper appraisal by regulatory authorities?

Heart failure is a dangerous condition and its treatment with β-blockers requires caution. When treating a malignant disease, it seems wise to use treatments that have passed the “acid-test” of official regulatory approval and that are manufactured to an adequate standard. In both the short- and long-term, it may be cheaper and more cost-effective to use carvedilol, which is available in the right doses and with the appropriate pharmacutical quality control, rather than preparations of β-blockers of uncertain strength and efficacy. If heart failure was cancerous rather than merely malignant, what do you think doctors and patients would choose?

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5. Gottlieb S. Carvedilol seems no better than metoprolol for heart failure. BMJ. 1999;318:1509.

Response

We read with interest the comments of Cleland concerning our comparative study of metoprolol and carvedilol. As shown in the published table, there were no statistically significant differences in any of the 15 baseline variables.

This is the first prospective peer-reviewed study comparing metoprolol and carvedilol. Cleland cites the Metra abstract (our reference 26), which showed a greater effect on ejection fraction and pulmonary wedge pressure with carvedilol; this study also showed a greater benefit in exercise with metoprolol. These, of course, are also surrogate end points. A more recent study by Sanderson confirms our findings in a double-blind, positive-controlled comparison of 51 patients; they showed that both metoprolol and carvedilol therapy created highly significant improvements in symptoms, exercise capacity, and ejection fraction, with no significant difference between the 2 β-blockers.

We agree that there are no widely accepted surrogates for morbidity and mortality in heart failure, and we appreciate Cleland commending our caution in our interpretation of the data. We stated that the primary end point of our study was to test for any measurable in vivo difference in measures of oxidative stress between carvedilol and metoprolol because carvedilol has in vitro antioxidant effects that have not been demonstrated in a population with heart failure. We showed parallel declines in thiobarbituric acid–reactive substances; this is an indirect measure of oxidative stress that is elevated in patients with heart failure. We also reported other clinical parameters (tolerability, withdrawals, ejection fraction, New York Heart Association class, symptoms, and exercise measures) that had parallel changes.

Currently, carvedilol is the only β-blocker approved for heart failure in the United States; thereby, it is the only β-blocker available in the low starting doses essential for initiation. We certainly do not advocate the “illicit, large-scale production of generic metoprolol in small doses.” In agreement with Cleland, we never proposed or even mentioned substituting maintenance carvedilol with metoprolol.

The Carvedilol or Metoprolol European Trial (COMET) is powered to prospectively compare the same 2 β-blockers used in our study for a mortality end point. However, questions have already been raised about the dose of metoprolol tartrate (50 mg BID) being used in COMET. Furthermore, COMET is not comparing carvedilol to either of the 2 β-1 selective preparations that have shown a favorable 34% reduction in mortality (bisoprolol and extended-release metoprolol succinate).

Thus, at the present time, the data show that no significant, clinically relevant differences exist between metoprolol and carvedilol in heart failure therapy.

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