Beta-Blocker Dose Does Not Influence the Beneficial Effects of Carvedilol Compared to Metoprolol in the Patients With Heart Failure: Results From the Carvedilol or Metoprolol European Trial (COMET)

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Background: Beta-blockers (BB) are often used at doses lower than those shown to be of benefit in controlled trials. It is important to know whether outcome differences between carvedilol and metoprolol in COMET may be influenced by the dose administered.

Methods: We compared the clinical characteristics and the outcome between the patients who reached target BB doses in COMET (carvedilol, 25 mg bid; metoprolol tartrate, 50 mg bid) and those who did not.

Results: At the end of uptitration, 4 months after randomization, the daily doses were 41.8 ± 14.6 mg (980/1308 patients [75%] reached target dose) for carvedilol and 82.8 ± 28.9 mg (1019/1313 [78%] on the target dose) for metoprolol. Compared to patients on low dose, those on the target doses were younger (61 ± 11 versus 64 ± 11 years), had higher body mass index (27.2 ± 4.2 vs. 26.4 ± 4.5 kg/m²), systolic and diastolic blood pressure (BP, 129 ± 19 versus 122 ± 19 mmHg and 78 ± 17 versus 75 ± 11 mmHg, respectively) and heart rate (HR, 82 ± 13 versus 79 ± 13 beats/min), a higher prevalence of NYHA class II symptoms (55% versus 39%) and a lower prevalence of ischemic heart disease (IHD, 48% versus 61%) (all p<0.001). Mortality rate was 29% in patients on target dose versus 41% in the others (RR 0.60; 95% CI 0.50-0.70; p<0.0001). The beneficial effect of reaching target dose remained significant by multivariate analysis (RR 0.78; 95% CI 0.66-0.92; p=0.0036). The mortality reduction achieved with carvedilol was similar in patients on target doses (25.4% on carvedilol versus 32.4% on metoprolol; RR 0.75; 95% CI 0.64-0.89; p=0.0008) and in patients on low dose (36.9% on carvedilol versus 45.6% on metoprolol; RR 0.69; 95% CI 0.60-0.81; p=0.02). No interaction between the effect of carvedilol, compared to metoprolol, and the dose administered was found (RR 0.99; 95% CI 0.73-1.33).

Conclusion: In COMET, patients titrated to higher BB doses were younger, with a higher baseline BP and HR, milder symptoms and a lower prevalence of IHD. Administration of the target BB doses was an independent predictor of a lower mortality risk. The survival benefits of carvedilol compared to metoprolol were maintained independently from the dose administered.

These findings were supported by a favorable change in the Overall Treatment Evaluation (OTE) in the carvedilol group compared to the placebo group (p=0.01).

Conclusion: In addition to reducing CV death and CHF hospitalization, carvedilol resulted in a favorable overall change in NYHA class in a broad spectrum of patients with CHF.