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CME

Relationship of Beta-Blocker Dose With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction

Results From the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) Trial

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Relationship of Beta-Blocker Dose With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction

Results From the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) Trial

Objectives This study sought to examine the association between baseline beta-blocker (BB) dose and outcomes in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial.

Background Beta-blockers reduce morbidity and mortality in chronic heart failure (HF) patients with reduced ejection fraction, but it is unclear whether titrating to higher BB doses improves outcomes in this setting.

Methods The HF-ACTION trial was a randomized, multicenter trial enrolling 2,331 ambulatory HF patients with systolic dysfunction (New York Heart Association functional class II to IV, left ventricular ejection fraction <0.35) randomized to exercise training versus usual care, with median follow-up of 2.5 years. The BB dose at baseline was standardized with carvedilol equivalents and analyzed as a continuous variable and by discrete dose groups. The relationship between BB dose and the primary endpoint of all-cause mortality or all-cause hospitalization and other cardiovascular secondary endpoints was determined before and after adjustment for variables significantly associated with outcomes in the HF-ACTION cohort.

Results Ninety-five percent of patients were receiving a BB. There was a significant inverse relationship between BB dose and all-cause death or hospitalization but not other cardiovascular endpoints after adjustment for other predictors of outcome, with a linear benefit up to the 50-mg daily dose. There was a significant association between BB dose and change in peak VO_2 at 3 months. There was no increase in bradycardia with higher doses of BB.

Conclusions There was a significant inverse relationship between BB dose and the endpoint of all-cause death or all-cause hospitalization in this well-treated HF cohort with systolic dysfunction, supporting recommendations that titrating doses up to 50 mg/day might confer a benefit in such patients. (Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure; NCT00047437) (J Am Coll Cardiol 2012;60:208–15)

Beta-blockers (BBs) are an important pharmacological therapy and reduce morbidity/mortality in patients with heart failure (HF) due to a reduced left ventricular ejection fraction (LVEF) (1). Guidelines recommend using BB therapy to treat outpatients with HF at doses consistent with those studied in randomized, controlled trials. There is little evidence, however, that clinical trial BB doses are being used in clinical practice (2). Furthermore, it is unclear whether there is a dose-response relationship between BBs and outcomes. In the only study prospectively designed to test dose-response relationships with the BB carvedilol in patients with systolic HF, Bristow et al. (3) reported dose-related improvements in LVEF and survival. However, this study was limited by a small sample size and a low number of deaths, making it difficult to interpret the association with survival. In a post hoc subgroup analysis of the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure) trial, no dose-response relationship with mortality was observed for metoprolol CR/XL in the overall cohort, but a wide variation in dose-response existed between patients (4). Heart rate reduction was similar across 3 dose groups, indicating the degree of beta-blockade might have been equivalent and thus limiting the ability to test a true association between dose and mortality benefit, because previous studies have demonstrated that the degree of heart rate reduction might be related to outcome (5–7).

The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial was the largest trial to date to test the effects of exercise training versus usual care in HF patients with moderate-to-severe left ventricular (LV) systolic dysfunction. In the HF-ACTION trial, approximately 95% of the 2,331 patients received a BB, providing a large, well-treated contemporary HF population in which to explore relationships between BB dose and outcomes. We aimed to examine the relationship between baseline BB dose and outcomes in the HF-ACTION study population, hypothesizing that patients taking higher doses might experience improved outcomes. In addition, we aimed to examine whether higher doses of BBs were associated with an increase in bradycardia and a decrease in other adverse cardiovascular events such as stroke and myocardial infarction (MI).

Methods

The HF-ACTION trial design and outcomes have been previously described (8,9). Briefly, the study was a multicenter, randomized, controlled trial testing the long-term safety and efficacy of aerobic exercise training plus evidence-based medical therapy versus evidence-based medical therapy alone in medically stable outpatients with LV systolic

Abbreviations and Acronyms

BB = beta-blocker
CPX = cardiopulmonary exercise
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
VO_2 = oxygen uptake

dysfunction (LVEF <35%) and New York Heart Association functional class II to IV HF. Adult patients receiving angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers and beta-adrenergic blockade for ≥6 weeks (unless there was a documented rationale for variation) were eligible. Investigators were provided with the followingx instructions in the operations manual with regard to use of evidence-based BB therapy and dose titration: patients must be receiving optimal HF therapy according to American Heart Association/American College of Cardiology and Heart Failure Society of America guidelines or have documented rationale for variation and be receiving stable doses for 6 weeks before enrollment. There was no specific forced titration strategy used, but there was education and reinforcement to achieve evidence-based levels of target doses on the basis of clinical trials. The primary endpoint was the composite of all-cause death or all-cause hospitalization. Patients were randomly assigned to usual care alone or usual care plus exercise training, consisting of a prescription of supervised aerobic exercise training at 60% to 70% of heart rate reserve 3×/week, followed by home-based training at the same intensity 5×/week, totaling 36 sessions. Randomization was stratified by center and HF etiology. Participants were followed for a median of 2.5 years.

Data considerations and outcome measures. Patient characteristics, health statuses, laboratory values, and physiological parameters at rest and during a cardiopulmonary exercise (CPX) test were collected on standardized forms at baseline and at several points throughout the study (laboratory values only at baseline). Beta-blocker dose at baseline was standardized with carvedilol equivalents and analyzed as a continuous variable and by discrete dose groups (0, 1 to 13, 14 to 25, 26 to 50, 51 to 200 mg daily). Dosing groups were selected on the basis of the common titration schedule for carvedilol (i.e., doubling of the dose every 2 to 4 weeks up to target doses recommended by guidelines) (1).

The composite primary endpoint of all-cause mortality and all-cause hospitalization and an endpoint of mortality alone were determined and adjusted with variables found to be significantly associated with outcomes (10). Other prespecified secondary endpoints included cardiovascular mortality or cardiovascular hospitalization, cardiovascular mortality alone, and cardiovascular mortality or HF hospitalization. Adverse cardiovascular events were collected throughout the study and included fatal or nonfatal HF hospitalization, MI, unstable angina pectoris, arrhythmia, bradycardia, stroke, or transient ischemic attack. Bradycardia was defined as symptomatic bradycardia with a heart rate <50 beats/min. All events were adjudicated by a blinded clinical events committee. Exercise and functional parameters of a 6-min walk test, exercise time on a CPX test, peak oxygen uptake (VO_2), and heart rate at peak exercise were also examined.

Statistical methods. Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables. The unadjusted relationship between BB dose at baseline and the primary endpoint was explored with piecewise regression models. The linear and piecewise linear models were compared with the null model with likelihood ratio tests. For the primary endpoint (all-cause death or hospitalization) and secondary endpoint (all-cause death), predictive models were developed with a broad range of candidate variables, including demographic data, medical history, laboratory values, exercise test values, and quality-of-life indexes (Kansas City Cardiomyopathy Questionnaire). These models provide a useful tool for estimating the risk of the given endpoint for specific patients and were used for adjustment in this analysis. Cox proportional hazards modeling was used to assess the relationship between outcomes and BB dose as a continuous variable before and after adjustment for the variables found to be significantly associated with each endpoint. A p value ≤0.05 was considered statistically significant for all analyses. The relationship between BB dose as a continuous variable and exercise parameters at 3, 12, and 24 months was analyzed with linear regression models that included the exercise parameters during follow-up as the response variables and the BB dose along with potential confounders as independent variables. Inverse probability weighting was used to adjust for missingness of the exercise parameters during follow-up. The exercise variables were transformed to achieve normality when needed. Statistical analysis was

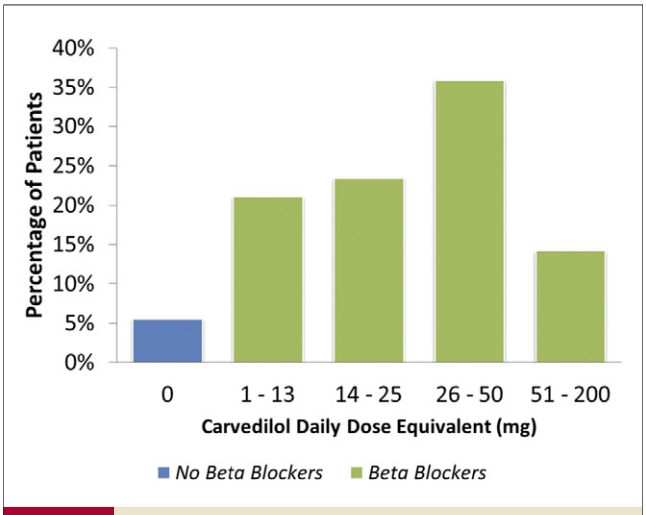

Figure 1 Distribution of Doses

Percentage of patients in each dose group (0 dose or no beta-blocker: 5.5%; 1 to 13 mg dose: 21%; 14 to 25 mg dose: 23%; 26 to 50 mg dose: 36%; 51 to 200 mg dose: 14%).

Table 1 Baseline Characteristics by BB Use at Randomization (N = 2,325)

Characteristics	BB Dose, mg					p Value
	No BBs (n = 128)	1–13 (n = 490)	14–25 (n = 544)	26–50 (n = 834)	51–200 (n = 329)	
Age, yrs	64	62	60	58	57	<0.0001
Female, %	27	32	27	29	24	0.11
Black, % (n = 2,290)	27	30	30	33	44	—
BMI, kg/m^2 (n = 2,318)	28	29	29	31	33	<0.0001
NYHA HF functional class, %						
II	56	59	65	65	68	—
III/IV	44	41	35	35	32	—
HF etiology, ischemic, %	56	56	57	46	46	<0.0001
SBP (n = 2,321), mm Hg	114	110	112	112	112	0.07
LVEF (n = 2,321), %	23	24	25	25	24	0.01
History of diabetes, %	5	19	21	37	18	0.0006
BUN (n = 2,022), mg/dl	23	21	20	20	19	0.002
Sinus rhythm (n = 2,287), %	76	79	81	81	83	0.41
HR at peak exercise (median) (n = 2,323), beats/min	126	122	120	118	117	0.0001
CPX duration (n = 2,303), min	9.0	9.3	9.7	10.0	9.2	0.05
6MWT distance (n = 2,274), m	351	366	372	375	374	0.37
Peak VO_2 (n = 2,269), ml/kg/min	14.6	14.0	14.7	14.5	14.3	0.46

BB = beta-blocker; BMI = body mass index; BUN = blood urea nitrogen; CPX = cardiopulmonary exercise; SBP = systolic blood pressure; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VO_2 = oxygen uptake; 6MWT = 6-min walk test.

performed by the Duke Clinical Research Institute with SAS software (version 9.2, Cary, North Carolina).

Results

Of the 2,331 patients enrolled in the HF-ACTION trial, 2,325 patients were included in this analysis; 6 patients with missing information at baseline were excluded. Only 128 (5.5%) patients were not receiving a BB. There was a broad distribution of doses in this cohort. Excluding those patients not receiving BB at randomization, the median BB dose was 38 mg carvedilol-equivalents daily (1st quartile = 25 mg, 3rd quartile = 50 mg). The most common dosing range was 26 to 50 mg daily (36%), followed by 14 to 25 mg daily (23%) (Fig. 1). In total, 73% of patients did not change BB dose groups during the study, 6% died, and 15% had missing data; therefore, only 6% of patients changed dose groups by the last assessment.

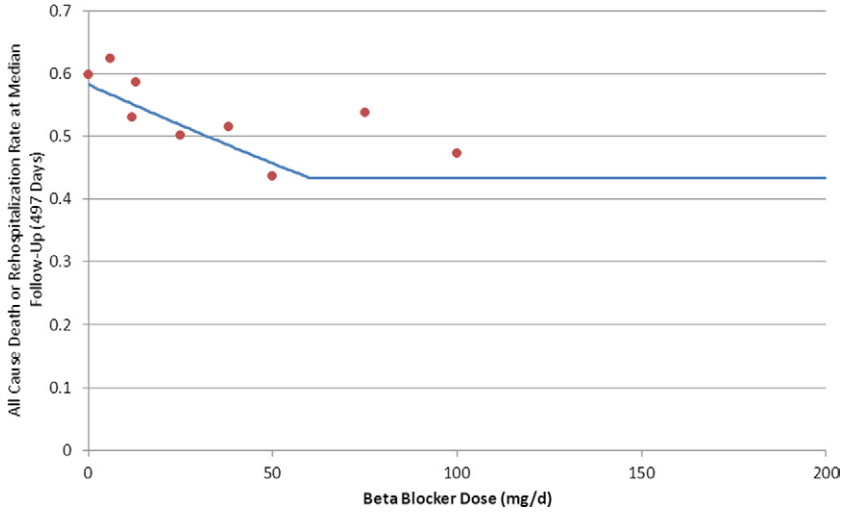

Figure 2 All-Cause Death or Hospitalization by Beta-Blocker Dose at Baseline

Piecewise linear fit statistically significant. All-cause death or hospitalization by beta-blocker dose at baseline, showing a linear relationship up to 50 mg daily dose. **Dots** represent event rate at most common doses on the basis of distribution of doses.

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Table 2 Outcomes and BB Dose at Randomization

	Chi-Square	p Value	HR (95% CI) (for 10 U Increase in BB Dose*)
All-cause death or all-cause hospitalization (1,430 events, 67%)			
Unadjusted	26.11	<0.0001	0.93 (0.91–0.96)
Adjusted†	5.43	0.02	0.96 (0.93–0.99)
All-cause death (307 events, 15%)			
Unadjusted	8.27	0.004	0.92 (0.88–0.98)
Adjusted‡	0.86	0.35	0.97 (0.92–1.03)

*Hazard ratios (HRs) are applicable for doses up to 50 mg/day. For dose >50 mg/day, HR = 1.00. †Adjusting by Kansas City Cardiomyopathy Questionnaire symptom stability, left ventricular ejection fraction, region, sex, ventricular conduction, Weber class, blood urea nitrogen, and mitral regurgitation. ‡Adjusting by sex, body mass index, loop diuretics, Canadian Cardiovascular Society angina class, creatinine, exercise duration, ventricular conduction, and left ventricular ejection fraction.

BB = beta-blocker; CI = confidence interval.

Baseline characteristics are shown in Table 1. Patients not receiving a BB were older and more often white, whereas black subjects were more often in the highest dose group. There was no difference in dose distribution on the basis of sex. Those not receiving a BB more often had a higher blood urea nitrogen level. Patients in the highest BB dose group had a higher body mass index and were younger. There was no difference between the dose groups in baseline exercise parameters. There was a significant reduction in maximal heart rate at peak exercise with increasing doses, indicating the degree of beta-blockade was indeed greater in the higher dose groups.

The relationship between all-cause death/hospitalization and dose is shown in Figure 2, and the clinical outcomes are shown in Table 2. The median follow-up was 2.5 years. A piecewise linear fit was used to model the relationship between the BB dose and the primary endpoint. When compared with a linear relationship, the piecewise linear model provided a better fit (likelihood ratio statistic = 25.8, $p < 0.0001$). The same relationship was used for all-cause death. After adjusting for the variables found to be significantly associated with the primary endpoint of all-cause death or hospitalization, higher BB dose remained significantly associated with a lower rate of the primary endpoint (hazard ratio: 0.96; $p = 0.02$). Although there was a significant inverse relationship between BB dose and all-cause death alone in a univariate model ($p = 0.004$), it became nonsignificant after adjusting for confounding variables ($p = 0.65$). This relationship remained significant when adjusted for sex, body mass index, loop diuretic dose, serum creatinine, and Canadian Cardiovascular Society angina class and became nonsignificant after adjustment for CPX testing duration. Although each of the other cardiovascular endpoints showed a similar significant inverse relationship with BB dose in a univariate model, these also became nonsignificant when adjusted for other clinical variables (data not shown).

The relationship between BB dose and exercise parameters (change in CPX duration, 6-min walk test, and peak VO_2 at 3, 12, and 24 months) was not significant when adjusted for baseline clinical variables, except for change in peak VO_2 at 3 months. Those in the highest BB dose group had the greatest increase in peak VO_2 at 3 months (3.9%; $p = 0.048$), but the relationship between these variables was not significant at 12 or 24 months. No relationship was observed between changes in CPX duration or 6-min walk distance and the dose of BB at 3, 12, or 24 months. The relationships between BB dose and cardiovascular adverse events are shown in Table 3. Patients who were not receiving a BB had the highest number of cardiovascular events, and those in the 26-to-50-mg daily dose group seemed to have the lowest cardiovascular adverse event rate. There was no increase in the incidence of bradycardia with increasing doses of BB.

Discussion

There were several important findings from this study. First, there was a significant relationship between BB dose and the adjusted risk for the primary outcome of all-cause death

Table 3 Cardiovascular Adverse Events by BB Use at Randomization

	BB Dose, mg					
Event Type, %	No BBs (n = 128)	1–13 (n = 490)	14–25 (n = 544)	26–50 (n = 834)	51–200 (n = 329)	p Value
Cardiovascular	45	43	41	33	43	0.0001
HF	34	32	29	22	30	0.0001
Myocardial infarction	4	3	5	4	3	0.59
Unstable angina	7	7	10	6	7	0.15
Arrhythmia	18	16	13	13	14	0.56
Bradycardia	3	2	1	2	1	0.35
Stroke	2	2	3	2	5	0.09
Cardiovascular events, n						0.004
0	56	57	59	68	57	
1	13	16	18	13	19	
2	12	10	8	7	9	
3 or more	20	17	16	13	15	

BB = beta-blocker; HF = heart failure.

or hospitalization; however, no significant relationship between BB dose and secondary outcomes was observed after adjustment for other clinical variables. Second, there was a significant relationship between BB dose and change in peak VO_2 at 3 months but not for other exercise or functional parameters. In addition, our study showed no increased incidence of bradycardia on higher doses of BB in this cohort; rather there were more cardiovascular and HF events in patients not receiving a BB compared with those receiving moderate-to-high doses even after adjustment for other key prognostic variables. Finally, approximately 50% of patients were not receiving target doses of BBs.

The relationship between higher doses of BB and an improvement in the adjusted risk for the primary composite endpoint of all-cause death or hospitalization seemed to be linear up to the highest dose group. Although guidelines recommend moderate-to-high doses of BB therapy, many patients are not titrated to doses demonstrated to be advantageous in large, multisite, randomized, controlled clinical trials, and registries (11). Data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry showed that, in patients hospitalized for HF, the mean daily dose of BBs before hospital admission was one-half the recommended target dose, and most patients were not titrated to target doses up to 90 days after discharge. In fact, at 60 and 90 days after discharge, only 17.5% and 7.9% of patients were receiving target doses of carvedilol and metoprolol, respectively (11). In part, this reluctance toward titration to evidence-based doses might be based on lack of definitive evidence that there is a dose-response relationship between BB therapy and clinical outcomes, health system barriers that prevent easy titration of the medications to target doses, and a concern about an increase in adverse events—particularly in those who are older and have significant comorbidities (12–14).

Recently, the CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) study evaluated the tolerability of bisoprolol and carvedilol in elderly patients; only 31% of patients were able to reach target doses (15). However, other studies have shown good BB tolerability in this patient population (16). The findings of the CIBIS-ELD study were more likely due to an aggressive titration schedule; this supports the titration scheme of the European Society of Cardiology guidelines, which allows for a slower titration to achieve dose targets (17).

The evidence for a dose-response relationship for cardiovascular drugs has been limited. Two studies have shown a benefit between higher doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and clinical outcome (18,19); these showed an advantage on a composite endpoint of HF hospitalization and death but not on death alone. Very little evidence exists with regard to BB dose and outcomes in HF patients. The REVERT (REversal of VEntricular Remodeling with Toprol-XL) trial examined the effects of BB therapy on LV remodeling in asymptomatic patients and showed that the benefits on LV end-systolic volume index and LVEF were dose-dependent (20). As previously mentioned, the MOCHA (Multicenter Oral Carvedilol Heart failure Assessment) study demonstrated a positive dose-response relationship between BB dose and LVEF improvement as well as an improvement in survival (3). However, given that this was a study of only 300 patients with only 30 deaths, the findings with regard to survival are difficult to interpret. A meta-analysis of BB dose and clinical outcome in HF patients found no significant relationship between all-cause mortality and BB dose (21); however, there were important limitations, as with any meta-analysis. In our study, all-cause mortality did not show a dose-related benefit with BB therapy when adjusted for other clinical variables, in particular when CPX duration was added to the model. This finding is not surprising, given that the strongest baseline predictor of both the primary and mortality endpoints in the HF-ACTION predictive model was exercise duration on CPX (10). Yet the primary endpoint of all-cause death/hospitalization remained significant even after adjustment for CPX duration, indicating this relationship was uniquely important in this cohort. There remains no definitive evidence of a dose-response relationship between BB therapy and outcomes in a randomized, controlled trial. In the absence of randomized testing, that an association exists might indicate the effect could be more or less pronounced than our results demonstrate.

The clinical improvement found with higher doses was consistent with the improvement in peak VO_2 at 3 months with higher doses of beta-blockade. This finding is noteworthy, because phase II studies of BB therapy have failed to demonstrate improvement in maximal exercise tolerance, peak VO_2, or 6-min walk with BB therapy versus placebo but have shown favorable trends on submaximal exercise (22–24). Certainly one of the concerns about BB therapy is potential impairment in exercise performance at higher BB doses. Our finding that there is no attenuation of exercise performance with higher doses of BBs should allow clinicians to feel more comfortable with BB titration, particularly in those patients who have important reductions in baseline exercise capacity, as seen in the HF-ACTION study. Furthermore, our study showed no increased incidence of bradycardia with higher BB doses, supporting the concept that patients might receive more benefit than harm with moderate-to-higher doses. This is particularly reassuring if adverse events are a concern preventing dose titration. We found approximately one-half of the patients were not at target doses. These findings suggest that there is considerable room for BB up-titration in clinical practice.

Interestingly, there seemed to be racial differences in the baseline dose of BB therapy. Black patients were more often receiving a higher baseline dose of BB than white patients or other races. It is unclear whether this finding was related to the need to have relatively higher doses of BB therapy to achieve similar efficacy. There was no statistical interaction

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between race and BB dose. This is an interesting finding that requires further analysis to better understand the differences between BB dosing and outcomes in black patients.

Study limitations. Our findings should be interpreted in the context of several potentially important limitations. First, this is a post hoc analysis. Although this study population is broad, patients who were not ambulatory and patients with preserved systolic function were excluded. This might have limited the number of elderly patients enrolled and conferred a generally younger population with an average age of 58 years, compared with the BB clinical trials in which the average age was roughly 62 years. By contrast, this study includes a relatively large cohort of women and black patients. Second, the use of dose conversions is an imperfect method for comparing doses. In this cohort, the median patient weight was 90 kg (1st quartile = 76 kg, 3rd quartile = 106 kg). Guideline dosing recommendations suggest that target carvedilol doses for patients >75 kg is 100 mg/day, relative to 200 mg/day for metoprolol. This would convert to a 2:1 dosing ratio with metoprolol. However, doses used in HF clinical trials might suggest a 4:1 conversion ratio. We therefore conducted a sensitivity analysis with both methods; there was no difference in heart rate reduction throughout the distribution of doses with a 4:1 conversion compared with the 2:1 conversion formula. There was also no difference in the clinical endpoint results. Finally, an important potential confounder is that sicker patients might be less able to tolerate higher BB doses. Although we adjusted for numerous known predictors of adverse outcome, the possibility of important unidentified prognostic indicators must be considered. A true dose-response relationship should be assessed in a randomized clinical trial.

Conclusions

Higher BB dose in ambulatory HF patients with reduced ejection fraction was associated with a significantly lower rate of all-cause death or all-cause hospitalization, even after adjustment for important prognostic covariates. Higher doses were not associated with increased incidence of bradycardia, with the best cardiovascular event profile in patients at target doses. These data support the current clinical guideline recommendations that BB therapy should be titrated to moderate-to-high doses as used in randomized, controlled clinical trials.

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Key Words: beta-blockers ■ dose ■ exercise ■ heart failure ■ mortality.

APPENDIX

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