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Heart Rate or Beta-Blocker Dose? Association With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction

Results From the HF-ACTION Trial

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ABSTRACT

OBJECTIVES This study aimed to compare whether reduced heart rate (HR) or higher beta-blocker (BB) dose affected outcomes to a greater extent in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial population.

BACKGROUND Recent data have shown that HR is an important modifiable factor in reducing mortality in heart failure (HF) patients. It has also been shown that titration of doses of BBs improves outcomes of morbidity and mortality in chronic HF patients with reduced ejection fraction. We aimed to compare whether reduced HR or higher BB dose affected outcomes to a greater extent in the HF-ACTION trial population.

METHODS HF-ACTION 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. BB dose at baseline was standardized by use of carvedilol equivalents. BB dose and HR were analyzed by discrete groups (higher/lower dose; higher/lower HR). The relationship of BB dose, HR, and the primary endpoint of all-cause mortality or all-cause hospitalization and other cardiovascular secondary endpoints were determined before and after adjustment for variables found to be significantly associated with outcome in the HF-ACTION cohort.

RESULTS There was a significant inverse relationship between either BB dose (higher was better) or HR (lower was better) and all-cause death or hospitalization in unadjusted analysis; however, only BB dose was significant for improved mortality outcomes. After adjustment for other predictors of outcome, only BB dose remained significant for improving all-cause death or hospitalization. BB dose, but not HR, was associated with improved outcomes of other cardiovascular endpoints in unadjusted analysis but did not remain significant when adjusted for other predictors of outcome in this cohort.

CONCLUSIONS There were more associated improvements in outcomes with higher BB dose than with reduced HR in this well-treated HF cohort with systolic dysfunction, which suggests that titration of BB doses may confer a greater benefit than reduction of HR in such patients. (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]; NCT00047437) (J Am Coll Cardiol HF 2016;4:109–15) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BB = beta-blocker

HF = heart failure

HR = heart rate

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

Beta-blockers (BBs) are an important pharmacological therapy that reduces morbidity/mortality in patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) (1).

In the only study prospectively designed to test dose-response relationships with the BB carvedilol in patients with systolic HF, Bristow et al. (2) reported dose-related improvements in LVEF and survival. We have previously shown that in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) cohort, higher BB dose was associated with a significant reduction in all-cause hospitalization and all-cause death, even after adjustment for important prognostic covariates, which suggests that BB therapy should be titrated to moderate to high doses (3).

Recent data have shown that heart rate (HR) is an important modifiable factor in reducing mortality in HF patients (4,5). Although HR lowering is an important effect of BBs, the prognostic benefits are not entirely related to reducing HR (1). In an analysis from the COMET (Carvedilol or Metoprolol European Trial), the investigators demonstrated that both the HR achieved during BB therapy and BB dose were independently associated with outcomes (6); however, studies have shown a survival benefit based on HR lowering alone rather than BB dose achieved (7,8). Furthermore, in a large randomized trial of the drug ivabradine, a selective HR-lowering agent, clinical outcomes were significantly improved compared with placebo (9).

The HF-ACTION 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 systolic dysfunction (10). We aimed to examine the relationship between baseline BB dose, baseline HR, and outcomes in the HF-ACTION study population, hypothesizing that titrating patients to higher BB doses versus lowering HR may confer a greater benefit on cardiovascular outcomes.

METHODS

The HF-ACTION trial design and outcomes have been described previously (10,11). 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 left ventricular systolic dysfunction (LVEF <35%) and New York Heart Association (NYHA) functional class II to IV HF. Adult subjects receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-adrenergic blockade for ≥6 weeks (unless there was a documented rationale for variation) were eligible. The primary endpoint was the composite of death or all-cause hospitalization. Patients were randomly assigned to usual care alone or usual care plus exercise training, which consisted of a prescription of supervised aerobic exercise training at 60% to 70% of HR reserve 3 times per week, followed by home-based training at the same intensity 5 times per week, totaling 36 sessions. Randomization was stratified by center and HF pathogenesis. Participants were followed up for a median of 2.5 years.

DATA CONSIDERATIONS AND OUTCOME MEASURES. Patient characteristics, health status, laboratory values, and physiological parameters at rest and during a cardiopulmonary exercise test were collected on standardized forms at baseline and at several points throughout the study (laboratory values only at baseline). HR was measured at rest after patients had been sitting for 5 min before assessment. BB dose at baseline was standardized by use of carvedilol equivalents and analyzed by discrete dose groups (high dose ≥25 mg daily vs. low dose <25 mg daily). Resting HR was also analyzed by discrete groups (high ≥70 beats/min vs. low <70 beats/min).

The composite primary endpoint of all-cause mortality and all-cause hospitalization, as well as an endpoint of mortality alone, were determined and adjusted with variables found to be significantly associated with outcomes (12). Other pre-specified secondary endpoints included cardiovascular mortality or cardiovascular hospitalization, cardiovascular mortality alone, and cardiovascular mortality or HF hospitalization. Although atrial fibrillation (AF) was not a predictor of outcomes in this cohort, we ran a sensitivity analysis to exclude patients with AF as well.

A subset of patients enrolled in the HF-ACTION study agreed to participate in the biomarker substudy and underwent plasma collection at baseline, 3 months, and 12 months. Changes were assessed in 928 patients with data available on serial changes.

STATISTICAL METHODS. Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables. For the primary endpoint (all-cause death or hospitalization) and secondary endpoint (all-cause death), adjustment models were developed with a broad range of candidate variables, including demographics, past medical history, laboratory values, exercise test values, and

quality-of-life indices (Kansas City Cardiomyopathy Questionnaire). These models were used for adjustment in this analysis. Cox proportional hazards modeling was used to assess the relationship between outcomes and BB dose or HR, before and after adjustment for the variables found to be significantly associated with each endpoint. The proportional hazard assumption was assessed with weighted Schoenfeld residuals. A 2-tailed p value ≤0.05 was considered statistically significant for all analyses. Statistical analysis was performed by the Duke Clinical Research Institute using SAS software version 9.2 (Cary, North Carolina).

RESULTS

Of the 2,331 patients enrolled in the HF-ACTION study, only 128 (5.5%) were not taking a BB. This analysis included 2,320 patients; 5 patients with missing HR information at baseline were excluded. Baseline characteristics are shown in Table 1. The clinical characteristics of patients across all groups were similar, particularly with regard to systolic blood pressure, LVEF, and functional capacity at baseline. Of note, HR at peak exercise was 118 beats/min in the high-dose group versus 122 beats/min in the low-dose group and 123 beats/min in the high-HR group versus 114 beats/min in the low-HR group, which indicates that there was a true beta-blockade effect with the higher doses.

The relationship between all-cause death/hospitalization and BB dose/HR groups is shown in Figure 1, and the clinical outcomes are shown in Table 2. There was a significant inverse relationship between either BB dose (higher was better) or HR (lower was better) and all-cause death or hospitalization in unadjusted analysis; however, after adjustment for the variables found to be significantly associated with the primary endpoint, higher BB dose remained significantly associated with improved outcomes regardless of high or low HR (hazard ratio: 0.77; p = 0.03 [95% confidence interval: 0.7 to 0.86]). A low BB dose combined with a high HR conferred the worst outcomes for this endpoint. The proportional hazard assumption was not met for HR for any of the 5 endpoints presented in Table 2 (unadjusted and adjusted) or for BB dose with all-cause death and cardiovascular death. The violation of the proportional hazard assumption was explored for each endpoint. In all cases, no crossing of the estimated hazard function was observed. Estimated hazard ratios in these cases represent average hazard ratios during the follow-up period and should be interpreted with caution. In a sensitivity analysis that excluded patients with AF or history of AF (n = 487), no difference was found from the primary results (Online Table 1).

Only BB dose was significant for improved outcomes on mortality in unadjusted analysis regardless of HR (Figure 2), but not after multivariable

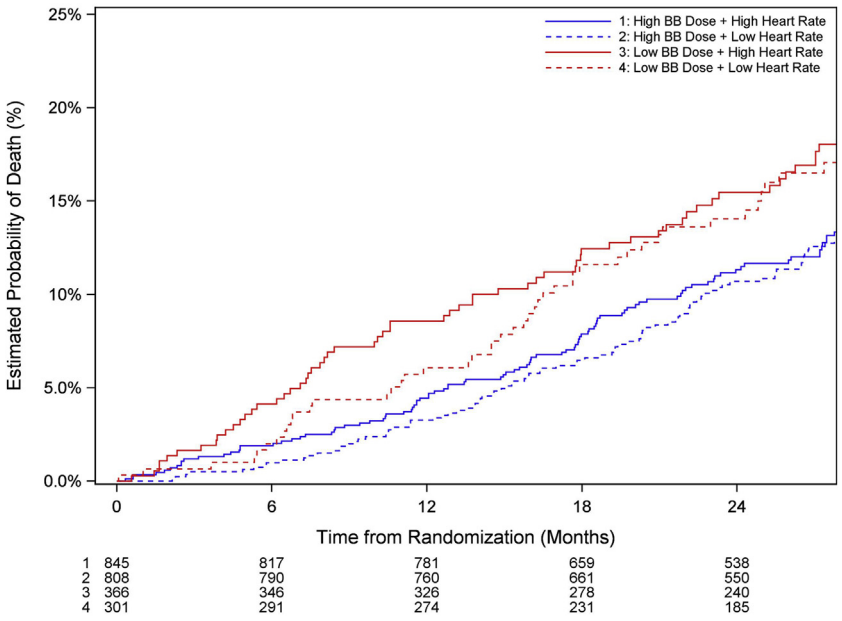
TABLE 1 Baseline Characteristics by Beta-Blocker Dose and HR at Randomization

Characteristics	Beta-Blocker Dose		HR	
	High (≥25 mg/d) (n = 1,655)	Low (<25 mg/d) (n = 670)	High (≥70 beats/min) (n = 1,211)	Low (<70 beats/min) (n = 1,109)
Age, yrs	59 (50–67)	62 (54–70)	57 (49–66)	61 (53–70)
Female	27.1	31.6	29.1	27.8
Black	34.4	28.4	35.2	30.0
BMI, kg/m^2	31 (27–36)	28 (25–33)	31 (27–36)	29 (26–34)
NYHA functional class II	65.4	58.5	60.0	67.1
Ischemic HF etiology	49.4	56.0	45.1	58.2
SBP, mm Hg	112 (100–126)	110 (100–124)	110 (100–124)	112 (100–128)
LVEF, %	25 (20–30)	24 (19–30)	24 (19–30)	25 (21–31)
History of diabetes	33.7	27.9	34.4	29.5
BUN, mg/dl	20 (15–27)	22 (16–31)	20 (15–28)	21 (16–28)
Sinus rhythm at baseline	81.3	78.8	78.8	82.6
HR at rest, beats/min	71 (64–79)	70 (62–76)	77 (72–84)	62 (60–66)
HR at peak exercise, beats/min	118 (103–133)	122 (107–139)	123 (111–139)	114 (98–129)
CPX duration, min	9.8 (7.0–12.0)	9.2 (6.5–11.8)	9.4 (6.6–11.6)	10.0 (7.2–12.7)
6MWT distance, m	374 (300–437)	366 (289–429)	366 (290–429)	377 (311–439)
Peak VO_2	14.5 (11.6–17.7)	14.1 (11.3–17.5)	14.2 (11.3–17.4)	14.7 (11.7–17.9)

Values are median (interquartile range) or %.

6MWT = 6-min walk test; BMI = body mass index; BUN = blood urea nitrogen; CPX = cardiopulmonary exercise; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure; Vo_2 = peak oxygen uptake.

FIGURE 1 All-Cause Death or Hospitalization by BB Dose (High/Low) and HR (High/Low) at Baseline



Estimated risk of death or hospitalization by discrete groups (high BB dose/high HR; high BB dose/low HR; low BB dose/high HR; low BB dose/low HR). BB = beta-blocker; HR = heart rate.

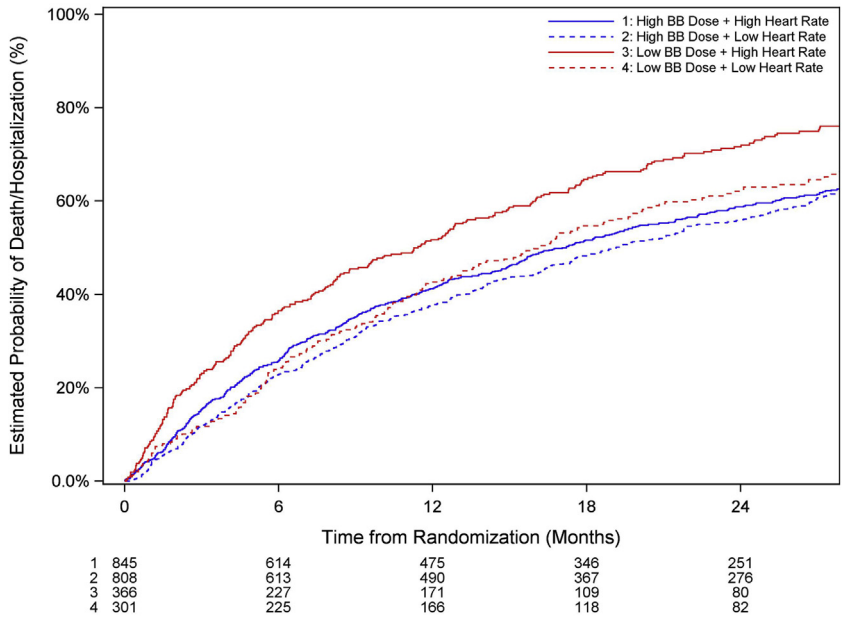
TABLE 2 Association Between Beta-Blocker Dose* at Baseline, Resting Heart Rate at Baseline, and Endpoints

	Unadjusted			Adjusted*†		
	Chi-Square	p Value	HR (95% CI)	Chi-Square	p Value	HR (95% CI)
All-cause death or all-cause rehospitalization						
Beta-blocker effect (high vs. low dose)‡	21.8	<.0001	0.77 (0.7–0.86)	4.7	0.03	0.87 (0.77–0.99)
Heart rate effect (heart rate ≥70 vs. <70 beats/min)	6.4	0.01	1.14 (1.03–1.26)§	2.9	0.09	1.11 (0.98–1.24)§
Beta-blocker by heart rate	3.5	0.06		1.8	0.19	
All-cause death						
Beta-blocker effect (high vs. low dose)	4.9	0.027	0.79 (0.64–0.97)§	0.32	0.57	0.94 (0.75–1.17)§
Heart rate effect (heart rate ≥70 vs. <70 beats/min)	0.05	0.82	0.977 (0.800–1.194)§	1.26	0.26	0.89 (0.72–1.09)§
Beta-blocker by heart rate	0.45	0.50		0.53	0.47	
CV death						
Beta-blocker effect (high vs. low dose)	2.74	0.098	0.80 (0.62–1.04)§	0.24	0.62	0.93 (0.71–1.23)§
Heart rate effect (heart rate ≥70 vs. <70 beats/min)	0.37	0.54	0.93 (0.72–1.19)§	2.45	0.12	0.81 (0.63–1.05)§
Beta-blocker by heart rate	0.02	0.88		0.06	0.80	
CV death or CV rehospitalization						
Beta-blocker effect (high vs. low dose)	10.43	0.001	0.82 (0.73–0.93)	1.22	0.27	0.93 (0.81–1.06)
Heart rate effect (heart rate ≥70 vs. <70 beats/min)	2.06	0.15	1.083 (0.971–1.207)§	0.05	0.8227	1.02 (0.89–1.15)§
Beta-blocker by heart rate	4.17	0.04		3.01	0.0828	
CV death or HF rehospitalization						
Beta-blocker effect (high vs. low dose)	10.71	0.001	0.77 (0.66–0.90)	1.40	0.2360	0.896 (0.747–1.074)
Heart rate effect (heart rate ≥70 vs. <70 beats/min)	5.83	0.016	1.197 (1.03–1.38)§	0.47	0.49	1.06 (0.9–1.26)§
Beta-blocker by heart rate	3.27	0.07		2.94	0.086	

*With adjustment by Kansas City Cardiomyopathy Questionnaire symptom stability, left ventricular ejection fraction, region, sex, ventricular conduction, Weber class, blood urea nitrogen, and mitral regurgitation. †With adjustment by sex, body mass index, loop diuretic agents, Canadian Cardiovascular Society angina class, creatinine, exercise duration, ventricular conduction, and left ventricular ejection fraction. ‡High-dose beta-blocker defined as ≥25 mg daily carvedilol equivalents; patients not taking beta-blockers were included in the low-dose group. §Proportional hazard assumption not valid; hazard ratio represents an average hazard ratio during follow-up.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio.

FIGURE 2 All-Cause Death by BB Dose (High/Low) and HR (High/Low) at Baseline



Estimated risk of death by discrete groups (high BB dose/high HR; high BB dose/low HR; low BB dose/high HR; low BB dose/low HR).
BB = beta-blocker; HR = heart rate.

adjustment. However, the lack of a significant association between BB dose and other events, in addition to the primary outcome of the study, may have been caused by the relative underpowering of the study group caused by the relatively low number of events. Although each of the other cardiovascular endpoints showed a similar significant inverse relationship with BB dose in a univariate model, these became nonsignificant when adjusted for other clinical variables.

With regard to biomarker changes, there did not appear to be any statistically significant difference in changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) between the groups, although there did appear to be a greater absolute change in the higher-dose groups (Table 3). It is likely the numbers were too small to detect a statistical difference. Finally, we have previously shown no increased risk of bradycardia with higher doses of BB in this cohort (3).

DISCUSSION

There are several important findings from this study. First, patients taking low-dose BB who had high HRs had the worse outcomes for the endpoint of all-cause mortality and hospitalizations; however, after adjustment for important clinical variables, only higher BB dose remained significantly associated with improved outcomes. There was a significant relationship between BB dose (higher was better) and all-cause death; however, no significant relationship between BB dose and death or secondary outcomes was observed after adjustment for other clinical variables.

This study found an association between higher doses of beta-blockade and an improvement in the primary composite endpoint of all-cause death/hospitalization, regardless of baseline HR being high

TABLE 3 Change in NT-proBNP From Baseline

	n	Median (25th–75th)	Minimum–Maximum
3 months			
Low BB dose/low heart rate	135	−4 (−299 to 253)	−4,010 to 7,112
Low BB dose/high heart rate	149	−54 (−449 to 231)	−6,224 to 17,235
High BB dose/low heart rate	340	−19 (−231 to 197)	−7,843 to 11,327
High BB dose/high heart rate	301	−64 (−365 to 130)	−8,675 to 18,216
12 months			
Low BB dose/low heart rate	85	−14 (−417 to 264)	−2,507 to 4,311
Low BB dose/high heart rate	101	−87 (−464 to 180)	−6,348 to 5,821
High BB dose/low heart rate	215	−46 (−255 to 175)	−8,376 to 4,379
High BB dose/high heart rate	191	−57 (−343 to 139)	−6,980 to 19,733

p Value for comparison of changes at 3 months = 0.12; p value for comparison of changes at 12 months = 0.45.
BB = beta-blocker; NT-proBNP = N-terminal pro-brain natriuretic peptide.

or low. The possibility for this has been demonstrated in other studies. For example, in a post-hoc subgroup analysis of the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure), 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. HR reduction was similar across 3 dose groups, which indicates the degree of beta-blockade may have been equivalent and thus limits the ability to test a true association between dose and mortality benefit, because previous studies have demonstrated that the degree of HR reduction may be related to outcome (13,14). With recent advances in therapies that target HR alone, this study suggests that BB dose should be optimized before HR is treated. Although guidelines recommend moderate to high doses of BBs, many patients' medications are not titrated to those doses. 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 at 90 days post-discharge. At 60 and 90 days post-discharge, only 17.5% and 7.9% of patients were receiving target doses of BBs, respectively (15). In part, this reluctance to titrate doses may be based on lack of definitive evidence that there are improved outcomes with higher doses, as well as 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 or frail or have significant comorbidities (16). A recent study of prescribing patterns in a community HF clinic showed that of 1,000 appointments for HF patients with reduced ejection fraction, 70 clinic visits were eligible for intervention (17). Of those, 58 patients were in sinus rhythm and had an HR ≥70 beats/min, and BB dose was increased in only 13 patients. Twenty additional patients were eligible for BB dose titration (15 were already at target doses, 10 were intolerant to higher doses) but did not have any change in dose. The authors concluded that 12% of patients would be eligible for ivabradine, an intervention to target HR alone.

The evidence for a BB dose-response relationship has been limited in cardiovascular medicine. The MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment) study demonstrated a positive dose-response relationship between BB dose and LVEF improvement and an improvement in survival (2); however, the cohort of 300 patients with only 30 deaths make the findings regarding survival 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 (7); however, there were important limitations, as with any meta-analysis. We have previously shown that approximately one-half the patients in HF-ACTION were not at target doses and that there was no increased risk of bradycardia with higher doses, which suggests there is considerable room for BB up-titration in clinical practice (3). This is particularly reassuring if adverse events are a concern that prevents dose titration. There remains no definitive evidence of a dose-response relationship between BB therapy and outcomes in a randomized controlled trial.

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 were excluded. On the other hand, this study includes a relatively large cohort of women and black patients. Additionally, changes in BB dose and HR during follow-up and incident AF were not captured in this analysis. An important potential confounder is that sicker patients may 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.

CONCLUSIONS

After adjustment for important clinic variables, a higher BB dose in ambulatory HF patients with reduced ejection fraction was associated with a significant reduction in all-cause hospitalization and all-cause death, regardless of baseline HR being high or low. This study suggests that the titration of BB doses may confer a greater benefit than a reduction in HR in such patients and supports 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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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study demonstrates an important question for patient care, particularly because new agents are available that target HR alone. Our data suggest that titration of BB doses should be considered as first-line therapy in clinical decision making.

TRANSLATIONAL OUTLOOK: These data support the need for a definitive randomized controlled trial examining a dose-response relationship between BB therapy and outcomes.

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KEY WORDS beta-blockers, dose, exercise, heart failure, heart rate, mortality

APPENDIX For a supplemental table, please see the online version of this article.