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ORIGINAL RESEARCH ARTICLE

Resting heart rate in ambulatory heart failure with reduced ejection fraction treated with beta-blockers

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Abstract

Aims Current guidelines recommend beta-blocker therapy in chronic heart failure with reduced ejection fraction (HFrEF) titrated according to tolerated target dose. The efficiency of this strategy to obtain adequate heart rate (HR) control remains unclear in clinical practice. The aim of this study was to determine, in a real-world setting, the proportion of HFrEF patients who fail to achieve beta-blocker target doses, whether target doses of beta-blockers have a relationship with the adequacy in reducing resting HR over time.

Methods and results Beta-blocker dose and resting HR of consecutive ambulatory patients with a diagnosis of HFrEF (ejection fraction $\leq$ 35%) in sinus rhythm were reviewed at the first outpatient contact in the Cleveland Clinic Health System from the year 2000 to 2015. Patients who did not receive beta-blocker therapy, have congenital heart disease and hypertrophic cardiomyopathy, were not in sinus rhythm, or have a history of heart transplant were excluded. Patients were followed up until their last known visit at the Cleveland Clinic. Median resting HR was 71 b.p.m. [inter-quartile range (IQR) 60–84 b.p.m.] in 8041 patients (median age 65; 68% male) with 67% on carvedilol, 32% on metoprolol succinate, and 1% on bisoprolol. In 3674 subjects (56%), resting HR was $\geq$70 b.p.m. At final follow-up after a median of 21 months (IQR 0.1–7.2 years), resting HR was 72 b.p.m. (IQR 60–84 b.p.m.) in the subset of patients with persistently low ejection fraction $\leq$ 35%. HR $\geq$ 70 b.p.m. was observed in 55% of this group. Beta-blocker target dose was achieved in 19%, 5%, and 15% of those receiving carvedilol, metoprolol succinate, and bisoprolol, respectively. In the subset of patients who experienced beta-blocker up-titration, reduced mortality or hospitalization due to heart failure was observed in patients who experienced the lowest HR after titration.

Conclusions In our single-centre experience, the majority of patients with chronic HFrEF treated with beta-blocker therapy did not achieve target doses over time, and a substantial proportion had inadequate control of resting HR. There was no relationship between achieved beta-blocker target dose and resting HR control.

Keywords Beta-blocker; Heart rate; Heart failure

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Introduction

Higher resting heart rate (HR) in heart failure with reduced ejection fraction (HFrEF) is associated with a higher incidence of cardiovascular disease and all-cause mortality,[1,2] as well as increased medical costs.[3] However, targeting low resting HR has not been utilized as a therapeutic approach. In fact, the ability to reach target doses of neurohormonal antagonists is often considered the main surrogate marker for adequacy of treatment and the basis of novel drugs that can directly target HR reduction.[4] This view has begun to change when results from the Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial (SHIFT) demonstrated that every heart beat per minute increase in resting HR was associated with a 3% relative risk of cardiovascular death or hospital admission for worsening heart failure and established the

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premise that resting HR of 70 b.p.m. or less should be considered as adequate control.[5]

Beta-blockers have become the cornerstone of pharmacological treatment of chronic HFrEF, with well-established HR-lowering effects.[6] Post-hoc analysis of major beta-blocker trials in HFrEF has suggested that their beneficial effects are predominately explained by their impact on resting HR.[7] Furthermore, reducing resting HR with ivabradine in patients already on beta-blocker therapy resulted in a significantly lower admission rate for heart failure in the SHIFT study.[8] Interestingly, this risk reduction was thought to be largely independent from beta-blocker dose.[9] However, a more recent post-hoc analysis of the HF-ACTION trial suggested that titration of beta-blocker doses might confer a greater benefit than reduction of HR in HFrEF patients.[10] In the contemporary clinical practice ambulatory setting, use and dosing of beta-blockers in HFrEF patients vary widely and are not well documented owing to higher co-morbidity and frailty that can affect drug tolerance.[11,12] Currently, it remains unclear what proportion of HFrEF patients fail to achieve beta-blocker target doses, whether target beta-blockers have any relationships with adequacy in HR control over time, and whether this is a metric that should be followed.

Methods

We identified consecutive HFrEF patients ages $\geq$ 18 years seen at our ambulatory clinics in the Cleveland Clinic Health System between 2000 and 2015 from electronic health records (EHRs). We used standard ICD9 codes (402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93; 428.0; 428.1; 428.20; 428.21; 428.22; 428.23; 428.30; 428.31; 428.32; 428.33; 428.40; 428.41; 428.42; 428.43; 428.9) to identify the diagnosis of HF. For the purpose of this study, we defined HFrEF as having a left ventricular ejection fraction (LVEF) $\leq$ 35% as documented from echocardiograms performed at our institution on the basis of the inclusion criteria for SHIFT. Also, patients were included only if they were on a beta-blocker and in sinus rhythm with or without ventricular pacing (i.e. atrial sensed pacing) at the time of first documentation of HFrEF ('baseline'). Patients were also excluded if they presented with a past history of congenital heart disease, hypertrophic cardiomyopathy, or a history of cardiac transplantation. This investigation complies with the principles outlined in the Declaration of Helsinki,[13] and the protocol was approved by the Cleveland Clinic Institutional Review Board. As this was a purely observational and retrospective study, the need for informed consent was waived, and patient data were de-identified.

All available clinical, laboratory, and drug histories of patients who met the eligibility criteria were extracted from their EHRs from baseline onwards until 31 December 2015. 'Last follow-up' is defined as the date of last documented clinic visit encounter. Target daily doses for beta-blockers in this analysis were defined by clinical trials and current practice guidelines: 50 mg for carvedilol, 200 mg for metoprolol succinate, and 10 mg for bisoprolol.[14] Adequate resting HR control was defined as a resting HR $<$ 70 b.p.m., according to the study design for SHIFT[15] as well as data that have shown reduction in hospital admissions for heart failure with a resting HR $>$ 70–72 b.p.m.[5] A subset analysis was carried out in patients who had their beta-blocker doses up-titrated and had at least three follow-up visits with resting HR recorded after the last titration, with follow-up documentation in EHR of heart failure hospitalization or all-cause mortality as primary endpoint. We defined baseline as closest HR ± 30 days from the baseline date, whereas follow-up was defined as closest HR within 180 ± 45 days since beta-blocker up-titration.

To identify factors associated with patients receiving higher vs. lower doses at baseline, a logistic regression model using an arbitrary cut-off of receiving $\geq$50% of guideline-directed beta-blocker dose was constructed by including all baseline clinical variables. The model reduction process was performed using Frank Harrell's stepdown method. The model's performance is measured by discrimination and calibration. Discrimination is measured by concordance statistic, which describes the model's ability to distinguish between patients who received $\geq$50% target doses of beta-blockers from patients who did not receive $\geq$50% target doses of beta-blockers. The calibration is a plot that measures relationship between the model's predicted probability and the actual fraction of patients who received beta-blocker dose $\geq$ 50% in the last visit. All measurements were internally validated using a 1000 bootstrap resampling process to correct bias.

Descriptive analysis of the cohort was calculated using median and inter-quartile ranges (IQRs) for continuous variables and counts and percentages for categorical variables. Significance testing was performed using χ^2 for comparing categorical variables and Wilcoxon sum rank test for continuous variables. Kaplan–Meier analysis of subset of patients who had their beta-blockers up-titrated stratified by highest (hyper-responder) vs. lowest (hypo-responder) quartile of HR reduction was performed with the composite of documented all-cause mortality and hospitalization due to heart failure was the primary outcome. Cox proportional hazards models were used to examine the association between HR responses to beta-blocker up-titration levels and time to all-cause mortality and HF hospitalizations after adjusting for potential confounders include age, sex, race, body mass index, systolic blood pressure, diastolic blood pressure, and serum creatinine. A *P*-value is considered to be significant if $<$0.05. All statistical analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, 2014, Vienna, Austria; url http://www.R-project.org/). All authors had full access to the data and contributed to the writing of the manuscript.

Together, they take responsibility for the integrity of the data and agree to the report as written.

Results

From a total of 40 064 unique patients identified by ICD9 codes with a diagnosis of heart failure, 11 832 (or 30%) had documented LVEF ≤ 35% in our EHR; and among them, 10 055 (85%) were also prescribed beta-blocker therapy. From this group, patients not in sinus rhythm or paced (*n* = 1530), those with hypertrophic cardiomyopathy (*n* = 37) and congenital heart disease (*n* = 158), and those with a history of heart transplantation (*n* = 289) were excluded, rendering a final study cohort of 8401 patients. Patients not in sinus rhythm were excluded, as the use adequacy of HR control might be difficult to compare with that of patients in sinus rhythm. A study flow chart is provided in *Figure* 1, with a median follow-up time of 1.4 years (IQR 0.1 and 7.2 years). Baseline characteristics of the study population are presented in *Table* 1, stratified by those with adequate (<70 b.p.m.) vs. inadequate (≥70 b.p.m.) resting HR at baseline.

Carvedilol was the most frequently used beta-blocker at 67%, metoprolol was second at 32%, and bisoprolol was only used in 1% of the study cohort. The proportion of patients prescribed the target dose for each beta-blocker, and the total study cohort at baseline vs. the end of follow-up is presented in *Figure* 2. At baseline, 13%, 3%, and 17% of patients were on target doses of carvedilol, metoprolol, and bisoprolol, respectively. At last follow-up, corresponding figures were 19%, 5%, and 19%. The change from 10% to 15% of the total cohort on the target dose of beta-blocker therapy was numerically small but significant (*P*-value < 0.01) for the total population (*Table* 2).

The median resting HR was 71 b.p.m. (IQR 60–84 b.p.m.) at baseline and increased to 72 b.p.m. (IQR 60–84 b.p.m.) at last follow-up (*P*-value < 0.0001, median duration of 21 months [IQR 0.1, 7.2 years]). Results at baseline were similar between carvedilol and metoprolol succinate, with 44% of patients having adequate resting HR control < 70 b.p.m., which did not change significantly from baseline to last follow-up (45%; *P*-value 0.39). From baseline to last follow-up, the overall percentage of patients with HR ≥ 70 b.p.m. taking carvedilol decreased from 59% to 54% (*P*-value: 0.01), whereas the percentage of patients with HR ≥ 70 b.p.m. taking metoprolol succinate increased from 52% to 58% (*P*-value: 0.03; *Figure* 3). Nevertheless, the proportion of patients with adequate resting HR control was similar among the three types of beta-blockers when compared at baseline or at last follow-up. Subgroups achieving ≥35%, ≥50%, and 100% of beta-blocker target dosescorresponded to adequate HR control (<70 b.p.m.) in 48%, 48%, and 49% of subjects (*P*-value: 0.93 between drugs), respectively. Patterns of resting HR control at baseline were similar across the study period of 15 years. Forty-two per cent of patients with HR < 70 b.p.m. were on beta-blocker doses ≥ 50% of the target dose;

Figure 1 Study design and STROBE diagram.

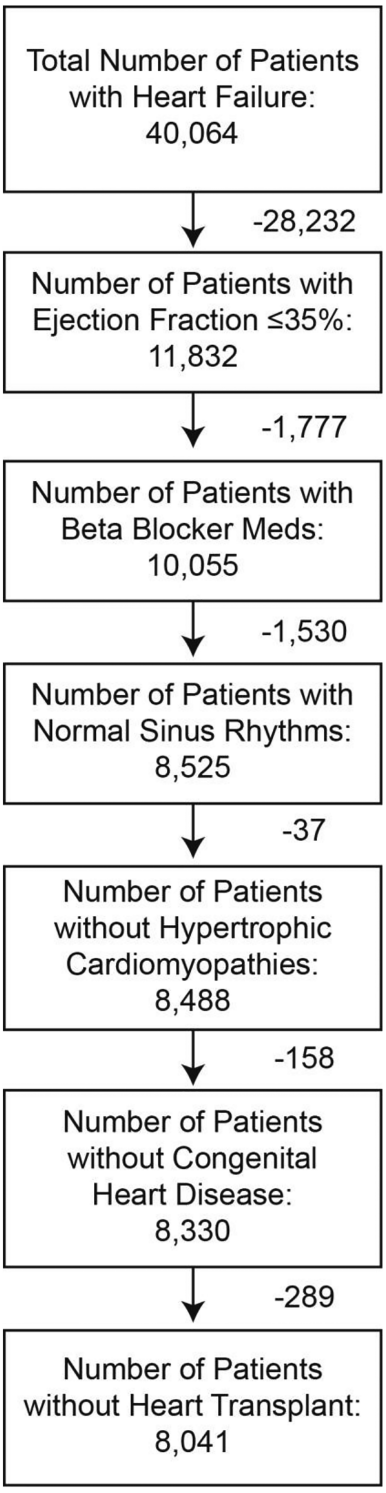

Table 1 Baseline characteristics of study population

	All (n = 8041[a])	Resting HR ≥ 70 b.p.m. (n = 4051)	Resting HR < 70 b.p.m. (n = 3023)	P value[b]
Demographics and vitals				
Age (years)	65 (55, 76)	65 (55, 76)	67 (58, 76)	<0.01
Male sex	68%	67%	70%	0.03
Black race	24%	29%	20%	<0.01
Systolic blood pressure (mmHg)	115 (102–130)	115 (102, 130)	116 (102, 130)	0.20
Diastolic blood pressure (mmHg)	67 (60–76)	67 (60, 76)	65 (59, 76)	<0.01
Body mass index (kg/m^2)	28 (23–33)	28 (24, 32)	28 (24, 32)	0.27
Co-morbidities and procedures				
Chronic kidney disease	27%	33%	25%	<0.01
Chronic obstructive pulmonary disease	11%	13%	10%	<0.01
Diabetes mellitus	40%	45%	36%	<0.01
History of malignancy	22%	24%	21%	0.01
Dyslipidaemia	66%	67%	69%	0.16
Haemorrhagic stroke	1%	1%	0%	0.01
Ischaemic stroke	10%	13%	8%	<0.01
Transient ischaemic attack	6%	6%	5%	<0.01
Hypertension	73%	78%	73%	<0.01
Percutaneous coronary intervention	9%	9%	9%	0.90
Coronary artery bypass surgery	19%	18%	20%	0.16
Peripheral arterial disease	37%	42%	37%	<0.01
Atrial fibrillation	42%	43%	45%	0.19
Cardiac devices				
Cardiac resynchronization therapy	38%	33%	55%	<0.01
Implantable cardioverter defibrillator	33%	28%	50%	0.01
Pacemaker	3%	3%	3%	<0.01
Medications				
Angiotensin-converting enzyme inhibitors	63%	59%	63%	<0.01
Angiotensin receptor blockers	20%	19%	21%	0.08
Beta-blockers	100%	100%	100%	1.00
Diuretics	84%	84%	85%	0.08
Calcium channel blockers	11%	11%	10%	0.29
Hydralazine	17%	19%	15%	0.01
Laboratory values				
Sodium (mmol/L)	138 (136–140)	138 (135, 140)	139 (136, 140)	0.01
Potassium (mmol/L)	4.2 (3.9–4.6)	4.2 (3.9, 4.6)	4.3 (4, 4.6)	<0.01
Chloride (mmol/L)	101 (98–103)	100 (97, 103)	101 (98, 103)	<0.01
Creatinine (mg/dL)	1.2 (0.9–1.6)	1.2 (0.94, 1.62)	1.2 (0.96, 1.62)	0.72
Blood urea nitrogen (mg/dL)	24 (17–35)	24 (17, 36)	24 (17, 36)	0.36
Albumin (mg/dL)	3.8 (3.3–4.2)	3.7 (3.2, 4.2)	3.9 (3.5, 4.2)	<0.01
Haemoglobin (g/dL)	12.1 (10.5–13.7)	11.9 (10.1, 13.6)	12.4 (10.8, 13.6)	<0.01

HR, heart rate.
[a]967 patients do not have heart rate record at baseline.
[b]Compared using Pearson's χ^2 test or Wilcoxon Mann–Whitney test.

37% of patients with HR ≥ 70 b.p.m. had HR ≥ 50% of the target dose.

A subset analysis was carried out in patients who had their beta-blocker doses up-titrated and had at least three follow-up visits with resting HR recorded after the last titration. The purpose of this was to allow for an adequate amount of time to pass to capture only longer lasting effects of beta-blocker dose on HR. Of the total 8041 patients, 997 met these criteria. The median duration between the two measurements was 205.7 days [IQR: 181 days, 286 days]. A wide range of HR changes following beta-blocker titration were observed. The 'hyper-responders' were defined as those with the greatest heart reduction (average reduction 22 [IQR: 17, 31], n = 260), and the 'hypo-responders' were defined as those with the least HR reduction (actually, average increase 13 b.p.m. [IQR: 8, 18], n = 237). *Figure* 4 shows a scatter plot of each patient with their baseline HR (x-axis) and HR after beta-blocker titration (y-axis). The white dots are patients who experienced an event of death or hospitalization due to heart failure, and the black dots represent patients who did not experience an event. The lowest event rates occurred in patients who started with low HR and ended with a low HR. Event rates in the lower left quadrant (those who started with a low HR and ended with a low HR) were significantly lower ($P < 0.05$) compared with the upper two quadrants (those who ended with an HR ≥ 70). There were no significant differences in baseline characteristics between hypo-responders and hyper-responders (*Table* 3). *Figure* 5 shows the Kaplan–Meier plot of hyper-responders vs. hypo-responders with Time 0 as the time after beta-blocker titration. Hyper-responders were significantly more likely to be free of mortality or hospitalization for heart failure during the follow-up period (P = 0.046). After multivariable adjustments, hypo-responders were

Figure 2 Proportion of patients reaching the beta-blocker target dose at baseline (black) vs. the end of follow-up (white).

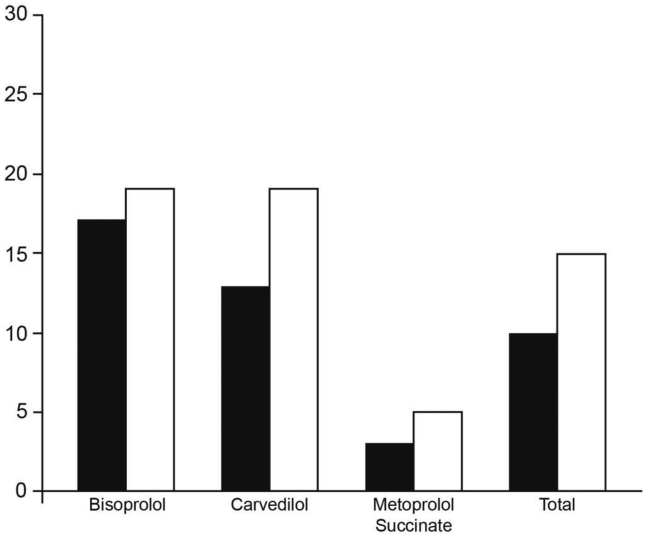

Table 2 Odds ratio of patients receiving ≥50% of guideline-directed beta-blocker dose

Variable	Coef	Odds ratio	Odds ratio 95% CI	*P*-value
Intercept	−8.16	0.00	0.00, 0.00	<0.01
Age	−0.01	0.99	0.98, 0.99	<0.01
Age*	−0.02	0.98	0.97, 0.99	<0.01
Race = Other	−0.34	0.71	0.54, 0.94	0.02
Race = White	−0.04	0.96	0.84, 1.09	0.50
Chronic obstructive pulmonary disease	−0.11	0.89	0.76, 1.06	0.19
Diabetes	0.11	1.12	0.99, 1.26	0.06
Dyslipidaemia	0.12	1.13	1.00, 1.28	0.05
Ischaemic stroke	−0.18	0.84	0.69, 1.01	0.07
Coronary artery bypass surgery	−0.11	0.90	0.78, 1.03	0.14
Peripheral arterial	−0.13	0.88	0.77, 0.99	0.04
Angiotensin receptor blockers	0.13	1.14	1.00, 1.30	0.05
Calcium channel blockers	0.41	1.51	1.28, 1.79	<0.01
Hydralazine	0.23	1.25	1.09, 1.45	<0.01
Systolic blood pressure	0.01	1.01	1.01, 1.02	<0.01
BMI	0.01	1.01	1.01, 1.02	<0.01
Sodium	0.01	1.01	1.00, 1.03	0.15
Potassium	0.15	1.16	1.05, 1.29	<0.01
Chloride	0.03	1.03	1.02, 1.05	<0.01
Blood urea nitrogen	0.00	1.00	0.99, 1.00	0.13
Haemoglobin	0.07	1.07	1.04, 1.10	<0.01

independently associated with increased all-cause mortality and HF hospitalizations compared with hyper-responders (adjusted hazard ratio 1.43, 95% confidence interval 1.08, 1.89, $P = 0.01$).

Discussion

This single-centre study provides contemporary academic clinical practice data on the routine use and dosing of beta-blocker agents and their effects on HR control in the current HFrEF treatment era. The key observations from this analysis are (i) only a minority of HFrEF patients were titrated to the guideline-recommended target dose of beta-blocker therapy at 'baseline'; (ii) up-titration of beta-blocker therapy was infrequently observed at 'last follow-up'; (iii) adequate resting HR control was substantially better than adherence to beta-blocker recommended target dose yet still occurred in a subset of patients; (iv) there was no relationship between achieving beta-blocker target dose and adequacy of resting HR control either at baseline or at follow-up; and (v), in the subset of patients who did have beta-blocker up-titration, those who had a larger reduction in their HR were less likely

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Figure 3 Resting heart rate ≥ 70 b.p.m. at baseline (black) vs. the end of follow-up (white) according to beta-blocker agent used.

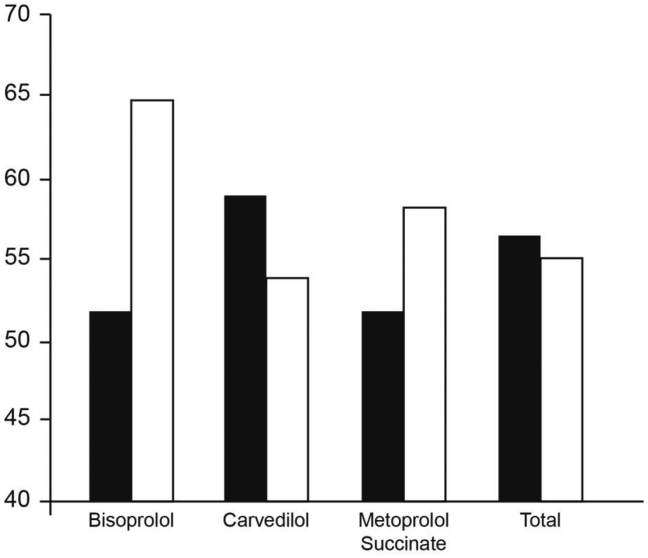
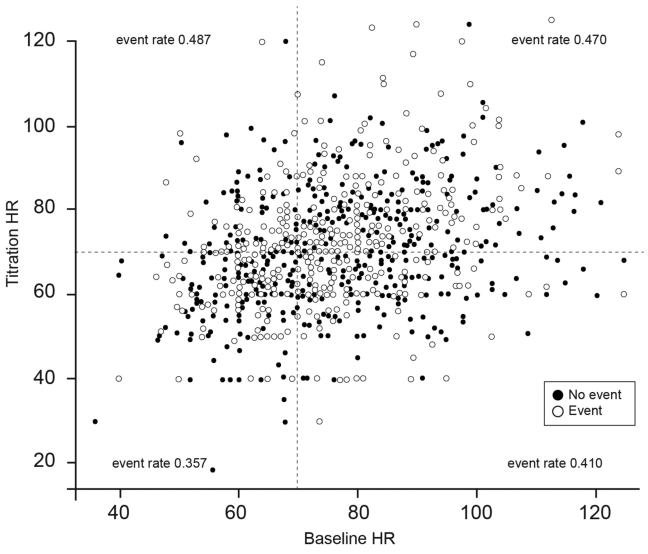


Figure 4 Scatter plot of individual patients with his/her baseline heart rate (HR) (*x*-axis) and HR after beta-blocker (BB) titration (*y*-axis). The white dots are patients who experienced an event of death or hospitalization due to heart failure, and the black dots represent patients who did not experience an event. Even rates in the lower left quadrant were significantly lower ($P < 0.05$) than the upper two quadrants.



to experience death or hospitalization from heart failure than were those who experienced increased HR despite beta-blocker titration. These observations highlight the overall inadequacy of resting HR control and challenges in achieving recommended target doses in patients with HFrEF in the contemporary clinical setting. Nevertheless, the lack of relationship between beta-blocker up-titration and adequacy of resting HR control also highlights the need to gain insight into factors that account for such discrepancies to better design strategies to improve clinical outcomes.

Large randomized clinical trials have shown that carvedilol,[16,17] metoprolol succinate,[18] and bisoprolol[19] improve morbidity and mortality in patients with HFrEF. It has been postulated (but not necessarily proven) that at least part of the observed benefit of beta-blocker therapy is derived from HR lowering. In an analysis of 35 beta-blocker

Table 3 Baseline characteristics between hyper-responders and hypo-responders

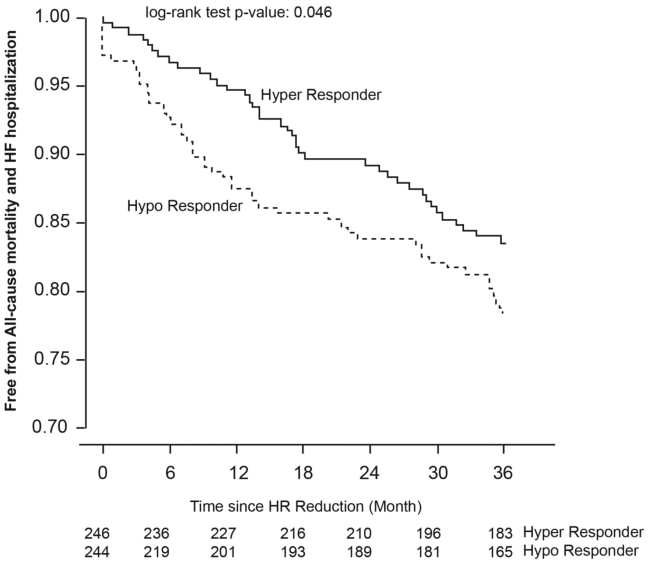
	Hyper-responders (n = 246)	Hypo-responders (n = 244)	P-value
Demographics and vitals			
Age (years)	63 (55, 74)	63 (53, 72)	0.381
Male sex	67%	67%	1.00
Black race	35%	31%	0.85
Systolic blood pressure (mmHg)	118 (108, 132)	116 (1006, 130)	0.49
Diastolic blood pressure (mmHg)	70 (62, 80)	72 (60, 80)	0.83
Body mass index (kg/m^2)	29 (25, 34)	30 (25, 35)	0.41
Co-morbidities			
Chronic kidney disease	7%	2%	0.02
Chronic obstructive pulmonary disease	3%	2%	0.55
Diabetes mellitus	5%	4%	0.66
History of malignancy	2%	2%	1.00
Dyslipidaemia	10%	4%	0.01
Haemorrhagic stroke	0%	0%	1.00
Ischaemic stroke	4%	0%	<0.01
Transient ischaemic attack	0%	0%	1.00
Hypertension	15%	4%	<0.01
Percutaneous coronary intervention	4%	1%	0.04
Coronary artery bypass surgery	0%	0%	<0.01
Peripheral arterial disease	15%	4%	<0.01
Atrial fibrillation	43%	45%	0.18
Cardiac devices			
Cardiac resynchronization therapy	57%	47%	0.04
Implantable cardioverter defibrillator	51%	43%	0.10
Pacemaker	11%	10%	0.67
Medications			
Angiotensin-converting enzyme inhibitors	78%	80%	0.45
Angiotensin receptor blockers	21%	23%	0.65
Beta-blockers	100%	100%	1.00
Diuretics	80%	81%	0.08
Calcium channel blockers	14%	6%	0.29
Hydralazine	6%	3%	0.15
Laboratory values			
Sodium (mmol/L)	139 (136, 141)	139 (135, 141)	0.98
Potassium (mmol/L)	4.2 (3.9, 4.6)	4.3 (4.1, 4.7)	0.14
Chloride (mmol/L)	101 (99, 104)	100 (98, 103)	0.27
Creatinine (mg/dL)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	0.18
Blood urea nitrogen (mg/dL)	20 (16, 28)	22 (16, 31)	0.45
Albumin (mg/dL)	3.9 (3.4, 4.2)	4.0 (3.5, 4.3)	0.49
Haemoglobin (g/dL)	12.7 (11.0, 14.1)	12.1 (10.9, 14.0)	0.65

Compared using Pearson's χ^2 test or Wilcoxon Mann–Whitney test.

trials in HFrEF, both HR achieved, and HR reduction with therapy was associated with improved clinical outcomes.[7] Other studies have shown that HR reduction from beta-blockers is the principle corollary for improvement in mortality.[20–22] In a recent meta-analysis of 11 double blinded randomized controlled trials, a higher HR was associated with greater all-cause mortality in patients with HFrEF.[23] Hence, the inability to reach therapeutic target has been speculated as inadequate delivery of life-saving therapy. In our study cohort, we observed that 15% of patients were prescribed the guideline-recommended target dose for beta-blocker therapy, which is consistent with prior reports between 13%[24] and 18%[25] of patients for similar analyses. The reasons for the lack of up-titration of beta-blockers, being either intolerability or therapeutic inertia, cannot be easily identified.

In search of a physiologic parameter to address this question, we sought to examine resting HR as a surrogate measure. Herein, we observed that ~55% of the study population had inadequate resting HR control and did not change significantly over time, which was similar than a recently reported cross-sectional series from Duke showing up to 70% with inadequate resting HR.[3] A recent publication by Ibrahim *et al*. retrospectively looked at resting HR in HFrEF patients in a real-world setting showed comparable findings to ours. In 6017 patients, 61% of patients had a resting HR $\geq$ 70 b.p.m. There was a low rate of target dose beta-blocker (27.9%), but in those patients, most (80.6%) had a resting HR $\leq$ 70 b.p.m. This is in stark contrast with prior studies from a community heart failure clinic showing 19% of patients with LVEF $\leq$ 50% (rather than $\leq$35%) had adequately controlled resting HR (<70 b.p.m.) at baseline and improved to 9% at 12 months.[26] Likewise, Elder *et al*. showed that after up-titration of beta-blockers only 19% of patients had a resting HR $\leq$ 75 b.p.m.[24] Yet our findings were in line with another study showing 64% of chronic HFrEF patients optimized on guideline-recommended

Figure 5 Kaplan–Meier plot of subset of patients who had their beta-blockers up-titrated stratified by the highest (hyper-responder) vs. lowest (hypo-responder) quartile of heart rate reduction. The composite of documented mortality and hospitalization due to heart failure was the primary outcome with median follow-up time of 36 months.



pharmacotherapy had a resting HR $\geq$ 70 b.p.m., despite 69% achieved at least half of the target dose of beta-blockers and 29% of patients reached the full target dose.[11] Several reports have not found an association between beta-blocker dosages and adequacy in resting HR control.[12,27,28] It is reassuring to observe in our cohort that chronic obstructive pulmonary disease was not a major determinant of low beta-blocker dosage, whereas those with other neurohormonal antagonists and hydralazine were associated with higher beta-blocker dosages. Taken together, resting HR control and beta-blocker dose likely capture different aspects of therapeutic adequacy that are influenced by several factors including age, sex, body habitus, comorbidities, side effects, and haemodynamic reserve, to name a few. However, it is also important to note that recent findings from the HF-ACTION study revealed that there was a significant inverse relationship between either higher beta-blocker dose or lower resting HR with all-cause death or hospitalization in unadjusted analysis. However, only beta-blocker dose maintained prognostic significance after multivariate adjustments.[29] These findings emphasize the importance of aggressive up-titration of beta-blocker therapy to maximally tolerated doses as the first-line therapeutic strategy (along with appropriate angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and also highlight the importance of validating the incremental value of other treatment modalities in the setting of inadequately controlled resting HR.

The degree to which beta-blockers are up-titrated in HFrEF patients in the clinical setting has been studied before. Carroll *et al*. showed that within a disease management programme, beta-blockers were up-titrated to optimal doses as defined by several major trials from 23% of participants to 49% of participants.[30] Gustafsson *et al*. studied the titration of beta-blockers in nurse-led heart failure clinics and found that 21% of participants achieved a target beta-blocker dose after titration.[31] Beta-blocker titration was studied in a multidisciplinary heart failure clinic by Jain *et al*. They found that in a protocol-driven heart failure clinic staffed by nurse and pharmacist specialists, the proportion of patients on 'medium' or 'optimal' doses of beta-blockers rose from a baseline of 18% to 57% for beta-blockers.[32] Given that improvement in dose escalation with the goal of guideline adherence may be associated with a decrease in long-term mortality of HFrEF patients,[33] further efforts to adhere to these guidelines should be pursued.

There are several important considerations based on our observations. First, better understanding of the reasons behind why there is inadequate beta-blocker up-titration is critical. Guideline recommendations have provided detailed information regarding management of drug intolerance. However, it is often difficult for clinicians to distinguish between inadequacies of treatment and intolerant to titration. For example, in our previous attempt to clarify this point a decade ago, we observed that the most common reasons for lack of beta-blocker therapy were obstructive lung disease and other drug intolerance (expected) and discontinuation during hospitalization (unexpected).[34,35] We speculate that concerns over side effects of hypotension and bradycardia may be playing a role in the lack of titration, even if these effects did not occur or at least were not documented. Clearly, quality improvement initiatives to provide consistent and

sustained emphasis of beta-blocker titration may be key to maximize its benefits. Second, resting HR itself may be an informative surrogate when combined with beta-blocker dosing when it comes to prognosis, but there are clear interaction and competing risks. In fact, both intolerant and insufficient beta-blocker therapy can lead to inadequate resting HR control. The ability to identify higher HR itself may serve as an opportunity to review beta-blocker dosing and considerations for re-challenge and/or up-titration over time.

Study limitations

The strength of this analysis is the sample size of consecutive HFrEF patients over the course of 15 years of EHRs. However, the findings should be interpreted in the light of some limitations inherent to its design. First, patients were captured only on appearance with beta-blocker treatment in the outpatient clinic. A potentially important phase of in-hospital up-titration or dose increases by primary physicians might not be reflected by these data, which probably better reflect the final beta-blocker dose reached compared with the up-titration process itself. Second, our tertiary care referral pattern may limit the external validity of our findings to smaller hospitals or a setting with less advanced heart failure care and may explain our higher rates of HFrEF patients not reaching target beta-blocker dosages. Third, because of the retrospective design, there was a wide range in follow-up time. Fourth, we can only speculate on the reasons for which beta-blocker up-titration was not performed in individual patients, as this was not prospectively adjudicated. There is potential selection bias from including those who survived at follow-up, not accounting for those lost to follow-up or clinical deterioration as reasons for lack of up-titration. It is also possible that the lack of improvement in HR and the lack of titration overall represent a combination of factors such as disease progression over time and individual dose-related adverse effects such as hypotension. It should be noted that these conclusions can only be applied to metoprolol succinate and carvedilol given that the number of patients on bisoprolol was too few in this study.

Conflict of interest

Dr Grodin has served as consultant for Pfizer Inc and Eidos Therapeutics. Dr Tang has served as consultant for Sequana Medical AG and received honorarium from Springer Nature and American Board of Internal Medicine. All other authors have no relationships to disclose.

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