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ORIGINAL ARTICLE

The prognostic value of heart rate at discharge in acute decompensation of heart failure with reduced ejection fraction

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Abstract

Aims The effect of elevated heart rate (HR) on morbidity and mortality is evident in chronic stable heart failure; data in this regard in acute decompensated heart failure (ADHF) setting are scarce. In this single-centre study, we sought to address the prognostic value of HR and beta-blocker dosage at discharge on all-cause mortality among patients with heart failure and reduced ejection fraction and ADHF.

Methods and results In this retrospective observational study, 2945 patients were admitted for the first time with the primary diagnosis of ADHF between January 2008 and February 2018. Patients were divided by resting HR at discharge into three groups (HR $<$ 70 b.p.m., HR 70–90 b.p.m., and HR $>$ 90 b.p.m.). Evidence-based beta-blockers were defined as metoprolol, bisoprolol, and carvedilol. The doses of prescribed beta-blockers were calculated into a percentage target dose of each beta-blocker and divided to four quartiles: 0 $<$ Dose $\leq$ 25%, 25% $<$ Dose $\leq$ 50%, 50% $<$ Dose $\leq$ 75%, and $>$75% of the target dose. Cox regression was used to calculate the hazard ratio for various HR categories and adjusting for clinical and laboratory variables. At discharge, 1226 patients had an HR $<$ 70 b.p.m., 1347 patients had an HR at range 70–90 b.p.m., and 372 patients with an HR $>$ 90 b.p.m. The 30 day mortality rate was 2.2%, 3.7%, and 12.1% ($P < 0.001$), respectively. Concordantly, 1 year mortality rate was 14.6%, 16.7%, and 30.4% ($P < 0.001$) among patients with HR $<$ 70 b.p.m., HR 70–90 b.p.m., and HR $>$ 90 b.p.m., respectively. The adjusted hazard ratio was significantly increased only in HR above 90 b.p.m. category (hazard ratio, 2.318; 95% confidence interval, 1.794–2.996).

Conclusions Patients with ADHF and an HR of $<$90 b.p.m. at discharge had significantly a lower 1 year mortality independent of the dosage of beta-blocker at discharge. It is conceivable to discharge these patients with lower HR.

Keywords Acute decompensated heart failure; Beta-blockers; Heart rate; Discharge

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Introduction

Heart failure (HF) is a growing public health concern worldwide, with high morbidity, mortality, and cost. The prevalence of HF is approximately 1–2% of the adult population in developed countries.[1]

Acute decompensated heart failure (ADHF) is defined as a gradual or rapid change in HF signs and symptoms resulting in a need for urgent therapy. These symptoms are primarily the result of pulmonary congestion due to elevated left ventricular (LV) end-diastolic filling pressures (with or without low cardiac output).[1] There is large heterogeneity in ADHF presentations; some patients are admitted with new onset HF. Others are with chronic disease and recurrent re-hospitalizations. The presentation of ADHF can be caused or triggered by acute coronary syndrome (ACS), atrial fibrillation, and several other aetiologies. In addition, the clinical presentation has a very wide spectrum, ranging from peripheral oedema,

mild dyspnoea, to pulmonary oedema and cardiogenic shock.[2]

Disease-modifying drugs that include neuro-hormonal antagonists (beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, and mineralocorticoid receptor antagonists) have been shown to improve survival and reduce mortality and re-hospitalization in patients with heart failure and reduced ejection fraction (HFrEF).[3,4]

Sympathetic tone blockage with beta-blockers has been proven to be one of the cornerstones of HFrEF treatment.[3] Levine showed an inverse semi-logarithmic relationship between resting heart rate (HR) and life expectancy in mammals and the questionable issue was whether human life can be extended by HR slowing.[5] Early initiation of beta-blockers, especially at discharge following a transient episode of ADHF, is beneficial and thought to be crucial. Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximal tolerated dose according to the European Society of Cardiology guidelines.[1,3,4]

In patients with HFrEF including those with ACSs, elevated resting HR is associated with increased risk of all-cause mortality and cardiovascular mortality.[6–9] Similarly, the SHIFT (Systolic Heart failure treatment with the If inhibitor Ivabradine Trial) trial had demonstrated that in patients with chronic HF and sinus rhythm, the risk of cardiovascular death or hospitalization due to HF was two-fold greater in patients with the highest HR as compared with those with the lowest HR.[10,11]

While the effect of elevated HR on cardiovascular morbidity and mortality is evident in chronic stable HF, data regarding acute HF are only starting to emerge, with the largest trial to date excluding patients younger than 65 years.[4,6,7,10–12]

In this single-centre study, we sought to address the prognostic value of HR and beta-blocker dosage and at discharge on all-cause mortality among patients with ADHF and reduced ejection fraction.

Methods

Study population

A retrospective observational study included all patients 18 years old or more that were admitted for the first time with the primary diagnosis of ADHF to Rambam Health Care Campus (RHCC), Haifa, Israel, between January 2008 and February 2018.

Data collection

The following parameters were noted: demographic data, vital signs on admission and discharge (including HR and blood pressure), and concomitant diseases (including chronic obstructive disease, hypertension, diabetes mellitus, ischaemic heart disease, chronic kidney disease, peripheral arterial disease, atrial fibrillation, valvular heart disease, and pulmonary hypertension). In addition, we included regular relevant medical therapy, laboratory results including blood urea nitrogen, creatinine, and electrolytes on admission and on discharge, recommended treatments on discharge, and mortality at 1 year. All data were collected by MdClone © software[13] for data gathering, Beersheba, Israel.

Inclusion criteria

First admission with HF as the primary diagnosis with left ventricular ejection fraction (LVEF) $\leq 40\%$. Echocardiographic data were collected for each patient that underwent echocardiographic study during the index hospitalization or in the last 6 months prior to admission.

Resting HR at discharge was divided into three groups (HR < 70 b.p.m., HR 70–90 b.p.m., and HR > 90 b.p.m.).

Based on the ESC guidelines,[1] the following evidence-based beta-blockers that improve survival were included in this study: bisoprolol 10 mg once daily; carvedilol 25 mg twice daily; and metoprolol succinate 200 mg once daily.

Other beta-blockers were excluded from the study. The doses of the prescribed beta-blockers were calculated into a percentage target dose of each beta-blocker and divided to four quartiles: $0 < \text{Dose} \leq 25\%$, $25\% < \text{Dose} \leq 50\%$, $50\% < \text{Dose} \leq 75\%$, and $75\% < \text{Dose} \leq 100\%$ of the guidelines target dose.

The use of a beta-blocker was evaluated at hospital discharge, and HR was noted at rest before discharge.

The study was approved by the local institutional review board for human research and complied with the Declaration of Helsinki: approval number, RMB-0310-20.

Exclusion criteria

Patients with primary diagnosis other than ADHF, younger than 18 years old, missing HR measurements at the day of discharge, and missing recent echocardiographic study or patients who died during their hospitalization were excluded from the study.

Study endpoints

The primary outcome was post-discharge all-cause mortality at 1 year.

Statistical analysis

Continuous variables were visually inspected for normal distribution and are summarized with mean ± standard

deviation. Categorical variables are presented with frequencies and proportions. The baseline characteristics were compared using the χ^2 test for categorical variables and the ANOVA (analysis of variance) test for continuous variables.

Kaplan–Meier curves were used to depict time to death. Comparison was made by the log-rank test.

Cox proportional hazard regression models were used to assess the association between HR groups and time to death; hazard ratios and 95% confidence interval (CI) were calculated for the groups using the patients with HR $<$ 70 as the reference category. Variables with *P* value below 0.2 in the univariate analysis were included in the multivariate model, in order to adjust for possible confounders.

For all analyses, a *P* value $<$ 0.05 for the two-tailed tests was considered statistically significant.

In order to explore a possible non-linear association between HR (continuous variable) and the risk of death (outcome), hazard ratio and 95% CI were assessed using cubic splining with 4 degrees of freedom; HR 70 was assigned as the reference value.[14] All statistical analyses were performed using SPSS 21.0 and R Version 3.6.1.

Results

Between January 2008 and February 2018, 11 383 patients were hospitalized with ADHF at RHCC, and 3957 patients had HFrEF. Among them, 3004 had HR measurement at discharge. Fifty-three patients were excluded due to recommendation of beta-blockers inadequate with the guidelines, and six patients had HR 40 or below, leaving the data of 2945 patients available for the final analysis (*Figure 1*).

The baseline characteristics of the study patients are shown in *Table 1*. Patients were divided into three groups (HR $<$ 70 b.p.m., HR 70–90 b.p.m., and HR $>$ 90 b.p.m.). Most patients in all subgroups were male 74%, 71.6%, and 74.2% (*P* = 0.116), respectively.

Acute coronary syndrome, atrial fibrillation, diabetes mellitus, and hypertension were less common in patients with HR above 90. Yet hypotension (systolic blood pressure $<$ 90) and lower doses of beta-blockers were more common in patients with HR above 90 as shown in *Table 1*.

Figure 1 Study flow diagram.

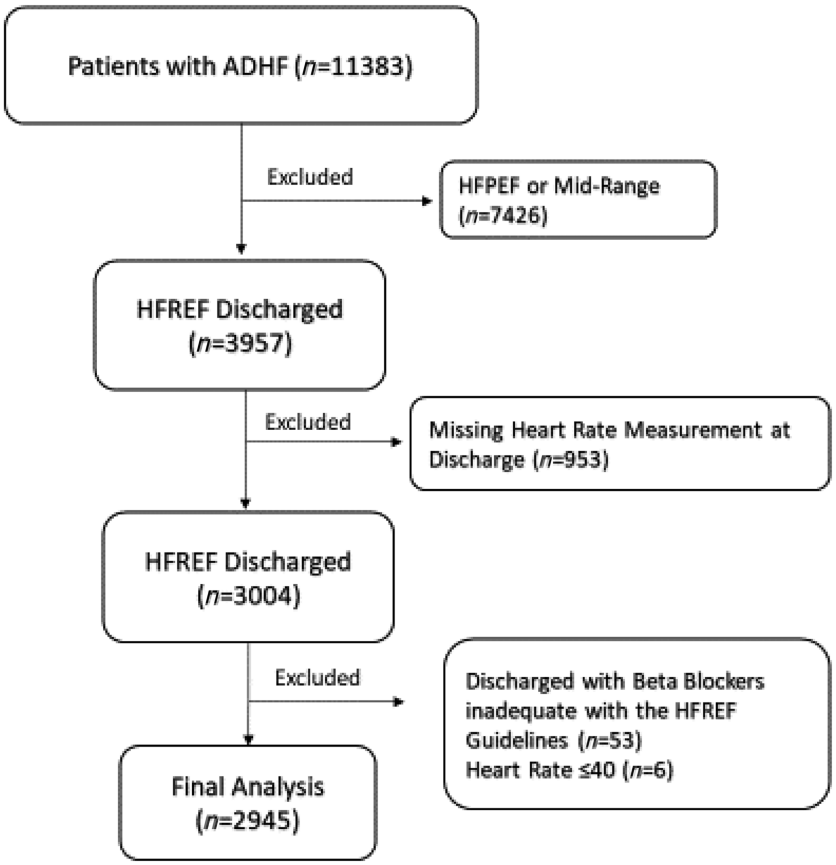

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Table 1 The baseline characteristics of the study population

	Heart rate < 70 $N = 1226$	Heart rate 70–90 $N = 1347$	Heart rate > 90 $N = 372$	*P* value
Age	69.7 ± 11.25	67 ± 12.15	64.8 ± 15.9	0.001
Female gender	319 (26%)	396 (29.4%)	96 (25.8%)	0.116
Systolic blood pressure	119.9 ± 19.4	118.6 ± 19.63	114.8 ± 20	0.001
Diastolic blood pressure	65 ± 13	68 ± 13	68 ± 14	0.001
Heart rate	61 ± 5.7	77.8 ± 5.5	99.9 ± 10.9	0.001
Ischaemic heart disease	901 (73.5%)	966 (71.7%)	235 (63.2%)	0.001
Diabetes mellitus	568 (46.3%)	708 (52.6%)	166 (44.6%)	0.001
Hypertension	939 (76.6%)	1029 (76.4%)	257 (69.1%)	0.008
Atrial fibrillation	623 (50.8%)	628 (46.6%)	163 (43.8%)	0.023
COPD	218 (17.8%)	238 (17.7%)	66 (17.7%)	0.997
Acute coronary syndrome	110 (9%)	152 (11.3%)	27 (7.3%)	0.03
Hypotension at discharge (SBP < 90)	29 (2.4%)	41 (3.0%)	36 (9.7%)	0.001
Ejection fraction				0.021
Moderate EF	318 (30.8%)	313 (27.9%)	73 (25.0%)	—
Moderate–severe EF	163 (15.8%)	154 (13.7%)	34 (11.6%)	—
Severely reduced EF	550 (53.3%)	656 (58.4%)	185 (63.4%)	—
Creatinine (mg/dL)	1.55 ± 1.15	1.59 ± 1.26	1.42 ± 0.92	0.05
GFR	53.55 ± 26.77	56.97 ± 27.83	65.93 ± 31.68	0.001
BUN (mg/dL)	29.17 ± 16.31	30.01 ± 18.47	29.41 ± 20.41	0.49
Haemoglobin (g/dL)	12.3 ± 1.98	12.18 ± 2.06	12.18 ± 2.07	0.27
ACE inhibitors	367 (29.9%)	410 (30.4%)	109 (29.3%)	0.9
Proportion of target dose ACE inhibitors[a]	0.45 ± 0.41	0.45 ± 0.39	0.42 ± 0.308	0.83
ARB	154 (12.6%)	116 (8.6%)	35 (9.4%)	0.004
Proportion of target dose ARB[a]	0.45 ± 0.24	0.38 ± 0.21	0.41 ± 0.17	0.031
Spironolactone	305 (24.9%)	320 (23.8%)	72 (19.4%)	0.09
Proportion of target dose spironolactone[a]	0.52 ± 0.27	0.48 ± 0.26	0.69 ± 0.44	0.001
Diuretics	1079 (88.0%)	1186 (88.0%)	310 (83.3%)	0.038
Beta-blockers				0.001
None	195 (15.9%)	224 (16.6%)	80 (21.5%)	—
0 < Dose ≤ 25%	410 (33.4%)	465 (34.5%)	124 (33.3%)	—
25% < Dose ≤ 50%	435 (35.5%)	406 (30.1%)	105 (28.2%)	—
50% < Dose ≤ 75%	18 (1.5%)	24 (1.8%)	15 (4.0%)	—
75% < Dose ≤ 100%	168 (13.7%)	228 (16.9%)	48 (12.9%)	—
Beta-blockers				0.005
None	195 (15.9%)	224 (16.6%)	80 (21.5%)	—
0 < Dose ≤ 33%	412 (33.6%)	468 (34.7%)	125 (33.6%)	—
33% < Dose ≤ 66%	433 (35.3%)	403 (29.9%)	104 (28.0%)	—
66% < Dose ≤ 100%	186 (15.2%)	252 (18.7%)	63 (16.9%)	—

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GFR, glomerular filtration rate; SBP, systolic blood pressure.
[a]Calculated only for patients receiving the drug.

The prevalence of ischaemic heart disease was 73.5%, 71.7%, and 63.5% in patients with HR < 70 b.p.m., 70–90 b.p.m., and >90 b.p.m., respectively ($P < 0.001$). Diabetes mellitus was found in 46.3%, 52.6%, and 44.6% of the patients with HR < 70 b.p.m., 70–90 b.p.m., and >90 b.p.m., respectively ($P < 0.001$). The prevalence of hypertension was 76.6%, 76.4%, and 69.1% in patients with HR < 70 b.p.m., 70–90 b.p.m., and >90 b.p.m., respectively ($P = 0.008$).

As shown in *Table 2*, all-cause mortality at 30 days occurred in 2.2%, 3.7%, and 12.1% of those with discharge HR < 70 b.p.m., 70–90 b.p.m., and >90 b.p.m., respectively ($P < 0.001$). All-cause mortality at 1 year follow-up occurred in 14.6%, 16.7%, and 30.4% of those with discharge HR < 70 b.p.m., 70–90 b.p.m., and >90 b.p.m., respectively ($P < 0.001$).

On Kaplan–Meier analysis, patients with an HR ≤ 90 at discharge had a better survival at 1 year after discharge (*Figure 2*) ($P < 0.001$).

Table 2 All-cause mortality in the subgroups of the study

	Heart rate < 70 $N = 1226$	Heart rate 70–90 $N = 1347$	Heart rate > 90 $N = 372$	*P* value
Mortality 30 days	27 (2.2%)	50 (3.7%)	45 (12.1%)	0.001
Mortality 90 days	59 (4.8%)	88 (6.5%)	64 (17.2%)	0.001
Mortality 6 months	98 (8.0%)	155 (11.5%)	92 (24.7%)	0.001
Mortality 1 year	179 (14.6%)	225 (16.7%)	113 (30.4%)	0.001

Under stratification according to beta-blocker prescription at discharge, patients discharged with no beta-blocker had poorer prognosis than those who received beta-blockers ($P < 0.001$) (*Figure 3*). Restricting the analysis to those who received guidelines adequate beta-blockers demonstrated no significant effect of beta-blocker dosage at discharge on survival ($P = 0.757$).

Figure 2 Kaplan–Meier survival curve from discharge to 1 year from discharge. Patients were divided for three groups by their heart rate at discharge: lower than 70 b.p.m., between 70 and 90 b.p.m., and above 90 b.p.m.

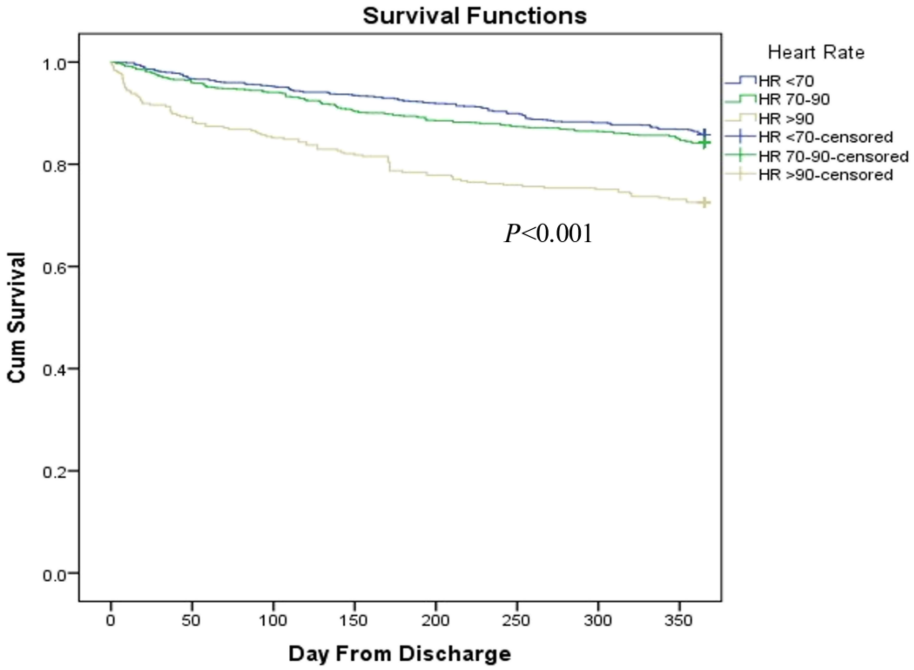
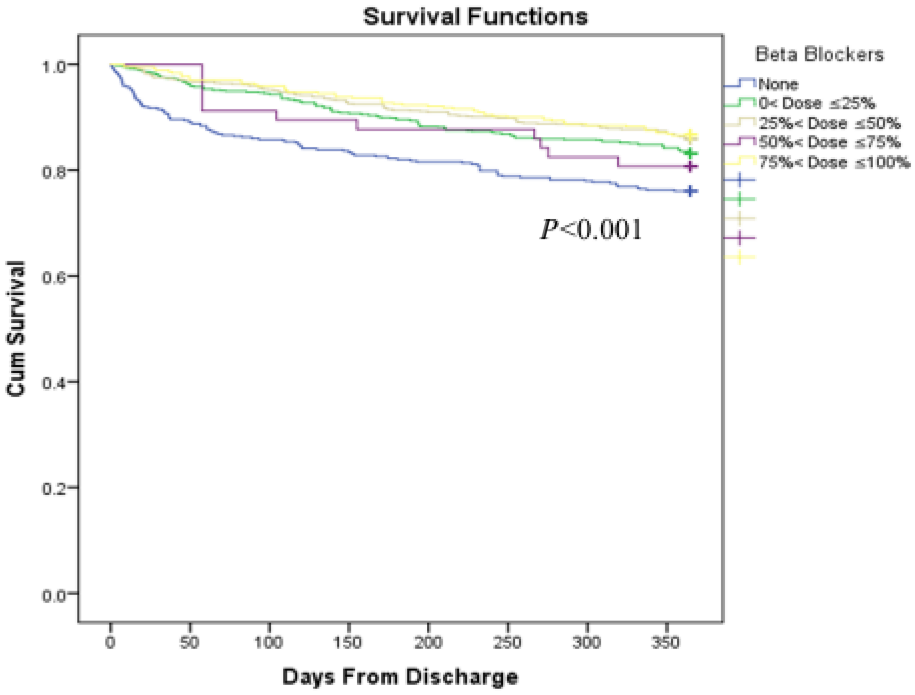


Figure 3 Kaplan–Meier survival curve from discharge to 1 year from discharge under stratification according to beta-blocker target dose prescription at discharge.



In unadjusted analysis, the hazard ratio for 1 year mortality was 1.132 (95% CI, 0.926–1.383) in patients with HR 70–90 b.p.m. and 2.172 (95% CI, 1.696–2.783) in patients with HR > 90 b.p.m. compared with patients with HR < 70 b.p.m. at discharge. There was statistically significant relationship between beta-blocker recommendation given at discharge and all-cause mortality reduction. The hazard ratio for 1-year mortality was 0.648 (95% CI, 0.509–0.821), 0.532 (95% CI, 0.414–0.68), 0.753 (95% CI, 0.405–1.398), and 0.503 (95% CI, 0.367–0.689) in patients who received 0 < Dose ≤ 25%, 25% < Dose ≤ 50%, 50% < Dose ≤ 75%, and 75% < Dose ≤ 100% of the optimal beta-blocker target dose, respectively, compared with patients who were discharged without beta-blockers (the reference group) (*Table 3*).

After adjustment for potential confounders, the hazard ratio for 1 year mortality was 1.073 (95% CI, 0.872–1.322) in patients with HR 70–90 b.p.m. and 2.318 (95% CI, 1.794–2.996) in patients with HR > 90 b.p.m. (*Table 3*). There was no significant interaction between HR and beta-blocker dose (P = 0.061).

Table 3 Univariable and multivariate Cox regression model for 1 year mortality

	Unadjusted		Adjusted Model 1[a]		Adjusted Model 2[b]	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (years)						
0–60	Reference	—	Reference	—	Reference	—
60–80	1.456 (1.12–1.893)	0.005	1.306 (0.989–1.724)	0.06	1.315 (0.997–1.735)	0.053
>80	3.943 (3.009–5.167)	<0.001	3.642 (2.708–4.899)	<0.001	3.676 (2.736–4.939)	<0.001
Female gender	1.225 (1.011–1.485)	0.038	1.121 (0.911–1.378)	0.280	1.12 (0.911–1.378)	0.281
Systolic blood pressure (per 10 mmHg)	0.88 (0.839–0.924)	<0.001	0.843 (0.798–.89)	<0.001	0.844 (0.799–0.891)	<0.001
Diastolic blood pressure (per 10 mmHg)	0.801 (0.744–0.861)	<0.001	0.973 (0.891–1.063)	0.54	0.974 (0.892–1.064)	0.563
Heart rate						
Heart rate < 70	Reference	—	Reference	—	Reference	—
Heart rate 70–90	1.132 (0.926–1.383)	0.227	1.073 (0.872–1.322)	0.504	1.072 (0.87–1.32)	0.515
Heart rate > 90	2.172 (1.696–2.783)	<0.001	2.318 (1.794–2.996)	<0.001	2.326 (1.8–3.01)	<0.001
Ischaemic heart disease	1.473 (1.187–1.827)	<0.001	1.065 (0.846–1.341)	0.593	1.069 (0.849–1.345)	0.572
Diabetes mellitus	1.666 (1.388–1.999)	<0.001	1.512 (1.236–1.850)	<0.001	1.511 (1.235–1.848)	<0.001
Hypertension	1.674 (1.317–2.128)	<0.001	1.345 (1.040–1.741)	0.024	1.341 (1.037–1.735)	0.025
Atrial fibrillation	0.859 (0.718–1.028)	0.097	0.760 (0.630–0.917)	0.004	0.760 (0.629–0.917)	0.004
COPD	1.181 (0.946–1.475)	0.141	1.288 (1.024–1.620)	0.03	1.290 (1.026–1.622)	0.03
Acute coronary syndrome	1.160 (0.870–1.547)	0.312	—	—	—	—
Ejection fraction		0.365				
Moderate EF	Reference		—	—	—	—
Moderate–severe EF	0.868 (0.626–1.203)		—	—	—	—
Severely Reduced EF	0.850 (0.677–1.068)		—	—	—	—
GFR (mL/min)						
>60	Reference	—	Reference	—	Reference	—
45–60	1.676 (1.295–2.168)	0.000	1.247 (0.953–1.633)	0.107	1.245 (0.951–1.63)	0.11
30–45	2.239 (1.753–2.86)	0.000	1.291 (0.976–1.707)	0.073	1.284 (0.971–1.69)	0.79
<30	2.980 (2.314–3.836)	<0.001	1.065 (0.736–1.541)	0.74	1.058 (0.731–1.53)	0.764
BUN (per 10)	1.24 (1.197–1.285)	<0.001	1.190 (1.124–1.260)	<0.001	1.190 (1.124–1.260)	<0.001
Haemoglobin	0.803 (0.768–0.839)	<0.001	0.886 (0.840–0.935)	<0.001	0.885 (0.839–0.934)	<0.001
ACE inhibitors/ARB	0.762 (0.632–0.919)	0.005	0.995 (0.817–1.212)	0.961	1.000 (0.821–1.217)	0.99
Spironolactone	0.931 (0.767–1.132)	0.475	—	—		
Diuretics	0.87 (0.665–1.138)	0.31	—	—		
Beta-blockers						
None	Reference	—	Reference	—	—	—
0 < Dose ≤ 25%	0.647 (0.509–0.821)	<0.001	0.764 (0.599–0.976)	0.031	—	—
25% < Dose ≤ 50%	0.532 (0.414–0.684)	<0.001	0.716 (0.553–0.927)	0.011	—	—
50% < Dose ≤ 75%	0.753 (0.405–1.398)	0.37	0.888 (0.472–1.673)	0.714	—	—
75% < Dose ≤ 100%	0.503 (0.367–0.689)	<0.001	0.71 (0.513–0.979)	0.037	—	—
Beta-blockers						
None	Reference	—	—		Reference	—
0 < Dose ≤ 33%	0.647 (0.510–0.821)	<0.001			0.765 (0.599–0.976)	0.031
33% < Dose ≤ 66%	0.532 (0.414–0.683)	<0.001			0.714 (0.551–0.924)	0.011
66% < Dose ≤ 100%	0.531 (0.394–0.715)	<0.001			0.732 (0.538–0.994)	0.46

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GFR, glomerular filtration rate.
Variables with *P* value below 0.2 in the univariate analysis were included in the multivariate model: age, sex, systolic blood pressure, diastolic blood pressure, heart rate, ischaemic heart disease, diabetes mellitus, hypertension, atrial fibrillation, COPD, GFR, BUN, haemoglobin, ACE inhibitors/ARB, and beta-blocker doses.
[a]Model 1 included beta-blocker doses stratified into five groups.
[b]Model 2 included beta-blocker doses stratified into four groups.

Furthermore, by using cubic splining, a near linear association between HR at discharge and the hazard ratio for 1 year mortality was demonstrated (*Figure 4*).

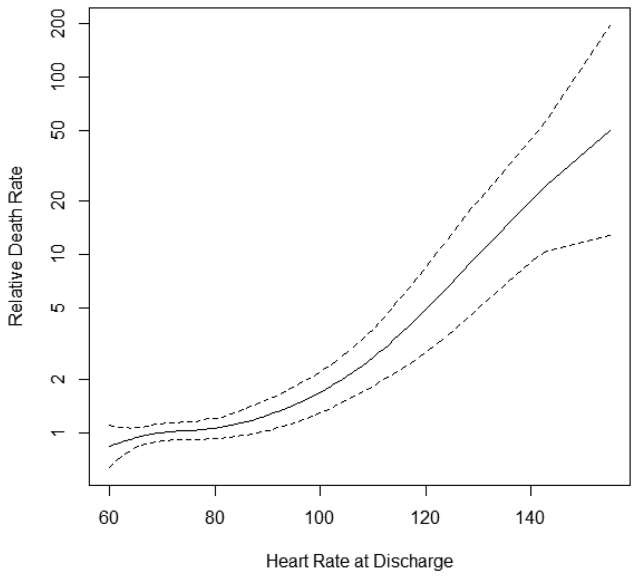
A number of sensitivity analyses was conducted according to the presence of atrial fibrillation, ACS, and hypotension. As demonstrated in *Table 4*, patients with HR above 90 b.p.m. were at higher risk for mortality independent of the presence/absence of atrial fibrillation or ACS (*Table 4*). The risk for 1 year mortality for those with HR 70–90 b.p.m. did not vary significantly from the reference group (*Figure 5*).

Stratifying patients according to the presence/absence of hypotension demonstrated a higher risk for death in those with HR $>$ 90 and normotension; the hazard ratio was 2.073 (95% CI, 2.073–2.732). However, the subgroup of patients with hypotension and HR above 90 did not differ significantly from other HR groups; the hazard ratio was 1.685 (95% CI, 0.458–6.193), probably due to the small number of patients (*Table 4*).

Discussion

The prognostic impact of HR in ADHF is still a matter of debate. In contrast to the predictive role of HR in chronic systolic HF,[15,16] the role of this measurement in ADHF is much more controversial. This is partly due to differences in the time point when HR was measured during an acute decompensation period and focusing on different endpoints like in-hospital mortality and readmission in various studies.

Figure 4 Adjusted association between heart rate at discharge and the hazard ratio for mortality, the (*Y*) axis presents the hazard ratio and 95% confidence interval, and heart rate values range from 60 to maximum (reference heart rate = 70). Variables adjusted for in the multivariate model: age, sex, systolic blood pressure, diastolic blood pressure, heart rate, ischaemic heart disease, diabetes mellitus, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, glomerular filtration rate, blood urea nitrogen, haemoglobin, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, and beta-blocker doses.



Heart rate and mortality

In this large cohort of HFrEF patients who were admitted with ADHF, it was found that resting HR at discharge of $>$90 b.p.m. was independently predictive of increased mortality at 1 year follow-up after discharge irrespective of the dosage of the prescribed beta-blockers on discharge. Based on the present study, it is conceivable to presume that the optimal target HR that improves prognosis is below 90 b.p.m. in patients with HFrEF.

These findings are in concordance with prior studies associating lower HR with decreased cardiovascular and all-cause mortality.[12,17,18] Maurer *et al*. reported that in HFrEF patients treated with carvedilol, the improvement on ejection fraction was primarily attributed to HR reduction and to lesser proportions was due to increased contractility and reduced systemic vascular resistance.[19]

Notably, Laskey *et al*. reported in both HFrEF and HFpEF patients, a positive near linear association between HR and mortality, especially in patients with HR above 85 b.p.m.[12] Similarly, this current study demonstrated a positive linear association between HR and mortality independent of beta-blockers dosage. Notably, it included patients only with HFrEF.

There are only few studies that have concentrated on HR at discharge among patients with acute decompensation of HFrEF.[4,12,20] Vollmert *et al*. demonstrated in patients with HFrEF that HR at discharge was a predictor of mortality. In this study, HR above 77 b.p.m. at discharge was associated with nearly two-fold mortality increment. HR increase by 5 b.p.m. was associated with an increase of mortality of 25%.[4]

In a retrospective study in 1669 chronic stable HF patients with LVEF $<$ 40%, Corletto *et al*. showed that by achieving guidelines recommended beta-blocker dose or to HR control (defined as 51–69 b.p.m.) has a similar positive impact on survival. When on target dose, supplemental HR control additionally improves survival.[21]

Beta-blockers and mortality

The current study showed that in patients receiving beta-blockers, regardless of the dose, mortality was decreased as compared with those discharged without any beta-blockers. This finding emphasizes the proven importance of beta-blockers recommendation at discharge. Yet there was no apparent benefit in those with higher doses of beta-blockers when dividing to by median, tertiles, or quartiles.

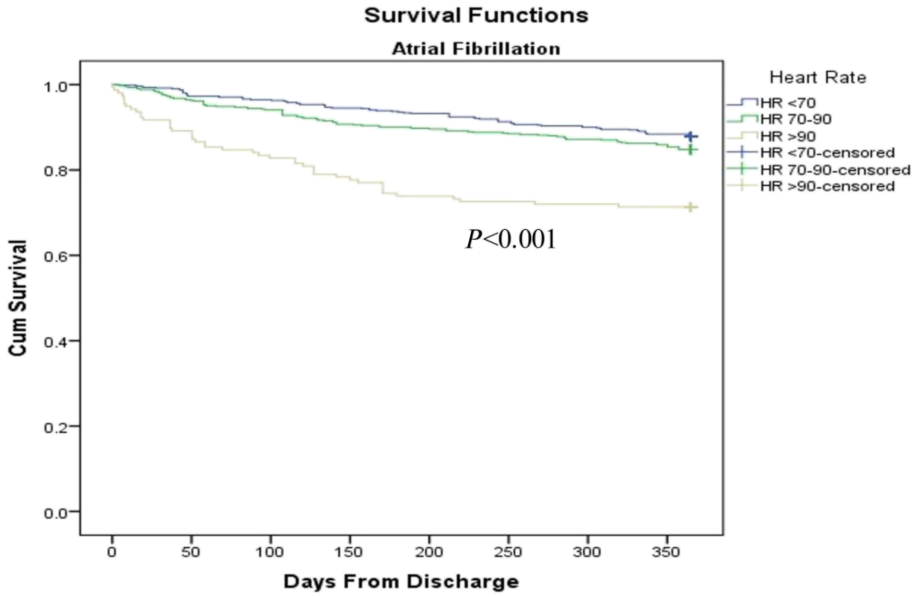
On the other hand, BIOSTAT-CHF study showed that HFrEF patients who were treated with $<$50% of the recommended

Table 4 All-cause mortality at 1 year after discharge following stratification according to atrial fibrillation, acute coronary syndrome, and hypotension

	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Strata	**Atrial fibrillation (*n* = 1414)**		**Without atrial fibrillation (*n* = 1531)**	
Heart rate < 70	Reference	—	Reference	—
Heart rate 70–90	0.914 (0.687–1.217)	0.539	1.244 (0.910–1.701)	0.171
Heart rate > 90	1.983 (1.385–2.84)	<0.001	2.595 (1.751–3.847)	<0.001
Strata	**Acute coronary syndrome (*n* = 289)**		**Without acute coronary syndrome (*n* = 2656)**	
Heart rate < 70	Reference	—	Reference	—
Heart rate 70–90	1.098 (0.881–1.37)	0.4	0.789 (0.388–1.603)	0.5
Heart rate > 90	2.282 (1.741–2.992)	<0.001	3.416 (1.382–8.439)	0.008
Strata	**Hypotension (*n* = 96)**		**Normotensive (*n* = 2837)**	
Heart rate < 70	Reference	—	Reference	—
Heart rate 70–90	0.696 (0.223–2.173)	0.53	1.082 (0.873–1.342)	0.47
Heart rate > 90	1.685 (0.458–6.193)	0.43	2.073 (1.573–2.732)	<0.001

CI, confidence interval.
Variables adjusted for in the multivariate model: age, sex, systolic blood pressure, diastolic blood pressure, heart rate, ischaemic heart disease, diabetes mellitus, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, glomerular filtration rate, blood urea nitrogen, haemoglobin, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, and beta-blocker doses.

Figure 5 Subgroup analysis for patients with atrial fibrillation—Kaplan–Meier survival curve from discharge to 1 year from discharge.



dose of beta-blockers were at increased risk of death and HF hospitalization compared with patients reaching ≥100% of the recommended dose.[20] One explanation for this discrepancy might be the available data on the up-titration of beta-blocker doses in the BIOSTAT-CHF; these data were unavailable in the current study.

Heart rate and mortality in patients with concomitant cardiac conditions

Due to the heterogeneous clinical presentations of patients with ADHF, several sensitivity analyses were performed according to the presence of atrial fibrillation, ACS, and hypotension.

Stratifying patients according to the presence of atrial fibrillation demonstrated similar trend with the highest risk of death in patients with HR above 90. These results are in contrast with the work of Cullington *et al*. and Mulder *et al*. who reported a better prognosis in HFrEF patients with slower HR and sinus rhythm but not in those with atrial fibrillation.[22,23]

Nevertheless, the aforementioned studies focused on patients with HFrEF in the outpatients setting as opposed to the current study that analysed patients with discharged following ADHF.

Furthermore, the present results remained unchanged following stratification according to the presence of ACS during hospitalization. This finding suggests that the benefit of lowering heart in ADHF is independent of the presence of myocardial ischaemia.

In the current cohort, patients with hypotension at discharge had similar risk of death regardless of the HR at discharge. One explanation is that hypotension reflects their low cardiac output and hypoperfusion; therefore, hypotensive HFrEF patients have poor prognosis regardless of the HR.[24] Yet the sample of this subgroup is statistically underpowered to draw any negative conclusions.

The strength of the current study is the large size of the cohort, inclusion of adults 18 and older, and adjusting to beta-blocker dosage.

Limitations

This is a single-centre retrospective study. Hospital factors and a rather high number of patients who had to be excluded due to incomplete chart record might have influenced the results. The results rely on the accuracy of documentation. Furthermore, the current study assessed the HR and beta-blockers dosage at a single time point; future studies are needed to explore serial HR measurements following discharge. Although adjustments were made for possible confounders such as demographic, comorbid conditions, haemodynamic, and laboratory variables, yet several important variables were unavailable such as New York Heart Association classification, brain natriuretic peptide, and physiological variables (cardiac output, pulmonary capillary wedge pressure, and systemic and pulmonary vascular resistance).

Conclusions

In patients with HFrEF and ADHF, lower HR at discharge can predict a better prognosis regardless of beta-blockers dosage. Therefore, HR at discharge may be a simple measurement to assist in identifying high-risk ADHF patients. Further multi-centre trails are needed to explore the benefit of HR reduction in the heterogeneous clinical presentations of ADHF.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200.
2. Allen LA, O'Connor CM. Management of acute decompensated heart failure. *Cmaj* 2007; **176**: 797–805.
3. Park JJ, Park HA, Cho HJ, Lee HY, Kim KH, Yoo BS, Kang SM, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ. β-Blockers and 1-year postdischarge mortality for heart failure and reduced ejection fraction and slow discharge heart rate. *J Am Heart Assoc* 2019; **8**: e011121.
4. Vollmert T, Hellmich M, Gassanov N, Er F, Yücel S, Erdmann E, Caglayan E. Heart rate at discharge in patients with acute decompensated heart failure is a predictor of mortality. *Eur J Med Res* 2020; **25**: 47.
5. Levine HJ. Rest heart rate and life expectancy. *J. Am. Coll. Cardiol.* 1997; **30**: 1104–1106.
6. Greene SJ, Vaduganathan M, Wilcox JE, Harinstein ME, Maggioni AP, Subacius H, Zannad F, Konstam MA, Chioncel O, Yancy CW, Swedberg K, Butler J, Bonow RO, Gheorghiade M. The prognostic significance of heart rate in patients hospitalized for heart failure with reduced ejection fraction in sinus rhythm. Insights from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial. *JACC Hear Fail* 2013; **1**: 488–496.
7. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. Resting heart rate in cardiovascular disease. *J. Am. Coll. Cardiol.* 2007; **50**: 823–830.
8. Jensen MT, Kaiser C, Sandsten KE, Alber H, Wanitschek M, Iversen A, Jensen JS, Pedersen S, Soerensen R, Rickli H, Zurek M, Fahrni G, Bertel O, de Servi S, Erne P, Pfisterer M, Galatius S. Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes—results from the BASKET PROVE trial. *Int J Cardiol* 2013; **168**: 3802–3806.
9. Alapati V, Tang F, Charlap E, Chan PS, Heidenreich PA, Jones PG, Spertus JA, Srinivas V, Kizer JR. Discharge heart rate after hospitalization for myocardial infarction and long-term mortality in 2 US registries. *J Am Heart Assoc* 2019; **8**: e010855.
10. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; **376**: 875–885.
11. Swedberg K, Komajda M, Böhm M, Borer J, Robertson M, Tavazzi L, Ford I. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: Is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I f inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012; **59**: 1938–1945.
12. Laskey WK, Alomari I, Cox M, Schulte PJ, Zhao X, Hernandez AF, Heidenreich PA, Eapen ZJ, Yancy C, Bhatt DL, Fonarow GC. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. *J Am Heart Assoc* 2015; **4**: e001626.
13. Benaim AR, Almog R, Gorelik Y, Hochberg I, Nassar L, Mashiach T, Khamaisi M, Lurie Y, Azzam ZS, Khoury J, Kurnik D, Beyar R. Analyzing medical research results based on synthetic data and their relation to real data results: systematic comparison from five observational studies. *JMIR Med Informatics* 2020; **8**: e16492.
14. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. *Bone Marrow Transplant* 2020; **55**: 675–680.
15. Castagno D, Skali H, Takeuchi M, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pfeffer MA, McMurray JJV, Solomon SD. Association of heart rate

and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. *J Am Coll Cardiol* 2012; **59**: 1785–1795.
16. Rao K, Fisher ML, Robinson S, Shorofsky S, Gottlieb SS. Effect of chronic changes in heart rate on congestive heart failure. *J Card Fail* 2007; **13**: 269–274.
17. Sarraf M, Francis GS. It is all about heart rate. Or is it? *J. Am. Coll. Cardiol.* 2012; **59**: 1946–1947.
18. Hjalmarson Å. Significance of reduction in heart rate in cardiovascular disease. *Clin Cardiol* 1998; **21**: II3–II7.
19. Maurer MS, Sackner-Bernstein JD, Yushak LEKRM, Rumbarger LEK, Yushak M, King DL, Burkhoff D. Mechanisms underlying improvements in ejection fraction with carvedilol in heart failure. *Circ Hear Fail* 2009; **2**: 189–196.
20. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017; **38**: 1883–1890.
21. Corletto A, Fröhlich H, Täger T, Hochadel M, Zahn R, Kilkowski C, Winkler R, Senges J, Katus HA, Frankenstein L. Beta blockers and chronic heart failure patients: prognostic impact of a dose targeted beta blocker therapy vs. heart rate targeted strategy. *Clin Res Cardiol* 2018; **107**: 1040–1049.
22. Cullington D, Goode KM, Zhang J, Cleland JGF, Clark AL, Rosa AB, Domingo PF, Francisco GS, Juan DJ, Rafael VP, Inés GO, Andreu FG, Jesús ÁG, Fernando WD, Jesús S, María Generosa CL, Juan CC, Francisco FA, Jose Ramón GJ, Cullington D, Goode KM, Zhang J, Cleland JGF, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? *IJC Hear Vasc* 2014; **2**: 213–220.
23. Mulder BA, Damman K, van Veldhuisen DJ, van Gelder IC, Rienstra M. Heart rate and outcome in heart failure with reduced ejection fraction: differences between atrial fibrillation and sinus rhythm—a CIBIS II analysis. *Clin Cardiol Wiley-Blackwell* 2017; **40**: 740–745.
24. Patel PA, Heizer G, O'Connor CM, Schulte PJ, Dickstein K, Ezekowitz JA, Armstrong PW, Hasselblad V, Mills RM, McMurray JJV, Starling RC, Tang WHW, Califf RM, Hernandez AF. Hypotension during hospitalization for acute heart failure is independently associated with 30-day mortality findings from ASCEND-HF. *Circ Hear Fail* 2014; **7**: 918–925.