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RESEARCH ARTICLE

Associations between baseline heart rate and blood pressure and time to events in heart failure with reduced ejection fraction patients: Data from the QUALIFY international registry

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Aims A high resting heart rate (RHR) and low systolic blood pressure (SBP) are a risk factor and a risk indicator, respectively, for poor heart failure (HF) outcomes. This analysis evaluated the associations between baseline RHR and SBP with outcomes and treatment patterns in patients with HF and reduced ejection fraction (HFrEF) in the QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) international registry.

Methods and results Between September 2013 and December 2014, 7317 HFrEF patients with a previous HF hospitalization within 1–15 months were enrolled in the QUALIFY registry. Complete follow-up data were available for 5138 patients. The relationships between RHR and SBP and outcomes were assessed using a Cox proportional hazards model and were analysed according to baseline values as high RHR (H-RHR) ≥75 bpm versus low RHR (L-RHR) <75 bpm and high SBP (H-SBP) ≥110 mmHg versus low SBP (L-SBP) <110 mmHg and analysed according to each of the following four phenotypes: H-RHR/L-SBP, L-RHR/L-SBP, H-RHR/H-SBP and L-RHR/H-SBP (reference group). Compared to the reference group, H-RHR/L-SBP was associated with the worst outcomes for the combined primary endpoint of cardiovascular death and HF hospitalization (hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.51–2.21, $p < 0.001$), cardiovascular death (HR 2.70, 95% CI 1.69–4.33, $p < 0.001$), and HF hospitalization (HR 1.62, 95% CI 1.30–2.01, $p < 0.001$). Low-risk patients with L-RHR/H-SBP achieved more frequently ≥50% of target doses of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers (BBs) than the other groups. However, 48% and 46% of low-risk patients were not well treated with ACEIs and BBs, respectively (≤50% of target dose or no treatment).

Conclusion In patients with HFrEF and recent hospitalization, elevated RHR and lower SBP identify patients at increased risk for cardiovascular endpoints. While SBP and RHR are often recognized as barriers that deter physicians from treating with high doses of recommended drugs, they are not the only reason leaving many patients suboptimally treated.

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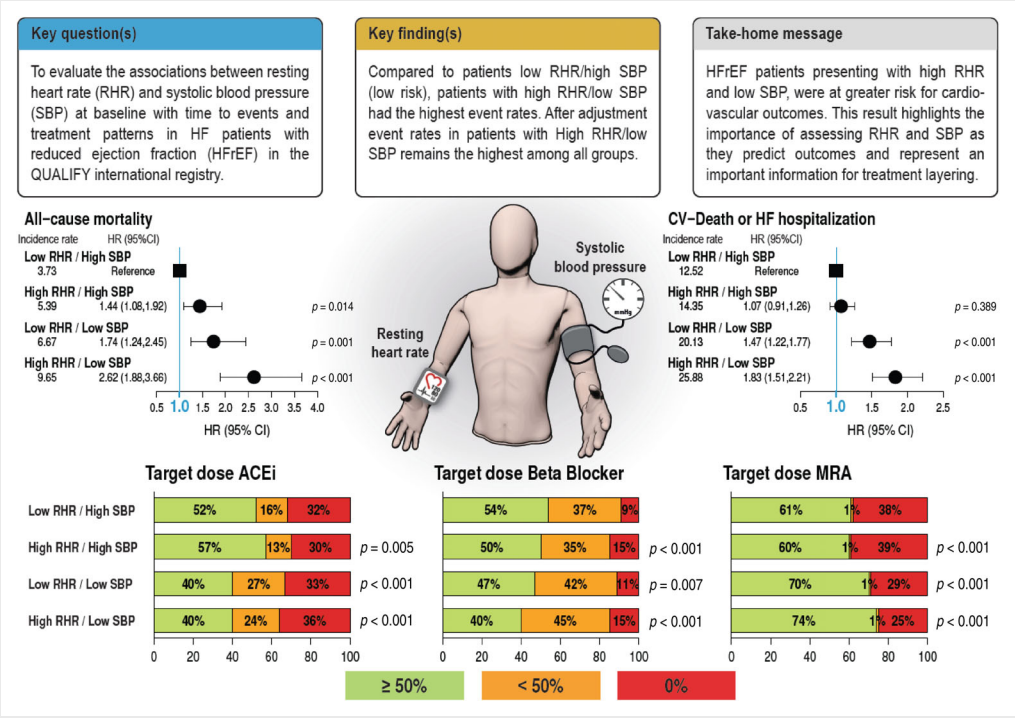
Graphical Abstract



Associations between baseline heart rate and blood pressure and time to events in HFrEF patients: summary of the key findings. ACEi, angiotensin-converting-enzyme inhibitor; BB, beta-blocker; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RHR, resting heart rate; SBP, systolic blood pressure.

Keywords Heart failure • Resting heart rate • Systolic blood pressure • Outcome • Treatment

Introduction

Heart failure (HF) is a global health problem and is the leading cause of hospitalization among elderly patients.[1] Systolic blood pressure (SBP) and resting heart rate (RHR) are strong predictors of cardiovascular (CV) mortality and morbidity in patients with HF and reduced ejection fraction (HFrEF).[2–4] In the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT),[5] a higher RHR (>70 bpm) in sinus rhythm was directly associated with an increased risk of CV death and HF hospitalization. While high SBP is an important risk factor for developing HF that is effectively ameliorated by antihypertensive treatment,[6–8] low SBP is associated with an increased risk of CV death and hospitalization for HF,[9] as well as in-hospital and post-discharge morbidity and mortality.[9,10] Accordingly, the assessment of SBP and RHR in HF patients, and their interactions, carry important clinical value in the assessment of HF patients and could predict tolerability of drugs.[11] The current HF guidelines from the European Society of Cardiology (ESC)[12] and the American Heart Association/American College of Cardiology[13] strongly recommend the rapid establishment of outcome-modifying therapies in HFrEF patients. Low SBP and low RHR frequently prevent physicians from initiating and up-titrating HF therapies.[14–16] Consequently, SBP and RHR have been introduced for patient 'profiling' supporting more personalized treatment sequencing during the initiation phase.[14,15]

We aimed to evaluate the associations between RHR and SBP at baseline and outcomes in addition to treatment patterns in patients with HFrEF in a global, prospective, observational, longitudinal registry. This analysis was performed in patients enrolled in the QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) registry.

Methods

QUALIFY is a global, prospective, observational, longitudinal survey of outpatients with chronic HFrEF with previous HF hospitalization (minimum of one overnight stay) within one to 15 months prior to enrolment.[17] QUALIFY was established to address the need for a long-term, global perspective on physician adherence to five classes of medications recommended for HFrEF management in the 2012 ESC guidelines: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), beta-blockers (BBs), mineralocorticoid receptor

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Table 1 Baseline characteristics by resting heart rate and systolic blood pressure profiles

	H-RHR/L-SBP	L-RHR/L-SBP	H-RHR/H-SBP	L-RHR/H-SBP
Age (years)	61.50 (19.00)*	65.00 (19.00)*	63.50 (17.00)*	66.50 (16.00)
Male sex	485 (77.5%)	594 (77.0%)	1344 (71.9%)	1387 (74.1%)
LVEF (%)	30.00 (10.00)*	30.00 (10.00)*	35.00 (9.00)	34.40 (10.00)
Systolic BP (mmHg)	105.00 (10.00)*	105.00 (10.00)*	135.00 (28.75)*	130.00 (20.00)
Diastolic BP (mmHg)	68.00 (10.00)*	65.00 (10.00)*	80.00 (15.00)*	80.00 (10.00)
RHR (bpm)	83.00 (12.00)*	65.00 (10.00)*	85.00 (13.00)*	66.00 (10.00)
Body mass index (kg/m^2)	26.45 (6.09)*	26.34 (5.49)*	28.73 (6.82)*	27.78 (6.10)*
Haemoglobin (g/L)	134.00 (27.25)	133.71 (26.00)	136.00 (27.00)*	134.00 (24.00)
Sodium (mmol/L)	139.00 (5.00)*	139.00 (5.00)*	139.00 (5.00)*	140.00 (5.00)
Potassium (mmol/L)	4.30 (0.74)	4.40 (0.60)	4.30 (0.70)	4.40 (0.78)
NT-proBNP (pmol/L)	382.44 (566.52)*	317.07 (576.84)*	298.21 (487.84)*	242.37 (389.52)
eGFR (ml/min/1,73 m^2)	65.92 (34.18)*	63.30 (36.59)*	66.19 (31.43)*	65.15 (33.82)
Total cholesterol (mmol/L)	4.26 (1.79)	4.14 (1.60)	4.92 (1.80)	4.50 (1.64)
Fasting glucose (mmol/L)	5.60 (1.76)	5.60 (1.60)	6.00 (2.54)	5.90 (2.07)
NYHA class				
I	47 (7.5%)*	93 (12.1%)*	171 (9.1%)*	303 (16.2%)*
II	280 (44.7%)	408 (52.9%)	790 (42.2%)	975 (52.1%)
III	269 (43.0%)	247 (32.0%)	799 (42.7%)	550 (29.4%)
IV	29 (4.6%)	22 (2.9%)	108 (5.8%)	37 (2.0%)
Coronary artery disease	339 (54.2%)*	448 (58.1%)*	1051 (56.2%)*	1182 (63.2%)
Hypertension	300 (47.9%)	368 (47.7%)	1418 (75.8%)	1388 (74.2%)
Diabetes mellitus	186 (29.7%)*	231 (30.0%)*	759 (40.6%)*	683 (36.5%)
Atrial fibrillation	223 (35.6%)	245 (31.8%)	601 (32.1%)	510 (27.3%)
Chronic kidney disease	121 (19.3%)	183 (23.7%)	331 (17.7%)*	394 (21.1%)
COPD	91 (14.5%)	99 (12.8%)	241 (12.9%)	233 (12.5%)
Myocardial infarction	277 (44.2%)	395 (51.2%)	849 (45.4%)*	999 (53.4%)
Peripheral artery disease	56 (8.9%)	61 (7.9%)*	197 (10.5%)	211 (11.3%)

Values are given as mean ± standard deviation, or *n* (%).
BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; H-RHR, high resting heart rate (≥75 bpm); H-SBP, high systolic blood pressure (>110 mmHg); L-RHR, low resting heart rate (<75 bpm); L-SBP, low systolic blood pressure (≤110 mmHg); LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RHR, resting heart rate.
*Statistically significant ($p < 0.05$) compared with L-RHR/H-SBP.

antagonists (MRAs) and ivabradine. Patients who were hospitalized for CV disease with in the 4 weeks before screening, or those for whom revascularization was planned, or those who were on a waiting list for heart transplantation or planned implantation of left ventricular assist device, and patients with conditions expected to hamper participation or 18-month follow-up (limited cooperation, limited legal capacity, any conditions with life expectancy less than 2 years, or recent valve intervention [<3 months]), or scheduled valve repair or replacement, were excluded from the survey.

Large patients population were recruited in Europe, the Middle East, Asia, Australia, and the Americas. Previous reports have presented baseline characteristics and guideline adherence scores (good, moderate, and poor) for the study population at enrolment,[17–20] and shown the beneficial impact of physicians' adherence to target doses of five guideline-recommended classes of HF medication on clinical outcomes. Data were collected from September 2013 through December 2014, with 7317 patients enrolled and fulfilling the inclusion criteria. Follow-up examinations were conducted at 6, 12, and 18 months after baseline. For this analysis, we investigated the relationship between RHR and SBP at baseline and clinical outcomes. The primary endpoint was a combined endpoint of CV death and hospitalization attributable to HF at 18 months of follow-up. We assessed also separately the component of the primary endpoint, and all-cause mortality at 18 months of follow-up. Events were reported by investigators and, as in many observational studies, there was no central adjudication of events, but formal guidance and training were provided to investigators to correctly classify the clinical outcomes of interest.

The relationship between RHR and SBP on outcomes were analysed according to each of the following four phenotypes:

- Low RHR/high SBP (L-RHR/H-SBP) defined as RHR <75 bpm and SBP ≥110 mmHg (reference group).
- High RHR/high SBP (H-RHR/H-SBP) defined as RHR ≥75 bpm and SBP ≥110 mmHg.
- Low RHR/low SBP (L-RHR/L-SBP) defined as RHR <75 bpm and SBP <110 mmHg.
- High RHR/low SBP (H-RHR/L-SBP) defined as RHR ≥75 bpm and SBP <110 mmHg.

Systolic blood pressure <110 mmHg was chosen as physicians might be reluctant to use medication at this level. Concerning SBP 110–120 mmHg is a grey zone, but outcomes increase below 110 mmHg in observational studies.[10,21] Concerning RHR, the cut-off for RHR was chosen according to previous literature in patients with

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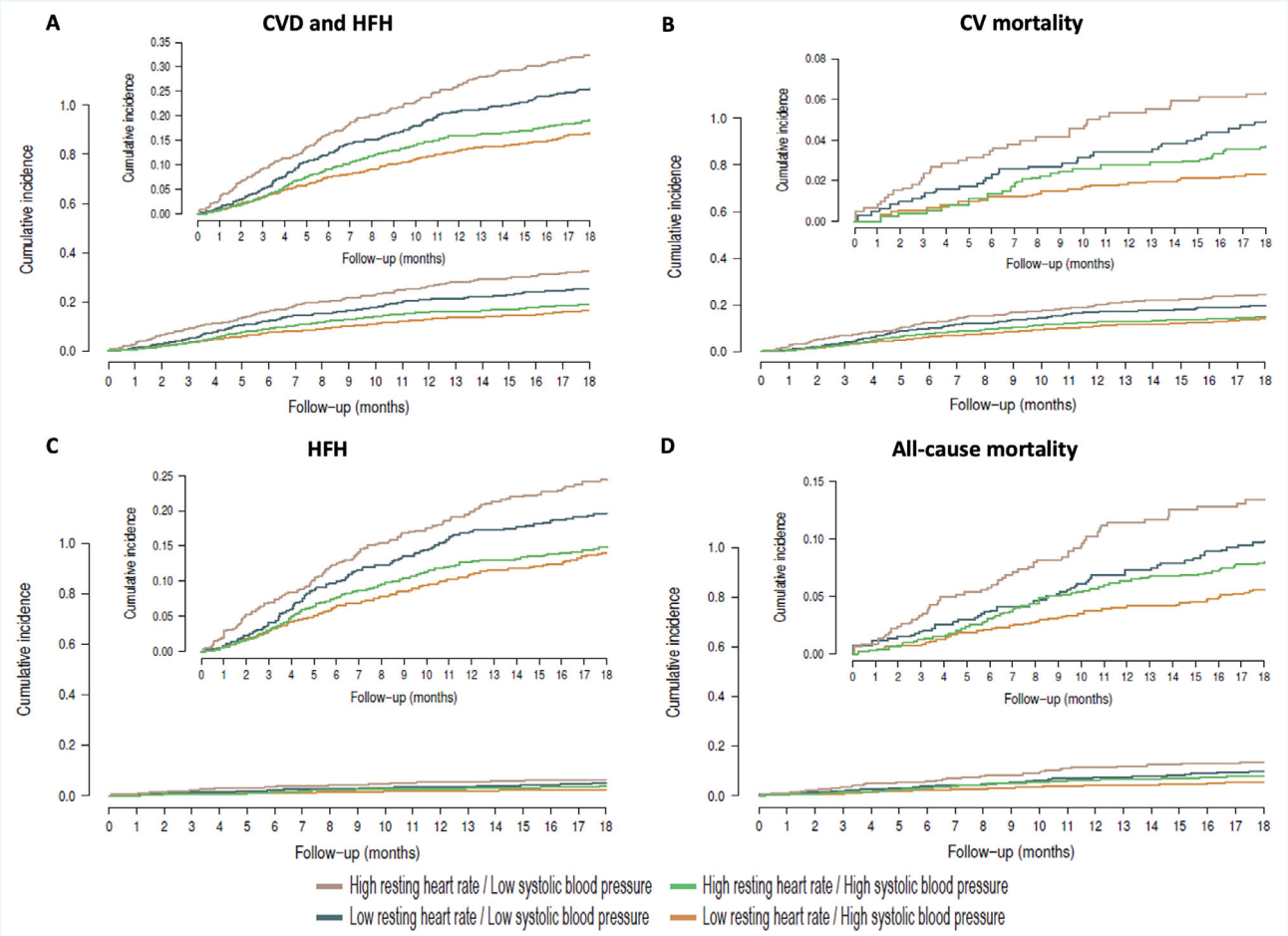

Figure 1 Incidence of the primary endpoint (cardiovascular death [CVD] and heart failure hospitalization [HFH]) and secondary endpoints (cardiovascular [CV] mortality, HFH and all-cause mortality) according to baseline resting heart rate and systolic blood pressure, displayed as time-to-first event.

HFrEF.[2,5,22,23] RHR >70 bpm is the cut-off from where risk for HF hospitalization is increased[5,9,10] while the risk is increased for CV disease at >75 bpm.[23] Therefore, these cut-offs define risk most clearly.

This analysis also examined dosing and subsequent titration to target doses of ACEIs, ARBs, BBs, MRAs, and ivabradine at 18 months according to RHR and SBP at baseline. Target doses were defined according to the ESC guidelines relevant at the time of data collection.

This registry has been approved by the local ethics committee and all patients or their legal representatives gave written informed consent.

Statistical analysis

Study participants without follow-up or incomplete data were excluded from the analysis. Continuous variables are presented as median and interquartile range. Categorical data are presented as counts or proportions with the corresponding percentages. For comparison of continuous variables Student's *t*-test was used; for comparison of categorical variables Fisher's exact test or χ^2 test were used, as appropriate. To study the effect of the relationship between RHR and SBP, and survival outcomes, we used Cox proportional hazards model, adjusted for age, sex, New York Heart Association (NYHA) class, atrial fibrillation (AF) and estimated glomerular filtration rate (eGFR) (threshold at 45 ml/min/1.73 m^2), to estimate hazard ratios (HR) with 95% confidence intervals (CI), respectively. Between-group differences (*p*-values) in adverse events were calculated with a χ^2 or Fisher's exact test, as appropriate. Any *p*-values are two-sided and subject to a local significance level of 5%. For statistical analyses, R version 4.1.2,[24] or SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) was used.

Results

A total of 7317 patients participating in the registry between September 2013 and December 2014 met the eligibility criteria. Complete follow-up data were available from 5138 patients (online supplementary *Figure S1*). The mean follow-up time was 17.48 ± 9.71 months. The baseline characteristics of patients according to baseline RHR and SBP are presented in *Table 1*. Out of the 5138 included patients, 626 (12.2%) had H-RHR/L-SBP, 771 (15%) had L-RHR/L-SBP, 1870 (36.4%) had H-RHR/H-SBP and 1871 (36.4%) had L-RHR/H-SBP. The majority of baseline characteristics did not vary between the four groups. Patients

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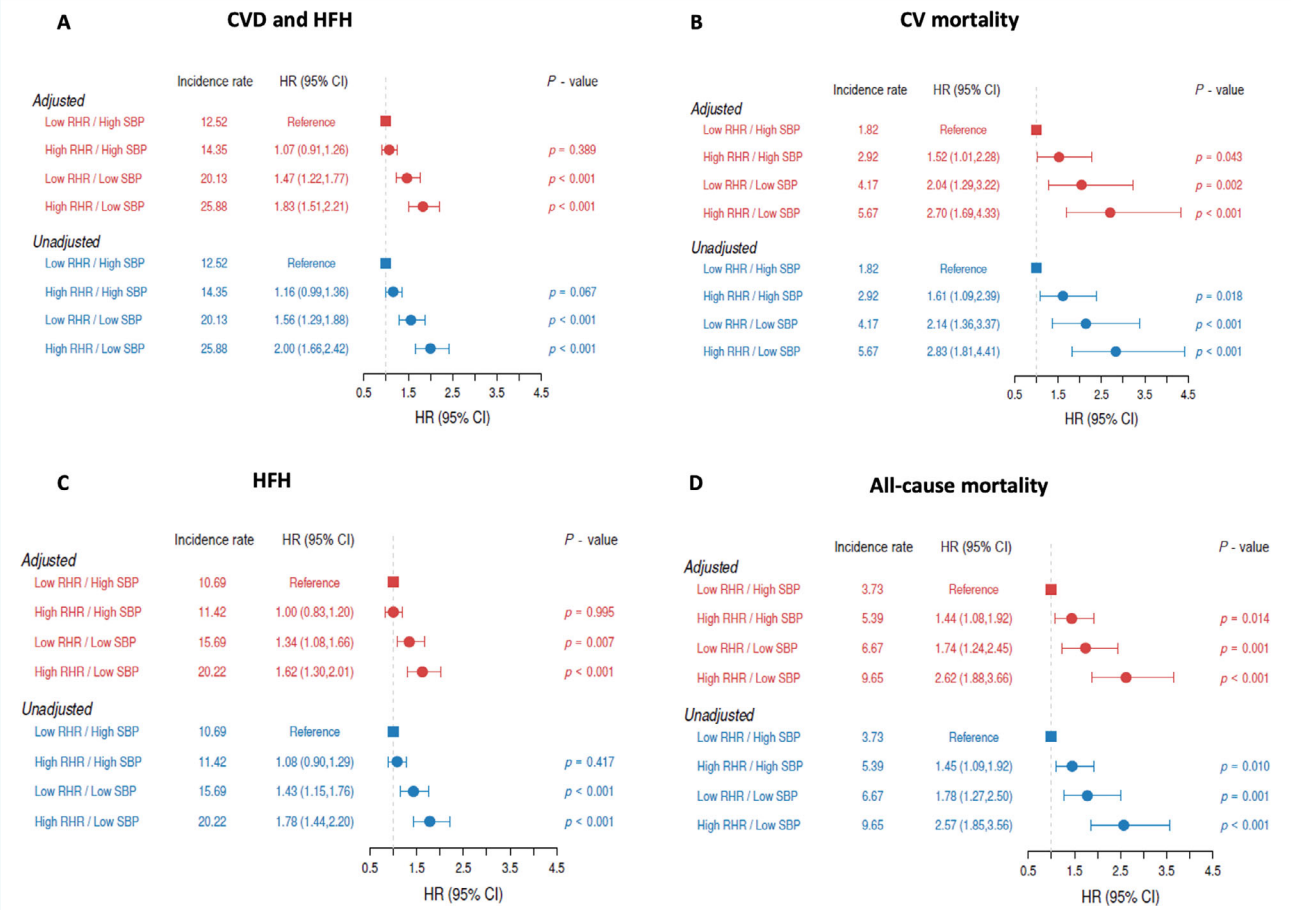

Figure 2 Association between resting heart rate (RHR) and systolic blood pressure (SBP) profiles at baseline and time to events, cardiovascular [CV] mortality and heart failure hospitalization (HFH) before and after adjusting for subject's age, sex, New York Heart Association class, atrial fibrillation, and estimated glomerular filtration rate (threshold at 45 ml/min/1.73 m^2). CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio. *P*-values versus reference group (low RHR/high SBP).

with H-RHR/L-SBP were slightly younger (61.5 ± 19 vs. 66 ± 16, $p < 0.05$) than the reference group, had a higher rate of AF (35.6% vs. 27.3%, $p < 0.05$) and lower rate of coronary artery disease (54.2% vs. 63.2%, $p < 0.05$).

The association between the combined endpoint and RHR/SBP groups is presented in *Figure 1*. Compared to the reference group, patients with H-RHR/L-SBP had the worst outcomes for CV death and HF hospitalization (HR 2.00, 95% CI 1.66–2.42, $p < 0.001$) (*Figure 1A*). After adjustment for age, sex, NYHA class, AF and eGFR, CV death and HF hospitalization in patients with H-RHR/L-SBP remained the highest between all groups (HR 1.83, 95% CI 1.51–2.21 $p < 0.001$), followed by L-RHR/L-SBP (HR 1.47, 95% CI 1.22–1.77 $p < 0.001$) and H-RHR/H-SBP (HR 1.07, 95% CI 0.91–1.26, $p = 0.4$) (*Figure 2*). H-RHR/L-SBP and after adjustment was associated with the worst outcomes for all other endpoints: all-cause mortality (HR 2.62, 95% CI 1.88–3.66, $p < 0.001$), CV mortality (HR 2.70, 95% CI 1.69–4.33, $p < 0.001$), and HF hospitalization (HR 1.62, 95% CI 1.30–2.01, $p < 0.001$) (*Figure 1B–D*).

Compared to patients with L-RHR/H-SBP (low-risk), the percentage of patients with H-RHR/L-SBP (high-risk) who achieved high treatment intensity (≥50% of the target dose of ACEIs, ARBs, or BBs) was significantly lower (40.3% vs. 51.2%, $p < 0.001$; 6% vs. 13%, $p < 0.001$%; and 40.7% vs. 53.3%, $p < 0.001$, respectively) (*Table 2*). Additionally, 48%, 87%, and 46% of L-RHR/H-SBP patients were not treated at all or treated with <50% of the target dose for ACEIs, ARBs and BBs, respectively. For MRAs and ivabradine, patients with H-RHR/L-SBP who achieved ≥50% of the target dose were significantly higher (74.2% vs. 61.8%, $p < 0.001$%, and 36.3% vs. 26.3%, $p < 0.001$, respectively) (*Table 2*, *Figure 3*).

Discussion

Our data show that for a large population of patients with HFrEF who were previously hospitalized for HF, patients with high RHR ≥75 bpm and low SBP <110 mmHg are at greater risk of CV death and HF hospitalizations, followed by L-RHR/L-SBP and H-RHR/H-SBP. This real-word data analysis also showed that H-RHR/L-SBP patients (high-risk) were undertreated with HF medications; and even L-RHR/H-SBP patients (low-risk) showed poor

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Table 2 Target dose of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and ivabradine by resting heart rate and systolic blood pressure profiles at baseline

	≥50%	<50%	0%	*p*-value vs. reference group
Angiotensin-converting enzyme inhibitors				
L-RHR/H-SBP	956 (51.2%)	299 (16%)	613 (32.8%)	Reference group
H-RHR/H-SBP	1053 (56.3%)	254 (13.6%)	563 (30.1%)	0.005
L-RHR/L-SBP	309 (40.1%)	201 (26.1%)	261 (33.9%)	<0.001
H-RHR/L-SBP	252 (40.3%)	152 (24.3%)	221 (35.4%)	<0.001
Angiotensin receptor blockers				
L-RHR/H-SBP	234 (12.6%)	203 (10.9%)	1427 (76.6%)	Reference group
H-RHR/H-SBP	208 (11.2%)	189 (10.2%)	1465 (87.7%)	0.81
L-RHR/L-SBP	61 (8.9%)	90 (11.7%)	620 (79.4%)	<0.001
H-RHR/L-SBP	38 (6.1%)	69 (11.1%)	517 (82.9%)	<0.001
Beta-blockers				
L-RHR/H-SBP	990 (53.3%)	685 (37%)	174 (9.4%)	Reference group
H-RHR/H-SBP	934 (50.5%)	635 (34.3%)	279 (15.1%)	<0.001
L-RHR/L-SBP	359 (46.9%)	328 (42.9%)	78 (10.2%)	0.007
H-RHR/L-SBP	253 (40.7%)	282 (45.3%)	87 (14%)	<0.001
Mineralocorticoid receptor antagonists				
L-RHR/H-SBP	1155 (61.8%)	11 (0.6%)	704 (37.6%)	Reference group
H-RHR/H-SBP	1305 (59.8%)	3 (0.2%)	562 (30.1%)	<0.001
L-RHR/L-SBP	544 (70.6%)	9 (1.2%)	218 (28.3%)	<0.001
H-RHR/L-SBP	463 (74.2%)	3 (0.5%)	158 (25.3%)	<0.001
Ivabradine				
L-RHR/H-SBP	481 (26.3%)	6 (0.3%)	1339 (73.3%)	Reference group
H-RHR/H-SBP	717 (38.6%)	8 (0.4%)	1131 (60.9%)	<0.001
L-RHR/L-SBP	197 (26.5%)	1 (0.1%)	545 (73.4%)	0.083
H-RHR/L-SBP	221 (36.3%)	1 (0.2%)	386 (63.5%)	<0.001

H-RHR, high resting heart rate (≥75 bpm); H-SBP, high systolic blood pressure (>110 mmHg); L-RHR, low resting heart rate (<75 bpm); L-SBP, low systolic blood pressure (≤110 mmHg).

implementation of HF drug therapy, with approximately 50% of these patients still receiving suboptimal doses of HF treatments (*Graphical Abstract*).

Patients with HFrEF and low SBP at baseline are at particularly high risk for adverse CV outcomes.[7,9,21,25] In addition, low SBP represents an important clinical situation that prevents physicians from using and titrating HF therapies in daily clinical practice.[16,20] Elevated RHR in patients with stable HF and sinus rhythm has been associated with adverse outcomes in patients with CV disease.[23,26] RHR is not only a marker for the increased incidence of adverse outcomes, but may also be a modifiable risk factor in patients with HF, and strategies to reduce heart rate improve outcome.[26]

As both low SBP and high RHR independently indicate poor outcomes in HF, their combination places HF patients at significantly higher risk for mortality and morbidity.[27] Initiation of HF treatments can be challenging in high-risk patients, who frequently present with low SBP and high RHR.[14–16] For illustration, renin–angiotensin–aldosterone system inhibitors have been shown to reduce outcomes in a broad population but are often limited in their applicability in the most critically ill patients because of hypotension.[7,18] In the present analysis, approximately 40% of patients with low SBP achieved ≥50% of the target dose of ACEIs and BBs. The results presented here have implications for the management of these patients, as it has been suggested that selective heart rate reduction with ivabradine, which does not affect contractility nor SBP,[27,28] could be used to treat patients with low SBP. This work also showed that in real-world, HFrEF patients are not on all recommended drugs or receive doses that are lower than those tested and achieved in clinical trials. This was shown in our analysis as only about 50% of the low-risk (L-RHR/H-SBP) patients were treated with ACEIs and BBs ≥50% of optimal dosages. This highlight that gap in implementation of guideline-directed medical therapy (GDMT) even in patients with high SBP. Furthermore, although this registry was performed prior to the angiotensin receptor–neprilysin inhibitor and sodium–glucose cotransporter 2 (SGLT2) inhibitor era, our results underscore the importance of GDMT implementation, as now with even more drugs and fast up-titration as recommended by guidelines may make physicians even more reluctant to use intensive drug treatments and may leave many patients on suboptimal treatment. Implementation of medical therapy in patients with HFrEF is often challenging because patient characteristics, including their physiological parameters and comorbidities, limit up-titration of lifesaving medications.[14–16] Patient phenotyping may guide personalized tailoring of drug therapies, whilst using all drug classes to improve outcomes.

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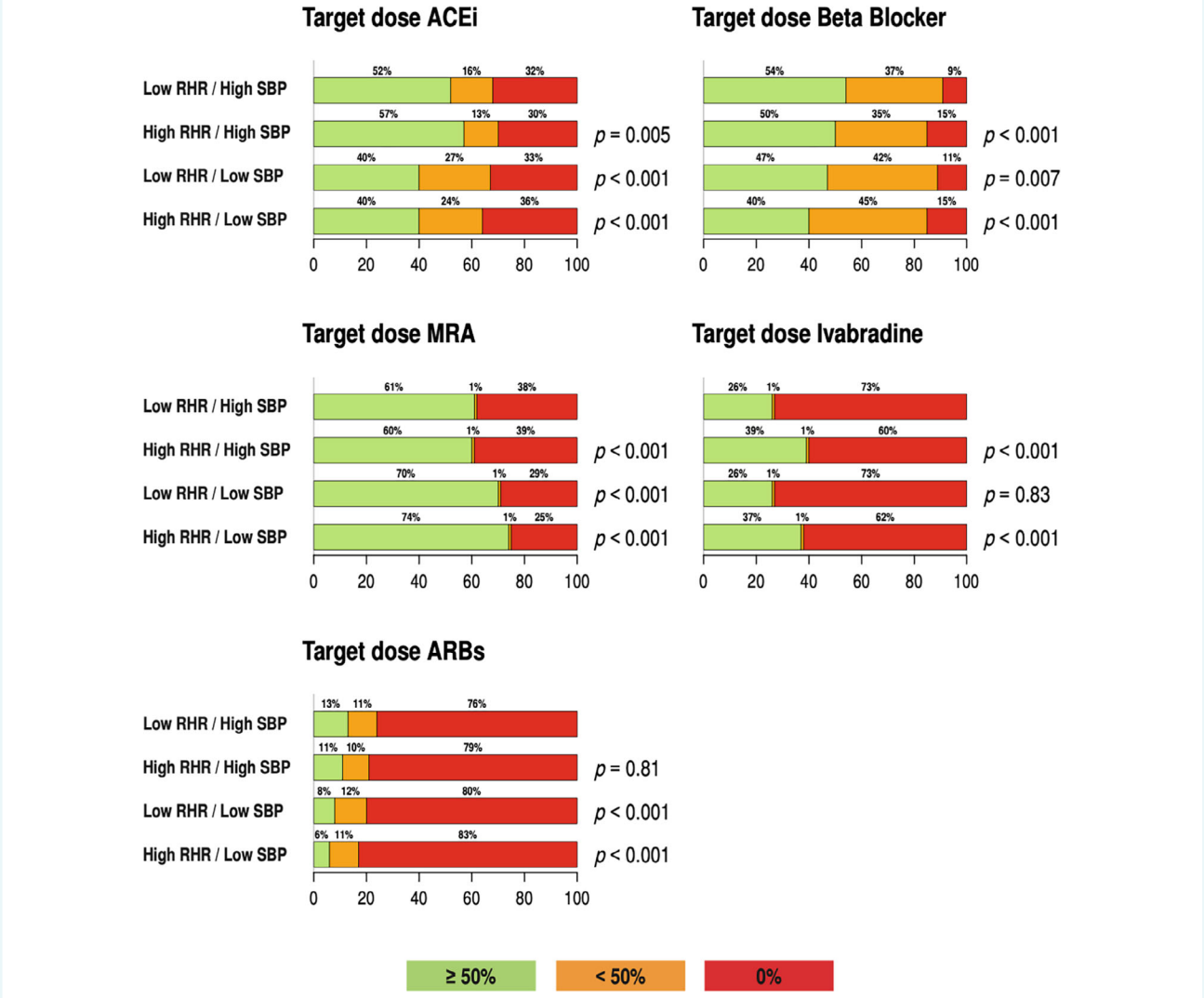

Figure 3 Target dose of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRA) and ivabradine by resting heart rate (RHR) and systolic blood pressure (SBP) profiles at baseline. High RHR is defined as ≥75 bpm, low RHR is defined as <75 bpm, high SBP is defined as >110 mmHg, low SBP is defined as ≤110 mmHg. *P*-values versus reference group (low RHR/high SBP).

Implementation of novel therapies such as SGLT2 inhibitors in HFrEF therapy is generally straightforward due to its favourable tolerability profile and its ease of administration (one dose, without titration). Furthermore, empagliflozin and dapagliflozin were effective and safe, with no significant interaction between SBP and their effects.[21,29]

Despite the large clinical heterogeneity of HFrEF, our data provide relevant clinical information and elucidate the importance of assessing RHR and SBP as simple profiling parameters, as well as the prevalence of the different patient profiles derived from these two parameters, their specific characteristics, and their treatment and outcomes in a large real-world HFrEF population. Furthermore, our results underscore the importance of implementing HF therapy even in patients with high SBP and low RHR, since many patients in our cohort receive suboptimal treatment.

Limitations

First, data obtained from registry and studied groups of RHR and SBP were not subject to randomization. Secondly, at the time the QUALIFY registry was initiated, international HF guidelines did not include a recommendation for angiotensin receptor–neprilysin inhibitor or SGLT2 inhibitor therapies as these drugs were not yet licensed for the treatment of HF and data on their use could not be collected. Out of 7317 patients enrolled in the registry, a total of 5138 (70%) with complete data were included in the present analysis. Patients from China were not included as the sponsor was facing logistical problems regarding data use from China at the time the registry was initiated. Therefore, a non-negligible proportion of patients enrolled in the registry (30%) were excluded from the present analysis. This introduces the risk

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that the analysed population is not fully representative of the entire cohort.

Conclusion

Our analysis shows that HFrEF patients, who presented with high RHR and low SBP, were at greater risk for CV death and HF hospitalization and all-cause mortality. Our result highlights the importance of assessing RHR and SBP in HFrEF patients as they predict outcomes, but additionally such phenotypes make physicians reluctant to use guideline-mandated therapy. Additional support to initiate and safely up-titrate such medications in routine clinical practice is likely to be needed.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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