Supplementary data: cumulative resting heart rate load and cardiovascular risk in patients with heart failure in sinus rhythm

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Appendix A of the supplementary data: supplementary methods

Appendix A1 of the supplementary data: detailed rationale and design of the 5 randomized controlled trials

In the BEST trial, 2708 patients with advanced chronic HF with LVEF ≤ 35% were recruited between 1995 and 1998 in the United States and Canada and were randomly assigned to receive either bucindolol (n = 1354) or placebo (n = 1354) with a mean follow-up of 2.0 years.[1] In the GUIDE-IT trial, 894 HF patients with LVEF ≤ 40% were enrolled in the United States and Canada between January 2013 and July 2016. Patients received either standard therapy or were titrated to achieve a target NT-proBNP level of less than 1000 pg/mL, with a minimum follow-up of 12 months.[2] In the HF-ACTION trial, 2331 medically stable HF outpatients with LVEF ≤ 35% and NYHA class II to IV were randomized to aerobic exercise training or usual care from 2002 to 2007, with 24 months of follow-up. Notably, although HF-ACTION was designed as a trial enrolling patients with HF with reduced EF (HFrEF) based on an LVEF ≤ 35% threshold, a small number of participants with LVEF > 40% were included. As our analysis classified heart failure phenotypes according to the original trial definitions, these participants were still included in the HFrEF group, resulting in a minor discrepancy of 27 patients between the number of patients with LVEF ≤ 40% and those categorized as HFrEF in our pooled cohort.[3] The RELAX trial included 216 stable HF outpatients with LVEF ≥ 50% who were randomized between October 2008 and February 2012 in North America, with a follow-up of 24 weeks.[4] In the TOPCAT trial, a total of 3445 HF patients with LVEF ≥ 45% were randomized to receive spironolactone (n = 1722) or matching

placebo (n = 1723) from 2006 to 2012, with an average follow-up duration of 3.3 years.[5]

Appendix A2 of the supplementary data: selection of the resting heart rate threshold

Several factors informed the selection of the 70 bpm threshold. First, current guidelines recommend a target resting heart rate of <70 bpm in patients with HFrEF to guide heart rate-lowering interventions. For HF with preserved EF (HFpEF), no specific target resting heart rate is recommended in the guidelines.[6,7] Second, our exploratory analysis using restricted cubic spline plots clearly demonstrated a marked increase in the risk of major cardiovascular events when resting heart rate exceeded approximately 70 bpm (**Supplementary figure 2**). Third, previous studies suggested that a baseline resting heart rate threshold around 70 bpm effectively identified high-risk populations for cardiovascular and noncardiovascular death, regardless of LVEF.[8] Based on these considerations, we selected 70 bpm as the threshold for resting heart rate in the primary analysis and 60 bpm and 80 bpm for sensitivity analyses.

Appendix A3 of the supplementary data: sensitivity and subgroup analyses

In the primary analysis, the study was included as a fixed effect. To account for within-trial clustering, we also fitted Cox frailty models with the study as a random effect. In addition, Fine and Gray competing risk models were used to account for competing events.[9] Noncardiovascular death was treated as a competing event for major cardiovascular events and cardiovascular death, whereas all-cause death was considered a competing event for hospitalization outcomes. Subdistribution hazard ratios with 95%CIs were reported.

We conducted a subgroup analysis based on HF type. It is important to emphasize that all subgroup analyses in our study were stratified by HF type (HFrEF or HFpEF) based on the original trial-defined classifications. For the sensitivity analyses, we evaluated different heart rate control targets of 60 bpm and 80 bpm in both the overall population and within HF subgroups.

Appendix B of the supplementary data: Figures and tables

Figure 1 of the supplementary data. Example calculation of cumulative heart rate load in 2 different scenarios
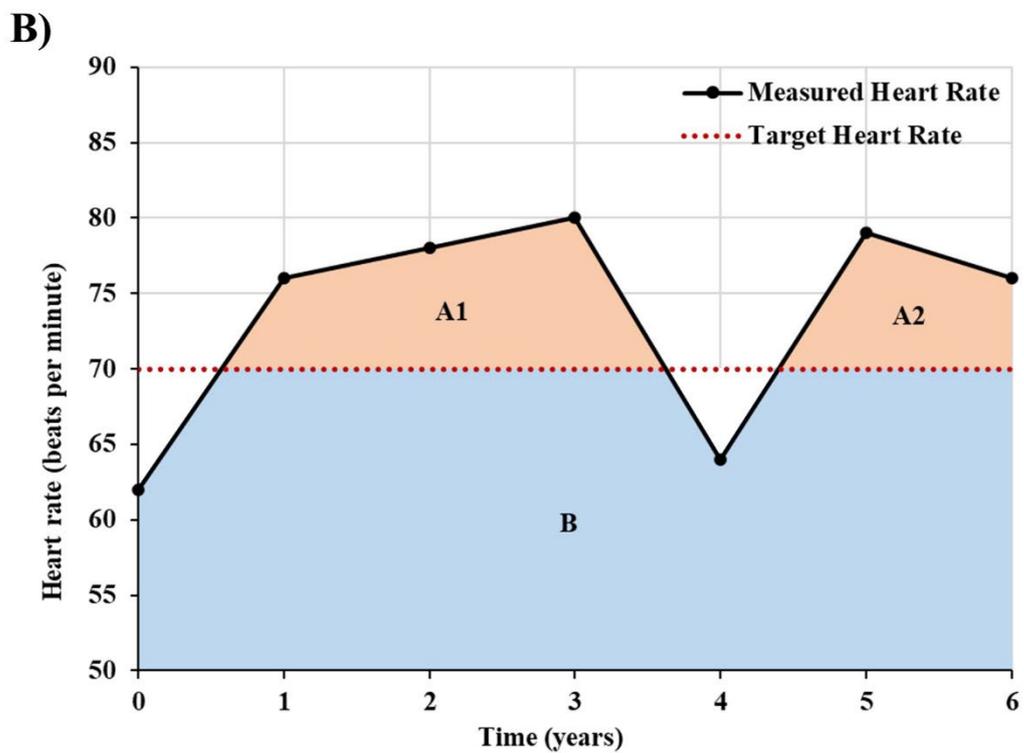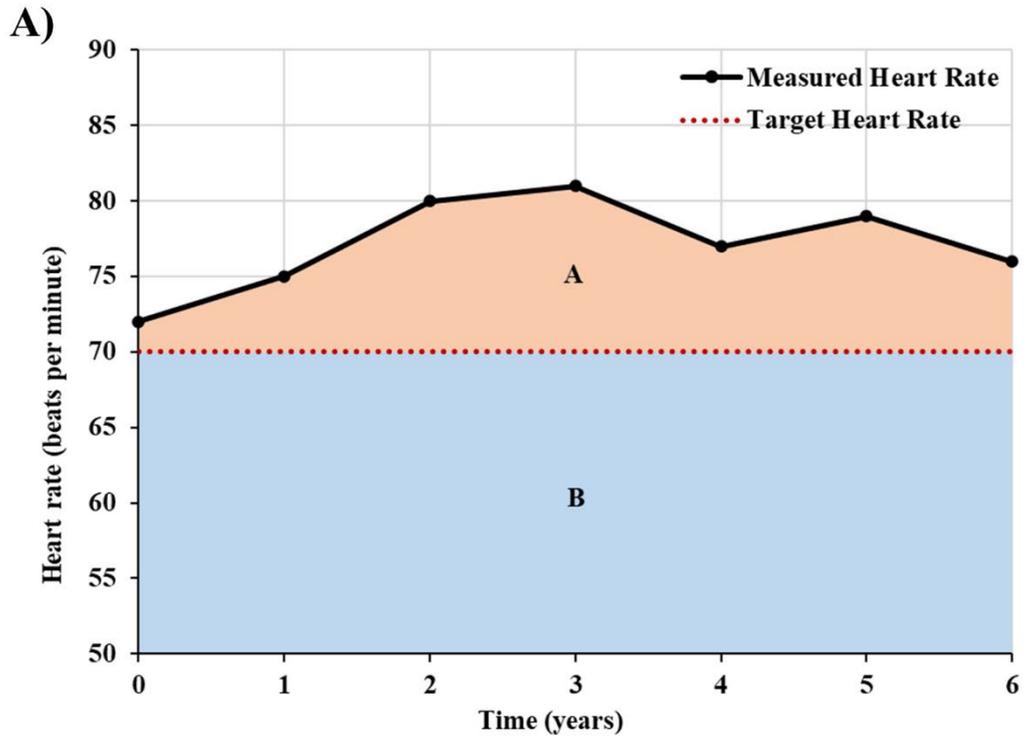
A) Cumulative heart rate load = A / (A + B) * 100%; B) Cumulative heart rate load = (A1+A2) / (A1+A2 + B) * 100%.

Figure 2 of the supplementary data. Association between mean resting heart rate and composite outcome among A) all participants, B) HFrEF, and C) HFpEF.
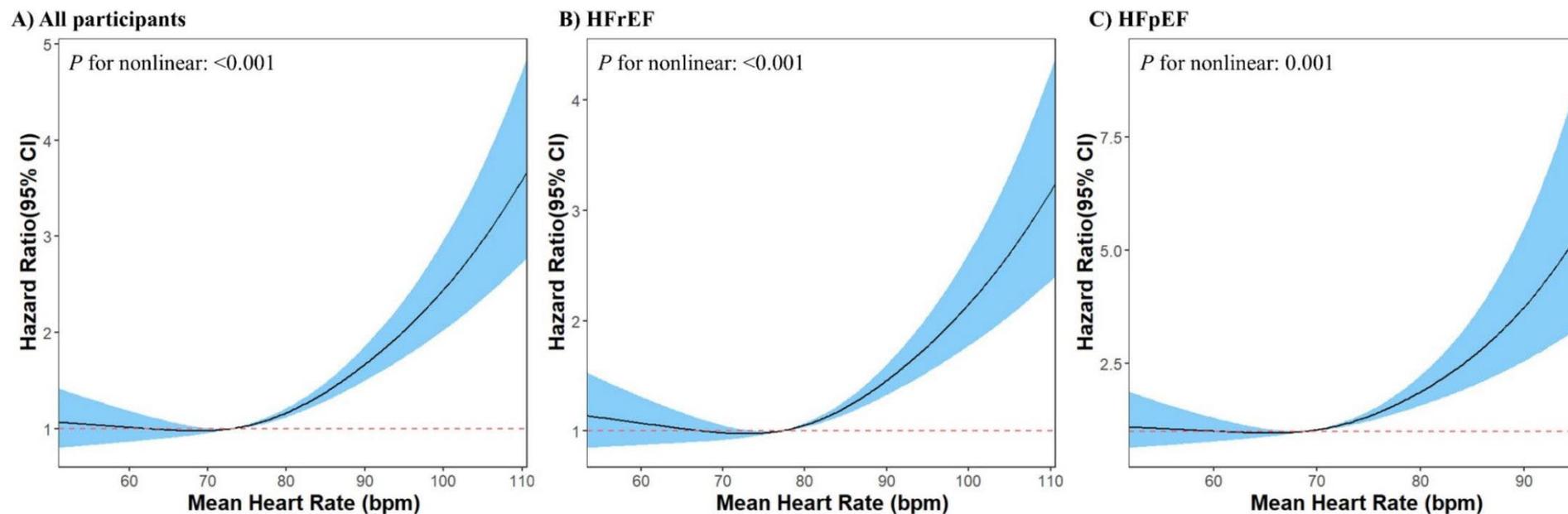
The analyses were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Figure 3 of the supplementary data. Frequency histograms showing the distribution for A) cumulative resting heart rate load, B) resting heart rate time at target, C) mean resting heart rate, D) resting heart rate standard deviation, and E) baseline resting heart rate.
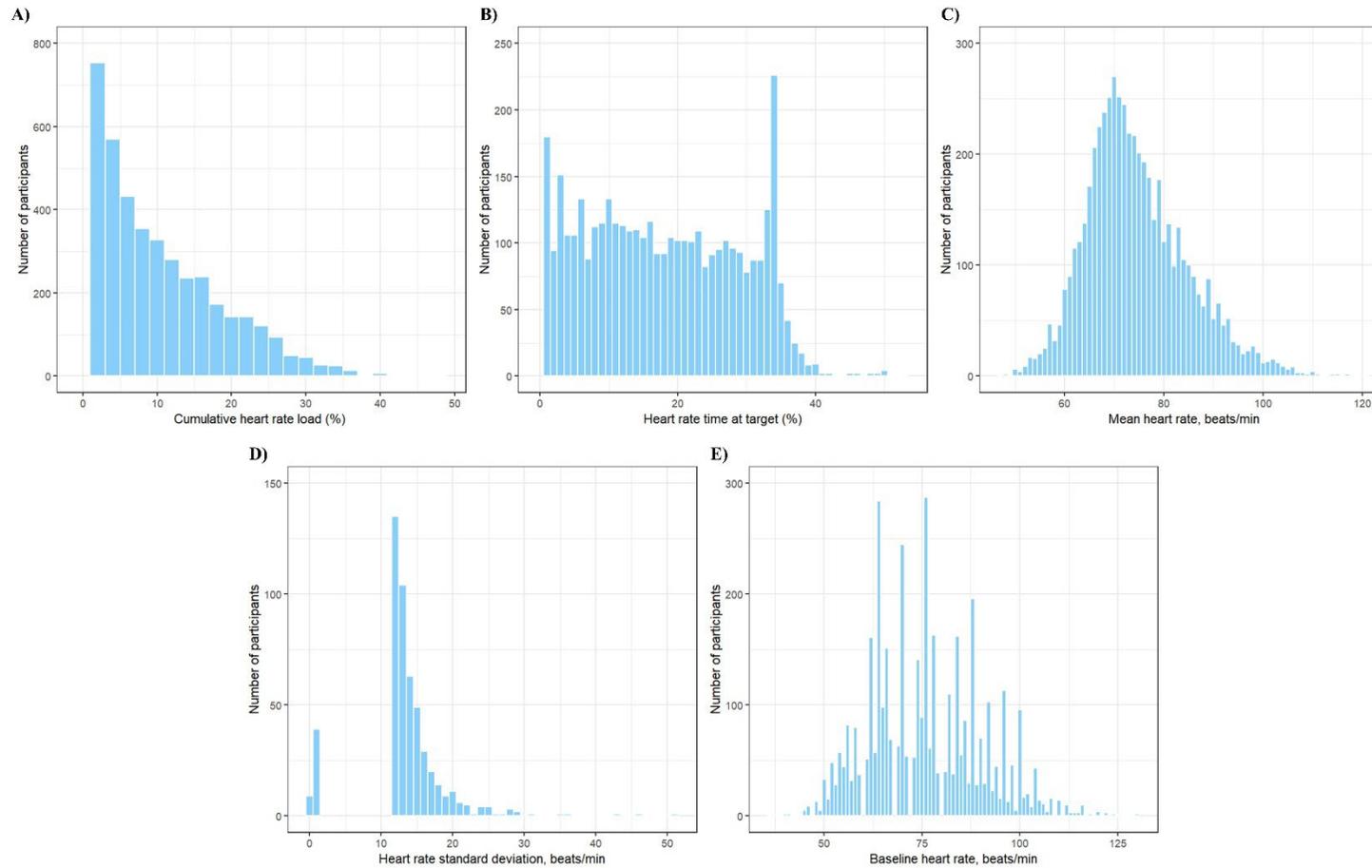
Figure 4 of the supplementary data. Scatterplots showing correlation between A) cumulative resting heart rate load and mean resting heart rate, B) cumulative resting heart rate load with resting heart rate time at target, C) resting heart rate time at target and mean resting heart rate, D) cumulative resting heart rate load and baseline resting heart rate, E) cumulative resting heart rate load and resting heart rate standard deviation, and F) resting heart rate time at target and baseline resting heart rate.
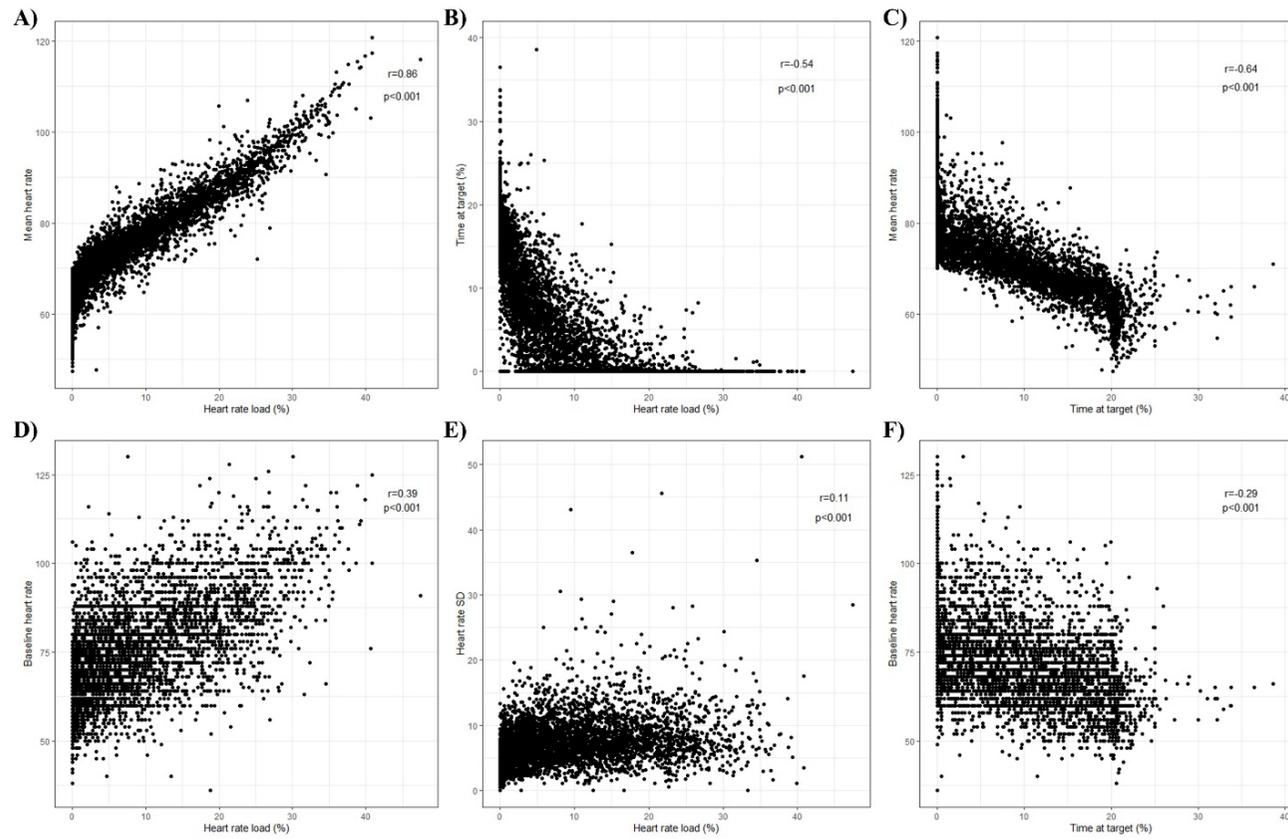
Figure 5 of the supplementary data. Calibration of Cox models comparing observed vs predicted risk of composite outcome at 1 year

Models were adjusted for the study, trial treatment, demographic information (age, sex, race, and body mass index), medical history (myocardial
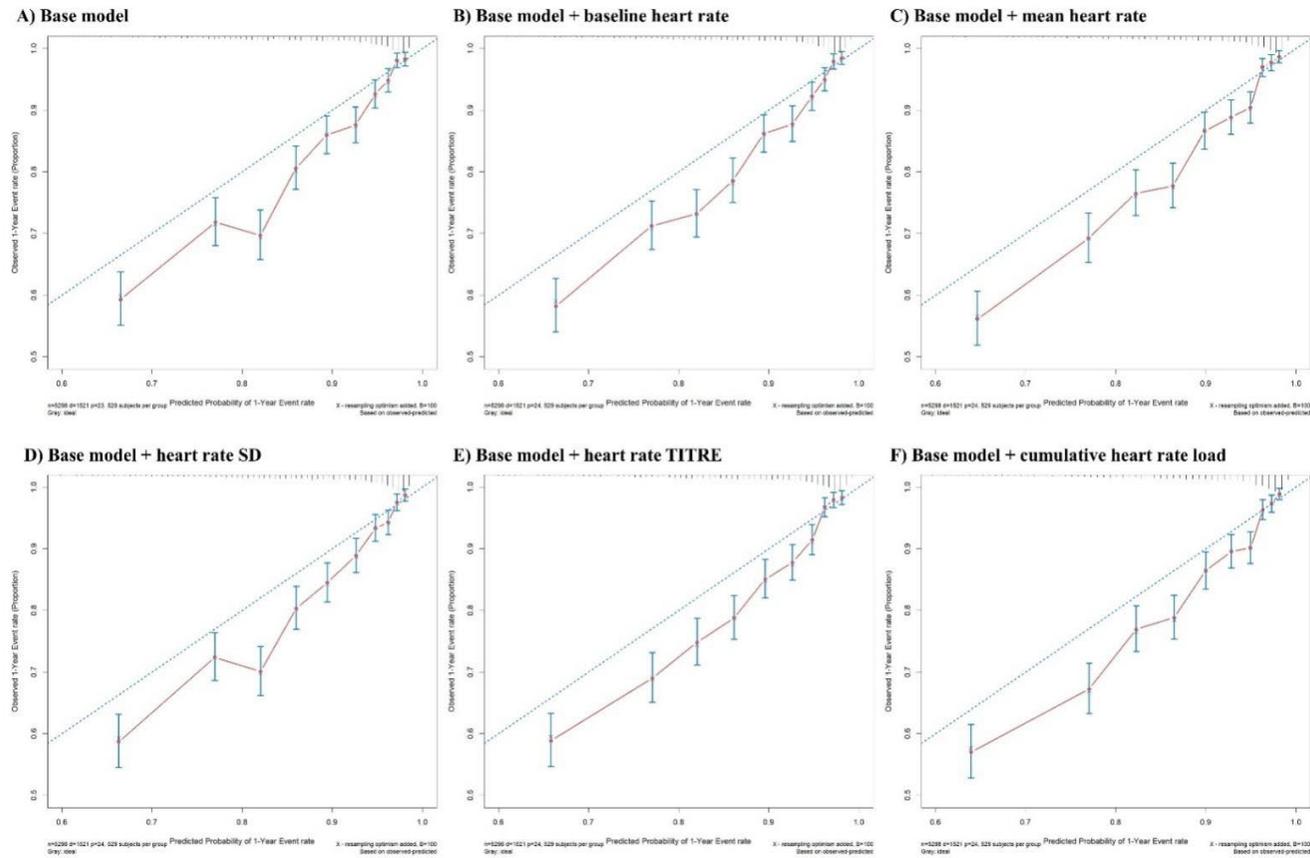
infarction, peripheral vascular disease, hypertension, dyslipidaemia, and diabetes), risk factors (NYHA functional class, current smoking),

creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 1 of the supplementary data. Trial characteristics of the included studies

Characteristics	BEST (1995-1999)		TOPCAT (2006-2012)		GUIDE-IT (2013-2016)		HF-ACTION (2003-2007)		RELAX (2008-2012)	
	Bucindolol	Placebo	Spironolactone	Placebo	NT-proBNP guided	Usual care	Aerobic exercise training	Usual care	Sildenafil	Placebo
No. of participants	1354	1353	1722	1723	446	448	1060	1070	113	103
Study population	HFrEF	HFrEF	HFpEF	HFpEF	HFrEF	HFrEF	HFrEF	HFrEF	HFpEF	HFpEF
LVEF, %	23.03 ± 7.17		57.21 ± 7.42		23.10 ± 8.17		25.39 ± 7.48		61.97 ± 6.24	
NYHA class III or IV	1973/1973 (100)		608/2125 (28.6)		156/442 (35.7)		277/792 (35.0)		47/96 (49.0)	
Follow-up, years	2.08 ± 1.05		3.48 ± 1.60		1.28 ± 0.64		2.59 ± 1.04		0.47 ± 0.06	
Number of heart rate measurements	10.74 ± 3.27		9.91 ± 3.69		6.82 ± 2.65		32.87 ± 11.61		3.90 ± 0.45	

Methods of resting heart rate measurement.	The protocol specified the timing of vital sign measurements at each visit but did not provide details on the method of heart rate assessment.	The protocol indicated that physical examinations, including HR measurement, would follow procedures outlined in the manual of procedures, which was not publicly available.	A physical examination, including vital signs such as heart rate, was performed at each study visit, with heart rate measured in the sitting and resting position.	Resting heart rate was measured after 5 min of quiet seated rest, in accordance with standard clinical practice.	Heart rate was obtained before and immediately after cardiopulmonary exercise testing, with the resting value typically measured in the standing position before the test.
Primary outcome	All-cause mortality	A composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.	A composite of time-to-first HF hospitalization or death from cardiovascular causes.	A composite of all-cause mortality or all-cause hospitalization.	Change in peak VO_2 after 24 weeks of therapy.

| Secondary outcome | Cardiovascular death, any hospitalization, heart failure hospitalization, a composite of death or heart transplantation, myocardial infarction, quality of life and any change in the need for concomitant therapy. | Death from any cause, any hospitalization, hyperkalemia, hypokalemia, an elevated serum creatinine level, and a serum creatinine level of 3.0 mg/dL or higher. | All-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components on the primary endpoint, health related quality of life, resource utilization, costs, cost effectiveness, and safety. | All-cause mortality, the composite of cardiovascular mortality or cardiovascular hospitalization, and the composite of cardiovascular mortality or heart failure hospitalization. | A composite hierarchical-rank clinical score based on time-to-death, time-to-hospitalization for cardiovascular or cardiorenal causes, and change in MLHFQ from baseline for patients alive without cardiovascular or cardiorenal hospitalization after 24 weeks of therapy. |

Unless otherwise indicated, values are expressed as mean ± standard deviation or No. (%).

Table 2 of the supplementary data. Association between cumulative resting heart rate load and clinical outcomes

	Events (No.)	HR (95%CI)	*P*	*P* for trend
Major cardiovascular events				
Q1 (0.00%-0.94%)	264	1 [Reference]		< .001
Q2 (0.94%-4.98%)	309	0.99 (0.84-1.17)	.880	
Q3 (4.99%-12.67%)	389	1.03 (0.88-1.22)	.697	
Q4 (12.68%-47.45%)	582	1.64 (1.39-1.93)	<.001	
Cardiovascular death				
Q1 (0.00%-0.94%)	131	1 [Reference]		< .001
Q2 (0.94%-4.98%)	161	1.01 (0.80-1.27)	.958	
Q3 (4.99%-12.67%)	188	1.06 (0.84-1.35)	.604	
Q4 (12.68%-47.45%)	269	1.57 (1.23-1.99)	<.001	
Hospitalization for heart failure				
Q1 (0.00%-0.94%)	185	1 [Reference]		< .001
Q2 (0.94%-4.98%)	222	1.00 (0.82-1.22)	.989	
Q3 (4.99%-12.67%)	299	1.07 (0.88-1.30)	.503	
Q4 (12.68%-47.45%)	453	1.64 (1.35-1.99)	<.001	
All-cause death				

Q1 (0.00%-0.94%)	192	1 [Reference]		< .001
Q2 (0.94%-4.98%)	205	0.90 (0.74-1.10)	.309	
Q3 (4.99%-12.67%)	246	1.05 (0.86-1.29)	.601	
Q4 (12.68%-47.45%)	325	1.55 (1.26-1.90)	<.001	

Hospitalization for any

reason

Q1 (0.00%-0.94%)	542	1 [Reference]		< .001
Q2 (0.94%-4.98%)	598	1.07 (0.95-1.20)	.291	
Q3 (4.99%-12.67%)	725	1.27 (1.13-1.43)	<.001	
	786	1.46 (1.28-1.65)	<.001	

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 3 of the supplementary data. Adjusted HRs for the association between resting heart rate measures and clinical outcomes using Cox

frailty models with study as a random effect

Outcomes	Events (No.)	Cumulative resting heart rate load		Resting heart rate TITRE		Mean resting heart rate		Resting heart rate SD		Baseline resting heart rate	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Major cardiovascular events	1544	1.31 (1.24-1.38)	< .001	0.93 (0.87-0.99)	.016	1.27 (1.20-1.35)	< .001	0.94 (0.89-1.00)	.055	1.09 (1.02-1.15)	.005
Cardiovascular death	749	1.17 (1.08-1.26)	< .001	0.93 (0.85-1.01)	.095	1.13 (1.04-1.23)	.003	0.99 (0.91-1.07)	.759	1.07 (0.98-1.16)	.110
Hospitalization for heart failure	1159	1.34 (1.26-1.43)	< .001	0.93 (0.86-1.00)	.040	1.31 (1.22-1.40)	< .001	0.96 (0.89-1.03)	.209	1.09 (1.02-1.17)	.010
All-cause death	968	1.20 (1.12-1.29)	< .001	0.94 (0.88-1.02)	.136	1.18 (1.09-1.27)	< .001	1.01 (0.94-1.09)	.776	1.10 (1.02-1.18)	.015
Hospitalization for any reason	2651	1.20 (1.15-1.25)	< .001	0.95 (0.91-0.99)	.016	1.17 (1.12-1.23)	< .001	1.10 (1.06-1.14)	< .001	1.06 (1.01-1.11)	.017

HR, hazard ratio; TITRE, time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load =

8.31%. A 1 SD increase in resting heart rate TITRE = 7.51%. A 1 SD increase in mean resting heart rate = 10.18 bpm. A 1 SD increase in resting heart rate SD = 3.54 bpm. A 1 SD increase in baseline

resting heart rate = 13.36 bpm.

Models were adjusted for trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidaemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretic use, pacemaker, implantable cardioverter-defibrillator, and with study as a random effect.

Table 4 of the supplementary data. Subdistribution HRs for the association between resting heart rate measures and clinical outcomes using

Fine and Gray competing risk models

Outcomes	Events (No.)	Cumulative resting heart rate load		Resting heart rate TITRE		Mean resting heart rate		Resting heart rate SD		Baseline resting heart rate	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Major cardiovascular events	1544	1.31 (1.24-1.38)	< .001	0.93 (0.88-0.99)	.014	1.28 (1.21-1.36)	< .001	0.95 (0.90-1.01)	.113	1.10 (1.04-1.16)	.001
Cardiovascular death	749	1.20 (1.12-1.29)	< .001	0.94 (0.88-1.02)	.135	1.18 (1.09-1.27)	< .001	1.01 (0.94-1.08)	.805	1.09 (1.01-1.18)	.021
Hospitalization for heart failure	1159	1.31 (1.24-1.38)	<.001	0.93 (0.88-0.99)	.015	1.28 (1.21-1.36)	< .001	0.95 (0.90-1.01)	.110	1.10 (1.04-1.16)	.001
Hospitalization for any reason	2651	1.20 (1.15-1.25)	< .001	0.96 (0.92-1.00)	.047	1.16 (1.11-1.21)	< .001	1.08 (1.04-1.12)	<.001	1.05 (1.01-1.10)	.019

HR, hazard ratio; TITRE, time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load is

8.31%. A 1 SD increase in resting heart rate TITRE = 7.51%. A 1 SD increase in mean resting heart rate = 10.18 bpm. A 1 SD increase in resting heart rate SD = 3.54 bpm. A 1 SD increase in baseline

resting heart rate = 13.36 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 5 of the supplementary data. Cross-adjusted associations of cumulative resting heart rate load and resting heart rate SD with clinical outcomes

Outcomes	Cumulative resting heart rate load Model adjusted for baseline variables +heart rate SD		Resting heart rate SD Model adjusted for baseline variables + cumulative resting heart rate load	
	HR (95%CI)	P	HR (95%CI)	P
Major cardiovascular events	1.35 (1.28-1.43)	< .001	0.87 (0.82-0.93)	< .001
Cardiovascular death	1.19 (1.09-1.28)	< .001	0.95 (0.87-1.03)	.203
Hospitalization for heart failure	1.38 (1.30-1.47)	< .001	0.88 (0.82-0.95)	.001
All-cause death	1.21 (1.13-1.30)	< .001	0.96 (0.89-1.03)	.282
Hospitalization for any reason	1.18 (1.13-1.24)	< .001	1.05 (1.01-1.09)	.020

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load = 8.31%. A 1 SD increase in resting heart rate SD = 3.54 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction,

peripheral vascular disease, hypertension, dyslipidaemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 6 of the supplementary data. Cross-adjusted associations of cumulative resting heart rate load and resting heart rate TITRE with clinical outcomes

Outcomes	Cumulative resting heart rate load		Resting heart rate TITRE	
	Model adjusted for baseline variables + resting heart rate TITRE		Model adjusted for baseline variables + cumulative resting heart rate load	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Major cardiovascular events	1.49 (1.38-1.60)	< .001	1.24 (1.14-1.35)	< .001
Cardiovascular death	1.22 (1.10-1.36)	< .001	1.07 (0.96-1.21)	.226
Hospitalization for heart failure	1.56 (1.44-1.69)	< .001	1.30 (1.18-1.43)	< .001
All-cause death	1.30 (1.19-1.43)	< .001	1.14 (1.03-1.26)	.011
Hospitalization for any reason	1.31 (1.23-1.38)	< .001	1.14 (1.07-1.21)	< .001

TITRE = time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load = 8.31%. A 1 SD increase in resting heart rate TITRE = 7.51%.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 7 of the supplementary data. Cross-adjusted associations of cumulative resting heart rate load and baseline resting heart rate with clinical outcomes

Outcomes	Cumulative resting heart rate load Model adjusted for baseline variables + baseline resting heart rate		Baseline resting heart rate Model adjusted for baseline variables + cumulative resting heart rate load	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Major cardiovascular events	1.36 (1.28-1.45)	< .001	0.92 (0.86-0.98)	.015
Cardiovascular death	1.19 (1.09-1.31)	< .001	0.96 (0.87-1.06)	.476
Hospitalization for heart failure	1.41 (1.31-1.52)	< .001	0.90 (0.83-0.98)	.010
All-cause death	1.21 (1.12-1.32)	< .001	0.98 (0.90-1.07)	.667
Hospitalization for any reason	1.24 (1.18-1.31)	< .001	0.94 (0.89-0.99)	.024

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load = 8.31%. A 1 SD increase in baseline resting heart rate = 13.36 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction,

peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular

ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 8 of the supplementary data. Baseline characteristics according to quarters of cumulative resting heart rate load (resting heart rate control target: 60 bpm)

Variables	Total (N = 5428)	Q1 0.00%-10.90% (n = 1357)	Q2 10.91%-17.33% (n = 1357)	Q3 17.33%-24.94% (n = 1357)	Q4 24.95%-54.95% (n = 1357)	P
Study						< .001
BEST	1973 (36.3)	300 (22.1)	359 (26.5)	561 (41.3)	753 (55.5)	
TOPCAT	2125 (39.1)	753 (55.5)	747 (55.0)	463 (34.1)	162 (11.9)	
GUIDE-IT	442 (8.1)	102 (7.5)	82 (6.0)	96 (7.1)	162 (11.9)	
RELAX	96 (1.8)	46 (3.4)	16 (1.2)	14 (1.0)	20 (1.5)	
HF-ACTION	792 (14.6)	156 (11.5)	153 (11.3)	223 (16.4)	260 (19.2)	
Age, y	62.0 ± 12.1	66.8 ± 9.9	64.6 ± 10.5	61.3 ± 11.8	55.3 ± 12.8	< .001
Male sex	3301 (60.8)	829 (61.1)	776 (57.2)	828 (61.0)	868 (64.0)	.004
Race						< .001
White	3991 (73.5)	1148 (84.6)	1097 (80.8)	969 (71.4)	777 (57.3)	
Black	1150 (21.2)	160 (11.8)	195 (14.4)	306 (22.5)	489 (36.0)	
Other	287 (5.3)	49 (3.6)	65 (4.8)	82 (6.0)	91 (6.7)	
HF type [a]						< .001
HFrEF	3207 (59.1)	558 (41.1)	594 (43.8)	880 (64.8)	1175 (86.6)	
HFpEF	2221 (40.9)	799 (58.9)	763 (56.2)	477 (35.2)	182 (13.4)	
LVEF category						< .001
≤ 40%	3180 (58.6)	551 (40.6)	587 (43.3)	875 (64.5)	1167 (86.0)	
41-49%	322 (5.9)	111 (8.2)	125 (9.2)	56 (4.1)	30 (2.2)	

⩾50%	1926 (35.5)	695 (51.2)	645 (47.5)	426 (31.4)	160 (11.8)	
Trial treatment [b]	3103 (57.2)	837 (61.7)	772 (56.9)	820 (60.4)	674 (49.7)	< .001
NYHA class III or IV	3061 (56.5)	619 (45.6)	612 (45.2)	839 (61.9)	991 (73.2)	< .001
BMI, kg/m²	33.46 ± 8.16	31.77 ± 7.06	31.99 ± 7.42	33.86 ± 8.04	36.21±9.18	< .001
Current smoker	926 (17.1)	183 (13.5)	209 (15.4)	247 (18.2)	287 (21.2)	< .001
Previous MI	1851 (34.1)	561 (41.3)	470 (34.6)	468 (34.5)	352 (25.9)	< .001
Previous stroke [b]	251 (7.3)	71 (6.7)	62 (6.2)	65 (8.2)	53 (8.8)	.164
Previous PAD	627 (11.6)	174 (12.8)	141 (10.4)	155 (11.4)	157 (11.6)	.263
Dyslipidemia	2971 (54.7)	871 (64.2)	730 (53.8)	701 (51.7)	669 (49.3)	< .001
Diabetes	1921 (35.4)	477 (35.2)	391 (28.8)	494 (36.4)	559 (41.2)	< .001
Hypertension	4015 (74.0)	1062 (78.3)	1046 (77.1)	991 (73.0)	916 (67.7)	< .001
SBP, mmHg	122.21 ± 18.12	124.63 ± 17.19	124.94 ± 17.03	122.15 ± 18.42	117.12 ± 18.70	< .001
DBP, mmHg	73.45 ± 11.61	71.64 ± 11.17	74.94 ± 11.11	74.18 ± 11.65	73.05 ± 12.23	< .001
Heart rate, beats/min	74.57 ± 13.36	64.91 ± 9.43	70.62 ± 9.57	76.12 ± 10.69	86.64 ± 12.72	< .001
LVEF	37.45 ± 18.21	44.18 ± 18.14	42.54 ± 17.99	35.54 ± 17.33	27.55 ± 14.19	< .001
Creatinine, μmol/L	104.21 ± 43.13	106.32 ± 43.33	100.07 ± 37.14	102.92 ± 34.23	107.56 ± 54.65	< .001
Potassium, mmol/L	4.33 ± 0.97	4.33 ± 1.16	4.31 ± 0.48	4.33 ± 0.48	4.33 ± 1.40	.947
ACEI	4230 (77.9)	964 (71.1)	1074 (79.1)	1093 (80.5)	1099 (81.0)	< .001
ARB [c]	687 (19.9)	227 (21.5)	157 (15.7)	155 (19.5)	148 (24.5)	< .001
Beta-blocker [c]	2912 (84.3)	888 (84.1)	836 (83.9)	678 (85.2)	510 (84.4)	.884
CCB [c]	951 (27.5)	361 (34.2)	302 (30.3)	202 (25.4)	86 (14.2)	< .001
Diuretic	4575 (84.3)	1079 (79.6)	1104 (81.4)	1159 (85.4)	1233 (90.9)	< .001
Antiarrhythmic drug [d]	443 (13.4)	91 (15.1)	91 (14.9)	113 (12.6)	148 (12.4)	.247

Pacemaker	421 (7.8)	82 (6.0)	101 (7.4)	114 (8.4)	124 (9.1)	.017
ICD	541 (10.0)	114 (8.4)	114 (8.4)	143 (10.5)	170 (12.5)	<.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BEST, Beta-Blocker Evaluation of Survival Trial; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; GUIDE-IT, Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in Heart Failure; HF-ACTION, A Controlled Trial Investigating Outcomes of Exercise Training; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; SBP, systolic blood pressure; TOPCAT, Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist.

Unless otherwise indicated, values are expressed as mean ± standard deviation or No. (%).

[a] The classification of HF type (HFrEF or HFpEF) was based on the original trial-defined criteria.

[b] In the BEST study, the trial drug was bucindolol; in the GUIDE-IT study, the trial treatment was natriuretic peptide–guided therapy; in the HF-ACTION study, the trial treatment was exercwase training; in the RELAX study, the trial drug was sildenafil; in the TOPCAT study, the trial

drug was spironolactone.

[c] Data were available for 3455 patients except in the BEST study.

[d] Data were available for 3303 patients except in the TOPCAT study.

Table 9 of the supplementary data. Baseline characteristics according to quarters of cumulative resting heart rate load (resting heart rate control target: 80 bpm)

Variables	Total (N = 5428)	Q1 0.00%-0.00% (n = 2168)	Q2 0.00%-0.19% (n = 546)	Q3 0.19%-3.00% (n = 1357)	Q4 3.00%-39.94% (n = 1357)	P V
Study						< .001
BEST	1973 (36.3)	421 (19.4)	221 (40.5)	590 (43.5)	741 (54.6)	
TOPCAT	2125 (39.1)	1386 (63.9)	173 (31.7)	382 (28.2)	184 (13.6)	
GUIDE-IT	442 (8.1)	128 (5.9)	31 (5.7)	125 (9.2)	158 (11.6)	
RELAX	96 (1.8)	61 (2.8)	5 (0.9)	14 (1.0)	16 (1.2)	
HF-ACTION	792 (14.6)	172 (7.9)	116 (21.2)	246 (18.1)	258 (19.0)	
Age, y	62.0 ± 12.1	66.2 ± 9.8	63.2 ± 10.8	61.4 ± 12.2	55.4 ± 12.9	< .001
Male sex	3301 (60.8)	1241 (57.2)	344 (63.0)	847 (62.4)	869 (64.0)	< .001
Race						< .001
White	3991 (73.5)	1862 (85.9)	413 (75.6)	940 (69.3)	776 (57.2)	
Black	1150 (21.2)	229 (10.6)	101 (18.5)	333 (24.5)	487 (35.9)	
Other	287 (5.3)	77 (3.6)	32 (5.9)	84 (6.2)	94 (6.9)	
HF type [a]						< .001
HFrEF	3207 (59.1)	721 (33.3)	368 (67.4)	961 (70.8)	1157 (85.3)	
HFpEF	2221 (40.9)	1447 (66.7)	178 (32.6)	396 (29.2)	200 (14.7)	
LVEF category						< .001
⩽ 40%	3180 (58.6)	712 (32.8)	365 (66.8)	955 (70.4)	1148 (84.6)	
41-49%	322 (5.9)	215 (9.9)	22 (4.0)	52 (3.8)	33 (2.4)	

⩾ 50%	1926 (35.5)	1241 (57.2)	159 (29.2)	350 (25.8)	176 (13.0)	
Trial treatment [b]	3103 (57.2)	1228 (56.6)	365 (66.8)	831 (61.2)	679 (50.0)	< .001
NYHA class III or IV	3061 (56.5)	911 (42.1)	313 (57.3)	850 (62.7)	987 (72.9)	< .001
BMI, kg/m^2	33.46 ± 8.16	31.64 ± 6.92	32.81 ± 7.96	33.86 ± 8.17	36.23 ± 9.20	< .001
Current smoker	926 (17.1)	311 (14.3)	80 (14.7)	254 (18.7)	281 (20.7)	< .001
Previous MI	1851 (34.1)	811 (37.4)	204 (37.4)	480 (35.4)	356 (26.2)	< .001
Previous stroke [b]	251 (7.3)	103 (5.9)	26 (8.0)	72 (9.4)	50 (8.1)	.012
Previous PAD	627 (11.6)	250 (11.5)	54 (9.9)	164 (12.1)	159 (11.7)	.610
Dyslipidemia	2971 (54.7)	1295 (59.7)	282 (51.6)	728 (53.6)	666 (49.1)	< .001
Diabetes	1921 (35.4)	708 (32.7)	185 (33.9)	480 (35.4)	548 (40.4)	< .001
Hypertension	4015 (74.0)	1758 (81.1)	388 (71.1)	950 (70.1)	919 (67.9)	< .001
SBP, mmHg	122.21 ± 18.12	126.39 ± 16.60	121.57 ± 18.15	120.46 ± 18.09	117.54 ± 19.00	< .001
DBP, mmHg	73.45 ± 11.61	74.11 ± 11.15	72.52 ± 11.16	72.95 ± 11.72	73.28 ± 12.33	< .001
Heart rate, beats/min	74.57 ± 13.36	66.11 ± 7.89	74.13 ± 10.11	76.71 ± 11.90	86.13 ± 13.38	< .001
LVEF	37.45 ± 18.21	46.51 ± 17.05	34.78 ± 17.33	33.54 ± 17.11	27.97 ± 14.49	< .001
Creatinine, μmol/L	104.21 ± 43.13	102.21 ± 39.30	104.06 ± 33.67	104.91 ± 40.17	106.80 ± 53.84	.021
Potassium, mmol/L	4.33 ± 0.97	4.32 ± 0.45	4.37 ± 1.76	4.32 ± 0.49	4.32 ± 1.40	.726
ACEI	4230 (77.9)	1603 (74.0)	440 (80.6)	1097 (80.8)	1090 (80.3)	< .001
ARB [c]	687 (19.9)	327 (18.7)	54 (16.6)	153 (19.9)	153 (24.8)	.004
Beta-blocker [c]	2912 (84.3)	1458 (83.6)	282 (86.8)	648 (84.5)	524 (85.1)	.471
CCB [c]	951 (27.5)	601 (34.4)	82 (25.2)	180 (23.5)	88 (14.3)	< .001
Diuretic	4575 (84.3)	1709 (78.9)	460 (84.2)	1181 (87.0)	1225 (90.3)	< .001
Antiarrhythmic drug [d]	443 (13.4)	108 (13.8)	60 (16.1)	137 (14.1)	138 (11.8)	.142

Pacemaker	421 (7.8)	133 (6.1)	58 (10.6)	113 (8.3)	117 (8.6)	.001
ICD	541 (10.0)	154 (7.1)	65 (11.9)	161 (11.9)	161 (11.9)	< .001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BEST, Beta-Blocker Evaluation of Survival Trial;

BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; GUIDE-IT, Guiding Evidence-Based Therapy

Using Biomarker Intensified Treatment in Heart Failure; HF-ACTION, A Controlled Trial Investigating Outcomes of Exercise Training;

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction;

NYHA, New York Heart Association; PAD, peripheral artery disease; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical

Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; SBP, systolic blood pressure; TOPCAT, Treatment of

Preserved Cardiac Function HF With an Aldosterone Antagonist.

Unless otherwise indicated, values are expressed as mean ± standard deviation or No. (%).

[a] The classification of HF type (HFrEF or HFpEF) was based on the original trial-defined criteria.

[b] In the BEST study, the trial drug was bucindolol; in the GUIDE-IT study, the trial treatment was natriuretic peptide-guided therapy; in

the HF-ACTION study, the trial treatment was exercise training; in the RELAX study, the trial drug was sildenafil; in the TOPCAT study,

the trial drug was spironolactone.

[c] Data were available for 3455 patients except in the BEST study.

[d] Data were available for 3303 patients except in the TOPCAT study.

Table 10 of the supplementary data. Association between cumulative resting heart rate load and clinical outcomes (resting heart rate control target: 60 bpm)

	Events (No.)	HR (95%CI)	*P*	*P* for trend
Major cardiovascular events				
Q1 (0.00%-10.90%)	278	1 [Reference]		< .001
Q2 (10.91%-17.33%)	304	1.03 (0.88-1.22)	.688	
Q3 (17.33%-24.94%)	379	1.05 (0.89-1.24)	.548	
Q4 (24.95%-54.95%)	583	1.67 (1.42-1.96)	< .001	
Cardiovascular death				
Q1 (0.00%-10.90%)	134	1 [Reference]		< .001
Q2 (10.91%-17.33%)	168	1.15 (0.92-1.45)	.221	
Q3 (17.33%-24.94%)	176	1.06 (0.84-1.35)	.602	
Q4 (24.95%-54.95%)	271	1.64 (1.30-2.07)	<.001	
Hospitalization for heart failure				
Q1 (0.00%-10.90%)	199	1 [Reference]		< .001
Q2 (10.91%-17.33%)	213	1.01 (0.83-1.23)	.938	
Q3 (17.33%-24.94%)	294	1.08 (0.90-1.31)	.396	
Q4 (24.95%-54.95%)	453	1.65 (1.37-1.99)	<.001	
All-cause death				

Q1 (0.00%-10.90%)	197	1 [Reference]		< .001
Q2 (10.91%-17.33%)	216	1.04 (0.86-1.27)	.694	
Q3 (17.33%-24.94%)	228	1.03 (0.85-1.26)	.762	
Q4 (24.95%-54.95%)	327	1.60 (1.31-1.96)	<.001	
Hospitalization for any reason				
Q1 (0.00%-10.90%)	589	1 [Reference]		< .001
Q2 (10.91%-17.33%)	565	0.95 (0.85-1.07)	.421	
Q3 (17.33%-24.94%)	713	1.16 (1.04-1.30)	.011	
Q4 (24.95%-54.95%)	784	1.34 (1.18-1.51)	<.001	

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoking), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemakers, and implantable cardioverter-defibrillators.

Table 11 of the supplementary data. Association between cumulative resting heart rate load and clinical outcomes (resting heart rate control target: 80 bpm)

	Events (No.)	HR (95%CI)	P	P for trend
Major cardiovascular events				
Q1 (0.00%-0.94%)	264	1 [Reference]		< .001
Q2 (0.94%-4.98%)	309	0.65 (0.53-0.79)	< .001	
Q3 (4.99%-12.67%)	389	0.86 (0.74-0.99)	.039	
Q4 (12.68%-47.45%)	582	1.30 (1.13-1.51)	< .001	
Cardiovascular death				
Q1 (0.00%-0.94%)	131	1 [Reference]		.371
Q2 (0.94%-4.98%)	161	0.67 (0.51-0.89)	.005	
Q3 (4.99%-12.67%)	188	0.82 (0.66-1.00)	.049	
Q4 (12.68%-47.45%)	269	1.11 (0.90-1.36)	.334	
Hospitalization for heart failure				
Q1 (0.00%-0.94%)	185	1 [Reference]		< .001
Q2 (0.94%-4.98%)	222	0.65 (0.51-0.83)	< .001	
Q3 (4.99%-12.67%)	299	0.91 (0.77-1.08)	.302	
Q4 (12.68%-47.45%)	453	1.37 (1.16-1.63)	< .001	
All-cause death				

Q1 (0.00%-0.94%)	192	1 [Reference]	.072
Q2 (0.94%-4.98%)	205	0.64 (0.50-0.83)	.001
Q3 (4.99%-12.67%)	246	0.86 (0.72-1.03)	.101
Q4 (12.68%-47.45%)	325	1.19 (1.00-1.43)	.055
Hospitalization for any reason			
Q1 (0.00%-0.94%)	542	1 [Reference]	< .001
Q2 (0.94%-4.98%)	598	0.96 (0.83-1.11)	.606
Q3 (4.99%-12.67%)	725	1.22 (1.10-1.36)	< .001
Q4 (12.68%-47.45%)	786	1.39 (1.24-1.56)	< .001

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoking), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 12 of the supplementary data. Adjusted HRs for the association between resting heart rate indexes and clinical outcomes (resting heart rate control target: 60 bpm)

Outcomes	Events (No.)	Cumulative resting heart rate load		Resting heart rate TITRE		Mean resting heart rate		Resting heart rate SD		Baseline resting heart rate	
		HR (95%CI)	P	HR (95%CI)	P e	HR (95%CI)	P v	HR (95%CI)	P	HR (95%CI)	P
Major cardiovascular events	1544	1.28 (1.21-1.36)	< .001	0.96 (0.90-1.02)	.171	1.27 (1.20-1.35)	< .001	0.94 (0.89-1.00)	.055	1.08 (1.02-1.15)	.007
Cardiovascular death	749	1.17 (1.07-1.27)	< .001	0.98 (0.90-1.07)	.603	1.14 (1.04-1.23)	.003	0.99 (0.91-1.07)	.733	1.06 (0.98-1.16)	.138
Hospitalization for heart failure	1159	1.32 (1.24-1.42)	< .001	0.96 (0.90-1.03)	.310	1.31 (1.22-1.40)	< .001	0.96 (0.89-1.03)	.214	1.09 (1.02-1.17)	.011
All-cause death	968	1.19 (1.10-1.28)	< .001	0.98 (0.91-1.05)	.561	1.18 (1.09-1.27)	< .001	1.01 (0.94-1.08)	.805	1.09 (1.01-1.18)	.021
Hospitalization for any reason	2651	1.17 (1.12-1.22)	< .001	0.99 (0.95-1.04)	.791	1.17 (1.12-1.22)	< .001	1.10 (1.06-1.14)	< .001	1.06 (1.01-1.10)	.022

TITRE, time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load = 9.93%. A 1 SD increase in resting heart rate TITRE = 3.81%. A 1 SD increase in mean resting heart rate = 10.18 bpm. A 1 SD increase in resting heart rate SD = 3.54 bpm. A 1 SD increase in baseline resting heart rate = 13.36 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 13 of the supplementary data. Adjusted HRs for the association between resting heart rate indexes and clinical outcomes (resting heart rate control target: 80 bpm)

Outcomes	Events (No.)	Cumulative resting heart rate load		Resting heart rate TITRE		Mean resting heart rate		Resting heart rate SD		Baseline resting heart rate	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Major cardiovascular events	1544	1.27 (1.21-1.33)		0.86 (0.81-0.91)	< .001	1.27 (1.20-1.35)	< .001	0.94 (0.89-1.00)	.055	1.08 (1.02-1.15)	.007
Cardiovascular death	749	1.13 (1.05-1.21)	.001	0.93 (0.86-1.01)	.087	1.14 (1.04-1.23)	.003	0.99 (0.91-1.07)	.733	1.06 (0.98-1.16)	.138
Hospitalization for heart failure	1159	1.30 (1.24-1.37)	< .001	0.85 (0.80-0.91)	< .001	1.31 (1.22-1.40)	< .001	0.96 (0.89-1.03)	.214	1.09 (1.02-1.17)	.011
All-cause death	968	1.16 (1.09-1.23)	< .001	0.91 (0.85-0.98)	.016	1.18 (1.09-1.27)	< .001	1.01 (0.94-1.08)	.805	1.09 (1.01-1.18)	.021
Hospitalization for any reason	2651	1.17 (1.13-1.22)	< .001	0.89 (0.85-0.93)	< .001	1.17 (1.12-1.22)	< .001	1.10 (1.06-1.14)	< .001	1.06 (1.01-1.10)	.022

TITRE, time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure. A 1 SD increase in cumulative resting heart rate load = 5.05%. A 1 SD increase in resting heart rate TITRE = 7.50%. A 1 SD increase in mean resting heart rate = 10.18 bpm. A 1 SD increase in resting heart rate SD = 3.54 bpm. A 1 SD increase in baseline resting heart rate = 13.36 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 14 of the supplementary data. Prognostic value of resting heart rate TITRE and cumulative resting heart rate load compared with traditional risk factors (resting heart rate control target: 60, 70, 80 bpm)

	Akaike information criterion	C-Statistic (95%CI)	Continuous net reclassification improvement (95%CI)	Integrated discrimination improvement (95%CI)
Major cardiovascular events				
Base model	23 781	0.7443 (0.7329-0.7557)		
Base model + resting heart rate TITRE (60 bpm)	23 781	0.7447 (0.7333-0.7561)	0.083 (-0.090-0.112)	0.001 (0-0.003)
Base model + resting heart rate TITRE (70 bpm)	23 775	0.7454 (0.7340-0.7568)	0.106 (0.058-0.147)	0.001 (0-0.004)
Base model + resting heart rate TITRE (80 bpm)	23 757	0.7466 (0.7351-0.7581)	0.135 (0.093-0.174)	0.004 (0.001-0.009)
Base model + cumulative resting heart rate load (60 bpm)	23 716	0.7525 (0.7411-0.7639)	0.116 (0.081-0.165)	0.010 (0.005-0.017)
Base model + cumulative resting heart rate load (70 bpm)	23 696	0.7542 (0.7428-0.7656)	0.153 (0.115-0.194),	0.013 (0.007-0.021)
Base model + cumulative resting heart rate load (80 bpm)	23 692	0.7546 (0.7431-0.7661)	0.167 (0.122-0.203)	0.015 (0.009-0.025)
Cardiovascular death				

Base model	11 490	0.7544 (0.7370-0.7718)		
Base model + resting heart rate TITRE (60 bpm)	11 492	0.7546 (0.7372-0.7720)	0.093 (-0.119-0.131)	0 (0-0.001)
Base model + resting heart rate TITRE (70 bpm)	11 488	0.7549 (0.7375-0.7723)	0.113 (-0.121-0.172)	0.001 (0-0.003)
Base model + resting heart rate TITRE (80 bpm)	11 489	0.7546 (0.7372-0.7720)	0.084 (-0.106-0.150)	0 (0-0.002)
Base model + cumulative resting heart rate load (60 bpm)	11 479	0.7569 (0.7397-0.7741)	0.089 (0.017-0.150)	0.002 (0-0.005)
Base model + cumulative resting heart rate load (70 bpm)	11 477	0.7573 (0.7400-0.7746)	0.132 (0.060-0.194)	0.002 (0-0.005)
Base model + cumulative resting heart rate load (80bpm)	11 481	0.7570 (0.7397-0.7743)	0.141 (0.060-0.194)	0.001 (0-0.005)
Hospitalization for heart failure				
Base model	17 796	0.7567 (0.7443-0.7691)		
Base model + resting heart rate TITRE (60 bpm)	17 797	0.7571 (0.7447-0.7695)	0.079 (-0.102-0.113)	0.001 (0-0.002)
Base model + resting heart rate TITRE (70 bpm)	17 792	0.7582 (0.7458-0.7706)	0.106 (0-0.152)	0.001 (0-0.004)
Base model + resting heart rate TITRE (80 bpm)	17 775	0.7597 (0.7471-0.7723)	0.144 (0.093-0.187)	0.004 (0.001-0.010)
Base model + cumulative resting heart rate load (60 bpm)	17 734	0.7667 (0.7544-0.7790)	0.126 (0.079-0.175)	0.011 (0.006-0.020)

Base model + cumulative resting heart rate load (70 bpm)	17 716	0.7684 (0.7560-0.7808)	0.165 (0.118-0.209)	0.014 (0.008-0.024)
Base model + cumulative resting heart rate load (80bpm)	17 708	0.7687 (0.7563-0.7811)	0.168 (0.108-0.209)	0.017 (0.009-0.029)
All-cause death				
Base model	14 832	0.7415 (0.7258-0.7572)		
Base model + resting heart rate TITRE (60 bpm)	14 834	0.7417 (0.7260-0.7574)	0.091 (-0.113-0.127)	0 (0-0.002)
Base model + resting heart rate TITRE (70 bpm)	14 831	0.7422 (0.7266-0.7578)	0.103 (-0.123-0.158)	0.001 (0-0.003)
Base model + resting heart rate TITRE (80 bpm)	14 828	0.7422 (0.7266-0.7578)	0.088 (-0.062-0.147)	0 (0-0.003)
Base model + cumulative resting heart rate load (60 bpm)	14 814	0.7456 (0.7302-0.7610)	0.113 (0.049-0.174)	0.002 (0-0.006)
Base model + cumulative resting heart rate load (70 bpm)	14 809	0.7464 (0.7309-0.7619)	0.135 (0.074-0.190)	0.003 (0-0.007)
Base model + cumulative resting heart rate load (80bpm)	14 814	0.7458 (0.7303-0.7613)	0.147 (0.083-0.198)	0.002 (0-0.006)
Hospitalization for any reason				
Base model	40 921	0.6681 (0.6576-0.6786)		

Base model + resting heart rate TITRE (60 bpm)	40 923	0.6681 (0.6576-0.6786)	0.019 (-0.03-0.045)	0 (0-0.001)
Base model + resting heart rate TITRE (70 bpm)	40 917	0.6690 (0.6585-0.6795)	0.071 (0.031-0.099)	0.001 (0-0.003)
Base model + resting heart rate TITRE (80 bpm)	40 896	0.6701 (0.6596-0.6806)	0.103 (0.071-0.130)	0.002 (0-0.005)
Base model + cumulative resting heart rate load (60 bpm)	40 878	0.6733 (0.6628-0.6838)	0.080 (0.046-0.110)	0.005 (0.002-0.009)
Base model + cumulative resting heart rate load (70 bpm)	40 858	0.6747 (0.6643-0.6851)	0.107 (0.080-0.136)	0.006 (0.003-0.011)
Base model + cumulative resting heart rate load (80bpm)	40 864	0.6739 (0.6634-0.6844)	0.107 (0.080-0.133)	0.006 (0.003-0.011)

TITRE, time at target.

The base model was adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 15 of the supplementary data. Association between cumulative resting heart rate load and clinical outcomes in HFrEF

	Events (No.)	HR (95%CI)	P	P for trend
Major cardiovascular events				
Q1 (0.00%-2.78%)	270	1 [Reference]		<.001
Q2 (2.78%-8.76%)	278	0.93 (0.79-1.11)	.430	
Q3 (8.77%-16.51%)	285	0.95 (0.79-1.13)	.553	
Q4 (16.51%-47.45%)	387	1.57 (1.31-1.87)	<.001	
Cardiovascular death				
Q1 (0.00%-2.78%)	141	1 [Reference]		.142
Q2 (2.78%-8.76%)	135	0.88 (0.69-1.12)	.304	
Q3 (8.77%-16.51%)	139	0.91 (0.71-1.16)	.439	
Q4 (16.51%-47.45%)	170	1.20 (0.93-1.55)	.155	
Hospitalization for heart failure				
Q1 (0.00%-2.78%)	190	1 [Reference]		<.001
Q2 (2.78%-8.76%)	226	1.08 (0.89-1.32)	.445	
Q3 (8.77%-16.51%)	217	1.05 (0.86-1.29)	.637	
Q4 (16.51%-47.45%)	315	1.84 (1.50-2.25)	<.001	
All-cause death				

Q1 (0.00%-2.78%)	178	1 [Reference]		.064
Q2 (2.78%-8.76%)	163	0.85 (0.69-1.06)	.155	
Q3 (8.77%-16.51%)	169	0.92 (0.74-1.16)	.483	
Q4 (16.51%-47.45%)	200	1.22 (0.97-1.54)	.083	
Hospitalization for any reason				
Q1 (0.00%-2.78%)	415	1 [Reference]		<.001
Q2 (2.78%-8.76%)	456	1.11 (0.97-1.27)	.142	
Q3 (8.77%-16.51%)	453	1.15 (1.00-1.33)	.050	
Q4 (16.51%-47.45%)	489	1.45 (1.25-1.69)	<.001	

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoking), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 16 of the supplementary data. Association between cumulative resting heart rate load and clinical outcomes in HFpEF

	Events (No.)	HR (95%CI)	*P*	*P* for trend
Major cardiovascular events				
Q1 (0.00%-0.21%)	74	1 [Reference]		.001
Q2 (0.22%-1.98%)	55	0.71 (0.50-1.00)	.053	
Q3 (1.99%-5.98%)	72	0.89 (0.64-1.24)	.486	
Q4 (6.02%-40.60%)	123	1.52 (1.13-2.05)	.006	
Cardiovascular death				
Q1 (0.00%-0.21%)	31	1 [Reference]		.002
Q2 (0.22%-1.98%)	34	1.03 (0.63-1.69)	.918	
Q3 (1.99%-5.98%)	43	1.26 (0.78-2.03)	.346	
Q4 (6.02%-40.60%)	56	1.97 (1.25-3.11)	.004	
Hospitalization for heart failure				
Q1 (0.00%-0.21%)	54	1 [Reference]		.057
Q2 (0.22%-1.98%)	31	0.58 (0.37-0.90)	.016	
Q3 (1.99%-5.98%)	43	0.76 (0.50-1.15)	.187	
Q4 (6.02%-40.60%)	83	1.28 (0.90-1.83)	.175	
All-cause death				

Q1 (0.00%-0.21%)	54	1 [Reference]		.001
Q2 (0.22%-1.98%)	54	0.94 (0.64-1.38)	.757	
Q3 (1.99%-5.98%)	61	1.02 (0.70-1.48)	.937	
Q4 (6.02%-40.60%)	89	1.74 (1.23-2.48)	.002	
Hospitalization for any reason				
Q1 (0.00%-0.21%)	188	1 [Reference]		<.001
Q2 (0.22%-1.98%)	180	0.94 (0.77-1.16)	.579	
Q3 (1.99%-5.98%)	189	0.98 (0.79-1.20)	.824	
Q4 (6.02%-40.60%)	281	1.56 (1.29-1.89)	<.001	

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoking), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 17 of the supplementary data. Adjusted HRs for the association between resting heart rate indexes and clinical outcomes by heart failure types

Outcomes	Events (No.)	Cumulative resting heart rate load		Resting heart rate TITRE		Mean resting heart rate		Resting heart rate SD		Baseline resting heart rate	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
HFrEF (n = 3207)											
Major cardiovascular events	1220	1.27 (1.20-1.36)	< .001	0.89 (0.84-0.96)	< .001	1.23 (1.15-1.32)	< .001	0.89 (0.83-0.96)	.001	1.06 (0.99-1.13)	.112
Cardiovascular death	585	1.12 (1.02-1.23)	.015	0.92 (0.84-1.01)	.093	1.07 (0.97-1.18)	.155	0.95 (0.86-1.04)	.270	1.01 (0.92-1.11)	.838
Hospitalization for heart failure	948	1.34 (1.24-1.44)	< .001	0.87 (0.80-0.94)	< .001	1.30 (1.21-1.40)	< .001	0.91 (0.84-0.98)	.013	1.09 (1.01-1.17)	.032
All-cause death	710	1.13 (1.04-1.23)	.005	0.94 (0.86-1.02)	.127	1.09 (1.00-1.19)	.044	0.96 (0.88-1.05)	.336	1.02 (0.94-1.12)	.581

	n										
Hospitalization for any reason	1813	1.17 (1.11-1.23)	< .001	0.92 (0.87-0.97)	.002	1.15 (1.09-1.21)	< .001	1.00 (0.95-1.05)	.999	1.03 (0.98-1.09)	.247
HFpEF (n = 2221)											
Major cardiovascular events	324	1.35 (1.23-1.48)	< .001	0.80 (0.71-0.90)	< .001	1.36 (1.22-1.51)	< .001	0.97 (0.86-1.09)	.609	1.17 (1.05-1.3)	.005
Cardiovascular death	164	1.33 (1.16-1.52)	< .001	0.79 (0.67-0.93)	.005	1.35 (1.15-1.57)	< .001	1.04 (0.89-1.21)	.601	1.23 (1.05-1.43)	.009
Hospitalization for heart failure	211	1.32 (1.18-1.47)	< .001	0.83 (0.72-0.96)	.011	1.32 (1.17-1.50)	< .001	0.97 (0.84-1.11)	.653	1.11 (0.97-1.26)	.135
All-cause death	258	1.32 (1.19-1.48)	< .001	0.81 (0.71-0.92)	.002	1.35 (1.20-1.53)	< .001	1.02 (0.90-1.15)	.756	1.23 (1.08-1.38)	.001
Hospitalization	838	1.20 (1.13-1.28)	< .001	0.93 (0.86-1.00)	.038	1.16 (1.08-1.24)	< .001	1.18 (1.11-1.25)	< .001	1.05 (0.98-1.13)	.013

for any reason

TITRE, time at target.

Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per 1-standard deviation (SD) increase in each resting heart rate measure.

HFrEF: a 1 SD increase in cumulative resting heart rate load = 8.90%. A 1 SD increase in resting heart rate TITRE = 6.95%. A 1 SD increase in mean resting heart rate = 10.53 bpm. A 1 SD increase in resting heart rate SD = 3.40 bpm. A 1 SD increase in baseline resting heart rate = 13.69 bpm.

HFpEF: a 1 SD increase in cumulative resting heart rate load = 5.52%. A 1 SD increase in resting heart rate TITRE = 7.44%. A 1 SD increase in mean resting heart rate = 7.28 bpm. A 1 SD increase in resting heart rate SD = 3.57 bpm. A 1 SD increase in baseline resting heart rate = 10.15 bpm.

Models were adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 18 of the supplementary data. Prognostic value of resting heart rate measures compared with traditional risk factors in HFrEF

	Akaike information criterion	C-statistic (95%CI)	Continuous net reclassification improvement (95%CI)	Integrated discrimination improvement (95%CI)
Major cardiovascular events				
Base model	17 777	0.6608 (0.6454-0.6762)		
Base model + baseline resting heart rate	17 777	0.6619 (0.6465-0.6773)	0.034 (-0.051-0.082)	0.001 (0-0.004)
Base model + mean resting heart rate	17 743	0.6710 (0.6556-0.6864)	0.080 (0.030-0.121)	0.009 (0.004-0.018)
Base model + resting heart rate SD	17 768	0.6630 (0.6474-0.6786)	0.059 (-0.001-0.100)	0.003 (0-0.009)
Base model + resting heart rate TITRE	17 774	0.6622 (0.6468-0.6776)	0.077 (0.015-0.119)	0.001 (0-0.005)
Base model + cumulative resting heart rate load	17 726	0.6747 (0.6593-0.6901)	0.106 (0.060-0.152)	0.013 (0.006-0.022)
Cardiovascular death				
Base model	8493	0.7012 (0.6797-0.7227)		
Base model + baseline resting heart	8495	0.7012 (0.6797-0.7227)	0.003 (-0.055-0.090)	0 (0-0.002)

rate				
Base model + mean resting heart rate	8493	0.7019 (0.6804-0.7234)	0.063 (-0.081-0.136)	0.001 (0-0.003)
Base model + resting heart rate SD	8494	0.7020 (0.6805-0.7235)	0.052 (-0.107-0.122)	0.001 (0-0.004)
Base model + resting heart rate TITRE	8494	0.7012 (0.6797-0.7227)	0.081 (-0.099-0.149)	0 (0-0.003)
Base model + cumulative resting heart rate load	8490	0.7034 (0.6819-0.7249)	0.071 (-0.026-0.141)	0.001 (0-0.005)
Hospitalization for heart failure				
Base model	13 841	0.6627 (0.6452-0.6802)		
Base model + baseline resting heart rate	13 839	0.6647 (0.6472-0.6822)	0.030 (-0.030-0.088)	0.001 (0-0.005)
Base model + mean resting heart rate	13 797	0.6777 (0.6602-0.6952)	0.081 (0.030-0.132)	0.012 (0.005-0.022)
Base model + resting heart rate SD	13 837	0.6641 (0.6465-0.6817)	0.051 (-0.022-0.099)	0.002 (0-0.008)
Base model + resting heart rate TITRE	13 836	0.6659 (0.6484-0.6834)	0.083 (0.027-0.124)	0.002 (0-0.006)

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Base model + cumulative resting heart rate load	13 783	0.6811 (0.6636-0.6986)	0.114 (0.064-0.163)	0.016 (0.008-0.027)
All-cause death				
Base model	10 274	0.6953 (0.6755-0.7151)		
Base model + baseline resting heart rate	10 275	0.6954 (0.6757-0.7151)	0.014 (-0.063-0.098)	0 (0-0.001)
Base model + mean resting heart rate	10 272	0.6966 (0.6769-0.7163)	0.062 (-0.059-0.139)	0.001 (0-0.004)
Base model + resting heart rate SD	10 275	0.6954 (0.6756-0.7152)	0.059 (-0.109-0.123)	0.001 (-0.001-0.004)
Base model + resting heart rate TITRE	10 275	0.6952 (0.6754-0.7150)	0.070 (-0.106-0.136)	0 (0-0.003)
Base model + cumulative resting heart rate load	10 268	0.6980 (0.6783-0.7177)	0.083 (-0.003-0.148)	0.002 (0-0.006)
Hospitalization for any reason				
Base model	25 856	0.6116 (0.5977-0.6255)		
Base model + baseline resting heart rate	25 857	0.6125 (0.5986-0.6264)	0.004 (-0.041-0.049)	0 (0-0.002)

Base model + mean resting heart rate	25 834	0.6187 (0.6048-0.6326)	0.033 (-0.006-0.069)	0.004 (0.001-0.010)
Base model + resting heart rate SD	25 858	0.6116 (0.5977-0.6255)	-0.022 (-0.038-0.058)	0 (0-0.001)
Base model + resting heart rate TITRE	25 852	0.6132 (0.5993-0.6271)	0.039 (-0.001-0.082)	0.001 (0-0.004)
Base model + cumulative resting heart rate load	25 827	0.6195 (0.6056-0.6334)	0.053 (0.014-0.090)	0.006 (0.002-0.012)

HFrEF, heart failure with reduced ejection fraction; TITRE, time at target.

The base model was adjusted for study, age, gender, race, trial treatment, New York Heart Association functional class, current smoking, medical history (myocardial infarction, peripheral arterial disease, hypertension, pacemaker, and implantable cardioverter-defibrillator), dyslipidemia, diabetes, body mass index, creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, and diuretics.

Table 19 of the supplementary data. Prognostic value of resting heart rate TITRE and cumulative resting heart rate load compared with traditional risk factors in HFrEF (resting heart rate control target: 60, 70, 80 bpm)

	Akaike information criterion	C-statistic (95%CI)	Continuous net reclassification improvement (95%CI)	Integrated discrimination improvement (95%CI)
Major cardiovascular events				
Base model	17 777	0.6608 (0.6454-0.6762)		
Base model + resting heart rate TITRE (60 bpm)	17 776	0.6619 (0.6465-0.6773)	0.065 (-0.065-0.094)	0.001 (0-0.004)
Base model + resting heart rate TITRE (70 bpm)	17 774	0.6622 (0.6468-0.6776)	0.077 (0.015-0.119)	0.001 (0-0.005)
Base model + resting heart rate TITRE (80 bpm)	17 762	0.6650 (0.6495-0.6805)	0.084 (0.037-0.129)	0.004 (0.001-0.010)
Base model + cumulative resting heart rate load (60 bpm)	17 738	0.6722 (0.6568-0.6876)	0.089 (0.048-0.137)	0.010 (0.005-0.018)
Base model + cumulative resting heart rate load (70 bpm)	17 726	0.6747 (0.6593-0.6901)	0.106 (0.060-0.152)	0.013 (0.006-0.022)
Base model + cumulative resting heart rate load (80 bpm)	17 715	0.6769 (0.6615-0.6923)	0.124 (0.080-0.168)	0.016 (0.008-0.027)
Cardiovascular death				

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Base model	8493	0.7012 (0.6797-0.7227)		
Base model + resting heart rate TITRE (60 bpm)	8495	0.7011 (0.6796-0.7226)	-0.059 (-0.086-0.100)	0 (-0.001-0.002)
Base model + resting heart rate TITRE (70 bpm)	8494	0.7012 (0.6797-0.7227)	0.081 (-0.099-0.149)	0 (0-0.003)
Base model + resting heart rate TITRE (80 bpm)	8495	0.7011 (0.6796-0.7226)	0.030 (-0.073-0.105)	0 (0-0.003)
Base model + cumulative resting heart rate load (60 bpm)	8492	0.7023 (0.6808-0.7238)	0.065 (-0.062-0.132)	0.001 (0-0.005)
Base model + cumulative resting heart rate load (70 bpm)	8490	0.7034 (0.6819-0.7249)	0.071 (-0.026-0.141)	0.001 (0-0.005)
Base model + cumulative resting heart rate load (80bpm)	8490	0.7042 (0.6828-0.7256)	0.078 (-0.023-0.156)	0.001 (0-0.005)
Hospitalization for heart failure				
Base model	13 841	0.6627 (0.6452-0.6802)		
Base model + resting heart rate TITRE (60 bpm)	13 839	0.6647 (0.6473-0.6821)	0.069 (-0.054-0.100)	0.002 (0-0.004)
Base model + resting heart rate TITRE (70 bpm)	13 836	0.6659 (0.6484-0.6834)	0.083 (0.027-0.124)	0.002 (0-0.006)
Base model + resting heart rate TITRE (80 bpm)	13 822	0.6692 (0.6515-0.6869)	0.106 (0.050-0.152)	0.006 (0.001-0.013)
Base model + cumulative resting heart rate load (60 bpm)	13 792	0.6797 (0.6623-0.6971)	0.098 (0.053-0.147)	0.013 (0.006-0.023)

Base model + cumulative resting heart rate load (70 bpm)	13 783	0.6811 (0.6636-0.6986)	0.114 (0.064-0.163)	0.016 (0.008-0.027)
Base model + cumulative resting heart rate load (80bpm)	13 772	0.6824 (0.6649-0.6999)	0.133 (0.084-0.181)	0.019 (0.010-0.032)
All-cause death				
Base model	10 274	0.6953 (0.6755-0.7151)		
Base model + resting heart rate TITRE (60 bpm)	10 276	0.6953 (0.6756-0.7150)	0.057 (-0.082-0.101)	0 (0-0.002)
Base model + resting heart rate TITRE (70 bpm)	10 275	0.6952 (0.6754-0.7150)	0.070 (-0.106-0.136)	0 (0-0.003)
Base model + resting heart rate TITRE (80 bpm)	10 274	0.6954 (0.6756-0.7152)	0.031 (-0.075-0.105)	0 (0-0.003)
Base model + cumulative resting heart rate load (60 bpm)	10 270	0.6972 (0.6775-0.7169)	0.074 (-0.032-0.138)	0.002 (0-0.005)
Base model + cumulative resting heart rate load (70 bpm)	10 268	0.6980 (0.6783-0.7177)	0.083 (-0.003-0.148)	0.002 (0-0.006)
Base model + cumulative resting heart rate load (80bpm)	10 267	0.6992 (0.6796-0.7188)	0.087 (0.011-0.157)	0.002 (0-0.006)
Hospitalization for any reason				
Base model	25 856	0.6116 (0.5977-0.6255)		

Base model + resting heart rate TITRE (60 bpm)	25 854	0.6130 (0.5991-0.6269)	0.034 (-0.004-0.064)	0.001 (0-0.003)
Base model + resting heart rate TITRE (70 bpm)	25 852	0.6132 (0.5993-0.6271)	0.039 (-0.001-0.082)	0.001 (0-0.004)
Base model + resting heart rate TITRE (80 bpm)	25 849	0.6134 (0.5994-0.6274)	0.046 (0.006-0.089)	0.002 (0-0.005)
Base model + cumulative resting heart rate load (60 bpm)	25 830	0.6194 (0.6055-0.6333)	0.058 (0.019-0.097)	0.005 (0.002-0.011)
Base model + cumulative resting heart rate load (70 bpm)	25 827	0.6195 (0.6056-0.6334)	0.053 (0.014-0.090)	0.006 (0.002-0.012)
Base model + cumulative resting heart rate load (80bpm)	25 824	0.6196 (0.6056-0.6336)	0.071 (0.036-0.108)	0.007 (0.002-0.013)

TITRE, time at target.

The base model was adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoker), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

Table 20 of the supplementary data. Prognostic value of resting heart rate measures compared with traditional risk factors in HFpEF

	Akaike information criterion	C-statistic (95%CI)	Continuous net reclassification improvement (95%CI)	Integrated discrimination improvement (95%CI)
Major cardiovascular events				
Base model	4516	0.7417 (0.7144-0.7690)		
Base model + baseline resting heart rate	4510	0.7474 (0.7203-0.7745)	0.144 (0-0.217)	0 (-0.003-0.005)
Base model + mean resting heart rate	4487	0.7523 (0.7250-0.7796)	0.121 (0.037-0.217)	0.008 (-0.001-0.023)
Base model + resting heart rate SD	4518	0.7418 (0.7146-0.7690)	0.115 (-0.184-0.215)	0.001 (-0.002-0.010)
Base model + resting heart rate TITRE	4514	0.7426 (0.7151-0.7701)	0.089 (-0.088-0.185)	0.001 (-0.002-0.008)
Base model + cumulative resting heart rate load	4483	0.7531 (0.7261-0.7801)	0.129 (0.022-0.214)	0.007 (-0.003-0.024)
Cardiovascular death				
Base model	2324	0.6978 (0.6571-0.7385)		
Base model + baseline resting heart	2320	0.7088 (0.6688-0.7488)	0.314 (0.147-0.442)	0.003 (0.001-0.009)

rate				
Base model + mean resting heart rate	2313	0.7097 (0.6691-0.7503)	0.182 (0.022-0.329)	0.006 (0.001-0.015)
Base model + resting heart rate SD	2326	0.6984 (0.6576-0.7392)	-0.127 (-0.257-0.240)	-0.001 (-0.003-0.002)
Base model + resting heart rate TITRE	2323	0.6982 (0.6572-0.7392)	0.121 (-0.111-0.276)	0.002 (0-0.009)
Base model + cumulative resting heart rate load	2312	0.7125 (0.6721-0.7529)	0.084 (-0.072-0.258)	0.004 (0-0.012)
Hospitalization for heart failure				
Base model	2858	0.8090 (0.7831-0.8349)		
Base model + baseline resting heart rate	2858	0.8116 (0.7860-0.8372)	0.090 (-0.119-0.181)	-0.002 (-0.005-0.002)
Base model + mean resting heart rate	2842	0.8173 (0.7921-0.8425)	0.110 (-0.023-0.208)	0.002 (-0.006-0.018)
Base model + resting heart rate SD	2860	0.8096 (0.7838-0.8354)	0.100 (-0.196-0.229)	0.001 (-0.002-0.014)
Base model + resting heart rate TITRE	2859	0.8095 (0.7838-0.8352)	0.065 (-0.153-0.180)	-0.001 (-0.004-0.007)

Base model + cumulative resting heart rate load	2839	0.8170 (0.7920-0.8420)	0.134 (-0.002-0.241)	0.002 (-0.006-0.021)
All-cause death				
Base model	3589	0.7086 (0.6756-0.7416)		
Base model + baseline resting heart rate	3581	0.7184 (0.6857-0.7511)	0.240 (0.080-0.359)	0.004 (0-0.010)
Base model + mean resting heart rate	3569	0.7246 (0.6920-0.7572)	0.174 (0.038-0.297)	0.008 (0.002-0.019)
Base model + resting heart rate SD	3591	0.7087 (0.6757-0.7417)	-0.123 (-0.202-0.223)	0 (-0.001-0.003)
Base model + resting heart rate TITRE	3588	0.7123 (0.6794-0.7452)	0.110 (-0.121-0.232)	0.001 (-0.001-0.006)
Base model + cumulative resting heart rate load	3569	0.7253 (0.6929-0.7577)	0.143 (0.009-0.277)	0.005 (0.001-0.014)
Hospitalization for any reason				
Base model	11 804	0.6890 (0.6707-0.7073)		
Base model + baseline resting heart rate	11 804	0.6898 (0.6715-0.7081)	0.002 (-0.122-0.062)	0.001 (0-0.004)

Base model + mean resting heart rate	11 788	0.6933 (0.6749-0.7117)	0.061 (-0.017-0.108)	0.005 (0-0.013)
Base model + resting heart rate SD	11 782	0.6941 (0.6758-0.7124)	0.063 (0.004-0.113)	0.004 (-0.001-0.010)
Base model + resting heart rate TITRE	11 803	0.6893 (0.6709-0.7077)	0.020 (-0.079-0.078)	0.001 (0-0.005)
Base model + cumulative resting heart rate load	11 776	0.6960 (0.6778-0.7142)	0.083 (0.022-0.143)	0.006 (0-0.015)

HFpEF, heart failure with preserved ejection fraction; TITRE, time at target.

The base model was adjusted for study, age, gender, race, trial treatment, NYHA functional class, current smoker, medical history (MI, PAD, hypertension, pacemaker, and ICD), dyslipidemia, diabetes, BMI, creatinine, LVEF, ACEI, and diuretics.

Table 21 of the supplementary data. Prognostic value of resting heart rate TITRE and cumulative resting heart rate load compared with traditional risk factors in HFpEF (resting heart rate control target: 60, 70, 80 bpm)

	Akaike information criterion	C-statistic (95%CI)	Continuous net reclassification improvement (95%CI)	Integrated discrimination improvement (95%CI)
Major cardiovascular events				
Base model	4516	0.7417 (0.7144-0.7690)		
Base model + resting heart rate TITRE (60 bpm)	4517	0.7410 (0.7134-0.7686)	0.077 (-0.174-0.145)	0 (-0.001-0.006)
Base model + resting heart rate TITRE (70 bpm)	4514	0.7426 (0.7151-0.7701)	0.089 (-0.088-0.185)	0.001 (-0.002-0.008)
Base model + resting heart rate TITRE (80 bpm)	4514	0.7412 (0.7135-0.7689)	0.065 (-0.156-0.153)	-0.002 (-0.006-0.005)
Base model + cumulative resting heart rate load (60 bpm)	4489	0.7514 (0.7242-0.7786)	0.135 (0.041-0.219)	0.008 (0-0.022)
Base model + cumulative resting heart rate load (70 bpm)	4483	0.7531 (0.7261-0.7801)	0.129 (0.022-0.214)	0.007 (-0.003-0.024)
Base model + cumulative resting heart rate load (80 bpm)	4494	0.7492 (0.7219-0.7765)	0.072 (-0.014-0.148)	0.005 (-0.004-0.027)
Cardiovascular death				

Base model	2324	0.6978 (0.6571-0.7385)		
Base model + resting heart rate TITRE (60 bpm)	2325	0.6966 (0.6558-0.7374)	0.153 (-0.206-0.236)	0.001 (-0.001-0.004)
Base model + resting heart rate TITRE (70 bpm)	2323	0.6982 (0.6572-0.7392)	0.121 (-0.111-0.276)	0.002 (0-0.009)
Base model + resting heart rate TITRE (80 bpm)	2323	0.6997 (0.6587-0.7407)	0.026 (-0.270-0.183)	0.001 (-0.002-0.011)
Base model + cumulative resting heart rate load (60 bpm)	2311	0.7108 (0.6706-0.7510)	0.211 (0.037-0.345)	0.006 (0.001-0.014)
Base model + cumulative resting heart rate load (70 bpm)	2312	0.7125 (0.6721-0.7529)	0.084 (-0.072-0.258)	0.004 (0-0.012)
Base model + cumulative resting heart rate load (80bpm)	2320	0.7066 (0.6660-0.7472)	0.108 (-0.098-0.240)	0.001 (-0.001-0.004)
Hospitalization for heart failure				
Base model	2858	0.8090 (0.7831-0.8349)		
Base model + resting heart rate TITRE (60 bpm)	2860	0.8090 (0.7830-0.8350)	0.047 (-0.115-0.135)	0 (-0.002-0.007)
Base model + resting heart rate TITRE (70 bpm)	2859	0.8095 (0.7838-0.8352)	0.065 (-0.153-0.180)	-0.001 (-0.004-0.007)
Base model + resting heart rate TITRE (80 bpm)	2860	0.8094 (0.7836-0.8352)	0.082 (-0.156-0.180)	-0.002 (-0.006-0.012)
Base model + cumulative resting heart rate load (60 bpm)	2845	0.8160 (0.7910-0.8410)	0.092 (-0.034-0.204)	0.003 (-0.005-0.018)

Base model + cumulative resting heart rate load (70 bpm)	2839	0.8170 (0.7920-0.8420)	0.134 (-0.002-0.241)	0.002 (-0.006-0.021)
Base model + cumulative resting heart rate load (80bpm)	2843	0.8141 (0.7884-0.8398)	0.051 (-0.165-0.148)	0.002 (-0.007-0.031)
All-cause death				
Base model	3589	0.7086 (0.6756-0.7416)		
Base model + resting heart rate TITRE (60 bpm)	3590	0.7087 (0.6756-0.7418)	0.122 (-0.210-0.199)	0.001 (-0.001-0.004)
Base model + resting heart rate TITRE (70 bpm)	3588	0.7123 (0.6794-0.7452)	0.110 (-0.121-0.232)	0.001 (-0.001-0.006)
Base model + resting heart rate TITRE (80 bpm)	3588	0.7111 (0.6781-0.7441)	0.078 (-0.186-0.207)	0 (-0.002-0.008)
Base model + cumulative resting heart rate load (60 bpm)	3572	0.7249 (0.6927-0.7571)	0.213 (0.079-0.328)	0.006 (0.002-0.015)
Base model + cumulative resting heart rate load (70 bpm)	3569	0.7253 (0.6929-0.7577)	0.143 (0.009-0.277)	0.005 (0.001-0.014)
Base model + cumulative resting heart rate load (80bpm)	3580	0.7185 (0.6857-0.7513)	0.097 (-0.022-0.226)	0.002 (0-0.008)
Hospitalization for any reason				
Base model	11 804	0.6890 (0.6707-0.7073)		

Base model + resting heart rate TITRE (60 bpm)	11 806	0.6892 (0.6709-0.7075)	0.056 (-0.090-0.108)	0 (0-0.002)
Base model + resting heart rate TITRE (70 bpm)	11 803	0.6893 (0.6709-0.7077)	0.020 (-0.079-0.078)	0.001 (0-0.005)
Base model + resting heart rate TITRE (80 bpm)	11 790	0.6926 (0.6743-0.7109)	0.079 (0.019-0.132)	0.002 (-0.002-0.008)
Base model + cumulative resting heart rate load (60 bpm)	11 791	0.6922 (0.6739-0.7105)	0.054 (-0.017-0.103)	0.005 (0-0.012)
Base model + cumulative resting heart rate load (70 bpm)	11 776	0.6960 (0.6778-0.7142)	0.083 (0.022-0.143)	0.006 (0-0.015)
Base model + cumulative resting heart rate load (80bpm)	11 787	0.6932 (0.6750-0.7114)	0.076 (-0.038-0.113)	0.003 (-0.001-0.011)

TITRE, time at target.

The base model was adjusted for study, trial treatment, demographic information (age, gender, race, and body mass index), medical history (myocardial infarction, peripheral vascular disease, hypertension, dyslipidemia, and diabetes), risk factors (NYHA functional class, current smoking), creatinine, left ventricular ejection fraction, angiotensin-converting enzyme inhibitors, diuretics, pacemaker, and implantable cardioverter-defibrillator.

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