Title

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Journal

Journal of the American Heart Association, 4(4)

ISSN

2047-9980

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Publication Date

2015-04-22

DOI

10.1161/jaha.114.001626

ORIGINAL RESEARCH

Heart Rate at Hospital Discharge in Patients With Heart Failure Is Associated With Mortality and Rehospitalization

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***Background*—**Whether heart rate upon discharge following hospitalization for heart failure is associated with long-term adverse outcomes and whether this association differs between patients with sinus rhythm (SR) and atrial fibrillation (AF) have not been well studied.

***Methods and Results*—**We conducted a retrospective cohort study from clinical registry data linked to Medicare claims for 46 217 patients participating in Get With The Guidelines®–Heart Failure. Cox proportional-hazards models were used to estimate the association between discharge heart rate and all-cause mortality, all-cause readmission, and the composite outcome of mortality/readmission through 1 year. For SR and AF patients with heart rate ≥75, the association between heart rate and mortality (expressed as hazard ratio [HR] per 10 beats-per-minute increment) was significant at 0 to 30 days (SR: HR 1.30, 95% CI 1.22 to 1.39; AF: HR 1.23, 95% CI 1.16 to 1.29) and 31 to 365 days (SR: HR 1.15, 95% CI 1.12 to 1.20; AF: HR 1.05, 95% CI 1.01 to 1.08). Similar associations between heart rate and all-cause readmission and the composite outcome were obtained for SR and AF patients from 0 to 30 days but only in the composite outcome for SR patients over the longer term. The HR from 0 to 30 days exceeded that from 31 to 365 days for both SR and AF patients. At heart rates <75, an association was significant for mortality only for both SR and AF patients.

***Conclusions*—**Among older patients hospitalized with heart failure, higher discharge heart rate was associated with increased risks of death and rehospitalization, with higher risk in the first 30 days and for SR compared with AF. **(*J Am Heart Assoc*. 2015;4: e001626 doi: 10.1161/JAHA.114.001626)**

Key Words: heart failure • heart rate • mortality

Heart rate has served as a marker for health and disease in humans for centuries. Prospective cohort studies and retrospective observational studies over the past several decades have contributed to a growing evidence base supporting an association between increased resting heart rate and adverse all-cause and cardiovascular outcomes.[1,2] Recent randomized clinical trial data from patients with heart failure (HF) have implicated heart rate as a potentially modifiable risk factor.[3,4] Most of these prior studies examined patients with chronic stable HF and reduced ejection fraction (EF) participating in a clinical trial.[4–10] The prognostic importance of discharge heart rate in unselected patients after hospitalization for HF has been less well studied. Few studies have included HF patients with preserved EF or those with atrial fibrillation (AF), or had sufficient power to evaluate potential time-dependent differences in the relationship between heart rate and outcomes.

Given this growing awareness as well as potential therapeutic import of an association between resting heart rate and

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/4/3/e001626/suppl/DC1

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Received November 17, 2014; accepted February 28, 2015.

outcomes in patients with HF,[11] we analyzed the relationship between heart rate at the time of hospital discharge and mortality and rehospitalization through 1 year in patients hospitalized for HF. We included patients in sinus rhythm (SR) as well as those in AF given the prevalence and prognostic importance of the latter in patients with HF.[12,13] Our specific objectives were to (1) examine baseline patient characteristics across the distribution of heart rates recorded at discharge in hospitalized patients with a primary discharge diagnosis of HF; (2) examine the association between discharge heart rate and all-cause mortality through 1 year in patients with SR and AF; and (3) examine the association between discharge heart rate and all-cause hospital readmission and the composite outcome of all-cause mortality or all-cause readmission through 1 year in patients with SR and AF.

Methods

Data Sources

The Get With The Guidelines®–Heart Failure (GWTG-HF) program is among the largest quality-improvement initiatives focusing on patients hospitalized with clinician-confirmed HF.[14] The design of the program has been previously described.[15,16] Hospitals participating in the registry use a web-based patient management tool (PMT, Quintiles) to collect data for consecutive patients admitted with HF and to receive recommendations for qualitative improvement in medical management. Patients hospitalized with new or worsening HF as primary diagnosis or patients who developed significant HF symptoms such that HF was the primary discharge diagnosis were included in the registry starting January 1, 2005. Patients were enrolled into the program regardless of their left ventricular function. Hospitals from all regions of the United States are represented and a variety of institutions participate, from community hospitals to large tertiary medical centers. Data collected for each HF patient include demographics, medical/surgical history including any history of AF, admission medications, admission and discharge vital signs, physical examination, rhythm at time of admission, serum laboratory tests, pharmacological and nonpharmacologic interventions, in-hospital outcomes, and discharge information. Trained hospital personnel enter the data by using standardized definitions. All participating hospitals were required to submit the GWTG-HF protocol to their institutional review board for approval. Because data collected were used for qualitative performance improvement, sites were granted a waiver of informed consent under the common rule. Quintiles is the data collection coordination center for the American Heart Association/American Stroke Association Get With the Guidelines® programs. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze de-identified data for research purposes.

We obtained clinical data from the GWTG-HF registry and Medicare claims data from the Centers for Medicare and Medicaid Services. The Medicare data include inpatient claims and corresponding denominator files for 2006 through 2011. The inpatient files contain hospitalization claims covered under Medicare Part A. The denominator files include date of death and information about program eligibility and enrollment. We linked data from the GWTG-HF registry to the research identifiable inpatient claims data with the use of indirect identifiers: admission date, discharge date, sex, and age or date of birth.[17] Combinations of these identifiers are almost always unique, enabling identification of registry hospitalizations in the Medicare claims data. For patients with multiple linked hospitalizations in the registry, we selected the first hospitalization for analysis.

Study Population

SR group

From January 1, 2005, to December 31, 2011, there were 65 032 admissions for patients ≥65 years of age with HF, at 292 sites fully participating in GWTG-HF. From these, we excluded (1) 2473 (3.8%) patients who were not enrolled in fee-for-service Medicare; (2) 2685 (4.1%) patients with missing EF information; and (3) 13 657 (21%) patients without discharge heart rate recorded. Finally, 20 197 patients without AF (defined as fitting none of the criteria for AF, ie, history of AF, AF at presentation or during hospitalization, or new-onset of AF) comprised the SR group. The final sample size for the SR group was 26 020 patients from 271 sites.

AF group

Above exclusions 1 to 3 were employed along with the exclusion of the 26 020 SR patients. The final sample size for the AF group was 20 197 patients from 262 sites.

Outcome measures

The primary outcome was all-cause mortality rate by 1 year. Secondary outcomes were all-cause readmission rate by 1 year and all-cause readmission or mortality rate by 1 year.

Heart rate and rhythm determination

Heart rhythm was electrocardiographically determined. Heart rate was determined in conformance with local protocol for obtaining vital signs. For SR patients, heart rate was determined by palpation or telemetry (depending on patient location). For AF patients, heart rate was electrocardiographically or telemetrically determined.

EF determination

EF in GWTG-HF patients is determined by 2-dimensional transthoracic echocardiography, gated scintigraphy, or contrast left ventriculography.

Statistical Analysis

Baseline patient characteristics were compared across heart rate tertiles for SR and AF patients. Medians and (25th to 75th) percentiles were determined for continuous variables and percentages for categorical variables. Chi-square tests were used to compare categorical variables across tertiles and Wilcoxon rank-sum statistics were used to compare continuous variables across tertiles. Kaplan–Meier survival estimates are plotted by tertile and log rank statistics assessed the difference in survival across the tertiles.

We fit models separately in SR and AF patients to allow for different relationships between patient and hospital characteristics and outcome(s) in each subgroup. The association of heart rate with each outcome for SR patients was assessed using unadjusted and adjusted Cox proportional-hazards regression models for 1-year follow-up. The functional form of heart rate was assessed by first comparing a linear fit to the fit of a restricted cubic spline. Evidence of a nonlinear relationship was identified and linear splines with and without truncation were considered. Several knot points were assessed, and the final transformation selected was the one that maximized model likelihood. The final linear spline was compared to the restricted cubic spline and suggested no lack of fit. Proportional hazards assumptions were assessed using Schoenfeld residuals. There was evidence of a nonproportional relationship over 1 year for each end point, but only for the upper portion of the linear spline (heart rate $\geq$75 beats per minute [bpm]). Subsequently, we determined that fitting a time-varying hazard held proportional on the interval 0 to 30 days and from 31 to 365 days fit the data well. Although risk does not change suddenly at any 1 point in time, this approach attempts to compromise between model fit and intuitive interpretation. A model assuming proportional hazards throughout 1-year follow-up is also reported. Adjusted models include age, gender, race (white versus other), insurance (none, Medicare, Medicaid, other), EF, history of atrial flutter, history of chronic obstructive pulmonary disease (COPD) or asthma, history of diabetes, history of hypertension, history of hyperlipidemia, history of peripheral vascular disease, prior myocardial infarction, prior stroke or transient ischemic attack, history of anemia, history of chronic renal insufficiency, smoking, US census-based geographic region, academic or teaching hospital, rural location, hospital size, and defect-free compliance score (defined as the frequency of patients with 100% compliance with all GWTG-HF-defined performance measures). Single imputation was used to reduce missingness in models. Missing values for categorical variables were imputed to the most likely category.

To determine whether cardiac resynchronization therapy (CRT) might serve as an effect modifier of the heart-rate-outcome relationship, an interaction term was included in adjusted models. The analysis plan specified that if significant, the relationship between heart rate and outcome would be described within CRT and no CRT subgroups; if not significant, the interaction term was dropped and the model was simply adjusted for CRT. Effect modification by EF group (EF$\leq$0.4 versus EF>0.4) was explored in a similar manner.

A sensitivity analysis was performed to determine whether the association between heart rate and the primary outcome (all-cause mortality at 1 year) might be biased by missing EF data. An indicator variable was defined reflecting the presence or absence of EF in each subject and an interaction term, heart rate$\times$EF missing status, was added to the model and a formal test for interaction was performed.

The analysis was repeated in similar fashion for AF patients. A 2-sided P value of $<$0.05 was considered statistically significant for each test. Analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Overall Sample

The overall sample (Table 1) comprised 46 217 patients from 273 sites with a primary discharge diagnosis of HF. The median (interquartile range) age was 80 (12) years with a slight female preponderance (54.3% female versus 45.7% male). Fifty-four percent had a past medical history of HF. Discharge heart rate, the primary variable of interest, appeared normally distributed. The difference between discharge and admission heart rates was statistically significant (mean [SD] difference, −8.8 [20]; P<0.0001). Vital signs at discharge, medications at discharge, and hospital characteristics are reported in Table S1.

SR Patients

There were 26 020 HF patients in the SR group. Discharge heart rates appeared normally distributed with a median of 72 bpm and interquartile range of 18 bpm.

Characteristics of SR Patients

Younger patients, women, and nonwhite patients were more likely to have a higher heart rate (Table 2). A higher heart rate and lower systolic blood pressure on both admission and discharge were more frequent in the highest discharge heart

Table 1. Baseline Patient Characteristics, Overall and by Heart Rate Tertiles

Variable	Level	Overall (N=46 217)		T1 (32 to 68 bpm) (N=16 273)		T2 (69 to 79 bpm) (N=14 574)		T3 (80 to 168 bpm) (N=15 370)		*P* Value
Demographics										
Age	Median	46 217	80	16 273	81	14 574	81	15 370	80	<0.0001
	25th		74		74		74		73	
	75th		86		86		86		86	
Gender	Female	25 088	54.3	8816	54.2	7734	53.1	8538	55.5	<0.0001
	Male	21 129	45.7	7457	45.8	6840	46.9	6832	44.4	
Race	Other (includes UTD)	1062	2.3	385	2.4	332	2.3	345	2.3	0.0761
	Asian	582	1.3	234	1.4	183	1.3	165	1.1	
	Hispanic (any race)	2211	4.8	803	4.9	704	4.9	704	4.6	
	Black	4474	9.8	1562	9.7	1374	9.5	1538	10.1	
	White	37 478	81.8	13 141	81.5	11 867	82.1	12 470	81.9	
	Missing	410	0.9	148	0.9	114	0.8	148	0.9	
Medical history										
Chronic or recurrent atrial fib	Yes	17 277	37.7	5749	35.6	5474	37.9	6054	39.7	<0.0001
Atrial flutter	Yes	1020	2.2	370	2.3	302	2.1	348	2.3	0.4140
COPD or asthma	Yes	13 223	28.8	4174	25.8	4065	28.1	4984	32.7	<0.0001
Diabetes—insulin treated	Yes	7632	16.6	2858	17.7	2425	16.8	2349	15.4	<0.0001
Diabetes—noninsulin treated	Yes	10 775	23.5	3869	23.9	3401	23.5	3505	22.9	0.1267
Hyperlipidemia	Yes	21 761	47.5	8160	50.5	6833	47.3	6768	44.4	<0.0001
Hypertension	Yes	35 584	77.6	12 908	79.9	11 197	77.5	11 479	75.3	<0.0001
PVD	Yes	6490	14.1	2403	14.9	2021	13.9	2066	13.5	0.0026
CAD	Yes	23 915	52.2	8921	55.2	7719	53.4	7275	47.7	<0.0001
Prior MI	Yes	8463	18.5	3185	19.7	2727	18.9	2551	16.7	<0.0001
CVA/TIA	Yes	7590	16.5	2809	17.4	2409	16.7	2372	15.6	<0.0001
ICD	Yes	3407	7.4	1212	7.5	1231	8.5	964	6.3	<0.0001
Heart failure	Yes	24 717	53.9	8755	54.2	7807	54.0	8155	53.5	0.4049
Anemia	Yes	9043	19.7	3231	20.0	2844	19.7	2968	19.5	0.4767
Pacemaker	Yes	6552	14.3	2406	14.9	2408	16.7	1738	11.4	<0.0001
CRT-P (CRT-pacing only)	Yes	323	0.7	126	0.8	107	0.7	90	0.6	0.1087
CRT-D (CRT with ICD)	Yes	885	1.9	277	1.7	365	2.5	243	1.6	<0.0001
Dialysis (chronic)	Yes	1319	2.9	402	2.5	388	2.7	529	3.5	<0.0001
Renal insufficiency	Yes	8927	19.5	3356	20.8	2779	19.2	2792	18.3	<0.0001
Depression	Yes	4711	10.3	1627	10.1	1489	10.3	1595	10.5	0.5264
Prior PCI	Yes	4679	10.2	1770	10.9	1523	10.5	1386	9.1	<0.0001
Prior CABG	Yes	6787	14.8	2620	16.2	2194	15.2	1973	12.9	<0.0001
Valvular heart disease	Yes	6692	14.6	2314	14.3	2102	14.5	2276	14.9	0.3188
CABG/PCI undetermined	Yes	6108	13.3	2261	14.0	2032	14.1	1815	11.9	<0.0001
Smoking	Yes	4188	9.1	1353	8.4	1271	8.8	1564	10.3	<0.0001

Continued

Table 1. Continued

Variable	Level	Overall (N=46 217)		T1 (32 to 68 bpm) (N=16 273)		T2 (69 to 79 bpm) (N=14 574)		T3 (80 to 168 bpm) (N=15 370)		*P* Value
Diagnosis										
Cardiac diagnosis	Heart failure with CAD	20 740	44.96	7734	47.60	6681	45.93	6325	41.23	<0.0001
	Confirmed AMI—non-STEMI	113	0.24	42	0.26	33	0.23	38	0.25	
	Confirmed AMI—STEMI	10	0.02	1	0.01	3	0.02	6	0.04	
	Confirmed AMI—STEMI/non-STEMI unspecified	13	0.03	3	0.02	7	0.05	3	0.02	
	Other	670	1.45	242	1.49	188	1.29	240	1.56	
	Peripheral vascular disease	38	0.08	15	0.09	10	0.07	13	0.08	
	Cerebral vascular disease	9	0.02	2	0.01	4	0.03	3	0.02	
	Unstable angina	52	0.11	23	0.14	6	0.04	23	0.15	
	Coronary artery disease	90	0.20	31	0.19	22	0.15	37	0.24	
	Heart failure, no CAD	24 398	52.89	8156	50.19	7591	52.19	8651	56.40	
	Missing	84	0.18	24	0.15	29	0.20	31	0.20	
Vital signs at admission										
Heart rate, bpm	Median	45 668	80	16 050	72	14 417	80	15 201	89	<0.0001
	25th		69		63		70		78	
	75th		94		85		92		103	
Systolic blood pressure, mm Hg	Median	45 664	139	16 059	143	14 409	139	15 196	134	<0.0001
	25th		120		124		120		117	
	75th		159		164		159		153	
Diastolic blood pressure, mm Hg	Median	45 692	73	16 072	72	14 416	73	15 204	74	<0.0001
	25th		63		62		63		64	
	75th		85		84		85		85	
Labs at admission										
BNP <100	Yes	2002	5.9	653	5.5	588	5.5	761	6.8	<0.0001
	No	31 670	94.1	11 237	94.5	10 018	94.5	10 415	93.2	
	Missing	12 545	27.1	4383	26.9	3968	27.2	4194	27.3	
Serum creatinine, mg/dL	Median	41 899	1.3	14 667	1.3	13 229	1.3	14 003	1.3	<0.0001
	25th		1.0		1.0		1.0		1.0	
	75th		1.8		1.8		1.8		1.8	
BUN, mg/dL	Median	41 563	25	14 564	26	13 120	25	13 879	25	<0.0001
	25th		18		18		18		18	
	75th		37		37		37		37	
Troponin, ng/dL	Median	34 666	0.05	12 262	0.05	10 875	0.05	11 529	0.05	0.0731
	25th		0.03		0.03		0.03		0.03	
	75th		0.10		0.10		0.10		0.11	
Ejection fraction	Median	46 217	45	16 273	50	14 574	45	15 370	45	<0.0001
	25th		30		30		30		30	
	75th		55		57		55		55	

AMI indicates acute myocardial infarction; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CVA/TIA, cerebrovascular accident/transient ischemic attack; ICD, implantable cardiac defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction; UTD, unable to determine.

Table 2. Baseline Patient Characteristics for Patients With Normal Sinus Rhythm, Overall and by Heart Rate Tertiles

Variable	Level	Overall (N=26 020)		T1 (33 to 67 bpm) (N=8544)		T2 (68 to 78 bpm) (N=8793)		T3 (79 to 148 bpm) (N=8683)		*P* Value
Demographics										
Age	Median	26 020	79	8544	80	8793	79	8683	79	<0.0001
	25th		72		73		73		72	
	75th		85		86		85		85	
Gender	Female	14 448	55.5	4763	55.7	4806	54.7	4879	56.2	0.1104
	Male	11 572	44.5	3781	44.2	3987	45.3	3804	43.8	
Race	White	19 799	76.9	6531	77.2	6689	76.8	6579	76.5	0.0011
	Black	3326	12.9	1024	12.1	1103	12.7	1199	13.9	
	Hispanic (any race)	1586	6.2	534	6.3	567	6.5	485	5.6	
	Asian	366	1.4	135	1.6	132	1.5	99	1.15	
	Other (includes UTD)	682	2.6	232	2.7	217	2.5	233	2.71	
	Missing	261	1.0	88	1.0	85	1.0	88	1.0	
Medical history										
Chronic or recurrent atrial fib	No	25 667	100	8435	100	8671	100	8561	100	
Atrial flutter	Yes	325	1.3	113	1.3	105	1.2	107	1.2	0.7430
COPD or asthma	Yes	7262	28.3	2105	24.9	2327	26.8	2830	33.1	<0.0001
Diabetes—insulin treated	Yes	4770	18.6	1690	20.0	1624	18.7	1456	17.0	<0.0001
Diabetes—non-insulin-treated	Yes	6446	25.1	2118	25.1	2196	25.3	2132	24.9	0.8153
Hyperlipidemia	Yes	12 284	47.9	4282	50.8	4221	48.7	3781	44.2	<0.0001
Hypertension	Yes	20 076	78.2	6813	80.8	6829	78.8	6434	75.2	<0.0001
PVD	Yes	3692	14.4	1254	14.9	1276	14.7	1162	13.6	0.0311
CAD	Yes	13 628	53.1	4759	56.4	4729	54.5	4140	48.4	<0.0001
Prior MI	Yes	4902	19.1	1759	20.8	1706	19.7	1437	16.8	<0.0001
CVA/TIA	Yes	3973	15.5	1390	16.5	1378	15.9	1205	14.1	<0.0001
ICD	Yes	1770	6.9	574	6.8	663	7.7	533	6.2	0.0011
Heart failure	Yes	12 722	49.6	4242	50.3	4327	49.9	4153	48.5	0.0504
Anemia	Yes	5011	19.5	1674	19.8	1687	19.5	1650	19.3	0.6300
Pacemaker	Yes	2786	10.8	980	11.6	1063	12.3	743	8.7	<0.0001
CRT-P (CRT-pacing only)	Yes	94	0.4	36	0.4	31	0.4	27	0.3	0.4789
CRT-D (CRT with ICD)	Yes	435	1.7	137	1.6	183	2.1	115	1.3	0.0004
Dialysis (chronic)	Yes	940	3.7	266	3.1	286	3.3	388	4.5	<0.0001
Renal insufficiency	Yes	5245	20.4	1810	21.5	1775	20.5	1660	19.4	0.0037
Depression	Yes	2594	10.1	815	9.7	905	10.4	874	10.2	0.2259
Prior PCI	Yes	2711	10.6	939	11.1	975	11.2	797	9.3	<0.0001
Prior CABG	Yes	3564	13.9	1329	15.8	1216	14.0	1019	11.9	<0.0001
Valvular heart disease	Yes	2857	11.1	940	11.1	946	10.9	971	11.3	0.6651
CABG/PCI undetermined	Yes	3745	14.6	1289	15.3	1366	15.7	1090	12.7	<0.0001
Smoking	Yes	2751	10.7	816	9.6	894	10.3	1041	12.1	<0.0001

Continued

Table 2. Continued

Variable	Level	Overall (N=26 020)		T1 (33 to 67 bpm) (N=8544)		T2 (68 to 78 bpm) (N=8793)		T3 (79 to 148 bpm) (N=8683)		*P* Value
Diagnosis										
Cardiac diagnosis	Heart failure with CAD	11 556	44.50	4050	47.48	4008	45.65	3498	40.39	<0.0001
	Confirmed AMI—non-STEMI	81	0.31	24	0.28	29	0.33	28	0.32	
	Confirmed AMI—STEMI	8	0.03	1	0.01	2	0.02	5	0.06	
	Confirmed AMI—STEMI/ non-STEMI unspecified	11	0.04	1	0.01	6	0.07	4	0.05	
	Other	432	1.66	140	1.64	136	1.55	156	1.80	
	Peripheral vascular disease	24	0.09	7	0.08	10	0.11	7	0.08	
	Cerebral vascular disease	6	0.02	2	0.02	2	0.02	2	0.02	
	Unstable angina	35	0.13	18	0.21	3	0.03	14	0.16	
	Coronary artery disease	58	0.22	23	0.27	14	0.16	21	0.24	
	Heart failure, no CAD	13 759	52.98	4264	49.99	4569	52.04	4926	56.88	
	Missing	50	0.19	14	0.16	14	0.16	22	0.25	
Vital signs at admission										
Heart rate, bpm	Median	25 681	80	8426	71	8687	80	8568	88	<0.0001
	25th		69		62		70		78	
	75th		93		84		91		101	
Systolic blood pressure, mm Hg	Median	25 666	142	8419	147	8680	141	8567	137	<0.0001
	25th		122		127		123		118	
	75th		163		169		163		157	
Diastolic blood pressure, mm Hg	Median	25 692	73	8430	72	8688	73	8574	73	0.0069
	25th		63		62		63		63	
	75th		85		84		85		85	
Labs at admission										
BNP <100 pg/mL	Yes	1183	6.3	316	5.1	404	6.4	463	7.4	<0.0001
	No	17 626	93.7	5865	94.9	5951	93.6	5810	92.6	
	Missing	7211	27.7	2363	27.7	2438	27.7	2410	27.8	
Serum creatinine, mg/dL	Median	23 562	1.3	7671	1.4	7972	1.3	7919	1.3	<0.0001
	25th		1.0		1.0		1.0		1.0	
	75th		1.8		1.9		1.8		1.8	
BUN, mg/dL	Median	23 352	25	7613	26	7903	25	7836	25	<0.0001
	25th		18		18		18		17	
	75th		37		37		37		37	
Troponin, ng/dL	Median	19 600	0.05	6454	0.05	6595	0.05	6551	0.06	<0.0001
	25th		0.03		0.03		0.03		0.03	
	75th		0.12		0.10		0.12		0.13	
Ejection fraction	Median	26 020	45	8544	50	8793	45	8683	40	<0.0001
	25th		30		30		30		26	
	75th		55		58		55		55	

AMI indicates acute myocardial infarction; BNP, brain natriuretic peptide; bpm, beats per minute; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CVA/TIA, cerebrovascular accident/transient ischemic attack; ICD, implantable cardiac defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction; UTD, unable to determine.

Table 3. Frequency of 1-Year Outcomes by Heart Rate Tertiles (Sinus Rhythm Patients)

Variable	Level	Overall (N=26 020)		T1 (33 to 67 bpm) (N=8544)		T2 (68 to 78 bpm) (N=8793)		T3 (79 to 148 bpm) (N=8683)		*P* Value
Mortality	Yes	7820	30.05	2283	26.72	2512	28.57	3025	34.84	<0.0001
All-cause readmission	Yes	16 154	62.09	5277	61.76	5500	62.56	5377	61.93	0.5236
Mortality or all-cause readmission	Yes	18 219	70.02	5835	68.29	6116	69.56	6268	72.20	<0.0001

rate tertile. Patients with higher discharge heart rate were more likely to have a history of COPD and smoking but less likely to have a history of diabetes, hypertension, peripheral vascular disease, prior myocardial infarction, prior stroke, and renal insufficiency. For SR patients with a history of COPD or asthma, and eligible for β-blocker therapy, 91.6% were prescribed β-blockers at discharge and 8.4% were not. For patients with a history of COPD or asthma, and eligible for evidence-based β-blocker therapy, 80.5% were prescribed evidence-based β-blockers at discharge and 19.5% were not. The quality of care composite measure, defect-free care, was lowest in the highest heart rate tertile. Importantly, this measure includes the use of β-blockers. Vital signs at discharge, medications at discharge, and hospital characteristics are reported in Table S2.

Study Outcomes in SR Patients

Overall all-cause mortality at 1 year was 30.1%, and the rate of all-cause readmission or mortality at 1 year was 70.0% (Table 3). There were significant differences in each outcome by 1 year across the discharge heart rate tertiles, with higher mortality and the composite outcome of mortality or all-cause readmission in the highest tertile (Table 3). Survival by 1 year was significantly different across the tertiles, with the lowest survival rate occurring in the highest tertile (log rank $P<0.0001$) (Figure 1). A similar pattern was observed for the composite outcome of readmission/mortality by 1 year.

Crude and adjusted measures of the association between discharge heart rate (expressed as a continuous variable) and each outcome are reported in Table 4. For patients with a discharge heart rate ≥75 bpm, there were worse outcomes with increasing heart rate. The slope of this relationship changed for patients with heart rate <75 bpm (Figure 2). After adjustment for differences in clinical characteristics, the risk for all-cause mortality at heart rate <75 increased by 6.0% (hazard ratio [HR] 1.060, 95% CI 1.018, 1.103; $P=0.0047$) per 10-bpm increment over the 1 year of follow-up. At heart rate ≥75 bpm, the risk for all-cause mortality increased by 18.5% (HR 1.185, 95% CI 1.149, 1.222; $P<0.0001$) per 10-bpm increment over the 1 year of follow-up. When the data were analyzed by time interval to better meet proportionality assumptions, there was a 19.2% higher risk for mortality (HR 1.192, 95% CI 1.075, 1.322; $P=0.0008$) per 10-bpm increment in heart rate <75 bpm over the first 30 days. There was a 30.0% higher risk for mortality (HR 1.300, 95% CI 1.219, 1.386; $P<0.0001$) per 10-bpm increment in heart rate ≥75 bpm over the first 30 days. Beyond that and through 365 days, the risk for all-cause mortality was not significant for heart rates <75 bpm but was 15.5% higher (HR 1.155, 95% CI 1.116, 1.196; $P<0.0001$) per 10-bpm increase in heart rate ≥75 bpm. Qualitatively similar patterns were observed for the association between discharge heart rate and all-cause readmission as well as the composite of all-cause mortality or readmission (Table 4). For all outcomes, the HR over the first 30 days was significantly different from 1.0 at heart rates <75 bpm but was not significantly different from 1.0 over the interval from 31 to 365 days.

There was no evidence for effect modification by CRT in models for mortality (interaction $P=0.374$), all-cause

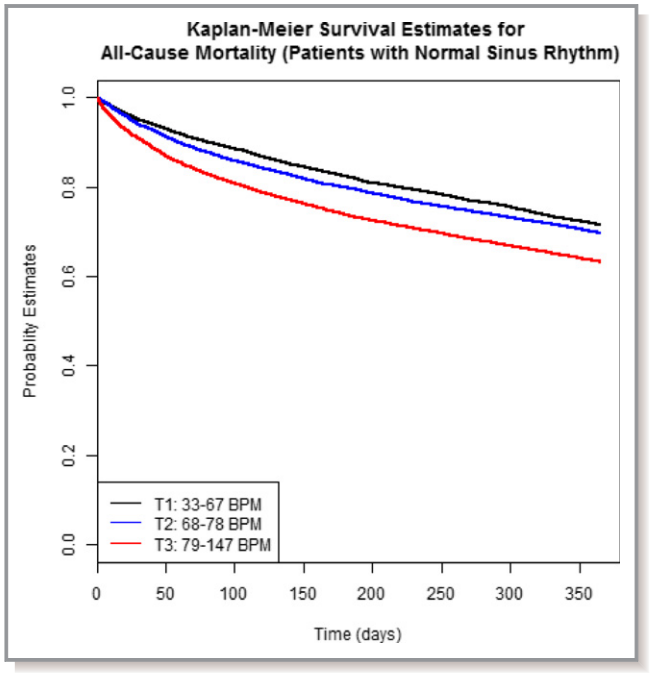

Figure 1. Kaplan–Meier plot of event-free survival by 1 year in patients with sinus rhythm (n=26 020). There was a significant difference across the discharge heart rate tertiles (log rank $P<0.0001$) with survival highest in the lowest tertile (see text for details). BPM indicates beats per minute.

Table 4. Hazard Ratios (HR) for Heart Rate per 10 bpm (Sinus Rhythm Patients, n=26 020)

	Unadjusted Model			Adjusted Model (Patient and Hospital Characteristics)		
Outcome	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Mortality						
Heart rate <75 bpm*	1.054	1.015, 1.094	0.0061	1.060	1.018, 1.103	0.0047
Heart rate <75 bpm						
[0, 30] days	1.125	1.034, 1.224	0.0061	1.192	1.075, 1.322	0.0008
[31, 365] days	1.045	1.002, 1.089	0.0417	1.040	0.995, 1.086	0.0794
Heart rate ≥75 bpm*	1.211	1.179, 1.245	<0.0001	1.185	1.149, 1.222	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.385	1.320, 1.454	<0.0001	1.300	1.219, 1.386	<0.0001
[31, 365] days	1.146	1.109, 1.184	<0.0001	1.155	1.116, 1.196	<0.0001
All-cause readmission						
Heart rate <75 bpm*	1.025	1.000, 1.052	0.0514	1.019	0.993, 1.046	0.1519
Heart rate <75 bpm						
[0, 30] days	1.056	1.011, 1.102	0.0141	1.045	0.999, 1.092	0.0530
[31, 365] days	1.013	0.982, 1.045	0.4309	1.009	0.977, 1.042	0.5787
Heart rate ≥75 bpm*	1.054	1.031, 1.077	<0.0001	1.063	1.039, 1.088	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.104	1.067, 1.142	<0.0001	1.128	1.089, 1.168	<0.0001
[31, 365] days	1.020	0.991, 1.050	0.1777	1.020	0.990, 1.051	0.1872
Composite readmission/mortality						
Heart rate <75 bpm*	1.024	1.000, 1.049	0.0541	1.023	0.998, 1.049	0.0769
Heart rate <75 bpm						
[0, 30] days	1.051	1.010, 1.094	0.0148	1.052	1.008, 1.097	0.0191
[31, 365] days	1.014	0.984, 1.044	0.3771	1.011	0.980, 1.042	0.4931
Heart rate ≥75 bpm*	1.098	1.077, 1.120	<0.0001	1.082	1.059, 1.105	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.171	1.137, 1.206	<0.0001	1.148	1.111, 1.186	<0.0001
[31, 365] days	1.044	1.016, 1.072	0.0018	1.037	1.008, 1.067	0.0125

*Ignoring violation of proportional hazards assumption (see text for details), model adjusted for the following covariates: age, gender, race (white vs other), insurance (none, Medicare, Medicaid, other), ejection fraction, history of atrial flutter, history of chronic obstructive pulmonary disease or asthma, history of diabetes, history of hyperlipidemia, history of hypertension, history of peripheral vascular disease, prior myocardial infarction, prior stroke or transient ischemic attack, history of anemia, history of chronic renal insufficiency, pacemaker, smoking, geographic region, academic or teaching hospital, rural location, hospital size, and defect-free compliance score.

readmission (*P*=0.952), or composite readmission/mortality (*P*=0.981). Including CRT in the adjusted model did not meaningfully change the HRs or 95% CIs for all-cause mortality or all-cause readmission at heart rate ≥75 bpm at either 0 to 30 days or 31 to 365 days. However, the HRs for heart rate <75 bpm at 0 to 30 days and heart rate ≥75 bpm at 31 to 365 days were no longer significant for the composite of all-cause mortality/readmission. There was no evidence of effect modification by EF in adjusted models for mortality (interaction *P*=0.292), all- cause readmission (*P*=0.054), or composite readmission/mortality (*P*=0.187).

EF data were missing in 6.06% of SR patients. There was no significant interaction between heart rate and the presence or absence of missing EF data (*P* for interaction 0.87), indicating no difference in the degree of association between heart rate and all-cause mortality between those with missing and nonmissing EF data.

AF Patients

There were 20 197 patients (43.7%) with either a history of AF or AF documented during the index hospitalization. Similar to the SR patients, discharge heart rates appeared normally

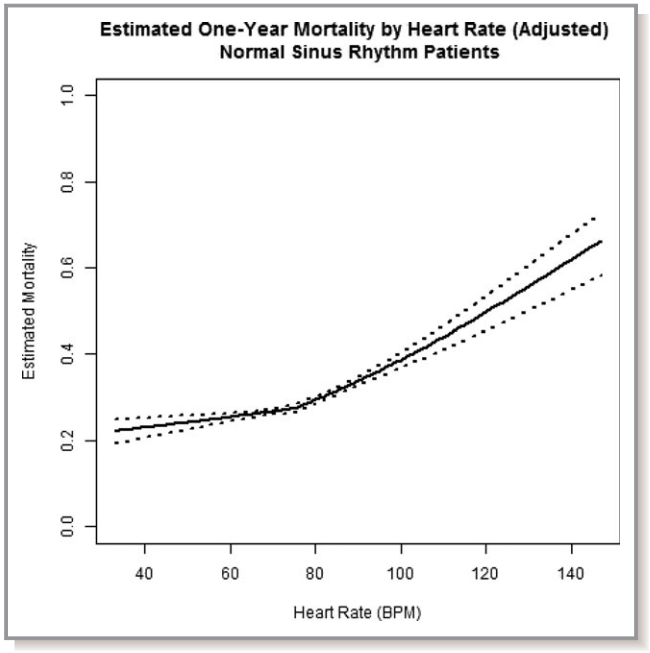

Figure 2. Estimated mortality at 1 year in patients with sinus rhythm (n=26 020). The inflection point represents a single linear spline at 75 bpm (see text for details). Risk of mortality rises steadily with heart rate. BPM indicates beats per minute.

distributed with a median of 74 bpm and interquartile range of 19 bpm.

Characteristics of AF Patients

Women and white patients were more likely to have higher heart rate (Table 5). A higher heart rate and lower systolic blood pressure on both admission and discharge were more frequent in the highest discharge heart rate tertile. Patients with higher discharge heart rates were more likely to have a history of COPD and smoking but less likely to have a history of diabetes, hypertension, peripheral vascular disease, prior myocardial infarction, prior stroke, and renal insufficiency. EF significantly varied by discharge heart rate tertile. For AF patients with a history of COPD or asthma, and eligible for β-blocker therapy, 91.4% were prescribed β-blockers at discharge, and 8.7% were not. For patients with a history of COPD or asthma, and eligible for evidence-based β-blockers, 78.8% were prescribed evidence-based β-blockers at discharge, and 21.2% were not. Defect-free care was lowest in the highest discharge heart rate tertile. Importantly, this measure includes the use of β-blockers. Vital signs at discharge, medications at discharge, and hospital characteristics are reported in Table S3.

Study Outcomes in AF Patients

Overall all-cause mortality at 1 year was 35.3% and the rate of all-cause readmission or mortality at 1 year was 72.4%. There was a significant difference in mortality by 1 year across the tertiles (log rank $P<0.0001$) (Figure 3). In contrast to the SR patients, the composite outcome of mortality/all-cause readmission was not significantly different across the discharge heart rate tertiles (Table 6).

Crude and adjusted measures of the association between discharge heart rate (expressed as a continuous variable) and each outcome are reported in Table 7. For patients with a discharge heart rate ≥75 bpm, there were worse outcomes with increasing heart rate. The slope of this relationship changed only slightly for patients with heart rate <75 bpm (Figure 4). After adjustment for differences in clinical characteristics, the risk for all-cause mortality increased, overall, by 8.4% (HR 1.084, 95% CI 1.039, 1.131; $P=0.0002$) per 10 bpm increase in heart rate for patients with discharge heart rate <75 bpm and 8.8% (HR 1.088, 95% CI 1.056, 1.120; $P<0.0001$) in patients with heart rate ≥75 bpm. There was a 22.8% (HR 1.228, 95% CI 1.165, 1.294; $P<0.0001$) per 10 bpm increment in heart in rate for the first 30 days at heart rate ≥75 bpm. Beyond that, and through 365 days, the risk for all-cause mortality was 4.9% higher (HR 1.049, 95% CI 1.014, 1.084; $P=0.0053$) for each 10-beat increment. Of note is that for heart rate <75 bpm, the risk for mortality increased by 8.7% (HR 1.087, 95% CI 1.042, 1.134; $P=0.0024$) per 10 bpm increment in heart rate. At heart rates <75 bpm there was no significant association between heart rate and risk for all-cause readmission or risk for the composite outcome of readmission/mortality. At heart rates ≥75 bpm, there was a 10.7% increase in risk (HR 1.107, 95% CI 1.073, 1.143; $P<0.0001$) per 10-beat increment for short-term (0 to 30 days) all-cause readmission and a 12.2% increased risk (HR 1.122, 95% CI 1.089, 1.155; $P<0.0001$) per 10-beat increment for the short-term composite outcome readmission/mortality. This increase in risk for the latter outcomes was not, however, present at heart rates ≥75 bpm from 31 to 365 days (Table 7).

There was no evidence of effect modification by CRT in the model for mortality (interaction $P=0.619$), and further adjusting for CRT status yielded mostly similar results as presented previously, although the HR for heart rates ≥75 bpm from 31 to 365 days was no longer significant ($P=0.2945$). There was evidence of effect modification by CRT in the models for all-cause readmission ($P=0.031$) and composite readmission/mortality ($P=0.033$) (Table 8). The interaction term (heart rate×EF) was statistically significant in adjusted models for mortality (interaction $P=0.010$), all-cause readmission ($P=0.003$), and composite readmission/mortality ($P=0.019$). The association between heart rate and mortality was more pronounced among patients with EF >0.40 compared to EF ≤0.40 (interaction $P=0.010$). Further evidence of effect modification was observed for all-cause readmission and composite all-cause mortality/readmission outcomes (interaction $P=0.003$, $P=0.019$, respectively) (Table 9).

Table 5. Baseline Patient Characteristics for Patients With Atrial Fibrillation, Overall and by Heart Rate Tertiles

Variable	Level	Overall (N=20 197)		T1 (32 to 68 bpm) (N=6692)		T2 (69 to 79 bpm) (N=6385)		T3 (80 to 168 bpm) (N=7120)		*P* Value
Demographics										
Age	Median	20 197	82	6692	82	6385	82	7120	81	0.0591
	25th		75		75		76		75	
	75th		87		87		87		87	
Gender	Female	10 640	52.7	3480	52.0	3264	51.1	3896	54.7	<0.0001
	Male	9557	47.3	3212	48.0	3121	48.9	3224	45.3	
Race	White	17 679	88.2	5835	87.8	5642	88.9	6202	87.9	0.0489
	Black	1148	5.7	409	6.2	329	5.2	410	5.8	
	Hispanic (any race)	625	3.1	193	2.9	186	2.9	246	3.5	
	Asian	216	1.2	86	1.3	60	0.95	70	1.0	
	Other (includes UTD)	380	1.9	123	1.9	126	1.99	131	1.8	
	Missing	149	0.7	46	0.7	42	0.66	61	0.9	
Medical history										
Chronic or recurrent atrial fib	Yes	17 277	85.6	5749	85.9	5474	85.8	6054	85.1	0.3493
Atrial flutter	Yes	695	3.4	245	3.7	203	3.2	247	3.5	0.3191
COPD or asthma	Yes	5961	29.5	1796	26.8	1888	29.6	2277	32.0	<0.0001
Diabetes—insulin treated	Yes	2862	14.2	964	14.4	926	14.5	972	13.7	0.2989
Diabetes—non-insulin-treated	Yes	4329	21.5	1481	22.1	1358	21.3	1490	20.9	0.2219
Hyperlipidemia	Yes	9477	46.9	3368	50.3	2937	46.0	3172	44.6	<0.0001
Hypertension	Yes	15 508	76.8	5265	78.7	4879	76.5	5364	75.4	<0.0001
PVD	Yes	2798	13.9	986	14.7	855	13.4	957	13.5	0.0410
CAD	Yes	10 287	51.0	3598	53.8	3334	52.3	3355	47.2	<0.0001
Prior MI	Yes	3561	17.6	1213	18.1	1158	18.1	1190	16.7	0.0431
CVA/TIA	Yes	3617	17.9	1252	18.7	1140	17.9	1225	17.2	0.0743
ICD	Yes	1637	8.1	569	8.5	607	9.5	461	6.5	<0.0001
Heart failure	Yes	11 995	59.4	3991	59.6	3797	59.5	4207	59.2	0.8272
Anemia	Yes	4032	20.0	1371	20.5	1254	19.7	1407	19.8	0.4329
Pacemaker	Yes	3766	18.7	1308	19.5	1423	22.3	1035	14.5	<0.0001
CRT-P (CRT-pacing only)	Yes	229	1.1	84	1.3	80	1.3	65	0.9	0.0921
CRT-D (CRT with ICD)	Yes	450	2.2	128	1.9	188	2.9	134	1.9	<0.0001
Dialysis (chronic)	Yes	379	1.9	113	1.7	110	1.7	156	2.2	0.0509
Renal insufficiency	Yes	3682	18.2	1326	19.8	1135	17.8	1221	17.2	0.0002
Depression	Yes	2117	10.5	706	10.5	658	10.3	753	10.6	0.8577
Prior PCI	Yes	1968	9.7	716	10.7	612	9.6	640	9.0	0.0030
Prior CABG	Yes	3223	16.0	1159	17.3	1056	16.5	1008	14.2	<0.0001
Valvular heart disease	Yes	3835	19.0	1259	18.8	1206	18.9	1370	19.3	0.7774
CABG/PCI undetermined	Yes	2363	11.7	823	12.3	769	12.1	771	10.8	0.0167
Medical history										
Smoking	Yes	1437	7.2	421	6.3	445	7.0	571	8.1	0.0003

Continued

Table 5. Continued

Variable	Level	Overall (N=20 197)		T1 (32 to 68 bpm) (N=6692)		T2 (69 to 79 bpm) (N=6385)		T3 (80 to 168 bpm) (N=7120)		*P* Value
Diagnosis										
Cardiac diagnosis	Heart failure with CAD	9184	45.55	3200	47.89	2983	46.81	3001	42.21	<0.0001
	Confirmed AMI—non-STEMI	32	0.16	12	0.18	10	0.16	10	0.14	
	Confirmed AMI—STEMI	2	0.01	0	0.00	1	0.02	1	0.01	
	Confirmed AMI—STEMI/ non-STEMI unspecified	2	0.01	2	0.03	0	0.00	0	0.00	
	Other	238	1.18	80	1.20	67	1.05	91	1.28	
	Peripheral vascular disease	14	0.07	7	0.10	1	0.02	6	0.08	
	Cerebral vascular disease	3	0.01	0	0.00	2	0.03	1	0.01	
	Unstable angina	17	0.08	4	0.06	4	0.06	9	0.13	
	Coronary artery disease	32	0.16	7	0.10	9	0.14	16	0.23	
	Heart failure, no CAD	10 639	52.76	3370	50.43	3295	51.71	3974	55.90	
	Missing	34	0.17	10	0.15	13	0.20	11	0.15	
Vital signs at admission										
Heart rate, bpm	Median	19 987	81	6601	73	6324	80	7062	90	<0.0001
	25th		70		63		70		78	
	75th		97		87		93		105	
Systolic blood pressure, mm Hg	Median	19 998	135	6615	138	6325	135	7058	132	<0.0001
	25th		118		120		118		115	
	75th		154		158		154		150	
Diastolic blood pressure, mm Hg	Median	20 000	73	6616	72	6326	73	7058	74	<0.0001
	25th		63		62		63		64	
	75th		85		83		84		86	
Labs at admission										
BNP <100 pg/mL	Yes	819	5.5	269	5.4	242	5.1	308	5.9	0.2406
	No	14 044	94.5	4690	94.6	4454	94.8	4900	94.1	
	Missing	5334	26.4	1733	25.9	1689	26.4	1912	26.8	
Serum creatinine, mg/dL	Median	18 337	1.3	6062	1.3	5795	1.3	6480	1.3	<0.0001
	25th		1.0		1.0		1.0		1.0	
	75th		1.7		1.7		1.7		1.7	
BUN, mg/dL	Median	18 211	26	6023	26	5750	26	6438	25	0.2853
	25th		18		18		18		18	
	75th		37		38		37		37	
Troponin, ng/dL	Median	15 066	0.05	5019	0.05	4737	0.05	5310	0.05	0.0117
	25th		0.03		0.03		0.03		0.02	
	75th		0.10		0.10		0.10		0.10	
Ejection fraction	Median	20 197	48	6692	50	6385	45	7120	48	<0.0001
	25th		30		32		30		30	
	75th		55		57		55		55	

AMI indicates acute myocardial infarction; bpm, beats per minute; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CVA/TIA, cerebrovascular accident/transient ischemic attack; ICD, implantable cardiac defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction; UTD, unable to determine.

Table 6. Frequency of 1-Year Outcomes by Heart Rate Tertiles (Atrial Fibrillation Patients)

Variable	Level	Overall (N=20 197)		T1 (32 to 68 bpm) (N=6692)		T2 (69 to 79 bpm) (N=6385)		T3 (80 to 168 bpm) (N=7120)		*P* Value
Mortality	Yes	7138	35.34	2161	32.29	2210	34.61	2767	38.86	<0.0001
All-cause readmission	Yes	12 543	62.10	4212	62.94	3976	62.27	4355	61.17	0.0940
Mortality or all-cause readmission	Yes	14 612	72.35	4795	71.65	4596	71.98	5221	73.33	0.0649

EF data were missing in 4.70% of AF patients. There was no significant interaction between heart rate and the presence or absence of missing EF data (*P* for interaction 0.81), indicating no difference in the degree of association between heart rate and all-cause mortality between those with missing and nonmissing EF data.

Discussion

In this analysis of over 46 000 patients discharged alive following treatment for HF in centers participating in the AHA GWTG-HF program from 2005 to 2011, we observed a significant and independent association of heart rate at the time of discharge on the risks for short- (discharge to 30 days) and longer-term (31 to 365 days) mortality in SR and AF patients. The associations between discharge heart rate and risks of all-cause readmission and the composite outcome of all-cause mortality/readmission were significant over the short term in both SR and AF, but only for the composite outcome over the longer term in SR. The magnitude of the association (HR) was greater over the short term and varied according to the cardiac rhythm status. Among patients with AF, the magnitude of association was significantly modified by discharge CRT status (all-cause readmission and the composite outcome) and by EF (all outcomes).

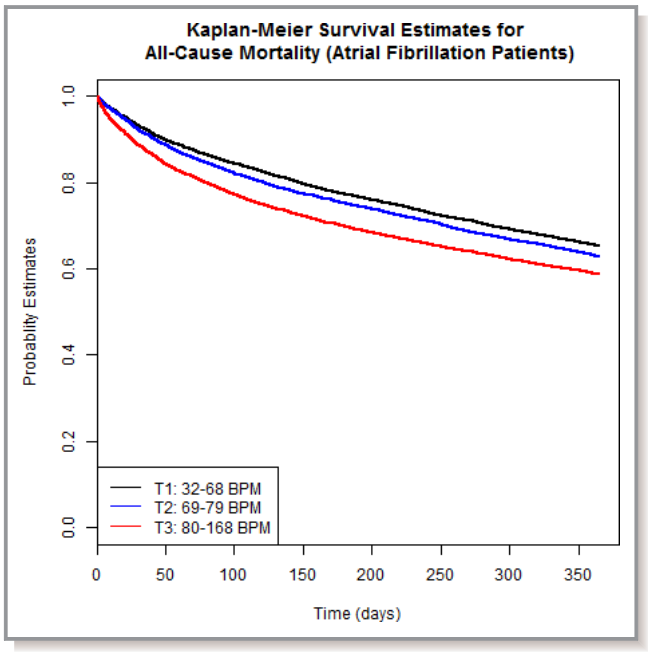

Figure 3. Kaplan–Meier plot of event-free survival by 1 year in patients with atrial fibrillation (n=20 197). There was a significant difference across the discharge heart rate tertiles (log rank *P*<0.0001), with survival highest in the lowest tertile (see text for details). BPM indicates beats per minute.

Our data are in qualitative agreement with conclusions from prior studies regarding an overall positive association between heart rate and adverse cardiovascular outcomes in patients with HF (Table 10). However, important differences exist. Studies derived from randomized clinical trials of specific therapies and which analyzed "baseline" (prerandomization) heart rate as the covariate of interest have been inconsistent in identifying a clinically meaningful association with postdischarge adverse outcomes.[5–7] Clinical trials that narrowed heart rate inclusion criteria[4] or studies in which post-hoc defined cut points for the analysis of the heart rate–outcome association[3,6] were employed differ methodologically from the present study and enrolled more selective patient populations. Most prior studies excluded patients with AF. Few studies included patients with HF and preserved EF. The majority of prior studies also failed to take into account, or report, the extent of guideline-based medical and device therapy. Finally, no study recognized, or reported, a time-dependence of the heart-rate-outcome association.

A prior study from the GWTG-HF program identified an association between the admission heart rate and in-hospital mortality.[19] Although the magnitude of the association in that study depended on the cardiac rhythm, the EF, and the absolute heart rate, there was, overall, a 23% increase in the adjusted odds of in-hospital death per 10-bpm increment in heart rate.[19] Differences between these 2 studies derive from a number of considerations. First, the latter study analyzed admission heart rate as the covariate of interest, whereas the current study analyzed discharge heart rate and, as such, an association between discharge heart rate and outcome will reflect the impact of treatment and the nature of the association will quite likely differ. Second, the latter study reported crude in-hospital mortality rates, whereas the current study reports the predicted probability of mortality obtained from the adjusted Cox multivariable model. Adjusted

Table 7. Hazard Ratios for Heart Rate, per 10 bpm (Atrial Fibrillation Patients, n=20 197)

	Unadjusted Model			Adjusted Model (Patient and Hospital Characteristics)		
Outcome	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Mortality						
Heart rate <75 bpm*	1.074	1.033, 1.117	0.0003	1.084	1.039, 1.131	0.0002
Heart rate <75 bpm	1.083	1.041, 1.126	<0.0001	1.087	1.042, 1.134	0.0001
Heart rate ≥75 bpm*	1.122	1.093, 1.151	<0.0001	1.088	1.056, 1.120	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.312	1.262, 1.364	<0.0001	1.228	1.165, 1.294	<0.0001
[31, 365] days	1.043	1.011, 1.076	0.0082	1.049	1.014, 1.084	0.0053
All-cause readmission						
Heart rate <75 bpm*	1.009	0.980, 1.038	0.5508	1.011	0.981, 1.041	0.4833
Heart rate <75 bpm	1.011	0.982, 1.040	0.4572	1.013	0.983, 1.043	0.4012
Heart rate ≥75 bpm*	1.026	1.004, 1.048	0.0224	1.033	1.010, 1.057	0.0046
Heart rate ≥75 bpm						
[0, 30] days	1.094	1.062, 1.128	<0.0001	1.107	1.073, 1.143	<0.0001
[31, 365] days	0.978	0.952, 1.006	0.1247	0.983	0.955, 1.012	0.2410
Composite readmission/mortality						
Heart rate <75 bpm*	1.008	0.982, 1.035	0.5531	1.012	0.984, 1.041	0.3902
Heart rate <75 bpm	1.012	0.985, 1.040	0.3812	1.015	0.986, 1.043	0.3167
Heart rate ≥75 bpm*	1.066	1.045, 1.086	<0.0001	1.048	1.026, 1.071	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.156	1.126, 1.186	<0.0001	1.122	1.089, 1.155	<0.0001
[31, 365] days	0.996	0.970, 1.022	0.7336	0.998	0.972, 1.025	0.8917

bpm indicates beats per minute; HR, hazard ratio.
*Ignoring violation of proportional hazards assumption (see text for details), model adjusted for the following covariates: age, gender, race (white vs other), insurance (none, Medicare, Medicaid, other), ejection fraction, history of atrial flutter, history of chronic obstructive pulmonary disease or asthma, history of diabetes, history of hyperlipidemia, history of hypertension, history of peripheral vascular disease, prior myocardial infarction, prior stroke or transient ischemic attack, history of anemia, history of chronic renal insufficiency, pacemaker, smoking, geographic region, academic or teaching hospital, rural location, hospital size, defect-free compliance score.

probabilities will likely differ from unadjusted crude rates. Third, the "plateau" in the curve for AF patients in the latter study appears outside of the 5% to 95% percentile distribution of heart rates and may reflect the paucity of data in this region, suggesting limited precision of an estimate. However, both studies agree in that mortality in AF patients exceeds that for SR patients for any heart rate. Finally, "flattening" of the association between heart rate and mortality in AF patients relative to SR patients in both the inpatient study and the present outpatient study are congruent observations.

In the present report from the GWTG-HF program, we extended the analysis to specifically examine the impact of the heart rate at the time of discharge on longer-term outcomes. The heart rate at the time of discharge is more likely to reflect the totality of the in-hospital treatment program including the extent of use of guideline-based therapies including β-blockers. Indeed, the average discharge heart rate was lower than that on admission, consistent with such treatment. By including the defect-free care measure in our adjusted analysis (and thereby accounting for differences in β-blocker use across the tertiles of heart rate), our findings not only differ from prior studies in this regard but also underscore the powerful, independent, and persistent effect of heart rate on longer-term outcomes.

In patients with AF, although early (0 to 30 days) and late (31 to 365 days) associations between heart rate and mortality were statistically significant at rates ≥75 bpm, the magnitude of this association decreased over the late term, mirroring the change in HR over time in SR patients. In contrast to the findings in patients in SR, the HRs for the association between discharge heart rate and all-cause readmission and the composite outcome were not statistically significant and suggest that in patients with AF, heart rate might be of lesser importance over the long term.[22] It should

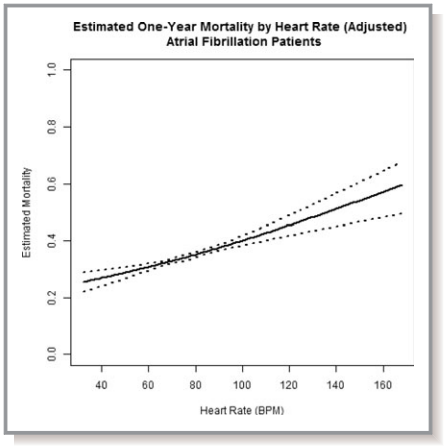

Figure 4. Estimated mortality at 1 year in patients with atrial fibrillation (n=20 197). The inflection point represents a single linear spline at 75 bpm (see text for details). Risk of mortality rises steadily with heart rate, although the slope of this relationship is less steep than the corresponding slope in sinus rhythm patients. BPM indicates beats per minute.

be recalled that patients with HF and AF are at intrinsically higher risk for death or readmission compared with patients in SR.[12,13] The decreased slope of the overall heart-rate-outcome relationship in patients with AF compared to patients with SR may reflect this increased baseline risk in patients with AF, which effectively attenuates a "heart rate" effect. Nevertheless, 50% of the patients in AF had a discharge HR >74 bpm, suggesting additional opportunity for potential benefit of further rate control on outcome.

We identified an early phase (0 to 30 days) HR and a later phase (31 to 365 days) HR for patients with either SR or AF. The HR for the association between heart rate and mortality between 0 and 30 days (early phase) and from 31 to 365 days (later phase) was numerically higher for SR patients compared to AF patients. In addition, in both groups of patients the magnitude of this association diminished over the interval from 31 to 365 days. These findings suggest that there may be potential early postdischarge benefit from lowering heart rate in patients hospitalized with HF in addition to benefit from decreasing the heart rate over the longer term.[4] In the present study, 25% of the patients in SR had a

Table 8. Hazard Ratios (HR) for Heart Rate, per 10 bpm Increase (Atrial Fibrillation Patients, n=20 197)

	Unadjusted Model			Adjusted Model		
Outcome	HR	95% CI	*P* Value	HR	95% CI	*P* Value
All-cause readmission						
No CRT						
Heart rate <75 bpm	1.001	0.959, 1.046	0.9509	1.008	0.963, 1.055	0.7312
Heart rate ≥75 bpm						
[0, 30] days	1.079	1.030, 1.130	0.0013	1.094	1.043, 1.147	0.0002
[31, 365] days	0.962	0.921, 1.004	0.0762	0.969	0.927, 1.013	0.1693
CRT						
Heart rate <75 bpm	1.072	0.928, 1.239	0.3434	1.071	0.924, 1.242	0.3614
Heart rate ≥75 bpm						
[0, 30] days	1.342	1.169, 1.541	<0.0001	1.297	1.120, 1.502	0.0005
[31, 365] days	0.909	0.762, 1.085	0.2910	0.880	0.736, 1.052	0.1608
Composite readmission/mortality						
No CRT						
Heart rate <75 bpm	1.010	0.970, 1.053	0.6211	1.015	0.972, 1.059	0.5070
Heart rate ≥75 bpm						
[0, 30] days	1.118	1.073, 1.165	<0.0001	1.098	1.050, 1.148	<0.0001
[31, 365] days	0.979	0.940, 1.019	0.2889	0.987	0.946, 1.028	0.5231
CRT						
Heart rate <75 bpm	1.102	0.960, 1.266	0.1665	1.091	0.946, 1.260	0.2324
Heart rate ≥75 bpm						
[0, 30] days	1.312	1.150, 1.497	<0.0001	1.282	1.112, 1.478	0.0006
[31, 365] days	0.918	0.778, 1.083	0.3101	0.898	0.760, 1.061	0.2044

bmp indicates beats per minute; CRT, cardiac resynchronization therapy.

Table 9. Hazard Ratios (HR) for Heart Rate, per 10 bpm Increase (Atrial Fibrillation Patients, n=20 197)

	Unadjusted Model			Adjusted Model		
Outcome	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Mortality						
LVEF ≤40%						
Heart rate <75 bpm	1.050	0.988, 1.117	0.1178	1.048	0.980, 1.120	0.1703
Heart rate ≥75 bpm						
[0, 30] days	1.311	1.240, 1.387	<0.0001	1.220	1.130, 1.316	<0.0001
[31, 365] days	0.991	0.943, 1.041	0.7090	1.005	0.953, 1.059	0.8634
LVEF >40%						
Heart rate <75 bpm	1.101	1.046, 1.159	0.0002	1.117	1.057, 1.180	<0.0001
Heart rate ≥75 bpm						
[0, 30] days	1.315	1.252, 1.380	<0.0001	1.234	1.156, 1.316	<0.0001
[31, 365] days	1.082	1.040, 1.125	<0.0001	1.080	1.035, 1.126	0.0004
All-cause readmission						
LVEF ≤40%						
Heart rate <75 bpm	1.010	0.964, 1.058	0.6845	1.008	0.960, 1.057	0.7588
Heart rate ≥75 bpm						
[0, 30] days	1.115	1.067, 1.165	<0.0001	1.127	1.076, 1.180	<0.0001
[31, 365] days	0.933	0.892, 0.976	0.0023	0.931	0.889, 0.975	0.0024
LVEF >40%						
Heart rate <75 bpm	1.011	0.975, 1.049	0.5601	1.017	0.980, 1.056	0.3806
Heart rate ≥75 bpm						
[0, 30] days	1.081	1.039, 1.123	<0.0001	1.094	1.051, 1.139	<0.0001
[31, 365] days	1.009	0.975, 1.044	0.6187	1.018	0.982, 1.055	0.3289
Composite readmission/mortality						
LVEF ≤40%						
Heart rate <75 bpm	1.009	0.967, 1.053	0.6788	1.006	0.962, 1.053	0.7826
Heart rate ≥75 bpm						
[0, 30] days	1.172	1.129, 1.217	<0.0001	1.141	1.093, 1.191	<0.0001
[31, 365] days	0.946	0.908, 0.985	0.0075	0.950	0.910, 0.991	0.0183
LVEF >40%						
Heart rate <75 bpm	1.012	0.978, 1.047	0.4974	1.021	0.985, 1.058	0.2575
Heart rate ≥75 bpm						
[0, 30] days	1.145	1.108, 1.183	<0.0001	1.108	1.067, 1.150	<0.0001
[31, 365] days	1.030	0.997, 1.063	0.0729	1.031	0.997, 1.066	0.0707

bmp indicates beats per minute; LVEF, left ventricular ejection fraction.

discharge heart rate <64 bpm and would likely not be candidates for aggressive attempts at further rate reduction. However, for the 50% of SR patients with a discharge heart rate >72 bpm, further efforts toward rate reduction during this critical time window might be of benefit.

Speculation regarding a fundamental pathophysiologic relationship between higher heart rate and the development[20,21] or worsening of HF[8–10] has ranged from myocardial energetic considerations[23] to favorable alterations in arterial afterload with heart rate reduction.[24] By targeting heart rate as a potentially modifiable risk factor in the progression of HF, the SHIFT trial[4] has implicated heart rate in the causal pathway of HF progression. Whether benefit from heart rate reduction derives from reduced myocardial oxygen consumption and

Table 10. Summary of Recent Clinical Trial and Population-Based Studies of the Association Between Heart Rate and Clinical Outcomes in Patients With and Without Prevalent HF

Study (Ref)	Year	Study Design/Patient Population	Specific Outcome(s)	Estimate of Magnitude of Association	Atrial Fibrillation Included?
BEAUTIFUL[3]	2008	RCT/CAD,LVD, heart rate ≥60 bpm	CV death HF admission	Post-Rx HR 1.08 per 5 bpm Post-Rx HR 1.16 per 10 bpm	No
SHIFT[4]	2010	RCT/HFrEF, heart rate ≥70 bpm	Composite (CV death/hospital admission)	Post-Rx HR 1.16 per 5 bpm	No
CHARM[5]	2012	RCT/HFrEF, HFpEF	All-cause mortality	"pre-Rx" HR 1.06 per 10 bpm	Yes
EVEREST[6]	2013	RCT/HFrEF	All-cause mortality	"baseline" HR 1.05 per 5 bpm* "discharge" HR 1.20 per 5 bpm†	No
Kapoor and Heidenreich[18]	2010	Prospective cohort/HFpEF	All-cause mortality	HR 1.47 for heart rate 70 to 90 (compared to rate <60)	No
AHA GWTG-HF[19]	2013	Prospective, registry design/HFrEF, HFpEF/in-patient	In-hospital mortality	Admission HR 1.20 per 10 bpm	Yes
FRAMINGHAM[20]	2014	Prospective cohort, population-based/no prevalent CV disease	All-cause mortality	HR 1.17 per 11 bpm	No
MESA[21]	2014	Prospective cohort, population-based/no prevalent CV disease	Incident HF	HR 1.04 per 1 bpm	No
EFFECT-HF[7]	2014	Retrospective, population-based, observational/post-hospital discharge/HFrEF, HFpEF	All-cause mortality	OR 1.41 for heart rate >90 (compared to heart rate 40 to 60)	No
Cullington, et al[22]	2014	Retrospective/prospective, community-based, observational/HFrEF	All-cause mortality	HR 1.10 per 10 bpm for SR patients only	Yes
Present study AHA GWTG-HF	2014	Prospective, registry design/HFrEF, HFpEF/post-hospital discharge	All-cause mortality All-cause mortality/ readmission	See Results	Yes

bpm indicates beats per minute; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVD, left ventricular dysfunction; OR, odds ratio; pEF, preserved ejection fraction; RCT, randomized clinical trial; rEF, reduced ejection fraction; SR, sinus rhythm.

*P=0.066, heart rate ≥70 bpm.

†P<0.001, heart rate ≥70 bpm.

improved myocardial efficiency, reduced total afterload, or alternative explanations[25] remains to be determined.

The present study has a number of limitations that merit discussion. This is a retrospective analysis from a prospectively designed and conducted registry. Data were collected by chart review and are, therefore, dependent on the quality and accuracy of data collection. Hospitals voluntarily participating in GWTG-HF may not be representative of all hospitals in the United States, although prior study has shown that GWTG-HF patients and hospitals have characteristics similar to hospitals nationwide. We restricted the analysis to fee-for-service Medicare beneficiaries ≥65 years of age in order to allow for assessment of postdischarge outcomes by linkage of GWTG-HF records with those from Medicare. However, the majority of patients hospitalized with HF in the United States are over the age of 65 years.[26] Characteristics and outcomes of Medicare beneficiaries in previous HF registries were similar to the broader Medicare population with HF, suggesting that findings from such registries may be generalizable.[27] The extent of missing biomarker data (eg, N-terminal pro-brain natriuretic peptide, brain natriuretic peptide) in this registry precludes more objective measures of disease severity. This study was not a prospective randomized trial, and residual measured and unmeasured confounders might have influenced reported outcomes notwithstanding extensive statistical adjusting of the crude rates. Although other medications potentially affecting heart rate (eg, calcium channel blockers, digoxin, amiodarone, and β-agonists in patients with COPD) are used in patients with HF, these medications are not systematically tracked in this quality assurance program. Consequently, the current models cannot adjust for their use. Attention is drawn, however, to the >90% prevalence of β-blockers and their dominant effect on heart rate at discharge. This registry does not record provider intention with respect

to the management of AF (rate versus rhythm control). Therefore, selection bias and residual confounding due to the use of β-blockers for rate control in patients with HF and AF is another limitation. As noted above, overall β-blocker use in AF patients exceeded 90%. The study is also limited in the absence of cause-specific outcomes. In the absence of independent clinical outcome assessment as would be the case in a clinical trial, we suggest that our choices for all-cause mortality and all-cause hospitalization are less subject to bias (eg, misclassification bias), which often limits inferences from observational studies. Increased sensitivity using an all-cause outcome allows for identification of clinical outcomes in these older subjects that are of broad clinical relevance. We believe that these considerations do not detract from our conclusions regarding the adverse effect of increased heart rate in patients with HF even after accounting for the extent of guideline-directed medical therapy.

In summary, our observations add to the growing evidence base for a positive association between heart rate and adverse clinical outcomes in patients with HF. Our findings expand on these prior observations and indicate a biphasic nature to the time-dependent hazard with an early (0 to 30 day) substantial increase in the HR for mortality and a longer-term (31 to 365 days) lower, albeit persistently and significantly increased, HR. These observations suggest additional opportunities to improve outcomes for HF patients in SR or AF, patients with preserved or depressed left ventricular systolic function, and patients with persistently increased heart rate at the time of hospital discharge.

Sources of Funding

The GWTG-HF program is provided by the American Heart Association. GWTG-HF has been funded in the past through support from Medtronic, GlaxoSmithKline, Ortho-McNeil, and the American Heart Association Pharmaceutical Roundtable.

Disclosures

Laskey, Alomari, Cox, Schulte, Zhao, Heidenreich, and Yancy have none declared. Hernandez: Research: Amgen, BMS, GSK, Novartis. Honoraria: Amgen, BMS, Novartis, Janssen. Eapen: Advisory Board: Novartis, Cytokinetics. Honoraria: Janssen. Consultant: Amgen. Bhatt: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Get With The Guidelines® Steering Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Associate Editor; Section Editor, Pharmacology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda. Fonarow: Research: Agency for Healthcare; Research and Quality, National Institutes of Health; Consulting: Bayer, Gambro, Novartis, Medtronic.

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