Prognostic Significance of Resting Heart Rate and Use of β-Blockers in Atrial Fibrillation and Sinus Rhythm in Patients With Heart Failure and Reduced Ejection Fraction

Findings From the Swedish Heart Failure Registry

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**Background**—In heart failure and reduced ejection fraction, the prognostic role of heart rate (HR) in atrial fibrillation (AF) is unknown and the effectiveness of β-blockers has recently been questioned in AF.

**Methods and Results**—A total of 18,858 patients with heart failure and reduced ejection fraction registered with Swedish Heart Failure Registry were included in this study: patients with sinus rhythm (SR; n=11,466) and patients with AF (n=7392). The outcome measure was all-cause mortality. Compared with HR ≤60 beats per minute, the adjusted hazard ratios for mortality in SR were 1.26 for HR=61 to 70 beats per minute, 1.37 for HR=71 to 80 beats per minute, 1.52 for HR=81 to 90 beats per minute, 1.63 for HR=91 to 100 beats per minute, and 2.69 for HR>100 beats per minute. However, in AF, the hazard ratio increased only for HR>100 beats per minute (1.30; P=0.001). β-blocker use was associated with reduced mortality in SR (hazard ratio, 0.77; P=0.011) and in AF (hazard ratio, 0.71; P<0.001). For β-blocker use in SR, the hazard ratio gradually increased with HR increment, whereas in AF, the hazard ratio significantly increased only for HR>100 beats per minute (1.29; P=0.003) compared with HR ≤60 beats per minute.

**Conclusions**—In patients with heart failure and reduced ejection fraction, a higher HR was associated with increased mortality in SR, but in AF, this is true only for HR>100 beats per minute. β-blocker use was associated with reduced mortality both in SR and in AF. (Circ Heart Fail. 2015;8:871-879. DOI: 10.1161/CIRCHEARTFAILURE.115.002285.)

**Key Words:** atrial fibrillation ■ heart failure ■ heart rate ■ mortality ■ registries

In patients with heart failure (HF) and reduced ejection fraction (HFrEF), a higher resting heart rate (HR) is associated with higher morbidity and mortality.1-3 β-blockers are recommended in patients with HFrEF, and their major effect in these patients is the control of HR.4 Previous studies have mainly examined sinus rhythm (SR), and whether a higher HR is associated with worse outcomes in HFrEF with concomitant atrial fibrillation (AF) has not been adequately studied. A recent study suggested that a slower resting ventricular rate is associated with better survival in HFrEF patients with SR but not in those with AF.5 In Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) trial, lenient rate control (<110 beats per minute) did not yield worse outcomes than strict rate control (<80 beats per minute) overall or in the subgroup of patients with HF, many of whom had preserved EF.6,7 A subgroup analysis from the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program showed that resting HR is an important predictor of outcome in patients with stable chronic HF without AF, independent of EF or β-blocker use; however, among patients with AF at baseline, HR had no predictive value.8 Importantly, a recent meta-analysis suggested that β-blockers improve outcomes in HFrEF patients with SR but not in those with AF.9 Therefore, the aims of this study were to confirm that a higher HR is associated with higher mortality and β-blocker use is associated with reduced mortality in SR and to assess the associations between HR and mortality and between β-blocker use and mortality in AF in HFrEF.

**Clinical Perspective on p 879**

**Methods**

**Study Protocol**

The Swedish Heart Failure Registry has been described previously.10,11 Between May 11, 2000 and August 1, 2013, there were 54,299
registrations from inpatient and outpatient units at 68 of ≈80 hospitals and from 102 of ≈1000 primary care outpatient clinics in Sweden. The criterion for entry in the registry was established HF diagnosis based on clinical judgment. Approximately 80 variables were recorded at discharge from the hospital or outpatient visits at cardiology, internal medicine, and primary care clinics, and patients were run against the population registry monthly for vital status (the protocol, case report form, and annual report are available at http://www.riksivikt.se). EF is reported in the registry as <30%, 30% to 39%, 40% to 49%, and ≥50%. For this study, we included only patients with an EF ≤40% (ie, HFrEF). Diagnosis of AF was based on ECG and medical history at enrollment, and if we found contradictory information (eg, if categorized as AF according to one and as SR according to the other, as may occur in paroxysmal AF), patients were excluded. Additional patients were excluded because of preserved EF or missing information on critical baseline variables or outcomes (Figure 1). A total of 18858 patients with HFrEF (11466 patients with SR and 7392 patients with AF) were included for in-depth analyses in this study.

Like other baseline variables, the last stable HR before deterioration and death during hospitalization and the HR at discharge from the hospital or outpatient visits at cardiology, internal medicine, and primary care clinics were recorded. HR was categorized into 6 strata and analyzed in a Cox regression model: ≤60, 61 to 70, 71 to 80, 81 to 90, 91 to 100, and >100 beats per minute.

Baseline Covariates
We collected data on 35 variables, including clinical characteristics, medical history, comorbidities, blood pressure, therapies, and interventions. Target doses for β-blockers were based on the 2012 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure. N-terminal pro–brain natriuretic peptide (NT-proBNP) was log transformed, and log-NT-proBNP, age, estimated glomerular filtration rate, hemoglobin, and systolic and diastolic blood pressure were included as continuous variables in the Cox regression models.

Outcome Measure
The outcome measure was all-cause mortality. Survival status was ascertained on July 21, 2013 by cross-referencing the population registry for vital status.12

Ethical Considerations
The registry and analysis of data were approved by a multisite ethics committee. The registry and this study conformed to the Declaration of Helsinki. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

Statistical Analysis
For baseline characteristics, categorical variables are presented as frequencies with percentages and continuous variables as median with quartiles. All continuous variables were tested for normality and homogeneity of variance; the continuous variables were not normally distributed. Therefore, differences in baseline characteristics were tested using the Mann–Whitney U rank-sum test or Kruskal–Wallis H rank-sum test for continuous variables, with nonnormality and Pearson χ² tests for categorical variables. We compared mortality outcomes by presenting Kaplan–Meier curves and performing Log-rank tests among HR strata. In addition, Cox proportional hazards models were used to calculate and test hazard ratios in the SR and AF subgroups separately. The covariates used in all adjusted Cox models were the variables listed in Table 1. There were no adjustments for multiple comparisons given the nature of the study.

Missing rates were <20% for all variables except the New York Heart Association class (23.9%), target β-blocker dose (21.2%), and NT-proBNP (67.1%). Missing data were handled by multiple imputations using fully conditional specification (multiple imputation algorithms). Scale variables were modeled with linear regression, dichotomous variables were imputed via logistic regression, and each model used all other variables as main effects. Multiple imputations were carried out with 5 imputations and 10 iterations per imputation. In addition, patient inclusion occurred largely before NT-proBNP was routinely used. Therefore, a consistency analysis was performed excluding NT-proBNP from the multiple imputation and Cox regressions.

Effect modification by heart rhythm (SR versus AF) was estimated by adding an interaction term between HR (continuous variable) and heart rhythm to the multivariable-adjusted Cox regression model. Similarly, the effect modification by β-blocker use (yes versus no) was estimated by adding an interaction term between HR and β-blocker use to the multivariable-adjusted Cox regression models in patients with SR and AF, respectively. The significance of the interaction term was evaluated by a Wald test.

We considered a 2-sided P value <0.05 as significant. We used IBM SPSS version 22 (IBM Corporation, Armonk, NY) for all analyses.

Results
Baseline Characteristics
The baseline characteristics of the study population are given in Table 1. The percentage of patients with New York Heart Association III/IV compared with patients with I/II increased with increasing HR in the SR subgroup but not in AF. An EF <30% was present in 3677 (50%) patients with AF and 6077 (53%) patients with SR (Table 1). The distribution of baseline HR in patients with SR and AF is shown in Figure 2. Overall, patients with AF had a higher HR. As shown in Figure 2, HR was roughly normally distributed.

Outcomes in Relation to Rhythm
The median follow-up was 2.4 (interquartile range [IQR], 1.0–4.4) years. A total of 3274 (44%) patients with AF and 3931 (34%) patients with SR died; the number of deaths per 1000 patient-years was 167.9 in AF versus 113.2 in SR (Table 2), and the adjusted hazard ratio for death in AF versus SR was 1.15 (95% confidence interval [CI], 1.08–1.22; P<0.001).

Outcomes in Relation to HR
We performed a formal assessment of potential effect modification, that is, the possibility that the effect of HR on mortality could be different depending on rhythm (AF or SR), and the P value for interaction was highly significant (P<0.001). This

Figure 1. Flowchart of study population enrollment. *Paroxysmal atrial fibrillation (AF) is often associated with sinus rhythm (SR) on ECG but with AF in the history. # When ECG is paced, information on underlying rhythm is not provided. EF indicates ejection fraction.
### Table 1. Baseline Characteristics Based on HR Strata

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sinus Rhythm (n=11466)</th>
<th>Atrial Fibrillation (n=7392)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, ≤70 (n=6077)</td>
<td>HR, &gt;100 (n=2416)</td>
</tr>
<tr>
<td></td>
<td>beats per min</td>
<td>(n=367)</td>
</tr>
<tr>
<td></td>
<td>Missing (%)</td>
<td>PValue</td>
</tr>
<tr>
<td>Age, y</td>
<td>≤6 mo</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Married</td>
<td>0.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>PFU specialty care*</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>PFU nurse-based HF clinic</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>30%–39%</td>
<td></td>
<td></td>
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<tr>
<td>Medical histories</td>
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<tr>
<td>Hypertension</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>IHD</td>
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<td>0.6</td>
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<tr>
<td>Lung disease</td>
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<td>0.5</td>
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<tr>
<td>Valvular disease</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>Valvular surgery</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>CRT</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>ICD</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Laboratory tests</td>
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<td></td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>0.3</td>
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<tr>
<td>Hemoglobin, g/L</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>NT-ProBNP, ng/L</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Medications</td>
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<td></td>
</tr>
<tr>
<td>ACEi</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>ARBs</td>
<td>1.7</td>
<td>1.7</td>
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<tr>
<td>β-blockers</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Target-dose β-blockers</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Statins</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Nitrate</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data are expressed either as median or n (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-ProBNP, N-terminal pro–brain natriuretic peptide; PCI, percutaneous coronary intervention; PFU, planned follow-up; and SBP, systolic blood pressure.

*Cardiology/internal medicine. Data are not imputed.
justifies separate analyses of the association between HR and mortality in AF and SR. In the unadjusted analysis, HR strata in SR were associated with a progressively increased risk of mortality compared with the reference HR strata ≤60 beats per minute ($\chi^2=187.40$; Log-rank test, $P<0.001$), whereas no significant difference in mortality was found among different HR strata in AF ($\chi^2=2.48$; Log-rank test, $P=0.780$) using Kaplan–Meier analysis (Figure 3).

Categorization of HR may impair granularity and lead to failure to detect a small risk, but when analyzed as a continuous variable, HR remained unassociated with outcomes. Compared with HR ≤60 beats per minute, the adjusted hazard ratios for mortality in SR were 1.26 (95% CI, 1.15–1.39; $P<0.001$) for HR=61 to 70 beats per minute, 1.37 (95% CI, 1.24–1.51; $P<0.001$) for HR=71 to 80 beats per minute, 1.52 (95% CI, 1.36–1.70; $P<0.001$) for HR=81 to 90 beats per minute, 1.55 (95% CI, 1.39–1.73; $P<0.001$) for HR=91 to 100 beats per minute, and 1.69 (95% CI, 1.56–1.84; $P<0.001$) for HR>100 beats per minute.

Table 2. Cox Regression Analyses of the Effect of HR on Mortality

<table>
<thead>
<tr>
<th>No. of Deaths/Patients (%) Per Person-Year</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>PValue</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation vs sinus rhythm (reference)</td>
<td>3274/7392 (16.8%)</td>
<td>1.45 (1.39–1.52)</td>
<td>&lt;0.001</td>
<td>1.15 (1.08–1.22)</td>
</tr>
<tr>
<td>HR strata, beats per min ≤60</td>
<td>1185/3697 (9.9%)</td>
<td>Reference</td>
<td>—</td>
<td>Reference</td>
</tr>
<tr>
<td>61–70</td>
<td>1819/4796 (12.9%)</td>
<td>1.29 (1.19–1.38)</td>
<td>&lt;0.001</td>
<td>1.18 (1.10–1.28)</td>
</tr>
<tr>
<td>71–80</td>
<td>1895/4772 (14.1%)</td>
<td>1.40 (1.30–1.50)</td>
<td>&lt;0.001</td>
<td>1.28 (1.19–1.38)</td>
</tr>
<tr>
<td>81–90</td>
<td>1184/2907 (15.2%)</td>
<td>1.50 (1.38–1.62)</td>
<td>&lt;0.001</td>
<td>1.37 (1.24–1.44)</td>
</tr>
<tr>
<td>91–100</td>
<td>637/1605 (15.0%)</td>
<td>1.49 (1.35–1.64)</td>
<td>&lt;0.001</td>
<td>1.39 (1.25–1.53)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>485/1081 (18.5%)</td>
<td>1.81 (1.63–2.02)</td>
<td>&lt;0.001</td>
<td>1.78 (1.59–2.00)</td>
</tr>
<tr>
<td>In sinus rhythm</td>
<td>751/2777 (8.0%)</td>
<td>Reference</td>
<td>—</td>
<td>Reference</td>
</tr>
<tr>
<td>≤60</td>
<td>1123/3300 (11.1%)</td>
<td>1.38 (1.26–1.51)</td>
<td>&lt;0.001</td>
<td>1.26 (1.15–1.39)</td>
</tr>
<tr>
<td>61–70</td>
<td>1028/2814 (12.4%)</td>
<td>1.53 (1.39–1.68)</td>
<td>&lt;0.001</td>
<td>1.37 (1.24–1.51)</td>
</tr>
<tr>
<td>71–80</td>
<td>588/1490 (14.2%)</td>
<td>1.74 (1.56–1.94)</td>
<td>&lt;0.001</td>
<td>1.52 (1.36–1.70)</td>
</tr>
<tr>
<td>81–100</td>
<td>267/718 (13.7%)</td>
<td>1.68 (1.46–1.93)</td>
<td>&lt;0.001</td>
<td>1.63 (1.40–1.88)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>174/367 (18.5%)</td>
<td>2.47 (2.10–2.92)</td>
<td>&lt;0.001</td>
<td>2.69 (2.26–3.21)</td>
</tr>
<tr>
<td>In atrial fibrillation</td>
<td>434/920 (16.9%)</td>
<td>Reference</td>
<td>—</td>
<td>Reference</td>
</tr>
<tr>
<td>≤60</td>
<td>696/1496 (17.3%)</td>
<td>1.02 (0.90–1.15)</td>
<td>0.782</td>
<td>1.02 (0.90–1.16)</td>
</tr>
<tr>
<td>61–70</td>
<td>867/1958 (16.7%)</td>
<td>0.98 (0.88–1.10)</td>
<td>0.762</td>
<td>1.09 (0.97–1.23)</td>
</tr>
<tr>
<td>71–80</td>
<td>596/1417 (16.3%)</td>
<td>0.95 (0.84–1.08)</td>
<td>0.458</td>
<td>1.07 (0.94–1.21)</td>
</tr>
<tr>
<td>81–100</td>
<td>370/887 (16.2%)</td>
<td>0.95 (0.83–1.09)</td>
<td>0.475</td>
<td>1.11 (0.96–1.28)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>311/714 (17.6%)</td>
<td>1.03 (0.89–1.19)</td>
<td>0.693</td>
<td>1.30 (1.11–1.52)</td>
</tr>
</tbody>
</table>

Multivariable Cox regression was performed with the variables listed in Table 1. CI indicates confidence interval; and HR, heart rate.
minute, 1.63 (95% CI, 1.40–1.88; \( P < 0.001 \)) for HR=91 to 100 beats per minute, and 2.69 (95% CI, 2.26–3.21; \( P < 0.001 \)) for HR >100 beats per minute. In contrast, in AF, the hazard ratio was significantly increased only for HR >100 beats per minute (1.30; 95% CI, 1.11–1.52; \( P < 0.001 \)) compared with HR \( \leq \) 60 beats per minute (Table 2; Figure 4). Figure 5 shows the adjusted hazard ratios for the association between HR and all-cause mortality in SR (left) and AF (right). It should be noted that this analysis was restricted to HR >50 and <140 beats per minute for presentational purposes and included only complete cases (missing data were not imputed). In a repeated analysis without NT-proBNP in the Cox regression model, the results were unchanged.

Outcomes in Relation to \( \beta \)-Blocker Use
We performed a formal assessment of potential effect modification, in other words, the possibility that the association between HR and mortality would be different in patients with \( \beta \)-blockers compared with patients without \( \beta \)-blockers. There was no evidence for a significant interaction between \( \beta \)-blocker use and HR in SR (\( P \) value for interaction=0.637) or in AF (\( P \) value for interaction=0.060). In SR, HR was significantly lower in patients using \( \beta \)-blockers compared with nonusers (70, IQR=61–80 versus 76, IQR=64–87; \( P < 0.001 \)). However, in AF, HR was higher in patients using \( \beta \)-blockers (79, IQR=69–90 versus 74, IQR=64–85; \( P < 0.001 \)). \( \beta \)-blocker use was associated with reduced mortality in both SR (hazard ratio, 0.77; 95% CI, 0.63–0.94; \( P = 0.011 \)) and AF (hazard ratio, 0.71, 95% CI, 0.61–0.84; \( P < 0.001 \); Table 3). In patients treated with \( \beta \)-blockers, there was a similar association between HR and all-cause mortality as in the overall population. In \( \beta \)-blocker use in SR, hazard ratio gradually increased with HR increment compared with HR \( \leq \) 60 beats per minute (hazard ratio, 1.29 for HR=61–70 beats per minute, 1.40 for HR=71–80 beats per minute, 1.50, for HR=81–90 beats per minute, 1.79 for HR=91–100 beats per minute, 2.60 for HR >100 beats per minute; \( P < 0.001 \)). In \( \beta \)-blocker use in AF, hazard ratio was significantly increased only for HR >100 beats per minute (1.29; 95% CI, 1.09–1.53; \( P = 0.003 \)) compared with HR \( \leq \) 60 beats per minute (Table 4).

Discussion
In this study, we report an association of HR strata and \( \beta \)-blocker use with all-cause mortality in patients with HFrEF in AF and SR. We show that AF was associated with higher mortality than SR and that higher resting HR was associated with increased mortality in SR, but in AF, this was true only if HR >100 beats per minute. Furthermore, \( \beta \)-blocker use was associated with reduced mortality in patients with SR or AF, and a lower HR was associated with reduced mortality in SR, but in AF, this was true only if HR \( \leq \) 100 beats per minute in \( \beta \)-blocker use.

HF and AF are both common and often coexist. AF is prevalent in 23% to 69% of patients with HFrEF in AF and SR. We show that AF was associated with higher mortality than SR and that higher resting HR was associated with increased mortality in SR, but in AF, this was true only if HR >100 beats per minute. Furthermore, \( \beta \)-blocker use was associated with reduced mortality in patients with SR or AF, and a lower HR was associated with reduced mortality in SR, but in AF, this was true only if HR \( \leq \) 100 beats per minute in \( \beta \)-blocker use.

Figure 3. Unadjusted overall survival according to heart rate strata in patients with heart failure and reduced ejection fraction in sinus rhythm (top) or atrial fibrillation (bottom); bpm indicates beats per minute.
outcome in patients with stable chronic HF without AF, independent of EF or β-blocker use; however, among patients with AF at baseline, HR had no predictive value. However, these studies were conducted either with a limited sample size or in a selected HF population. Moreover, no studies have been designed to assess the target HR in patients with AF, specifically those with HFrEF. Our current study is the first large-scale investigation with a large sample size, a representative HFrEF population, and an extensive covariate adjustment. Our results demonstrate that a higher HR is associated with increased mortality in SR, but in AF, this is true only for HR >100 beats per minute. One possible explanation is that AF results in the loss of atrial contraction, and consequently, a decrease in left ventricular filling and therefore a decrease in stroke volume. Physiologically, this has to be compensated by an increase in ventricular rate to maintain sufficient cardiac output. Therefore, slightly higher ventricular rates for patients with AF ensure hemodynamic stability. Accordingly, HR has less effect on outcome in AF than in SR. This assumption is supported by RACE studies. One possible explanation is that incremental increase from 61 to 100 beats per minute has less effect on mortality, even with delimited diastolic flow time, if the left atrial is large with increased reservoir capacity to modulate higher filling pressure. Another possible explanation is that AF reflects the mechanical consequences of both HFrEF (myocardial weakness) and left atrial remodeling.

Figure 4. Forest plots of hazard ratios (95% confidence intervals [CIs]) for mortality in different heart rate strata.

Figure 5. Adjusted hazard ratios for the association between the heart rate and all-cause mortality in sinus rhythm (left) and atrial fibrillation (right). bpm indicates beats per minute.
HF and AF are at intrinsically higher risk for death, and this was also supported by a study in patients with heart failure with concomitant AF at HRs <100 beats per minute. In a recently published study,28 in patients with AF, HR might be of lesser importance over the long term.28 These support the notion that patients with HFrEF in AF are at intrinsically higher risk, independent of HR. Indeed, as shown in the results, the independent hazard ratio was 1.15 (95% CI, 1.08 to 1.22; P<0.001). It might be that this intrinsically higher baseline risk explains the attenuation of the association for mortality both in SR and AF, and a lower HR was also associated with reduced morbidity and mortality in patients with HFrEF.29,30 Accordingly, β-blockers are recommended by current guidelines as part of the first-line therapy for HFrEF.4,31 However, a meta-analysis showed that β-blockers are less effective in HFrEF patients with AF compared with those with SR.32 This concern was recently reinforced by another meta-analysis demonstrating that β-blockers do not improve outcomes in concomitant HFrEF and AF.9 Therefore, the benefit of β-blockers shown in HFrEF patients with SR may not necessarily be extrapolated to HFrEF patients with AF. These findings are consistent with our observations that HR does not independently predict outcomes in AF. However, this study showed that β-blocker use was associated with reduced mortality both in SR and AF, and a lower HR was also associated with a lower risk of death.

**Table 3. Cox Regression Analyses for the Association of β-Blockers With Mortality in Sinus Rhythm and Atrial Fibrillation Subgroups**

<table>
<thead>
<tr>
<th>β-Blockers (yes vs no)</th>
<th>No. of Deaths/Patients (% Per Person-Year)</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In sinus rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers (yes vs no)</td>
<td>3347/10291 (10.6%)</td>
<td>0.56 (0.52–0.62)</td>
<td>&lt;0.001</td>
<td>0.77 (0.63–0.94)</td>
<td>0.011</td>
</tr>
<tr>
<td>In atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers (yes vs no)</td>
<td>2835/6739 (15.7%)</td>
<td>0.52 (0.47–0.58)</td>
<td>&lt;0.001</td>
<td>0.71 (0.61–0.84)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable Cox regression was performed with the variables listed in Table 1 except atrial fibrillation. CI indicates confidence interval; and HR, heart rate.

Only when HR exceeds 100, diastolic flow time would be so curtailed as to elevate left atrial and pulmonary capillary pressure, resulting in acute heart failure, rehospitalization, and death. In addition, patients with HFrEF in AF are at intrinsically higher risk, independent of HR. Indeed, as shown in the results, the independent hazard ratio was 1.15 (95% CI, 1.08 to 1.22; P<0.001). It might be that this intrinsically higher baseline risk explains the attenuation of the association for patients with AF at HRs <100 beats per minute. In a recently published study,28 in patients with heart failure with concomitant AF, although early (0–30 days) and late (31–365 days) associations between HR and mortality were statistically significant at rates ≥75 beats per minute, the magnitude of this association decreased over the late term. Furthermore, in contrast to the findings in patients with heart failure and SR, the association between discharge HR and all-cause readmission and the composite outcome (all-cause mortality or all-cause readmission) were not statistically significant, suggesting that in patients with AF, HR might be of lesser importance over the long term.28 These support the notion that patients with HF and AF are at intrinsically higher risk for death, and this increased baseline risk attenuates an HR effect. However, it is noteworthy to mention that this study is different from our study because it included patients with both HFrEF and heart failure with preserved EF and only patients aged >65 years.

β-blockers have been used preferentially over other rate control medications for HFrEF because previous large randomized controlled trials demonstrated that β-blockers can significantly reduce morbidity and mortality in patients with HFrEF.28,30 However, a meta-analysis showed that β-blockers are less effective in HFrEF patients with AF compared with those with SR.32 This concern was recently reinforced by another meta-analysis demonstrating that β-blockers do not improve outcomes in concomitant HFrEF and AF.9 Therefore, the benefit of β-blockers shown in HFrEF patients with SR may not necessarily be extrapolated to HFrEF patients with AF. These findings are consistent with our observations that HR does not independently predict outcomes in AF. However, this study showed that β-blocker use was associated with reduced mortality both in SR and AF, and a lower HR was also associated

**Table 4. Cox Regression Analyses for the Association of HR Strata With Mortality in Heart Failure and Reduced Ejection Fraction With β-Blockers**

<table>
<thead>
<tr>
<th>HR strata, beats per min</th>
<th>β-Blocker use in sinus rhythm</th>
<th>No. of Deaths/Patients (% Per Person-Year)</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td></td>
<td>670/2565 (7.7%)</td>
<td>Reference</td>
<td>&lt;0.001</td>
<td>Reference</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>61–70</td>
<td></td>
<td>1022/3063 (10.9%)</td>
<td>1.41 (1.27–1.55)</td>
<td>&lt;0.001</td>
<td>1.29 (1.17–1.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>71–80</td>
<td></td>
<td>861/2507 (11.5%)</td>
<td>1.48 (1.34–1.64)</td>
<td>&lt;0.001</td>
<td>1.40 (1.26–1.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>81–90</td>
<td></td>
<td>464/1274 (12.7%)</td>
<td>1.63 (1.45–1.84)</td>
<td>&lt;0.001</td>
<td>1.50 (1.33–1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>91–100</td>
<td></td>
<td>203/824 (15.1%)</td>
<td>1.58 (1.35–1.85)</td>
<td>&lt;0.001</td>
<td>1.79 (1.52–2.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;100</td>
<td></td>
<td>127/659 (15.8%)</td>
<td>2.30 (1.90–2.78)</td>
<td>&lt;0.001</td>
<td>2.60 (2.14–3.17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-Blocker use in atrial fibrillation</th>
<th>HR strata, beats per min</th>
<th>No. of Deaths/Patients (% Per Person-Year)</th>
<th>Univariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Multivariable Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td></td>
<td>358/792 (15.7%)</td>
<td>Reference</td>
<td>&gt;0.05</td>
<td>Reference</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>61–70</td>
<td></td>
<td>595/1348 (16.2%)</td>
<td>1.03 (0.90–1.17)</td>
<td>0.697</td>
<td>1.03 (0.90–1.18)</td>
<td>0.700</td>
</tr>
<tr>
<td>71–80</td>
<td></td>
<td>753/1787 (15.6%)</td>
<td>0.99 (0.87–1.12)</td>
<td>0.871</td>
<td>1.11 (0.97–1.27)</td>
<td>0.119</td>
</tr>
<tr>
<td>81–90</td>
<td></td>
<td>536/1329 (15.5%)</td>
<td>0.98 (0.86–1.12)</td>
<td>0.761</td>
<td>1.10 (0.96–1.27)</td>
<td>0.162</td>
</tr>
<tr>
<td>91–100</td>
<td></td>
<td>325/824 (15.1%)</td>
<td>0.96 (0.82–1.11)</td>
<td>0.547</td>
<td>1.09 (0.94–1.28)</td>
<td>0.260</td>
</tr>
<tr>
<td>&gt;100</td>
<td></td>
<td>268/659 (15.8%)</td>
<td>1.00 (0.90–1.11)</td>
<td>0.995</td>
<td>1.29 (1.09–1.53)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Multivariable Cox regression was performed with the variables listed in Table 1 except atrial fibrillation β-blockers and target dose β-blockers. CI indicates confidence interval; and HR, heart rate.
Conclusions

In patients with HFrEF, a higher HR was associated with increased mortality in SR, and in AF, this is true only for HR >100 beats per minute. β-blocker use was associated with reduced mortality both in SR and in AF.

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Disclosures

Dr Lund declares speaker’s honoraria from Servier. Dr Fu declares speaker’s honoraria from Servier, Novartis, Resmed, and AstraZeneca. The other authors report no conflicts.

References

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**CLINICAL PERSPECTIVE**

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