CLINICAL RESEARCH STUDY

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# Repeated Heart Rate Measurement and Cardiovascular Outcomes in Left Ventricular Systolic Dysfunction

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## ABSTRACT

**BACKGROUND:** Elevated resting heart rate is associated with increased cardiovascular risk, particularly in patients with left ventricular systolic dysfunction. Heart rate is not monitored routinely in these patients. We hypothesized that routine monitoring of heart rate would increase its prognostic value in patients with left ventricular systolic dysfunction.

**METHODS:** We analyzed the relationship between heart rate measurements and a range of adverse cardiovascular outcomes, including hospitalization for worsening heart failure, in the pooled placebo-treated patients from the morBidity-mortality EvAlUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) trial and Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine (SHIFT) Trial, using standard and time-varying covariate Cox proportional hazards models. By adjusting for other prognostic factors, models were fitted for baseline heart rate alone or for time-updated heart rate (latest heart rate) alone or corrected for baseline heart rate or for immediate previous time-updated heart rate.

**RESULTS:** Baseline heart rate was strongly associated with all outcomes apart from hospitalization for myocardial infarction. Time-updated heart rate increased the strengths of associations for all outcomes. Adjustment for baseline heart rate or immediate previous time-updated heart rate modestly reduced the prognostic importance of time-updated heart rate. For hospitalization for worsening heart failure, each 5 beats/min increase in baseline heart rate and time-updated heart rate was associated with a 15% (95% confidence interval, 12-18) and 22% (confidence interval, 19-40) increase in risk, respectively. Even after correction, the prognostic value of time-updated heart rate remained greater.

**CONCLUSIONS:** In patients with left ventricular systolic dysfunction, time-updated heart rate is more strongly related with adverse cardiovascular outcomes than baseline heart rate. Heart rate should be measured to assess cardiovascular risk at all assessments of patients with left ventricular systolic dysfunction.

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**KEYWORDS:** BEAUTIFUL; Heart rate; Left ventricular systolic dysfunction; Prognosis; SHIFT

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Resting heart rate is directly associated with cardiovascular mortality and morbidity in a range of diseases and in the general population.[1] These results suggest that the slower the heart rate, the fewer the cardiovascular complications. In particular, in patients with left ventricular systolic dysfunction, with and without clinical heart failure, resting heart rate in sinus rhythm has been associated with increased risk for morbidity and mortality. In the Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial (SHIFT), in patients with heart failure in sinus rhythm and left ventricular ejection fraction ≤35%, isolated heart rate reduction with ivabradine resulted in a diminution in clinical outcomes in patients with a resting heart rate ≥70 beats/min.[2] Ivabradine slows the heart by selective $I_f$ current inhibition and, unlike beta-blockers, has no known cardiovascular effects other than heart rate reduction. These results support the notion that heart rate is a modifiable risk factor for patients with heart failure. In the morBidity-mortality EvAlUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) trial in patients with coronary heart disease and left ventricular ejection fraction <40%, ivabradine did not reduce cardiovascular outcomes in the overall trial, but post hoc analyses suggested benefit in the subgroup with resting heart rates ≥70 beats/min.[3] In the placebo groups of both trials, heart rate was directly associated with rate of cardiovascular morbidity and mortality.[3,4]

To further assess these results, we analyzed outcomes in the placebo-treated patients in a pooled population from SHIFT and BEAUTIFUL according to baseline heart rates and heart rates achieved to (1) study the overall association between baseline heart rate and a variety of cardiovascular outcomes; (2) investigate whether or not time-updated heart rate (obtained from repeated measurements over follow-up) exhibited greater prognostic value than baseline; and (3) determine whether time-updated heart rate remained a significant predictor after correcting for baseline and after correcting for the immediate previous time-updated heart rate.

## CLINICAL SIGNIFICANCE

- Time-updated heart rate is more strongly related with cardiovascular outcomes than baseline heart rate in patients with left ventricular systolic dysfunction.
- Current heart rate provides significant additional information about increased cardiovascular risk in left ventricular systolic dysfunction and therefore should be measured at all assessments of patients with left ventricular systolic dysfunction with or without heart failure.
- More information on the optimal frequency of heart rate assessment and the role of continuous monitoring of resting heart rate would complement these findings.

## MATERIALS AND METHODS

The study designs of BEAUTIFUL and SHIFT, both randomized, double-blind, placebo-controlled, parallel-group trials, have been described.[5,6] Briefly, SHIFT included patients if they had symptomatic heart failure and a left ventricular ejection fraction ≤35%, were in sinus rhythm with heart rate ≥70 beats/min, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a beta-blocker if tolerated. In BEAUTIFUL, eligible patients had coronary artery disease with or without heart failure, left ventricular ejection fraction of <40%, and resting heart rate ≥60 beats/min.

This analysis focuses on pooled data from the placebo-treated patients in SHIFT and BEAUTIFUL with heart rate recorded at baseline. In SHIFT, heart rates were obtained from 12-lead electrocardiography after at least a 5-minute rest at baseline, at 2 weeks, 4 weeks, 4 months post-baseline, and 4 months thereafter. In BEAUTIFUL, measurements were recorded at baseline, 2 weeks, 4 weeks, 3 months, 6 months, and 6 months thereafter.

In the present analysis, we explored the relationship between the heart rate and the composite outcomes of cardiovascular mortality or hospital admission for worsening heart failure (the SHIFT primary end point), as well as their individual components, and cardiovascular mortality or hospital admission for myocardial infarction (components of the BEAUTIFUL primary end point).

### Statistical Analysis

Continuous variables are presented for the 2 studies as means (± standard deviation), and categoric variables are presented as frequencies. In the pooled BEAUTIFUL and SHIFT placebo populations, associations between heart rate and the clinical outcomes listed earlier were analyzed using Cox proportional hazards models. Baseline heart rate was analyzed, and estimated hazard ratios (HRs) were calculated for the baseline heart rate groups: <65 beats/min; 65 to 69 beats/min; 70 to 74 beats/min; 75 to 79 beats/min; 80 to 84 beats/min; and ≥85 beats/min, with corresponding 95% confidence intervals (CIs) and $P$ values. In analyses incorporating follow-up heart rates, because of regression to the mean, it was possible to split the lowest heart rate group (<65 beats/min) into 2 groups: <60 beats/min and 60-64 beats/min. Statistical models of risk markers usually relate a baseline measurement to the risk of a future event. However, if the risk marker changes dynamically over time and it is believed that risk will more closely relate to recently measured levels of the risk marker, then alternative approaches are of interest. In this analysis, time-updated heart rates (the most recent previously measured heart