

EDITORIAL COMMENT

Prognostic Significance of Ventricular Rate at Discharge in Patients With Persistent Atrial Fibrillation and HF



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Atrial fibrillation is the most common arrhythmia and is associated with an increased risk of heart failure (HF), systemic thromboembolism, and mortality. It is seen in 10% to 45% of patients with congestive HF at initial presentation.¹ Its presence in HF patients is associated with worse prognosis in terms of morbidity and mortality.² Frequently, cause-effect relationship cannot be established at the time of presentation, as persistent atrial fibrillation with a rapid ventricular rate can lead to HF, and on the contrary, severe HF can be complicated by atrial fibrillation with a rapid ventricular rate.

In atrial fibrillation, the relationship between ventricular rate and congestive HF is complex. Optimal management of HF, through neuro-hormonal influences, decreases sympathetic activity and thus slows ventricular rate. Slowing ventricular rate by atrioventricular blockade leads to improved ventricular filling and cardiac output. In individual patients, it is very difficult to establish which of the above is more critical; however, controlling ventricular rate is intuitive and is associated with improvement in HF. The optimal ventricular rate that is associated with the best long-term outcome remains a matter of debate.

Early rhythm control, when feasible, has become the mainstay of treatment for atrial fibrillation.^{3,4} However, there is an important subset of patients who require rate control as the primary modality of

treatment, either as a short- or long-term goal of therapy.⁵ Multiple studies have reported the effect of ventricular rate control in patients with atrial fibrillation and HF. RACE II (The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) trial⁶ is the sole randomized trial to evaluate clinical outcomes associated with a specific target heart rate. In this study, patients with permanent atrial fibrillation were randomized to a lenient rate-control strategy (resting heart rate <110 beats/min) or a strict rate-control strategy (resting heart rate of <80 beats/min or <110 beats/min during moderate exercise). There was no difference in the composite primary outcome of cardiovascular death, HF hospitalizations, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events (absolute difference of -2.0 percentage points [90% CI: -7.6 to 3.5; $P < 0.001$] for the noninferiority margin). This study was primarily designed to evaluate chronic outpatient management of rate control in atrial fibrillation. Importantly, however, patients with HF were under-represented and it remained unclear whether the results could be extrapolated to such a population. Hess et al⁷ used registry data that included 13,981 patients to assess optimal rate control strategy in patients with atrial fibrillation and HF. The study demonstrated that after multivariable adjustment, compared with strict rate control, lenient rate control was associated with higher adjusted risks of death (HR: 1.21; 95% CI: 1.11-1.33; $P < 0.001$), all-cause readmission (HR: 1.09; 95% CI: 1.03-1.15; $P < 0.002$), death or all-cause readmission (HR: 1.11; 95% CI: 1.05-1.18; $P < 0.001$), but not cardiovascular readmission (HR: 1.08; 95% CI: 1.00-1.16; $P = 0.051$) at 90 days. The authors of this study concluded that heart rates higher than 80 beats/min were associated with adverse outcomes,

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irrespective of left ventricular ejection fraction. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)⁸ investigated optimal heart rate control in 2,812 outpatients with permanent atrial fibrillation. The authors reported a nonlinear J-shaped relationship between heart rate and mortality, where decreasing heart rate ≤ 65 beats/min was associated with increasing all-cause mortality (adjusted HR: 1.15 per 5-beats/min increase; 95% CI: 1.01-1.32; $P = 0.04$), and increasing heart rate > 65 beats/min was associated with worse all-cause mortality (adjusted HR: 1.10 per 5-beats/min increase; 95% CI: 1.05-1.15; $P < 0.0001$). Similar observations were noted in the multicenter prospective observational registry - Clinical Implications of Heart Rate Control in Heart Failure with Atrial Fibrillation (CODE-AF).⁹ It was shown that in patients with atrial fibrillation and HF with preserved ejection fraction, the resting heart rate has U-shaped associations with the composite endpoint of death and hospitalization. No studies have specifically reported long-term outcomes of the degree of heart rate control in patients with atrial fibrillation and HF.

In this issue of *JACC: Advances*, Kishihara et al¹⁰ attempt to answer this question. This was an observational study that involved 334 patients with persistent atrial fibrillation hospitalized for HF syndrome at Tokyo's Women Medical University Hospital. Patients with pacemakers and implantable defibrillators were excluded. The study population was classified into 4 groups at 10 beats/min increments of heart rate at discharge: heart rate < 60 beats/min, heart rate 61 to 70 beats/min, heart rate 71 to 80 beats/min, and heart rate > 81 beats/min. The primary end point was a composite of death from any cause and rehospitalization due to HF. Follow-up with the patients was conducted through office visits or telephone calls. During the median follow-up period of 389 days, 39.8% of patients experienced the primary composite endpoint. Patients with heart rate at discharge > 81 beats/min had a higher rate of the primary end point (log-rank test for trend: $P = 0.039$). Multivariable Cox regression analysis indicated that heart rate > 81 beats/min was an independent predictor for the composite end point (HR: 1.87; 95% CI: 1.11-3.17). Death from any cause contributed to the composite endpoint more than rehospitalization for HF. Notably, a heart rate of > 81 beats/min remained a

predictor of composite end point across the spectrum of left ventricular ejection fraction.

There are several important limitations to this study. This was a single-center study subject to selection bias. A significant number of patients with persistent atrial fibrillation and HF were excluded if their heart rates were not recorded on admission and discharge. There is a lack of documentation of the rhythm during outpatient follow-up, which limits the understanding of how the hospital discharge heart rate was associated with the presence of sinus rhythm on follow-up and whether such association could have impacted the composite end point. This study excluded patients with pacemakers and implantable cardiac defibrillators, which represent a considerable proportion of patients with atrial fibrillation and HF. Finally, since this study is of an observational nature, it only suggests association between a particular heart rate and future cardiovascular outcomes. Thus, it remains unclear whether patients who had lower heart rates at discharge are simply different due to unmeasurable confounders and self-select themselves for more favorable outcomes on follow-up, regardless of the medical treatment for HF or rate control.

Despite all limitations, the authors are to be commended for studying this specific patient population who had HF decompensation and atrial fibrillation and limiting their study to an inpatient setting, which has significant challenges when it comes to study design. It is of note that favorable outcomes associated with a heart rate lower than 81 beats/min persisted across the range of left ventricular ejection fraction, which provides a good reminder that patients with HF with preserved ejection fraction and decompensated HF syndrome should also have a very nuanced approach to managing rate control. Lower ventricular rate in patients with atrial fibrillation is a good indicator of improved HF. Although, at present, rhythm control is preferable for the management of patients with atrial fibrillation in HF, it is not feasible for a large proportion of patients related to the inability to restore and/or maintain sinus rhythm. Overall, the data presented here can make us pause when discharging this group of patients and potentially think about who needs a closer follow-up and vigilant, comprehensive management of HF and other cardiovascular comorbidities in a timely manner.

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