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EDITORIAL COMMENT

Does Slow and Steady Win the Race?*

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Heart rate is 1 of the 4 vital signs that have provided a basis for making medical decisions for centuries (1). In recent years, we have learned that heart rate is also a powerful predictor of outcomes in unselected populations, patients with hypertension (2), and coronary artery disease, among other conditions (3). In patients with systolic heart failure (HF), higher heart rate at baseline and lower reduction of heart rate from baseline to follow-up in response to beta blockade are strong predictors of worse outcomes (4,5).

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In this issue of the *Journal*, Castagno et al. (6) report on the association of baseline heart rate with cardiovascular outcomes in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) Program. In this multicenter, randomized, placebo-controlled study, 7,599 patients with stable chronic HF were enrolled into 1 of 3 subgroups before randomization, 1 of which allowed only patients with a resting left ventricular ejection fraction (LVEF) >40%. The authors used baseline heart rate obtained by either palpation or auscultation and a concomitant 12-lead electrocardiogram to determine whether the rhythm was sinus or atrial fibrillation (AF). The outcomes included all-cause mortality (the primary outcome of the study) and the composite cardiovascular mortality plus hospital stay for worsening HF.

In the results, the authors provide us with 3 major findings. First, they show that baseline resting heart rate is associated with increased mortality, with every 10-beat/min increase associated with respective increases of 8% for all-cause mortality and 10% for the composite endpoint. This perhaps unsurprising finding was not affected by dosage or usage of beta-blocker or any other therapy and serves to confirm similar findings previously made. Second, this finding is extended to the 3,023 patients with LVEF >40% (nonsystolic HF), as we are shown that the relationship between resting heart rate and adverse outcomes continues irrespective of baseline LVEF. Third, and paradoxically, we are shown that this association is not observed in the 1,148 (15%) patients with AF at baseline. The conclusions reported in this study are made in a well-defined, well-treated group of patients with HF and so are applicable to current medical practice.

Indeed, it is now a popular notion in HF guidelines that optimal treatment of HF includes the use of beta-blocker therapy to achieve a resting heart rate <60 beats/min or as low as tolerated by the patient (7). Recent studies have shown that administration of pure heart rate-lowering medications to patients with chronic systolic HF and mildly increased heart rate (>70 beats/min at rest)—such as the potassium channel blocker ivabradine—results in improvement in ventricular reverse remodeling, improved symptoms, and fewer cardiovascular hospital stays (8,9). Although undoubtedly effective, the precise mechanism(s) underlying the benefit of beta-blockade for systolic HF remain elusive. Studies to date have suggested the reduction of baseline heart rate as well as follow-up heart rate on therapy is predictive of beta-blocker efficacy (5). Perhaps reduction of heart rate by beta-blocker therapy underpins their beneficial effects, although other agents that reduce resting heart rate have not shown efficacy. Perhaps careful evaluation of other therapies that reduce heart rate, such as ivabradine or vagal stimulation, should be tested in patients not receiving beta-blockade.

The contrast in therapeutic evidence base between HF patients with reduced versus preserved systolic function is also noted when considering the issue of heart rate. Unlike the former group, there is little information with regard to the impact of heart rate and survival for those in the latter group. Only 1 previous study, a subgroup analysis performed in the DIG (Digitalis Investigator Group) study, reported in their cohort with LVEF >45% a lack of relationship between baseline heart rate and mortality (10). This is in contrast to the current study, where the relationship was similar to that in the overall trial. Why this disagreement? The cohort in the DIG trial was smaller than Castagno et al. and did show a significant correlation with HF hospital stay. Perhaps the failure to find an association with mortality occurred in this lesser-powered cohort through play of chance. Alternatively, a higher rate of usage of digoxin in the DIG trial (50% by definition!) might have played a role. This study was undertaken before the current era of lower target serum digoxin levels, which might have led to higher rates of digoxin toxicity and propensity for lethal arrhythmias, especially in women. Finally, the higher cut point for LVEF (45% vs. 40%) might have influenced the results in the 2 analyses. Other supporting data, such as the robust positive association between resting heart rate in a variety of clinical settings as previously mentioned, suggest

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that the current report by Castagno et al. (6) has it correctly. Nevertheless, other large data sources that include patients with HF and preserved systolic function should be interrogated to determine the heart rate and outcome relationship. After all, we have been surprised before where agents such as angiotensin-converting enzyme inhibitors and beta blockers exerted profoundly positive effects upon systolic HF only to show a lack of similar effects in HF patients with preserved ejection fraction. This might be yet another reminder that, with all their similarities, the 2 forms of HF retain fundamentally important differences.

Atrial fibrillation is an independent predictor of mortality in patients with HF and is associated with other markers of worse prognosis, such as history of hypertension, advanced age, higher New York Heart Association functional classification, and lower ejection fraction (11). A major therapeutic tenet is to control heart rate adequately in these patients, with many clinicians ascribing a lower heart rate to therapeutic efficacy. On the surface then, Castagno et al. (6) report the most intriguing and paradoxical finding in this study—the lack of association of resting heart rate and cardiovascular outcomes in the 15% of patients in this study with AF. The authors themselves look closely at their data and quite rightly suggest several reasons why this finding is likely correct. First, the statistical interaction ($p < 0.001$) is very indicative of a very strong interaction. Second, the authors' own analysis suggests that patients with AF really are different. Patients in sinus rhythm who were in the highest tertile of heart rate had lower ejection fraction and higher New York Heart Association functional class and were more likely to be diabetic than those in the lower tertiles. Among patients with AF, this was not seen. Additionally, the authors point out that other smaller cohorts have suggested there is no heart rate–outcome relationship when AF is present. In contrast, it must be pointed out that heart rate was determined by either auscultation or palpation and might thus have been inaccurate in those with AF (the so called "pulse deficit") and so affected the analysis. It would be quite helpful, for purposes of verification, to review the heart rate in patients with AF by both electrocardiogram and physical exam to determine whether there is likely an issue with pulse deficit. The population of patients with implanted cardiac devices could be an important source of information. The question of heart rate and outcomes for patients in AF could be further evaluated—in fact expanded upon—with potential for analysis of peak heart rate, temporal trends, and other factors that might instead predict outcomes for this subgroup.

Several potential explanations exist for this apparent paradox. Patients with AF and lower heart rates might also have conduction system disease, which might be associated with worse prognosis. Secondly, such patients might have concomitant autonomic dysfunction or adrenergic stimulation from impaired diastolic filling, with the need for a resultant increase in heart rate for delivery of cardiac output. In this scenario, those who are unable to increase their atrioventricular conduction, perhaps due to beta receptor down-regulation, will fare poorly in the long term. Atrial fibrillation is notorious for its irregularity. Many patients with uncontrolled AF also suffer periodic pauses, which might result in syncopal or pre-syncopal symptoms (or, even if asymptomatic, cause for clinician concern). This in turn limits the amount of rate control that is tolerable. Recent evidence suggests that the degree of heart rate irregularity (as well as rate) and a measured "atrial fibrillatory rate" might impact outcomes in AF (the more irregular, the worse the outcome) (12). This might serve as a marker of the overall conductive and autonomic state or a driver of outcomes. One potential therapeutic option then might be to ablate the atrioventricular node and place a pacemaker (or biventricular pacemaker) to control heart rate. This strategy, perhaps combined with AF ablation, is under consideration as a trial in the stable systolic HF population.

Castagno et al. (6) have provided us with important confirmatory, expansive, and surprising data in the field of heart rate and outcomes, and for that they should be congratulated. From this further questions arise. For example, can pure heart rate reduction be as efficacious as beta blockade in patients with systolic HF? Will heart rate reduction in patients with nonsystolic HF reduce morbidity and mortality? Will this strategy work for patients with cardiovascular disease but without HF? For now, slow and steady wins the race for most patients with HF and sinus rhythm, but for those with AF, the race is far from over.

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