How Many Patients Will Benefit From a New Therapy for Chronic Systolic Heart Failure, and What Difference Does it Make?*

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The importance of heart rate lowering in optimizing natural history among patients with chronic systolic heart failure (HF) has been increasingly clear for 15 years, certainly at least since Kjekshus and Gullestad reported a cross-sectional analysis of the HF mortality trials then completed (1). This assessment revealed that placebo-subtracted mortality changes among the trials were directly proportional to placebo-subtracted heart rate changes. This relationship was most strongly influenced by the trials of beta-blocking drugs by then available, but extended to non-beta-blockers as well. Subsequent meta-regression analyses confirmed these findings (2,3) and further indicated that the mortality benefit was highly significantly related to heart rate reduction, but not at all to beta-blocker dose (2).

However, the beta-blocker trials were based on hypotheses about the net effect of all beta-blocker pharmacological actions, in addition to heart rate slowing, which might, in theory, improve myocardial function; no target heart rates were developed for use of the drugs. The relatively recent availability of ivabradine, a “pure” heart rate-slowing drug, has allowed evaluation specifically of the benefit of heart rate reduction, separate from other pharmacological effects. Ivabradine seems to have only 1 action on the cardiovascular system, that of blocking f-channels in sinoatrial nodal cells, thereby reducing or eliminating the small f-current (If) generated across these channels. Physiologically, this current increases heart rate by increasing the slope of spontaneous sinoatrial diastolic depolarization (itself a function of ion movement through calcium and potassium channels). Administration of ivabradine enables rigorous testing of the hypothesis that heart rate lowering, alone, provides important benefit to patients with systolic HF. This hypothesis is highly plausible: the “mechanism” of such benefit is not fully understood, but it is known that in the failing myocardium, high-energy substrates are relatively deficient; increasing heart rate increases demand for this resource while decreasing the myocardial perfusion that could help to replenish it. Consistent with this putative mechanism, increasing the frequency of electrical stimulation of isolated papillary muscle strips from the hearts of humans with New York Heart Association functional class IV HF results in progressively diminishing contractile force, whereas similarly stimulating normal human papillary muscle strips increases contractile force (4). With this background, SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) was designed to test the hypothesis that heart rate lowering in addition to that achievable with beta-blockade, and on a background of evidence-based doses of the other drugs now routinely applied in chronic systolic HF, would diminish the frequency of either cardiovascular death or hospitalizations for worsening HF (the primary pre-specified composite endpoint).

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among patients with moderate-to-severe symptoms, left ventricular ejection fraction $\approx 35\%$ and heart rate at rest $\geq 70$ beats/min (5). The trial was highly positive, demonstrating an 18% reduction of the primary composite endpoint compared with placebo, 26% reduction in HF hospitalizations, and 26% reduction in death attributable specifically to HF. Importantly, by virtue of the study design, benefit only could be inferred in patients whose heart rate, for whatever reason (drug intolerance, adverse drug effects, insensitivity to drugs, and so on) could not be lowered to $< 70$ beats/min with beta-blockers alone. Moreover, though beta-blockade is a mainstay of therapy for systolic HF, multiple registries indicate that more than one-half the affected patients maintain heart rates in excess of 70 beats/min (often far in excess) despite beta-blockade (6,7) and other therapies. Therefore, it is expected that many patients can benefit from addition of ivabradine. However, this assumption never had been rigorously evaluated. In this issue of JACC: Heart Failure, Dierckx et al. (8) now have provided this evaluation, in a single-center cohort. These investigators collected data from 1,000 consecutive HF clinic visits. They found, as has been documented in several epidemiological studies, that one-half of the 824 individual patients who reported for these 1,000 visits had systolic HF and the remainder had diastolic HF (for which no evidence-based natural history-altering therapy now exists), that many already had achieved heart rates $< 70$ beats/min on their beta-blocker regimen and that several others were likely to have been brought there with more aggressive beta-blockade. This left only 3% of the 824 patients likely to qualify for addition of ivabradine (perhaps even fewer since the European Medicines Agency has labeled the drug for use only in patients with heart rates $> 75$ beats/min, for whom there is high likelihood of reduction in mortality alone). Conversely, ivabradine is devoid of several of the adversities associated with beta-blockers (exacerbation of pulmonary disease [9], conduction abnormalities [10], diabetes [11], and so on), thus suggesting that the drug will be prescribed in many patients whose heart rate could be lowered with higher beta-blocker doses alone but who cannot tolerate such dose increases.

The Dierckx et al. (8) data differ from those of recent large multicenter registries noted in the preceding text that indicate a larger proportion of patients with systolic HF whose heart rates are not optimally controlled despite current therapy. (Moreover, the SHIFT data suggest that optimal outcomes require achievement of heart rates $\leq 60$ beats/min [12], though this is not yet accepted as a target of therapy.) Nonetheless, even accepting the authors’ estimates at face value, current data indicate that approximately 10,000,000 people have HF in the United States today (13), and similar or even greater numbers elsewhere in the world (14). Using the authors’ proportions, this suggests that at least 600,000 persons in the United States and elsewhere can benefit from addition of ivabradine to lower heart rate to improve survival and/or reduce hospitalization frequency (and in addition, to enhance quality of life [15], not affected by beta-blockers); these numbers increase annually.

Most importantly, however, what impact should the findings of Dierckx et al. (8) have on the algorithm for treatment of patients with chronic systolic HF? Clearly, they suggest that clinicians often can achieve currently accepted goals by optimizing treatment with standard therapies, including maximization of beta-blockers. However, if heart rate on such therapy remains $> 70$ beats/min (or, according to the European labeling instructions, $> 75$ beats/min), ivabradine should be added. The issue of the proportion of patients who will be appropriate for ivabradine is interesting, but not nearly so important as that patients who are eligible should be treated because they will benefit.

**REFERENCES**


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