How Many Heart Failure Patients Might We SHIFT to a Lower Heart Rate?

See Article by Das et al

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For fast acting relief, try slowing down.

–Lily Tomlin

For years, β-blockers were strongly contraindicated in patients with heart failure. The pendulum has swung far from that position, and for patients with heart failure with reduced ejection fraction, β-blockers are now standard of care. It has been argued that persistent tachycardia may pose ongoing risk, and additional efforts to slow heart rate may further relieve a failing heart. Ivabradine presents an alternative option for reducing heart rate through I_f channel current inhibition. SHIFT (Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial) studied its use in patients with New York Heart Association functional class II-IV heart failure with ejection fraction ≤35% and heart rate >70 beats per minute, despite background medical therapy, and found a reduction in the end point of cardiovascular death or heart failure hospitalization.[1] This finding was driven mostly by reduction in hospitalization, and 2 important outstanding questions were highlighted in the accompanying editorial: concern over generalizability/applicability and whether the findings may have been an association with and not a consequence of treatment.[2] Despite these limitations, SHIFT was a landmark heart failure trial of a novel agent, and ivabradine has earned a IIa recommendation (level of evidence: B-R) in the recently published American College of Cardiology/American Heart Association/Heart Failure Society of America HF Guideline Focused Update.[3] Ongoing awareness of the importance of adequate background β-blocker therapy was highlighted in the commentary, "Given the well-proven mortality benefits of β-blocker therapy, it is important to initiate and uptitrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation."

Das et al[4] are to be congratulated for their work, providing important insights into the generalizability of ivabradine in contemporary clinical practice. Simply put, they addressed the question of how many in the chronic heart failure population on guideline-directed medical therapy would be eligible for ivabradine, based on the criteria from the SHIFT trial. They used the Swedish Heart Failure Registry (SwedeHF), a large database of heart failure patients, to tackle the question of generalizability of SHIFT. Although 53% in SwedeHF were inpatients, the fraction of ivabradine eligibility was similar between inpatients and outpatients, implying that this may not be a major limitation. Substantial baseline information, including medication profiles and medical history, was otherwise available. Some important limitations with the database are acknowledged, including the inability to assess for hospitalization prior to database enrollment, whether medications were stable for 4 weeks, and the category of ejection fraction did not explicitly include ≤35%. Given the typical uncer-

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tainty in ejection fraction measurements of ±5%, the cutoff of <40% chosen was reasonable. Approximately half of the patients had been diagnosed within the prior 6 months, raising the question of whether they had enough time for uptitration to maximally tolerated dose of β-blocker. This is also another substantial difference from the SHIFT trial, where the duration of heart failure prior to enrollment was 3.5 years. The small proportion with cardiac resynchronization therapy is also notable because higher cardiac resynchronization therapy utilization might have facilitated more aggressive uptitration of β-blockers. On the other hand, the lower rate limit on cardiac resynchronization therapy devices is sometimes set at 70 or 75 beats per minute to improve the percentage of biventricular pacing through suppression of premature ventricular contractions. Currently available data does not support the use of ivabradine in such patients, so it is not clear how increased cardiac resynchronization therapy utilization would change ivabradine eligibility. It is also likely that the number of patients in the study with atrial fibrillation is an underestimate, given the frequent asymptomatic nature of this common diagnosis. Despite these limitations, Das et al[4] provide a valuable estimate on the generalizability of SHIFT.

Are the SHIFT inclusion criteria the most appropriate benchmark to assess how broadly this agent might be used? It is of interest to compare the present study to the population of the recently published RELIf-CHF study (Long-Term Treatment With Ivabradine in Ambulatory Patients With CHF).[5] RELIf-CHF was a multicenter, prospective observational study of ivabradine in 767 patients in clinical practice in Germany. Left ventricular ejection fraction (LVEF) ≤35% was not required, but the median duration of heart failure was 33.8 months. The distribution of New York Heart Association functional class and ischemic burden were similar to the SwedeHF population, but the RELIf-CHF study had lower β-blocker use—65% versus 89% in the cohort described by Das et al.[4] The authors speculated that the low rate of β-blocker use could be driven by intolerance or contraindication to β-blockers and that this was a likely indication for ivabradine use. They observed a reduction in hospitalization from 23% to 5%, reduction in BNP (B-type natriuretic peptide), increase in LVEF, improved quality of life, and low rate of adverse drug reactions. Although this was not a randomized trial, it provides some evidence of real-world benefit in a broader cohort than SHIFT. On the other hand, EDIFY (Effect of Ivabradine in Patients With Heart Failure With Preserved Ejection Fraction) was a prospective, randomized trial of 179 patients with New York Heart Association II/III symptoms, sinus rhythm >70 beats per minute, and LVEF ≥45% with elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide).[6] Despite the expected decrement in heart rate, no improvement was observed in any of the 3 coprimary end points (echo-Doppler *E*/*e*', distance on 6 MW, or plasma NT-proBNP). Thus, SHIFT inclusion criteria currently offer the most evidence-based parameters of which patients are likely to have a favorable risk/benefit ratio from ivabradine treatment.

Overall, 14.2% of patients in the registry were comparable to participants in the SHIFT trial within the limitations of the data set. Focusing on the heart failure with reduced ejection fraction population (defined as LVEF <40% for this study), estimated eligibility was 24.3% (3741/15 367). Barring additional clinical trial results demonstrating efficacy in a broader population, this seems more likely to be a ceiling than a floor. This estimate includes some with LVEF ≥35%, and the non-SHIFT-type patients were also more likely to have achieved >50% of the target β-blocker dose, suggesting that additional β-blocker uptitration would be possible in some fraction of the SHIFT-type patients. Das et al[4] also estimated shifts in eligibility over time, based on the subset of patients with serial data points. The fraction whose eligibility changed was small, and we must be particularly cautious in our understanding of the group who moved from eligible to ineligible. Detailed information on medications during follow-up was not available in the SwedeHF database, so we must consider the possibility that new ineligibility based on a lower heart rate could occur in the result of treatment with ivabradine, a treatment success rather than a change in eligibility!

Quantification and understanding of the differences between clinical trial participants and the broader population are important for efforts to improve quality of care on a population basis. Current quality initiatives appropriately focus on utilization of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and aldosterone antagonists, for example. Initiatives to evaluate and increase evidence-based utilization of ivabradine now have a foundation on which to develop reasonable population-based targets. Although the cost of ivabradine is modest (annualized wholesale acquisition cost has been reported[7] at ≈$4500) compared with some medications, such as the hepatitis C antivirals and proprotein convertase subtilisin kexin 9 inhibitors, it is substantial compared with β-blockers. Cost-effectiveness has been of interest, and recent publications have suggested favorable economics, albeit over a 10-year time horizon, driven predominantly by estimated reductions in hospitalization rates.[8] The insights from Das et al[4] will improve our ability to estimate the value of this therapy.

Although as a result of the present work, we now have a better estimate of how many would be eligible for treatment based on the SHIFT criteria, outstanding questions on the role of ivabradine remain. Most importantly, we do not know why more patients were not on target doses of β-blockers. Was it too early to have completed the uptitration process? Are we as clinicians too quick to decrease dose in response to side effects? Is there a group of patients who simply cannot

tolerate β-blockers at the doses that were studied in clinical trials and could ivabradine provide benefit in this population, despite the lower doses of β-blockers? The fundamental role of β-blockers in treating heart failure with reduced ejection fraction is well documented, but we have a great deal yet to learn about the role and relationship of ivabradine.

DISCLOSURES

None.

AFFILIATIONS

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FOOTNOTES

Circ Heart Fail is available at http://circheartfailure.ahajournals.org.

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