Ivabradine
Role in the Chronic Heart Failure Armamentarium

Mitchell A. Psotka, MD, PhD; John R. Teerlink, MD

Abstract—Ivabradine is approved to reduce hospitalizations for patients with symptomatic heart failure, reduced ejection fraction, and persistently elevated heart rate despite otherwise maximal medical therapy. However, the eligible patient population is a small fraction of those with heart failure overall. This review summarizes the major clinical evidence supporting the use of ivabradine, identifies and discusses areas of uncertainty from the clinical trial data, helps describe the population most likely to benefit, and attempts to place ivabradine within the multifaceted treatment scheme currently used for patients with heart failure and reduced ejection fraction. (Circulation. 2016;133:2066-2075. DOI: 10.1161/CIRCULATIONAHA.115.018094.)

Key Words: clinical studies as topic ▪ drug therapy ▪ heart failure

The current treatment regimen for chronic heart failure (HF) has markedly improved survival and quality of life; however, the burden of HF hospitalization and mortality remains substantial. The heart rate (HR)–lowering therapeutic ivabradine was recently approved by the US Food and Drug Administration for the treatment of stable chronic HF. Because ivabradine has been the subject of multiple controlled trials and authorized by the European Medicines Agency since 2005, substantial clinical data are available for review. The efficacy, adverse effects, and evidence-based use of ivabradine for patients with chronic HF are reviewed here, with emphasis on the role of ivabradine within the contemporary framework for treatment of chronic HF. The ivabradine data also refine the current understanding of the impact of HR control on the progression and management of chronic HF.

HR Management in HF

The epidemiological association between elevated HR and cardiovascular outcomes is well established. Observational cohorts and controlled trials have shown a consistent correlation between elevated HR and morbidity and mortality in general and HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) specifically. In the Get With The Guidelines–Heart Failure registry, resting HR ≥70 bpm in sinus rhythm on hospital admission was associated with increased in-hospital mortality, and resting HR on discharge predicted 1-year hospital readmission and mortality.7,12 These data, however, do not distinguish whether HR is a risk factor or a modifiable therapeutic target.

The beneficial effects of β-blockers on both morbidity and mortality in HFrEF suggest that HR can be a therapeutic target, but there is disagreement as to whether these effects derive from HR reduction or from other results of adrenergic receptor inhibition. Analyses of individual trials have demonstrated no relationship between improved outcomes and HR change, a trend to dose-dependent reduction in all-cause mortality, and an association of target β-blocker dosing with improved outcomes.16–19 Additionally, analysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) found that after multivariable adjustment only β-blocker dose, not HR, remained associated with improved mortality and hospitalizations.20 Alternatively, meta-analyses of >19,000 β-blocker–treated patients with HFrEF found that the magnitude of HR lowering directly correlated with improved all-cause mortality and left ventricular ejection fraction (LVEF), with no significant relationship between β-blocker dose and HR or all-cause mortality.14 Although these analyses are confounded because β-blockers were titrated to maximally tolerated doses in the included trials, they suggest the potential for an alternative targeted HR-lowering therapy in HF.

A niche for an HR-reducing therapeutic distinct from β-blockers exists because, despite the incontrovertible benefit of β-blockers for HFrEF, uncertainty surrounding their mechanism, their known side effects, particularly in patients already perceived to have borderline low blood pressures or pulmonary disease, and the reluctance of the parts of patients and prescribers have prevented their universal use.21 Even for patients in the landmark clinical trials, successful titration was modest. Target dosing was achieved by 43% (10 mg daily bisoprolol) in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), 64% (200 mg daily metoprolol succinate) in the Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF), and 65% and 75% (25 mg twice daily carvedilol) in the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS)
Ivabradine and $I_f$

Ivabradine possesses multiple characteristics suitable for an adjunctive therapy for patients with HFrEF on maximally tolerated $\beta$-blocker therapy or intolerant of $\beta$- Blockers. It is a specific inhibitor of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels create the diastolic depolarization or “funny” pacemaker current ($I_f$) of the sinoatrial node, so termed because it is uniquely activated by the membrane hyperpolarization that follows systolic depolarization. $I_f$ was first discovered in 1970s animal studies, found to be primarily mediated in humans by abundant sinoatrial HCN4, and determined to be clinically relevant in part by genetic studies linking HCN4 mutations and asymptomatic bradycardia. Ivabradine directly blocks HCN channels in a use-dependent manner, which decreases the sinus rate in both healthy and diseased hearts at rest and with exertion (Figure 1). The primary cardiac effect of ivabradine appears to result from this HR reduction, and ivabradine does not directly change inotropy, diastolic function, cardiac output, vascular resistance, or blood pressure. Ivabradine has no activity at the atrioventricular node and does not alter the ventricular rate in atrial fibrillation. Although HCN channels are not expressed in normal ventricular myocardium, expression is increased in the ventricular myocardium of patients with HFrEF, raising the possibility that the mechanism of action of ivabradine may be multifaceted in these patients, perhaps by reducing ventricular ectopy.23–26

Ivabradine pharmacology is well described. The half-life of oral ivabradine and its primary active metabolite require twice-daily dosing. It is metabolized predominantly by the cytochrome P450 3A4 system (CYP3A4), and concomitant use of strong inhibitors, including azoles, macrolides, and protease inhibitors, is contraindicated. Because of its use dependence, HR reduction with ivabradine is proportional to pretreatment HR. In healthy volunteers, a single 10-mg oral dose of ivabradine decreased resting HR 16±8% and peak exercise HR 11±4%.3 There is no direct effect on the HR-adjusted QT interval by ivabradine. There are no data on subjects with creatinine clearance <15 mL/min, but no dose adjustment is otherwise necessary. The off-target visual effects of ivabradine, sensations of increased brightness not mediated by retinal stimuli called phosphenes, appear to be mediated by inhibition of similar hyperpolarization-activated channels in the retina.36

**Initial Chronic Stable Angina Trials**

The HR-lowering effect of ivabradine was initially evaluated as a therapeutic for symptomatic coronary artery disease in a series of international, double-blind, randomized efficacy studies quantified by exercise tolerance testing. Patients with New York Heart Association (NYHA) class III to IV HF symptoms were excluded. In 300- to 900-patient trials, ivabradine decreased HR and significantly lengthened exercise tolerance testing duration for patients with chronic stable angina, and ivabradine was not inferior to atenolol and amlodipine.37–39 However, ivabradine achieved only a mild additive exercise tolerance testing benefit with low-dose, untitrated atenolol, and no significant advantage was seen when ivabradine was added to full-dose amlodipine.40,41

**Morbidity-Mortality Evaluation of the $I_f$ Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction Study**

The Morbidity-Mortality Evaluation of the $I_f$ Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) study invoked the association between HR and outcomes as rationale. In this international, double-blind trial, 10917 predominantly male patients with stable ischemic HFrEF and LVEF <40% were randomized to ivabradine or placebo (Table). Of these patients, 85% had NYHA class II or III HF symptoms, and standard HF medication use was similar to that in a recent large European registry, with 87% taking $\beta$-blockers. Four percent of subjects had incomplete follow-up. There was no difference in the primary composite end point of first cardiovascular death, hospitalization for myocardial infarction (MI), or hospitalization for worsening HF over a median of 19 months of follow-up despite a sustained placebo-corrected mean decrease in HR of 6.4 bpm by ivabradine (Table). There was no benefit on secondary end points either, although there were improvements in LVEF and left ventricular dimensions with ivabradine in the 426-patient echocardiographic substudy.43
Table. Characteristics of the Large Ivabradine Trials

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>BEAUTIFUL (n=10,917)</th>
<th>BEAUTIFUL (HR ≥70 bpm) (n=5392)</th>
<th>SIGNIFY (n=19,102)</th>
<th>SHIFT (n=65,050)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>≥55</td>
<td>≥55</td>
<td>≥55</td>
<td>≥18</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>≥60</td>
<td>Post hoc (≥70)</td>
<td>≥70</td>
<td>≥70</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>≤39</td>
<td>≤39</td>
<td>&gt; 40</td>
<td>≤35</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>≤180</td>
<td>≤180</td>
<td>No “severe uncontrolled hypertension; or hypotension”</td>
<td>≥85 and ≤180</td>
</tr>
</tbody>
</table>

Recruitment

<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Median follow-up (IQR), mo</td>
<td>19 (16–24)</td>
<td>...</td>
<td>28 (21–35)</td>
<td>23 (18–28)</td>
</tr>
</tbody>
</table>

Baseline characteristics

| Age, y              | 65.2±8.5  | 64.6±8.6 | 65±7.3    | 60.4±11.4  |
| Male, %             | 83        | 82       | 72        | 76         |
| HR, bpm             | 71.6±9.9  | 79.2±8.6 | 77.2±7.1  | 79.9±9.6   |
| LVEF, %             | 32.4±5.5  | 32.0±5.6 | 56.4±8.6  | 29.0±5.1   |
| History of CAD, %   | 100       | 100      | 100       | 68         |
| Angina present, %   | 14        | 13       | 75        | ...        |
| NYHA class, %       | I         | 15       | 14        | ...        | 0 |
|                     | II        | 61       | 59        | ...        | 49 |
|                     | III       | 23       | 27        | ...        | 50 |
|                     | IV        | 0        | 0         | ...        | 2 |

Baseline medications, %

| β-Blocker   | 87        | 84 | 83 | 89 |
| ACEi/ARB    | 90        | 90 | 83 | 93 |
| MRA         | 27        | 30 | ... | 60 |
| Diuretic    | 59        | 63 | ... | 83 |
| Cardiac glycosides | 8 | ... | ... | 22 |

Devices, %

| CRT | ... | ... | ... | 1 |
| ICD | ... | ... | ... | 3 |

Treatment regimen, mg twice daily

<table>
<thead>
<tr>
<th>Ivabradine starting dose</th>
<th>5; if ≥75 y of age, start with 2.5</th>
<th>5; if ≥75 y of age, start with 2.5</th>
<th>7.5; if ≥75 y of age, start with 5</th>
<th>5; if ≥75 y of age, start with 2.5</th>
</tr>
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<tbody>
<tr>
<td>Ivabradine target dose</td>
<td>7.5</td>
<td>7.5</td>
<td>10</td>
<td>7.5</td>
</tr>
<tr>
<td>Mean dose achieved</td>
<td>6.2</td>
<td>...</td>
<td>8.2±1.7</td>
<td>6.4±1.6</td>
</tr>
</tbody>
</table>

Outcomes (ivabradine vs placebo)

<table>
<thead>
<tr>
<th>Primary composite end point</th>
<th>Cardiovascular death, MI, or HHF</th>
<th>Cardiovascular death, MI, or HHF</th>
<th>Cardiovascular death or MI</th>
<th>Cardiovascular death or HHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-corrected HR change (95% CI), bpm</td>
<td>6.4 (6.0–6.8) at 1 y</td>
<td>7.9 (7.3–8.5) at 1 y</td>
<td>9.8 (9.6–10.0) at 3 mo</td>
<td>9.1 (8.5–9.7) at 1 y</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or HHF, n (%)</td>
<td>844 (15.4) vs 832 (15.3)</td>
<td>463 (17.2) vs 498 (18.5)</td>
<td>654 (6.8) vs 611 (6.4)</td>
<td>825 (25) vs 979 (30)</td>
</tr>
<tr>
<td>P</td>
<td>0.94</td>
<td>0.17</td>
<td>0.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause death, n (%)</td>
<td>572 (10.4) vs 547 (10.1)</td>
<td>331 (12.3) vs 324 (12.0)</td>
<td>485 (5.1) vs 458 (4.8)</td>
<td>503 (16) vs 552 (17)</td>
</tr>
</tbody>
</table>

(Continued)
Baseline HR ≥70 bpm modified the effect of ivabradine on the primary outcome (P=0.03 for interaction), and a prespecified subgroup analysis of those patients was performed.42 The placebo-corrected mean HR reduction in the subgroup was 7.9 bpm, and although a higher proportion of patients were not taking β-blocker or had NYHA class III symptoms, there was still no significant difference in the primary composite end point (Table). Statistically fewer patients on ivabradine in the subgroup analysis were admitted with MI, but event rates were low. A separate subgroup analysis of the 14% of patients with activity-limiting angina demonstrated a reduction in hospitalizations for MI and a borderline reduction in the composite end point (hazard ratio, 0.76; 95% confidence interval, 0.58–1.0; P=0.05).44 Of those patients with angina and HR ≥70 bpm, differences in the same outcomes appeared statistically significant.

### Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients With Coronary Artery Disease

The Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients With Coronary Artery Disease (SIGNIFY) international, randomized, placebo-controlled, double-blind trial was undertaken to validate the potential ischemic benefit seen in BEAUTIFUL subgroups.37–41,44,45 The population of 19 102 patients with stable coronary artery disease, with an HR ≥70 bpm, and without clinical HF was predominantly male; 75% had angina; 83% were taking β-blockers; 40% were taking nitrates; 4% were taking dihydropyridine calcium channel blockers; the mean LVEF was 56%; and only 2% had incomplete follow-up (Table). Although HR was significantly reduced by ivabradine therapy, with target and mean dosing higher than in BEAUTIFUL, there was no statistically significant benefit from ivabradine on the primary composite outcome of cardiovascular death or nonfatal MI over a median of 28 months. There was also a trend toward increased HF hospitalization and no benefit on the incidence of MI.

When the prespecified 63% of the population with activity-limiting angina was analyzed for the primary outcome, there was evidence of harm with ivabradine, with a hazard ratio of 1.18 (95% confidence interval, 1.03–1.35; P=0.02; P=0.02 for interaction) and an absolute risk increase of 1.1%.45 This was despite improved angina class severity with ivabradine, consistent with prior exercise treadmill studies.37–41 The reason for a harmful effect, in contrast to BEAUTIFUL, remains unclear. Perhaps the increased ivabradine dosing and concomitant administration of the CYP3A4 inhibitors verapamil and diltiazem increased adverse events to overwhelm any potential benefit, or perhaps HR lowering in the presence of stable angina...
has only symptomatic benefit. Whatever the cause, SIGNIFY clearly shows that ivabradine offers no benefit besides symptomatic improvement for patients without HF and that those patients with angina symptomatically helped by ivabradine may also be most likely to suffer an associated unwanted clinical outcome.

**Systolic Heart Failure Treatment With the I1 Inhibitor Ivabradine Trial**

Building on BEAUTIFUL, the Systolic Heart Failure Treatment With the I1 Inhibitor Ivabradine Trial (SHIFT) randomized 6505 patients with ischemic and nonischemic stable HFrEF and LVEF ≤35% to ivabradine or placebo (Table).46 Like BEAUTIFUL, SHIFT included no patients from the United States, most patients were male, and evidence-based use of HF medications was similar to that in a European registry, with 89% of patients taking β-blockers, 60% taking aldosterone antagonists, and 22% taking digitals.29 All patients had NYHA class II to IV symptoms (predominantly class II or III); 68% were ischemic in pathogenesis; 70% achieved the target ivabradine dose of 7.5 mg twice daily; and only 3% were lost to follow-up over a median of 23 months.

Fewer patients treated with ivabradine suffered the primary composite end point of first cardiovascular death or hospitalization for HF (hazard ratio, 0.82; 95% confidence interval, 0.75–0.90; P<0.0001); this was almost exclusively driven by a 5% absolute risk reduction for HF hospitalization.46 Although not statistically significant, there was a trend toward less benefit with concomitant baseline β-blocker use (P=0.103 for interaction) and a trend toward greater ivabradine effect for nonischemic patients (P=0.059 for interaction). Patients also experienced statistically significant improvements in NYHA class, global assessments, and Kansas City Cardiomyopathy Questionnaire summary scores with ivabradine.46,47 A pooled analysis of the 11 897 patients from SHIFT and BEAUTIFUL with baseline HRs ≥70 bpm demonstrated comparable findings; however, there remained no statistically significant effect on all-cause or cardiovascular mortality.46

SHIFT substudies supported the beneficial effects of ivabradine found in the main trial. Ivabradine-mediated improvement showed no interaction with comorbidity load, even when adjusted for the lower use of β-blockers with more comorbidities.49 Ivabradine therapy also reduced recurrent all-cause and HF hospitalizations, with a 23-month incidence rate ratio of 0.75 (95% confidence interval, 0.65–0.87; P=0.0002).50 The 275-patient echocardiographic substudy demonstrated a mild augmentation of LVEF (4±10%; P=0.004) and mild decreases in end-systolic and -diastolic volumes after 8 months of ivabradine relative to placebo.31,52 Concomitant significant reductions in effective arterial elastance and improved total arterial compliance, without changes in systemic vascular resistance, suggested that dimension changes may have followed from enhanced ventricular-arterial interaction, particularly from improved vascular function, rather than a direct effect on ventricular function.

There was significant effect modification of the primary end point by baseline HR (P=0.029 for interaction).46 SHIFT patients in the highest HR quartile (resting HR ≥87 bpm) had the greatest HR reduction with ivabradine (23±13 bpm) and the largest reduction in clinical end points.43 These patients were younger; more had NYHA class III symptoms and nonischemic origins and took mineralocorticoid receptor antagonists; and fewer used β-blockers. After statistical adjustment for known prognostic factors and baseline HR, the beneficial effect of ivabradine was eliminated, which the trial investigators cited as evidence that ivabradine exerts its effect only though HR change. Still, this statistical relationship does not prove a causal link, yet it may be that alternative pathways mediate the effects independently of HR reduction, perhaps as a result of changes in ivabradine targets in the failing myocardium or afterload effects on the vasculature.32–34,51

There are, however, several peculiarities about the SHIFT population and trial results that limit its applicability:

1. Although a large proportion of the population were eligible for device therapy, only 1% had cardiac resynchronization therapy and 3% had an implantable cardioverter-defibrillator compared with 13% and 24%, respectively, of all HF patients in a European registry.29
2. Although trial investigators urged maximum dosing of β-blocker, only 75% of patients were taking an evidence-based β-blocker for HFrEF (carvedilol, bisoprolol, or metoprolol succinate), with only 26% at target dose and only 56% taking >50% the target dose.46
3. Subgroup analysis found that ivabradine did not significantly reduce any end point in those with baseline HR <75 bpm.44 Ivabradine was associated with an almost 3% absolute risk reduction in all-cause mortality (P=0.01) in the 4150 patients with baseline HR ≥75 bpm, but there was a statistically nonsignificant trend toward increased risk for all-cause and HF mortality in the 2351 patients with HR <75 bpm (P=0.21).
4. Although the primary investigator-reported reason for failure to achieve target β-blocker dosing was hypotension, the mean baseline systolic blood pressure was 122 mm Hg, similar to untreated baseline values in the landmark β-blocker trials.3,4,23–26,55
5. Compared with the marked and consistent reduction in all-cause mortality found in the benchmark β-blocker trials, a similar HR reduction by ivabradine provided no all-cause mortality benefit (Table). In contrast to ivabradine, the absolute risk reduction in cumulative mortality at 1 year for carvedilol compared with placebo was 7.1% (P=0.0014), and treated patients spent 27% fewer days per year hospitalized.3,56 The absolute reduction in mortality with bisoprolol over 1.3 years was 5.5% (P<0.0001), and over 1 year, it was 3.8% for metoprolol succinate (P=0.00009).24,25 Meta-analyses have reinforced these findings.3,4 Additionally, carvedilol was compared with HR reduction alone mediated by metoprolol tartrate in COMET, in which carvedilol and metoprolol tartrate decreased resting HR 13.3 and 11.7 bpm from baseline, respectively.21 Although the HR reductions were similar to those observed with ivabradine, carvedilol outperformed metoprolol tartrate, with an absolute reduction in all-cause mortality of 6% over 58 months.
6. In another SHIFT subgroup analysis, ivabradine demonstrated a statistically significant improvement for the
primary composite end point of cardiovascular death or HF admission only for patients taking <50% of target β-blocker doses.57 Even though this analysis was likely biased away from an interaction by including the 13% of subjects taking metoprolol tartrate and nebivolol, the absolute risk for the primary end point was reduced 10% (P=0.012) in patients taking no baseline β-blocker but was not reduced at all in those taking 100% of their target β-blocker dose.57 There remained no statistically significant benefit on cardiovascular mortality at any β-blocker dose. The authors argue that because the statistical test for multiplicative interaction did not cross their threshold, particularly after adjustment for baseline HR, there was no interaction between efficacy of ivabradine and β-blocker dose; however, the statistically weak test for heterogeneity was borderline (P=0.056). Thus, it should not be strongly concluded that the effect of ivabradine is independent of β-blocker dosing, and the results of SHIFT remain muddled by idiosyncrasies in the population and the suggestion that ivabradine may be effective in only a subset of the trial population.

Adverse Events

Although generally well tolerated, with total adverse event rates similar to those of placebo in BEAUTIFUL and SHIFT, ivabradine increased the frequency of asymptomatic and symptomatic bradycardia, atrial fibrillation, and phosphenes (Table).24,47,48 In SIGNIFY, 13% of patients discontinued ivabradine because of adverse events compared with 7% of those treated with placebo (P<0.001). However, those numbers were 14% and 13% for ivabradine and placebo, respectively, in SHIFT (P=0.051).46 For reference, permanent treatment withdrawals were similar or decreased with the study medications compared with placebo in the landmark β-blocker trials.24-26 Phosphenes were reversible with ivabradine withdrawal and reportedly not associated with medication discontinuation.

The incidence of bradycardia was greater in SIGNIFY than in SHIFT or BEAUTIFUL, possibly because of higher ivabradine dosing and concomitant use of the CYP3A4 inhibitors verapamil and diltiazem (Table). Fortunately, no association was found between emergent bradycardia (HR<50 bpm) and the primary SIGNIFY end point, either in the total population or in those with activity-limiting angina.46

Given the worse prognosis for patients with HF and atrial fibrillation compared with those with HF alone, the 1.5% absolute risk increase in atrial fibrillation over 28 months with ivabradine therapy (0.7% yearly absolute increase risk) in SIGNIFY is striking.55,59 In the pooled analysis from SHIFT and BEAUTIFUL with baseline HR ≥70 bpm, there was a similar 1.7% increase in the absolute risk of atrial fibrillation (P<0.001) with ivabradine.48 A meta-analysis that included multiple small trials with unclear follow-up found similar results, and the mechanism remains unclear.56 When only emergent atrial fibrillation in SIGNIFY was considered, 74% of patients had no history of atrial fibrillation, and most cases were paroxysmal.59 Although the incidence of the primary composite end point and stroke was comparable for those who developed atrial fibrillation on ivabradine and on placebo in SIGNIFY, this analysis lacked power, and a detectable downstream harm may manifest only when a large population can be analyzed for a longer duration.58

HF With Preserved Ejection Fraction

Two small, randomized, placebo-controlled trials have assessed the effects of ivabradine on exercise tolerance and echocardiographic parameters in HFrEF patients with conflicting results. The first dosed ivabradine 5 mg twice daily in 61 HFrEF patients with significant improvements in exercise capacity, peak oxygen uptake, and echocardiographic parameters over 7 days.59 The second study administered ivabradine 7.5 mg twice daily in a crossover design to 22 patients with HFrEF.60 Although ivabradine improved echocardiographic parameters of diastolic function over 2 weeks, it diminished peak oxygen consumption and submaximal exercise performance measured by oxygen uptake efficiency slope.

Interpretation of these disparate results is challenging. Baseline peak oxygen uptake values were similar in both trials, but the first trial selectively included subjects with echocardiographic suggestion of increased left ventricular filling pressures and used a lower ivabradine dose. HR decreased ≥10 bpm in the low-dose trial compared with 20 bpm in the higher-dose trial.61,62 Given the heterogeneity of HFrEF diagnoses, additional uncharacterized differences in the subjects were likely.63 More evidence is needed to determine the potential role for ivabradine in patients with HFrEF.

Role in Chronic HF Therapy

Both the US Food and Drug Administration and the European Medicines Agency approved ivabradine for the treatment of patients with stable HFrEF in sinus rhythm with LVEF ≤35% taking a β-blocker at the maximum tolerated dosing. However, the US Food and Drug Administration used the SHIFT entry criteria, specifically HR ≥70 bpm, whereas the European Medicines Agency approved ivabradine only for those with HR >75 bpm. Because higher β-blocker dosing correlated with lower baseline HR, the increased HR cutoff potentially addressed the lack of benefit seen for ivabradine both below an HR of 75 bpm and with higher β-blocker dosing.54,57 Both agencies contraindicated ivabradine with significant sinoatrial or atrioventricular block in the absence of a pacemaker or with strong CYP3A4 inhibitors among other prohibitions. Both warned of fetal toxicity suggested by animal studies and advised clinical monitoring of patients for atrial fibrillation and bradycardia.

The critical prerequisite for ivabradine initiation in HFrEF is the use of guideline-directed medical therapy, including a maximally titrated β-blocker or true β-blocker intolerance, because ivabradine appears inferior to evidence-based β-blocker therapy with respect to mortality (Figure 2). The correlations with diminished ivabradine efficacy at a lower HR and with target β-blocker dosing suggest the same and indicate that appropriate measurement of resting HR is mandatory. In SHIFT, baseline HR was measured by ECG after a 5-minute rest at 2 consecutive visits.46 Although it remains unclear whether β-blockers should be titrated to an HR goal or a target dose, it is reasonable to attempt to achieve both while acknowledging that guideline-quoted targets are derived from
the doses achieved in major clinical trials and not prospective dose-ranging outcomes studies.21,22

For symptomatic patients with HFrEF with elevated HR in sinus rhythm taking the major classes of therapeutic medications who are legitimately intolerant of or ineligible for increased β-blocker therapy, ivabradine appears to be a reasonable choice. Because digoxin was not studied with a modern regimen, did not affect mortality, and reduced all-cause and HF hospitalization similarly to ivabradine (3% and 8%, respectively, with digoxin; 4% and 5%, respectively, in SHIFT), ivabradine has a superior evidence base.9,46 Even so, the mechanism by which an ivabradine-mediated HR reduction improves HFrEF is not entirely clear. It could involve improving autonomic function, diminishing ischemic supply-demand mismatch, changing afterload or ventricular-vascular interaction, or altering myocardial energetics.51,64 Ivabradine is not without risk, but those with an HR >75 bpm or prescribed <50% target β-blocker dosing appear to derive the most benefit.

The proportion of patients with HFrEF eligible for ivabradine will nonetheless be modest, and it is conceivable that greater benefits on a population scale could be generated with diligent titration of β-blockers in qualified individuals. In an analysis of 1000 consecutive community HF clinic appointments by 824 patients, 58 patients had LVEF ≤35%, sinus rhythm, and HR ≥70 bpm.65 Of these, 25 (3% overall, 12% of those with LVEF ≤35%) were taking maximally dosed β-blockers or were intolerant to β-blockers and eligible for ivabradine. However, 20 of the 33 patients taking submaximally dosed β-blockers were inappropriately not uptitrated, almost as many as were suitable for ivabradine. Thus, the availability of ivabradine should remind practitioners to appropriately prescribe all evidence-based HFrEF medications while appreciating the ability to tailor therapy for patients intolerant of β-blockers.

Conclusions

Medical therapy has markedly improved morbidity and mortality for patients with HFrEF. Hospitalization can be further decreased with the addition of ivabradine to select symptomatic patients already treated with maximized guideline-directed therapy with persistently elevated HR and reduced ejection fraction. The benefits of ivabradine treatment suggest the importance of HR reduction in the causal HF pathway, but the superiority of β-blockers suggests that their pleiotropic effects contribute to improved patient outcomes and should remind practitioners to use them vigorously.

Disclosures

Dr. Teerlink has received research funding and honoraria from Amgen, Bayer, Cytokinetics, Medtronic, Novartis, St. Jude, Trevena, and ZS Pharma. Dr. Psotka reports no conflicts.

Figure 2. Evidence-based medical therapy. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atroventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and PI, HIV protease inhibitors.


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