Ivabradine (Corlanor®): A novel agent to reduce hospitalization due to worsening heart failure

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Heart failure (HF) is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood. This progressive syndrome can result from defects in ventricular filling (diastolic HF) or impaired ventricular contractility (systolic HF), both leading to cardiac remodeling and decreased stroke volume and cardiac output. The neurohormonal imbalance associated with chronic HF contributes to a progressive decline of heart function. The heart cannot keep up with oxygen demands of the body, resulting in symptoms like dyspnea, fatigue, exercise intolerance, and fluid retention. Typical causes of HF are hypertension (HTN), coronary artery disease (CAD), and cardiomyopathies; some medications can also induce HF.

Heart failure is associated with significant morbidity, mortality, and economic burden. The absolute mortality rate for HF remains approximately 50% within 5 years of diagnosis. Despite established therapeutic options, more than 1 million HF-related hospitalizations occur each year, and rehospitalization continues to be an issue. Hospitalized patients are at high risk of rehospitalization, with a 25% one-month readmission rate. The total cost of HF care in the U.S. exceeds $30 billion annually, over half of which is attributed to hospitalizations. Interestingly, HF is the leading cause of hospitalization among Medicare patients, representing about 80% of overall HF hospitalizations. The need for repeat hospitalization is also an important marker for poor prognosis and is associated with a higher risk of mortality. However, clinical trials have demonstrated that certain drugs, devices, or care strategies improve survival rates and reduce risk of hospitalization in patients with HF. Evidence-based guidelines recommend the use of a beta-blocker (β-blocker), an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB), a mineralocorticoid/aldosterone receptor antagonist (MRA), and a diuretic to improve survival and quality of life for patients with HF with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction (LVEF) ≤40%. ACE-I or ARBs, β-blockers, and MRAs are pivotal in modifying the course of chronic HF and are recommended in all patients with HFrEF.

ACE-I and β-blockers reduce morbidity, mortality and hospitalizations, slow the progression of disease, and improve signs and symptoms of HF. ARBs provide similar morbidity and mortality benefits and are useful in patients who are ACE-I intolerant. MRAs reduce the risk of HF hospitalization and mortality in patients with persisting symptoms despite ACE-I (or ARB) and β-blocker therapy. Diuretics are indicated for symptomatic relief of fluid retention, but do not reduce hospitalizations or improve mortality.

Clinical outcome of HF patients can be predicted by numerous clinical and laboratory variables. For example, increased heart rate (HR) is an established risk factor for cardiovascular (CV) events and is correlated with a poor prognosis in patients with HF. Accordingly, reducing HR may result in improved clinical outcome. Certain β-blockers are known to improve survival in HF patients, and this effect might be partly mediated by HR lowering. However, a large portion of HF patients do not achieve optimal doses of β-blockers. Patients frequently experience side effects that limit the use of β-blockers and the achievement of target doses. A further issue is that a significant proportion of HF patients on target doses of β-blockers continue to have relatively high resting HR ≥ 70 bpm. Difficulties achieving an appropriate target HR solely with β-blockers and the potential negative effects of elevated HR on clinical outcomes prompted investigations into the use of new agents that target HR-lowering, specifically.

One such agent, ivabradine, has been on the market in Europe since 2005. The 2012 European Society of Cardiology (ESC) HF guideline included a weak recommendation for ivabradine use in patients with HF. In April 2015, the FDA granted an approved indication for ivabradine (Corlanor®; Amgen, Inc.) to reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35%, who are in sinus rhythm with resting HR ≥70 bpm and either are on a maximally-tolerated dose of β-blocker or have a contraindication to β-blocker use. The use of ivabradine in conjunction with β-blockers, as well as other mainstays of HF treatment, to achieve a target HR <70 bpm is desirable. The objectives of this article are to discuss the pharmacology, relevant clinical studies, safety and tolerability, cost, and potential role of ivabradine in heart failure.

**Mechanism of Action**

Ivabradine belongs to a new class of agents called the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers. Ivabradine is a novel HR-lowering agent that selective-
ly inhibits the I\textsubscript{f} current (or funny current) by acting specifically on the sinoatrial (SA) node, which is responsible for spontaneous pacemaker activity. The “funny current” is named after its unusual behavior of flowing inward and being activated by hyperpolarization during the resting phase of the cardiac action potential. Inhibition of the active, open I\textsubscript{f} channel current prolongs diastolic depolarization of the sinus node.\textsuperscript{14} The spontaneous pacemaker activity of the SA node is reduced, thereby lowering the HR. Importantly, ivabradine does not significantly influence the funny current when HR reaches 60 bpm or lower, or when I\textsubscript{f} channels start closing.\textsuperscript{15}

**Pharmacodynamics**

Ivabradine causes a dose-dependent reduction in HR. The effect size depends on baseline HR, with greater HR reductions occurring in patients with higher baseline HR.\textsuperscript{13} The average HR reduction is approximately 10 bpm at rest and during exercise, and a plateau effect is seen at doses greater than 20 mg twice daily.\textsuperscript{13} Ivabradine decreases myocardial oxygen consumption, and by improving diastolic perfusion time, enhances myocardial oxygen supply and relieves myocardial stress.\textsuperscript{14} Ivabradine does not elicit negative inotropic effects, intracardiac conduction effects, or ventricular repolarization effects.\textsuperscript{16} The QT interval is prolonged as expected with HR slowing; however, after appropriate correction for HR by atrial pacing, ivabradine displayed no significant effect on QT prolongation.\textsuperscript{17} Subsequently, ivabradine has no direct torsadogenic potential. Lastly, ivabradine did not have any deleterious influence on ejection fraction (EF) in those with baseline EF between 30% and 45%.

**Pharmacokinetics**

The pharmacokinetic properties of ivabradine are summarized in Table 1.\textsuperscript{13,18} Ivabradine, a highly water-soluble drug, is rapidly and almost entirely absorbed after oral administration. However, the drug only has moderate bioavailability due to first-pass effect in the gut and liver. Ingestion of ivabradine with food results in a one-hour delay to peak plasma concentration and increases AUC from 20% to 40%. Thus, ivabradine should be taken with food to reduce variability in exposure. The pharmacokinetics of ivabradine are linear over a large dose range of 0.5 mg to 24 mg, without time effect. The drug has extensive tissue distribution with 70% protein binding and a distribution half-life of about 2 hours. Ivabradine undergoes extensive metabolism via CYP3A4 into several metabolites, including the N-desmethylated derivative S-18982. This major active metabolite circulates in the blood at a concentration about 40% of that of ivabradine and has shown equipotent HR reduction activity in animals and humans.\textsuperscript{18} This metabolite is similarly metabolized by CYP3A4, and has a half-life of 13 hours. Metabolites are excreted unchanged at a similar extent to active drug via the feces and urine.

**Drug Interactions**

The metabolic clearance of ivabradine accounts for about 80% of its total clearance, and only involves CYP3A4.\textsuperscript{19} Concomitant use of CYP3A4 inducers decreases ivabradine serum concentrations, and use of CYP3A4 inhibitors increases ivabradine serum concentrations. Increased serum concentrations of ivabradine may exacerbate bradycardia and conduction disturbances. Use of strong CYP3A4 inhibitors such as azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone is contraindicated.\textsuperscript{13} Moderate CYP3A4 inhibitors, such as diltiazem, verapamil, and grapefruit juice, should be avoided with ivabradine.\textsuperscript{13} Similarly, CYP3A4 inducers, such as St. John’s wort, barbiturates, rifampicin, and phenytoin, should be avoided.\textsuperscript{13} Most patients taking ivabradine will also be treated with other HR-lowering medications, such as \(\beta\)-blockers, digoxin, or amiodarone; combined use of these agents increases the risk of bradycardia. Additionally, concomitant use with loop or thiazide diuretics should be monitored as these agents may enhance the arrhythmogenic effect of ivabradine. No dose adjustments are required when ivabradine is concomitantly administered with digoxin, sildenafil, simvastatin, omeprazole, warfarin, or metformin, among many others.\textsuperscript{13} Grapefruit juice consumption should be avoided while taking ivabradine, as ivabradine exposure increased twofold after the ingestion of grapefruit juice.\textsuperscript{19}

**Clinical Trials**

As summarized in Table 2, two large, multi-center, double-blind, randomized, placebo-controlled trials have been conducted with ivabradine for the treatment of HF: BEAUTIFUL (morbidity-mortality EvAlUAtion of the I\textsubscript{f} inhibitor ivabradine in patients with coronary artery disease and left-ventricular dysfunction) and SHIFT (Systolic Heart failure treatment with the I\textsubscript{f} inhibitor ivabradine Trial).\textsuperscript{20,21} The approved indication of ivabradine is based on SHIFT.

The effect of ivabradine in HF was initially investigated in the BEAUTIFUL trial, which enrolled 10,917 patients with stable CAD, LVEF ≤40% and resting HR ≥60 bpm.\textsuperscript{20} Patients had stable symptoms of HF or angina for ≥3 months, and were receiving conventional cardiovascular medications at stable doses for ≥1 month. \(\beta\)-blocker therapy was not required, nor were there specific protocols for target dosing of \(\beta\)-blockers. Exclusions include age <55 years (except diabetics aged ≥18 years were allowed), recent MI or coronary revascularization, recent stroke, severe HF (NYHA class IV), presence of pacemaker/cardioverter, and sick sinus syndrome or heart block. Patients were randomly assigned to ivabradine, adjusted based on HR, or placebo.

At a median follow-up of 19 months, ivabradine decreased mean HR by 6 bpm, from a mean ± SD baseline rate of 71.9 ± 9.9 bpm. However, ivabradine did not significantly reduce the rate of the primary composite outcome of cardiovascular death and hospitalization for acute MI or HF compared with placebo (RR 1.00; 95% CI 0.91 to 1.1; \(p=0.94\)).\textsuperscript{20} Limitations of this trial are that it included patients with a wide range of HRs and it only included patients with CAD, or with ischemic HF.

A post-hoc analysis of the effects of ivabradine in patients with angina, baseline HR ≥70 bpm and LVEF ≤40% found a
Table 2 | Summary of major clinical trials for ivabradine.

<table>
<thead>
<tr>
<th>Study</th>
<th>BEAUTIFUL&lt;sup&gt;20&lt;/sup&gt;</th>
<th>SHIFT&lt;sup&gt;21&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Stable coronary artery disease and LVEF &lt;40%</td>
<td>Symptomatic HF, LVEF ≤35%, sinus rhythm with HR ≥70 bpm, HF hospitalization within previous year, and stable background therapy incl. β-blocker if tolerated</td>
</tr>
<tr>
<td>Treatment Arms</td>
<td>• Ivabradine: 5 mg to 7.5 mg BID with meals (N=5479)</td>
<td>• Ivabradine 5 mg to 7.5 mg BID with meals, according to HR and tolerability (N=3241)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Composite of CV death or hospitalization for acute MI or new onset of worsening HF</td>
<td>Composite of CV mortality or hospitalization for worsening HF</td>
</tr>
<tr>
<td>Results</td>
<td>Primary composite endpoint:</td>
<td>Primary endpoint:</td>
</tr>
<tr>
<td></td>
<td>• No difference between ivabradine vs. placebo: hazard ratio 1.00; 95% CI 0.91 to 1.10; p=0.94</td>
<td>• Occurred in 24% of ivabradine- vs. 29% of placebo-treated patients: 18% relative risk reduction (hazard ratio 0.82; 95% CI 0.75 to 0.90; p&lt;0.0001) after 3 months of treatment</td>
</tr>
<tr>
<td></td>
<td>Baseline HR &gt;70 bpm:</td>
<td>Other results:</td>
</tr>
<tr>
<td></td>
<td>• No difference in primary endpoint (hazard ratio 0.91; 95%CI 0.81 to 1.04; p=0.17)</td>
<td>• No difference in all-cause mortality (hazard ratio 0.90; 95% CI 0.80 to 1.02), cardiovascular mortality (hazard ratio 0.91; 95% CI 0.80 to 1.03), but ivabradine reduced risk of death from HF (hazard ratio 0.74; 95% CI 0.58 to 0.94)</td>
</tr>
<tr>
<td></td>
<td>• Ivabradine reduces hospital admission for fatal or nonfatal MI (hazard ratio 0.64; 95% CI 0.49 to 0.84; p=0.001) and coronary revascularization (hazard ratio 0.70; 95% CI 0.52 to 0.93; p=0.016)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No difference in HF outcomes</td>
<td></td>
</tr>
<tr>
<td>Conclusions</td>
<td>No significant difference in primary outcome, regardless of baseline HR</td>
<td>Ivabradine significantly reduced primary outcome, occurrence, primarily due to reduced hospitalization for worsening HF</td>
</tr>
<tr>
<td></td>
<td>Ivabradine reduced secondary outcomes, including hospitalization for fatal or nonfatal MI, and coronary revascularization in patients with baseline HR &gt;70 bpm</td>
<td>Significant reduction in HF deaths (seen in BEAUTIFUL subgroup analysis) confirmed</td>
</tr>
</tbody>
</table>

BPM = beats per minute; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

36% reduction of hospital admissions secondary to fatal MI or nonfatal MI and a 30% reduction of coronary revascularization in the ivabradine group.<sup>20</sup> Thus, the HR lowering effect of ivabradine in this population appeared to improve ischemic endpoints, particularly in those with a high baseline HR. However, these results should be interpreted in the context of post-hoc analysis limitations.

Based on the subgroup analyses of BEAUTIFUL, a second trial was designed to further investigate the effects of ivabradine in those with HF and elevated HR. SHIFT aimed to evaluate the effects of ivabradine in 6,588 patients with chronic HF of any cause and LVEF ≤35%, who were in sinus rhythm with HR ≥70 bpm, in NYHA class II-IV despite optimal medical therapy, and who had a hospitalization for HF in the prior 12 months.<sup>21</sup> Patients with recent MI, ventricular or atrioventricular pacemakers, atrial fibrillation, or symptomatic hypotension were excluded from the study. Patients were randomly assigned to ivabradine (titrated based on HR) or placebo. At baseline, 90% of patients were taking a β-blocker, 84% a diuretic, 22% digoxin, 79% an ACE-I, 14% an ARB, and 60% taking an MRA. However, only 20% of patients were on a full-dose β-blockers. About 75% of study subjects were men, nearly 90% of subjects were White, and the average age was 60 years.

Ivabradine treatment was associated with an average HR reduction of 15 bpm from baseline HR 79.7 ± 9.5 bpm.<sup>21</sup> The difference in HR between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months, and 8.3 bpm at 24 months. At a median follow-up of 22.9 months, in the placebo arm, patients with the highest baseline HRs were at more than twofold higher risk for the primary endpoint compared with those

Table 3 | Treatment effect of ivabradine on the primary endpoint and its components in the SHIFT trial.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3421)</th>
<th>Placebo (n=3264)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint&lt;sup&gt;a&lt;/sup&gt;</td>
<td>793 (24.5%)</td>
<td>937 (28.7%)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>449 (13.9%)</td>
<td>491 (15.0%)</td>
<td>0.91 (0.80-1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>514 (15.9%)</td>
<td>672 (20.6%)</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup>First occurrence of cardiovascular death or hospitalization for worsening heart failure. CV = cardiovascular; HF = heart failure.
with the lowest HRs. The risk increased by 3% for every 1-bpm and by 5% for every 5-bpm increase from baseline HR. The addition of ivabradine on top of recommended therapy for HF significantly reduced the relative risk of the primary endpoint (first occurrence of CV mortality or HF hospitalization), by 18% compared with placebo (Table 3). The primary composite endpoint occurred in 937 (29%) of the placebo group versus 793 (24%) of patients receiving ivabradine. The risk of hospitalization for HF was reduced by 26% and deaths from HF were significantly reduced by 26% (hazard ratio 0.74; 95% CI 0.58 to 0.94; p=0.014). The treatment effect in the ivabradine group was driven primarily by the reduction in the risk of hospitalization for worsening HF, as no difference was observed in CV mortality between groups. On the basis of this absolute risk reduction, 26 patients would need treatment for 1 year to prevent one primary outcome event.

In the subgroup of patients receiving at least 50% of the full target dose of β-blocker, the reduction in HR was similar to that of the overall population. Effects on CV outcomes were not significantly different compared with the overall study population, aside from hospital admission for HF, which was significantly reduced by 19%. This finding may be related to a lower event rate in this group (13% per year for primary outcome) versus the overall population. Additionally, in the subgroup of patients with HR ≥75 bpm (n=4150), a modestly greater reduction was observed in the primary endpoint (24% relative risk reduction) comparing patients treated with ivabradine versus placebo (hazard ratio 0.76; 95% CI 0.68 to 0.85; p<0.0001).

A sub-analysis of SHIFT sought to explain whether the clinical benefit observed with ivabradine was related to the β-blocker dose or to the baseline HR. Patients were grouped by quintiles of HR (<72 bpm, 72 to <75 bpm, 75 to <80 bpm, 80 to <87 bpm, 87 to 287 bpm) and of β-blocker dose at baseline (none, <25%, 25% to <50%, 50% to <100%, 100% of target dose). Although there was a trend towards reduction in magnitude of ivabradine treatment effect with increasing β-blocker dose, statistical tests for interaction were not significant when adjusted for baseline HR (p=0.35). The sub-analysis led to the conclusion that the effect of ivabradine seen in SHIFT was driven by baseline HR and its reduction, and not by baseline β-blocker dose. This finding is rather important, considering only 56% of patients were receiving at least 50% of target dose of β-blocker.

A post-hoc analysis of the SHIFT study evaluated the safety and efficacy of ivabradine across three different blood pressure groups: low systolic blood pressure (SBP), defined as <115 mm Hg (n=2,010); intermediate SBP, defined as 115-130 mm Hg (n=1,968); and, high SBP, defined as ≥130 mm Hg (n=2,427). This analysis confirmed that chronic HF with low SBP is associated with poor outcomes, and that ivabradine, compared with placebo, reduced the primary composite endpoint independent of baseline SBP (SBP <115 mm Hg, hazard ratio=0.84; SBP ≥115 but <130 mm Hg, hazard ratio=0.86; SBP ≥130 mm Hg, hazard ratio=0.77; p for interaction=0.68). Safety was similar across the three SBP groups.

An additional sub-analysis of SHIFT confirmed the benefits of ivabradine in reduction of baseline HR and its acceptable profile, independent of baseline clinical status and objective severity of HF (NYHA class).

### Table 4 | Adverse drug reactions in SHIFT

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>Ivabradine (N=3260)</th>
<th>Placebo (N=3278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>10%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hypertension or ↑ BP</td>
<td>8.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Phosphenes, visual brightness</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Adverse drug reactions with rates >1% in ivabradine-treated patients and occurring more frequently with ivabradine than placebo.

Adverse Events & Precautions

The most common adverse drug reactions associated with ivabradine in SHIFT were bradycardia, increased BP, atrial fibrillation, and phosphenes (Table 4). Overall, ivabradine was well tolerated. The rate of asymptomatic and symptomatic bradycardia was higher in the ivabradine group than in the placebo group (both p<0.0001), but led to permanent withdrawal from the study in only 48 ivabradine-treated patients (1%) versus 10 placebo-treated patients (<1%). The rate of bradycardia was 6.0% per patient-year in ivabradine-treated patients (2.7% asymptomatic, 3.4% asymptomatic) and 1.3% per patient-year in placebo-treated patients. Extreme bradycardia is uncommon at therapeutic doses. Bradycardia risk factors include sinus node dysfunction, conduction defects, ventricular dysynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone).

Visual symptoms are rare, but have been experienced in clinical trials. The phenomena, phosphenes, are described as transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (such as stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistence). Phosphenes are believed to be mediated by effects on retinal photoreceptors via inhibition of the retinal I<sub>1</sub> current. The onset is within the first 2 months of treatment, after which they may occur repeatedly under triggering circumstances. Phosphenes occurred in 89 patients in the ivabradine group versus 17 patients in the placebo group (p<0.0001). The phenomena are generally reported to be of mild or moderate intensity and led to discontinuation of ivabradine in <1% of patients. Overall, visual symptoms are rare, mild-to-moderate, and most symptoms resolved during or after treatment.

Patients treated with ivabradine are at increased risk of developing atrial fibrillation, characterized by heart palpitations, chest pressure, or worsening shortness of breath. In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in those on ivabradine and 3.9% per patient-year with placebo. In another recent study (SIGNIFY), atrial fibrillation was observed in 5.3% of patients treated with ivabradine compared to 3.0% of patients treated with placebo.

More patients experienced episodes of increased BP while being treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). Episodes occurred more frequently following BP treatment modifications, were transient, and did not affect the treatment effect of ivabradine. Thus, BP may require closer monitoring following treatment ivabradine initiation or subsequent titration.

Adverse reactions associated with ivabradine use during postmarketing include syncope, hypotension, angioedema, erythema, rash, pruritus, urticarial, vertigo, diplopia, and visual impairment. Reactions are voluntarily reported from the population, and it is not possible to estimate frequency reliably or establish a causal relationship from these data.

Precautions for ivabradine include fetal toxicity, atrial fibrillation, and bradycardia and conduction disturbances. Women of reproductive potential should be advised to use effective contra-
ceusion while on ivabradine. Due to the risk of atrial fibrillation, cardiac rhythm should be regularly monitored and ivabradine should be discontinued if atrial fibrillation develops. Bradycardia, sinus arrest, and heart block have occurred with ivabradine. Ivabradine should be avoided in patients with 2nd degree atrioventricular block, unless a functioning demand pacemaker is present.

DOSING AND ADMINISTRATION

Corlanor® (ivabradine) is available in 5-mg (oval, scored) tablets and 7.5-mg (triangular) tablets in bottles of 60 and 180.12 The recommended starting dose is 5 mg twice daily administered with meals in patients with stable HF. Ivabradine should be initiated at a dose of 2.5 mg twice daily in patients with a history of conduction defects or in whom bradycardia could lead to hemodynamic compromise. After two weeks of treatment, patients should be assessed and the dosage adjusted to achieve a resting HR between 50 and 60 bpm (Table 5). Thereafter, the dose should be adjusted, as needed, based on resting HR and tolerability. The maximum dose is 7.5 mg twice daily.12

Use in Special Populations

No dosage adjustment is required in patients with mild-to-moderate hepatic impairment or with creatinine clearance 15 to 60 mL/min.12 No data exists for patients with creatinine clearance <15 mL/min or for patients with severe hepatic impairment. Ivabradine has only been studied in a limited number of patients aged 75 years or older. Although no differences in effects were observed in elderly patients age 65 years or older, lower initial doses of ivabradine may be considered in this population. Safety and efficacy of ivabradine in pediatric patients has not been established.

Based on findings in animal studies, ivabradine is present in rat milk. However, whether the same presence occurs in humans is not known. Breastfeeding is not recommended due to potential risks to breastfed infants.15 Based on findings from animal reproduction studies, embryo/fetal harm may occur if ivabradine is administered to pregnant women. Effective contraception is recommended in women of reproductive potential.15 Women in their third trimester of pregnancy who are taking ivabradine should be monitored for preterm birth. All pregnant patients started on ivabradine should be followed closely for deterioration of their HF that could potentially result from HR slowing, especially during the first trimester. These patients may be particularly HR-dependent to alter cardiac output.

Contraindications

Ivabradine is contraindicated in persons with acute decompensated HF, with baseline HR <60 bpm prior to treatment, or with BP <90/50 mm Hg.13 Due to its effects on the sinus node, ivabradine is contraindicated in patients with sick sinus syndrome, sinoatrial block, or third-degree AV block in patients without pacemakers.13 Pacemaker dependence, i.e., when HR is completely maintained by a pacemaker, is also a contraindication for use.13 Ivabradine has not been studied in the setting of severe hepatic impairment (Child-Pugh C), although increased systemic exposure is anticipated; thus, ivabradine use is contraindicated in this population.13 Concomitant use with strong CYP3A4 inhibitors is also contraindicated, as discussed above (see CLINICAL PHARMACOLOGY section).

Cost

Twice-daily ivabradine has a monthly wholesale acquisition cost (WAC) of $375 or about $4,500 per patient per year.12 The prices are the same for all tablet strengths and bottle sizes. High costs for patients may be a challenge for ivabradine to make ground since most other HF drugs are relatively low-cost generic drugs. Nevertheless, considering its potential be cost-effective by reducing hospitalizations and associated costs of care, as well as improvements in quality of life, ivabradine may have a promising role in the treatment regimens of select patients with HF.20

Conclusion

Ivabradine reduces HR by selectively and specifically inhibiting the I1 current, which is responsible for regulating the intrinsic pacemaker activity in the sinoatrial node. Ivabradine is indicated to reduce the risk of hospitalization for worsening HF in stable, symptomatic patients in sinus rhythm with resting HR ≥70 bpm and who are on either maximally tolerated β-blocker doses or have a contraindication to β-blocker use. The recommended starting dose is 5 mg twice daily with meals and can be titrated after two weeks to achieve a resting HR between 50 and 60 bpm. Heart rate reduction with ivabradine has a significant impact on risk reduction in patients with HFrEF with an elevated HR when given concomitantly with guideline-based therapies. Ivabradine is generally well-tolerated with the most common side effects being bradycardia and phosphenes. Patients taking ivabradine should be advised regarding avoidance of pregnancy, atrial fibrillation, other precautions and contraindications, as well as potential CYP3A4 drug interactions.

References

5. Krumholz HM, Merrill AR, Schone EM, et al. Patterns of

Table 5 | Dose adjustments for ivabradine.

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 bpm</td>
<td>Increase dose by 2.5 mg twice daily (max: 7.5 mg twice daily)</td>
</tr>
<tr>
<td>50-60 bpm</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt;50 bpm or bradycardia</td>
<td>Decrease dose by 2.5 mg twice daily; discontinue if current dose is 2.5 mg twice daily</td>
</tr>
</tbody>
</table>

http://pharmacy.ufl.edu/pharmanote/

**EDITOR’S CORNER**

**Antithrombotic Therapy for VTE Disease: Updates from the CHEST 2016 Guidelines**

Updates are currently underway to the 9th edition of the CHEST Antithrombotic Guidelines, which were originally published in February 2012. These guidelines have become a staple resource in guiding antithrombotic therapy for various diseases, such as atrial fibrillation and venous thromboembolism (VTE) disease. In January 2016, CHEST published the most recent chapter to be updated for the 10th edition, “Antithrombotic Therapy for VTE Disease.”

A notable update in the new guideline is the recommendation of direct oral anticoagulants (DOACs) over warfarin for treatment of VTE disease that is not associated with cancer. Recent studies have shown that DOACs are as effective as warfarin therapy with similar or reduced bleeding risk and increased convenience. Low molecular weight heparin (LMWH) still remains the treatment of choice for cancer-associated thrombosis.

The recommended duration of antithrombotic therapy has remained relatively unchanged from the 9th edition. Treatment for 3 months is recommended in patients with provoked VTE disease; regardless of bleeding risk. Unprovoked VTE disease should be treated for at least 3 months and consideration for extended treatment depends on the timing of the occurrence and the patient’s individual bleeding risk. Patients receiving extended therapy should be reassessed periodically to determine whether cessation of antithrombotic therapy is appropriate. CHEST now also recommends that aspirin should be considered for prevention of recurrence in patients who are stopping anticoagulant therapy.

Also provided in the 10th edition are new recommendations regarding recurrent VTE while taking anticoagulation therapy. Patients with recurrent VTE while taking warfarin or a DOAC should be switched temporarily to a LMWH. If the VTE recourses during therapy with a long-term LMWH, the guidelines suggest increasing the dose of LMWH by up to one-third.

Pharmacogenetic Testing for Clopidogrel: Is There a Benefit?

Clopidogrel blocks the platelet P2Y12 receptor to inhibit platelet activation and aggregation and is commonly prescribed after percutaneous coronary intervention (PCI) to prevent adverse cardiovascular (CV) events. This prodrug is converted to its active form via a two-step bioactivation process mediated in large part by the cytochrome P450 (CYP) 2C19 enzyme. Approximately 30% to 40% of individuals are heterozygotes or homozygotes for loss-of-function alleles in the CYP2C19 gene, which leads to reduced or absent CYP2C19 activity. These patients may not attain sufficient levels of the active clopidogrel metabolite to inhibit platelet aggregation.1

Multiple studies have shown a higher rate of CV events among clopidogrel-treated patients with a CYP2C19 loss-of-function genotype compared with similarly-treated patients without this genotype.2 The data are strongest with clopidogrel use after acute coronary syndrome (ACS) and PCI.3 The FDA-approved clopidogrel label contains a boxed warning about decreased drug effectiveness in individuals with the loss-of-function genotype and recommends considering alternative treatment in these patients. Although prasugrel and ticagrelor are more expensive than clopidogrel, these alternatives are not affected by CYP2C19 genotype.4,5 Clinical Pharmacogenetic Implementation Consortium guidelines strongly recommend considering prasugrel or ticagrelor after an ACS and PCI for individuals with a loss-of-function variant in the absence of contraindications (e.g., history of transient ischemic attack or stroke).6

These data have led to CYP2C19 genotyping in clinical practice at some institutions to assist with choosing antiplatelet therapy after PCI. Investigators at the University of Florida presented data at the 2015 American Heart Association Scientific Sessions which suggested improved outcomes with clinical implementation of CYP2C19 genotype-guided clopidogrel therapy.7 Over 400 patients, most of whom had ACS, were genotyped after PCI. Approximately 30% of patients had a loss-of-function genotype, and 54% of these were switched to an alternative (prasugrel or ticagrelor). The risk for major adverse CV events, defined as a composite of cardiovascular death, myocardial infarction, cerebral vascular accident or stent thrombosis, was significantly lower among patients with a loss-of-function genotype switched to an alternative antiplatelet compared to those with a loss-of-function genotype who remained on clopidogrel (HR 0.09, 95% CI 0.01–0.84, p=0.034).

Contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) for more information about these findings or for assistance with interpreting CYP2C19 pharmacogenetic test results clinically.

References: