New Agents for Heart Failure: Ivabradine

Jeffrey S. Borer, MD

Professor of Medicine, Cell Biology, Radiology and Surgery
Director, The Howard Gilman Institute for Heart Valve Disease
and the Schiavone Institute for Cardiovascular Translational Research
Formerly Chairman, Department of Medicine and Chief, Division of Cardiovascular Medicine
SUNY Downstate Medical Center and College of Medicine
Brooklyn and New York, NY
Overall Program Learning Objective
Integrate ivabradine into patient management

Module Learning Objectives
After completing this activity, the learner will be able to:

• Describe the mechanism of action of ivabradine in heart failure
• Describe the benefits of ivabradine in patients with heart failure
• List common adverse events
• Select appropriate patients for treatment with ivabradine
Heart Rate Control: The Sino-Atrial Node

Acetylcholine
Muscarinic receptor

Norepinephrine
Beta receptor

$c_\text{AMP}$

PKA

$f$-channel

$\text{Ca}_{\text{in},T}$

$\text{Ca}_{\text{in},L}$

$\text{K}$
Heart Rate Reduction with Ivabradine

Acetylcholine → Muscarinic receptor → cAMP → PKA

Norepinephrine → Beta receptor

Ivabradine → f-channel

$I_{ca,T}$, $I_{ca,L}$, $I_K$, $I_f$

Sinus node cell

↓ HR
Ivabradine: Pure Heart Rate Reduction

$I_f$ inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

$\Delta RR$, change in the R-R interval

Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT)

- **Objective:** To test the hypothesis that heart rate slowing with ivabradine improves **cardiovascular outcomes, LV function, and quality of life**
- **Patients:**
  - Moderate to severe (Class II to IV NYHA) chronic heart failure with left ventricular (LV) systolic dysfunction (LV ejection fraction \([EF] \leq 35\%\))
  - Heart rate \(\geq 70\) bpm in sinus rhythm and
  - Receiving guideline-based recommended therapy **including maximally tolerated/guideline-recommended doses of beta-blockers**

Study duration:
• Median: 22.9 months
• Maximum: 41.7 months

*Based on heart rate and tolerability

BID, twice daily
SHIFT: Improved Quality of Life with Ivabradine (prespecified analysis using Kansas City Cardiomyopathy Questionnaire [KCCQ])

**ΔKCCQ Overall Summary Score**  
基线 12个月 

**ΔKCCQ Clinical Summary Score**  
基线 12个月

HR Slowing and Cardiac Function in HF: Change ($\Delta$) in LV End Systolic Volume Index (LVESVI)

$\Delta\Delta = -5.8; \ P=0.0002$

Baseline  Month 8  
Ivabradine (n=208)  
Baseline  Month 8  
Placebo (n=203)

D - 7.0 mL/m²  
D - 0.9 mL/m²

# SHIFT: Adverse Events

<table>
<thead>
<tr>
<th>Adverse events with rates ≥1.0% higher on ivabradine than placebo occurring in &gt;1% on ivabradine</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, blood pressure increased</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>

BEAUTIFUL: Patients and Follow-up

Patients with chronic stable CAD, LVEF <40%, HR ≥60 bpm; some had mild HF

12,138 screened

10,917 randomized

5479 to ivabradine 5-7.5 mg BID
5438 to placebo

5479 analyzed
5438 analyzed

Study duration:
- Median: 19 months
- Maximum: 35 months
SIGNIFY: Patients and Follow-up

Patients with chronic stable CAD, LVEF >40%, HR ≥70 bpm; none had HF

23,164 screened

19,102 randomized

9550 to ivabradine 5-10 mg BID

9550 analyzed [6037 angina; 3513 no angina]

9552 to placebo

9552 analyzed [6012 angina; 3540 no angina]

Study duration:
- Median: 27.8 months
- Maximum: 42 months

### Differences in Design of BEAUTIFUL, SIGNIFY, and SHIFT That May Have Influenced Outcomes

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>BEAUTIFUL CAD and LVSD</th>
<th>SIGNIFY CAD without HF or LVSD</th>
<th>SHIFT HF and LVSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I-III HF; ~50% had Class II symptoms</td>
<td>All CAD LVEF &lt;40% HR ≥60 bpm</td>
<td>All CAD No HF LVEF &gt;40% HR ≥70 bpm</td>
<td>All hospital admissions for HF during 12 months prior to randomization LVEF ≤35% HR ≥70 bpm</td>
</tr>
<tr>
<td>Administration Regimen</td>
<td>Starting dose: 5 mg BID Titrated to 7.5 mg BID Up-titration 1 visit</td>
<td>Starting dose: 7.5 mg BID* Titrated to 5, 7.5, or 10 mg BID Titration any visit</td>
<td>Starting dose: 5 mg BID Titrated to 7.5 mg BID or 2.5 BID at any visit</td>
</tr>
<tr>
<td>Diltiazem/Verapamil</td>
<td>2.2%</td>
<td>4.4%</td>
<td>0</td>
</tr>
</tbody>
</table>

*5 mg BID for patients age ≥75 years LVSD, left ventricular systolic dysfunction

Understanding SIGNIFY vs BEAUTIFUL vs SHIFT: Effect of LV Function

• SIGNIFY indicates that the main target of heart rate lowering in CVD is the myocardium (the ventricle) rather than the coronary arteries

• When the ventricle is normal, heart rate lowering minimizes (transient) exercise-induced O₂ consumption and angina but not adverse outcomes

• When the ventricle is damaged, heart rate lowering reduces further damage (LV remodeling) and improves outcomes
SIGNIFY vs BEAUTIFUL vs SHIFT: Clinical Implications

• In patients with chronic HF and in sinus rhythm with heart rate $\geq 70$ bpm and already receiving recommended therapies, isolated HR reduction substantially improves outcomes in addition to those achievable with beta blockade, including
  – Reduction in CV death or HF hospitalizations
  – Improvement in LV function
  – Reduction in total hospitalizations during prolonged interval
  – Improvement in health-related quality of life

• These benefits reduce the total burden of HF
  – Reduction in hospitalizations also can be expected to substantially reduce health care costs
Ivabradine: Tips for Use

- Indication: to reduce the risk of hospitalization for worsening heart failure
- Appropriate patients
  - Stable, symptomatic chronic heart failure and
  - Left ventricular ejection fraction ≤35% and
  - Sinus rhythm with resting heart rate ≥70 bpm and
  - Taking maximally tolerated dose of beta-blocker unless beta blockers are contraindicated
Ivabradine: Tips for Use (cont)

- Inappropriate patients
  - Acute decompensated heart failure
  - Blood pressure <90/50 mm Hg
  - Sick sinus syndrome, sinoatrial block, 3rd degree AV block, unless functioning demand pacemaker
  - Heart rate (resting) <60 bpm
  - Severe hepatic impairment
  - In combination with strong CYP3A4 inhibitors
  - Pacemaker dependent
Ivabradine: Tips for Use (cont)

- Females should use effective contraception
  - Pregnant females should not use ivabradine
- Monitor for atrial fibrillation
- Monitor heart rate decreases, symptoms of bradycardia
- Not recommended in presence of 2nd degree AV block unless a functioning pacemaker is in place
Summary

- Ivabradine is an $I_f$ inhibitor that slows heart rate
- In patients with “HFrEF”, ivabradine
  - Significantly reduces the frequency of cardiovascular death or hospitalization for worsening heart failure
  - Improves quality of life