New Drug Updates: Ivabradine
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Objectives
Participants will be able to identify patients who may benefit from treatment with ivabradine for heart failure

Heart Failure Statistics
- ~5.7 million people in the United States have heart failure (HF)\(^1\)
- lifetime risk of developing HF for both sex at age 40 is 1 in 5\(^1\)
- HF is the leading cause of rehospitalization in Medicare patients\(^2\)
- ~50% of hospitalized patients with HF are readmitted within 6 months of discharge\(^3\)

Managing Heart Failure

Ivabradine Introduction

• Available internationally for years as Procoralan and Corlentor for the treatment of stable angina and heart failure, manufactured by Amgen

• Indication: for reduction of hospitalization in patients with chronic heart failure, who have the following characteristics:
  – Stable, symptomatic heart failure
  – Left ventricular ejection fraction (LVEF) of <35%
  – Sinus rhythm with resting heart rate of >70 beats per minute
  – On maximum tolerated doses of beta-blockers or have a contraindication to beta-blockers

What’s the Problem with ↑ HR

• Accelerates production of atherosclerosis (Int J Cardiol 2008;126:302-12)

• Associated with coronary plaque disruption (Circulation 2001;12:1477-82)

• Framingham Study: progressive increase in all cause and cardiovascular mortality in relation to antecedent HR (Am Heart J 1987; 113:1489-94)

• Continuous increase in death rates in survivors of Acute MI starting at HR > 70 (J Am Coll Cardiol 2007;50:853-30)
Ivabradine Mechanism of Action

- Class: hyperpolarization-activated cyclic nucleotide-gated channel blocker
- Slows HR by inhibiting cardiac pacemaker If current
  - No effect on ventricular repolarization or myocardial contractility
  - Does not alter BP

The If Current

- The funny current is highly expressed in spontaneously active cardiac regions, such as the Sinoatrial (SA) node, the Atrioventricular (AV) node and the Purkinje fibers.
- The funny current is a mixed sodium-potassium current, inward and slowly activating on hyperpolarization at voltages in the diastolic range (normally from -60/-70 mV to -40 mV).
- When at the end of a sinoatrial action potential, the membrane repolarizes below the If threshold (about -40/-50 mV), the funny current is activated and supplies inward current, which is responsible for starting the diastolic depolarization phase
- By this mechanism, the funny current controls the rate of spontaneous activity of sinoatrial myocytes, hence the cardiac rate.
Ivabradine Mechanism of Action

Systolic Heart failure treatment with the Inhibitor Ivabradine Trial
SHIFT Trial

Efficacy
SHIFT Trial
- Randomized, double-blind, placebo-controlled
- N=6558 patients in 37 countries and 677 centers with NHYA Class II-IV HF, LVEF ≤35%, resting HR ≥70 bpm (sinus rhythm)
- Hospitalized due to HF within 12 months of study
- Treatment: ivabradine 5 mg BID, can ↑ 2.5 mg BID or 7.5 mg BID to maintain resting HR of 50-60 or placebo
- Duration: 2 years


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DOI:10.1016/S0140-6736(10)61198-1
Efficacy

- Primary composite endpoints:
  - Cardiovascular death
  - Hospitalization for worsening heart failure
- Other endpoints:
  - All-cause / CV / HF death
  - All-cause / CV / HF hospitalization
  - Composite of CV death, hospitalization for HF or non-fatal MI
  - NYHA class / Patient & Physician Global Assessment

Mean Heart Rate Reduction

- **Mean ivabradine dose:** 6.4 mg bid at 1 month
- **6.5 mg bid at 1 year**

Primary Composite Endpoint

- **Cumulative frequency (%)**
  - Ivabradine n=793 (14.5%PY)
  - Placebo n=937 (17.7%PY)
- **HR = 0.82 [95% CI 0.75-0.90] p<0.0001**
Efficacy

- Results:
  - Fewer patients on ivabradine vs placebo (SS, 24% vs 29%)
  - Reduced risk of hospitalization for worsening HF (SS, 16% vs 21%)
  - Death due to HF (3% vs 5%)
  - No significant effect on CV death (14% vs 15%)
Efficacy

MorBidity-mortality EvAlUation of The I f inhibitor Ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL Trial)

- Patients with coronary artery disease and left ventricular dysfunction with a heart rate \( \geq 70 \) bpm have a higher risk of cardiovascular mortality, hospitalization for myocardial infarction (HR=1.46; \( p=0.0066 \)), and coronary vascularization (HR=1.38; \( p=0.037 \)).
- In patients with heart rate \( \geq 70 \) bpm, ivabradine reduces the composite of fatal and nonfatal myocardial infarction (HR=0.64; \( p=0.001 \); RRR 36%) and coronary revascularisation (HR=0.70; \( p=0.016 \); RRR 30%).
- In angina patients, ivabradine reduces the primary end point of cardiovascular death, hospitalization for heart failure, or for myocardial infarction (HR=0.76; \( p=0.05 \); RRR 24%).

Safety

Safety with an event; \( n=6492 \)

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>45% (1450)</td>
<td>48% (1553)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>75% (2439)</td>
<td>74% (2423)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25% (204)</td>
<td>29% (237)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>5% (150)</td>
<td>1% (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6% (194)</td>
<td>1% (48)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Atrial fibrillation</td>
<td>9% (306)</td>
<td>8% (251)</td>
<td>0.012</td>
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<tr>
<td>Phosphenes</td>
<td>3% (89)</td>
<td>1% (17)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Blurred vision</td>
<td>1% (17)</td>
<td>&lt;1% (7)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Safety

- SHIFT Trial
  - Bradycardia, hypertension, afib, visual disturbances (transient increases in brightness)
- Fetal toxicity and teratogenic effects have occurred in animal studies
- CYP3A4 substrate so many drug interactions
  - Contraindicated with inhibitors
  - Avoid with inducers or moderate inhibitors
Safety

Contraindications to Ivabradine:

▶ Acute decompensated heart failure
▶ Blood pressure <90/50 mmHg
▶ Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
▶ Resting heart rate <60 bpm prior to treatment
▶ Severe hepatic impairment (Child-Pugh C)
▶ Pacemaker dependence
▶ Concomitant use of strong CYP3A4 inhibitors

Convenience

• Starting doses is 5 mg BID
  – After 2 weeks if HR is between 50-60, keep dose
  – If HR>60, increase to 7.5 mg BID
  – If HR<50, decrease to 2.5 mg BID
• For 30 days treatment, 5 mg BID, costs ~$375.00

Summary

• Ivabradine is a new novel drug that reduces HR by inhibiting cardiac pacemaker, AV node, \( I_f \) current
• Adjunct to standard of care for HF patients who is on max beta blocker but resting HR>70, in sinus rhythm, and is symptomatic or have contraindication to beta blocker use
• Ivabradine might reduce hospitalization for worsening HF in some patients
• However, not shown to reduce mortality
A 54-year-old man with a history of HF presented to clinic for follow up after starting metoprolol succinate 50 mg daily. Physical examination was unremarkable. Left ventricular ejection fraction (LVEF) was 35% and a stress test was negative for ischemia. The patient was taking aspirin, a statin, and an angiotensin converting enzyme (ACE) inhibitor. No complaints of tiredness, dizziness, and chest pain. Vitals: BP 138/72 HR 65. Should ivabradine be started for this patient?

A. Yes, start ivabradine 5 mg BID today
B. Yes, should start lower dose of 2.5 mg BID
C. No, we need to maximize the beta blocker dose first
D. No, I should never start ivabradine for this patient