SHIFT: Ivabradine versus Placebo in Chronic Systolic Heart Failure

Systolic Heart failure treatment with the I<sub>F</sub> inhibitor ivabradine Trial

**BOTTOM LINE**

- In **SHIFT**, patients with stable moderate to severe HF-rEF NYHA Class II 49%, Class III 50%; mean LVEF 29% in sinus rhythm & a resting HR ≥70 bpm treated with ivabradine, compared to placebo, had:
  - ↓ risk of CV death or hospital admission for worsening of HF (ARR 5%, NNT=20/1.9 years)
  - the primary endpoint (composite of both CV death or hospital admission for worsening of HF) was driven by hospitalisation, as CV & all-cause mortality alone were non-statistically significant
  - subgroup analyses: this benefit was most prominent in those with a baseline HR of ≥77 bpm, & primary endpoint was NS for those on ≥50% of target β-blocker
  - ↑ risk of symptomatic bradycardia (NNH=25), asymptomatic bradycardia (NNH=20), phosphenes (NNH=50), & AF (NNH=100)
- The **SHIFT** trial was published in 2010. Ivabradine was approved by Health Canada in February 2017, & is indicated for treatment of stable chronic HF (NYHA Classes II-III) with reduced LVEF (≤35%) & a resting HR of ≥77 bpm. Clinical experience in Canada is lacking; however, ivabradine is approved / used in other countries (since 2015 in US, 2005 in Europe).
- At time of print, ivabradine is not on the Saskatchewan Drug Plan; cost $38 (2.5mg BID), $66 (5mg BID) & $113 (7.5mg BID)/month.
- Either ivabradine or digoxin may be considered as an add-on to HF triple therapy to further ↓ HR see below comparison. The β-blocker should be titrated to the target or maximally tolerated dose prior to adding either of these agents.

**BACKGROUND**

- A raised resting HR has been linked to an ↑ risk of morbidity & mortality in HF patients. A resting HR of 50 to 60 bpm is considered an acceptable target, providing the patient is not experiencing symptomatic bradycardia. Some HF patients will have a raised resting HR (HR >70 bpm) despite being on the target or maximally tolerated β-blocker dose.
- Ivabradine is a selective inhibitor of the I<sub>F</sub> current in the sinoatrial (SA) node, which is a relatively new class of medication with a unique mechanism of action. The I<sub>F</sub> current controls spontaneous electrical pacemaker activity in the SA node, which subsequently determines HR. Ivabradine inhibits the I<sub>F</sub> current, thereby ↓ HR (without ↓ BP or acting on cardiac ion channels or receptors).
- Ivabradine can also inhibit the I<sub>F</sub> current in the retina, resulting in visual disturbances (e.g. phosphenes).

- The 2015 CCS HF Companion suggested ivabradine may be considered in patients on standard HF triple therapy (i.e. ACEi/ARB/ARNI + β-blocker + MRA) with ↑ HR (>70-75 bpm) after β-blocker titration is complete. The 2016 ACC/AHA/HFSA and 2016 ESC HF Guidelines have incorporated ivabradine into their updated recommendations for patients with symptomatic HF (NYHA class II-III) with LVEF ≤35%, in sinus rhythm & a resting HR of ≥70 bpm despite triple therapy, or contraindications to β-blockers.

- Ivabradine versus Digoxin:
  - at time of print, there are no published head-to-head trials comparing ivabradine to digoxin in patients with HF-rEF
  - In 2012, a UK research group conducted a retrospective analysis of the **DIG** trial data (digoxin versus placebo in HF-rEF patients in sinus rhythm) using the **SHIFT** primary composite endpoint. The investigators concluded ivabradine & digoxin’s benefit of reducing CV death or HF hospitalization was the same (ARR 5%, NNT=20), which was driven by a reduction in HF hospitalization (**SHIFT** ARR 5%, NNT=20; **DIG** ARR 8%, NNT=13) as CV death was non-statistically significant in both data sets.
  - the baseline patient characteristics between the **DIG** and **SHIFT** trials were similar (e.g. age, HR, LVEF, NYHA class, comorbidities); ACEi/ARB and diuretic usage was also similar, however, β-blocker & MRA use was not reported in the **DIG** trial compared to digoxin, ivabradine has less real-world experience / post-marketing surveillance, cannot be used in AF patients, is more expensive & not listed on the SK Drug Formulary; however, ivabradine has less drug interactions, does not need to be dose adjusted in renal dysfunction, & does not require therapeutic drug monitoring.
  - Ivabradine has also been studied in stable coronary artery disease, however this is not an approved indication in Canada:
    - **BEAUTIFUL**: 7 ivabradine vs placebo in 10,917 patients with CAD & LVEF <40% x 19 months
      - CV death, hospitalization for MI, hospitalization for new/worsening HF (primary endpoint): NS
      - subgroup analysis: patients with a baseline resting HR ≥70 bpm had ↓ hospitalizations for acute MI (p=0.001) & ↓ hospitalizations for acute MI or unstable angina (p=0.023) compared to those with a baseline resting HR of <70 bpm
    - **SIGNIFY**: 8 ivabradine vs placebo in 19,102 patients with CAD without HF & a HR of ≥70 bpm x 27.8 months
      - CV death or non-fatal MI: NS (subgroup analysis: ivabradine ↑ risk in patients with activity-limiting angina, p=0.02 for interaction)
      - ↑ risk of AF with ivabradine (ARI 1.5%, NNH=67)

**TRIAL BACKGROUND**

**DESIGN**: event-driven, multinational 37 countries, 677 centers, randomized, double-blind, placebo-controlled, parallel-group ITT trial with concealed allocation. Funding: Servier. Enrollment: October 2006 to June 2009.

**INTERVENTION**: ivabradine 7.5mg BID versus placebo, in addition to standard HF therapy

**Study Phases**:

1. run-in phase without study treatment x 14 days, then
2. ivabradine 5mg BID or placebo x 14 days, then
3. if resting HR >60 bpm: ↑ ivabradine to 7.5mg BID; if resting HR 50 to 60 bpm: continue ivabradine 5mg BID;
   if resting HR <50 bpm or persistent symptomatic bradycardia: ↓ ivabradine 2.5mg po BID x 14 days
4. dose reassessed at Day 28 & q4 months and adjusted as above; if resting HR <50 bpm or persistent symptomatic bradycardia: discontinuation of therapy
**INCLUSION:** patients ≥18 years with moderate to severe HF, LVEF ≤35%, sinus rhythm, resting HR of ≥70 bpm, stable symptomatic chronic HF for ≥4 weeks, admitted to the hospital within the last 12 months due to worsening HF, on optimal drug therapy for ≥4 weeks prior.

**EXCLUSION:** HF due to congenital heart disease or primary severe valvular disease; any of the following events in the past 2 months were also excluded: MI, ventricular or AV pacemakers pacing ≥40% of the day, permanent atrial fibrillation/flutter, or symptomatic hypotension; CRT started within previous 6 months. Patients were not allowed to take non-DHP CCBs, class I antiarrhythmics, and strong CYP3A4 inhibitors.

**POPULATION:** at baseline: n=6505 6558 randomized but 7 patients were not dispensed the drug, one site was removed due to misconduct
- mean age 60.4 years (SD 11.4yrs), 11% ≥75 years, 76% 49, 89% Caucasian
- mean HR 79.9 bpm (SD 9.6 bpm), LVEF 29% (SD 5.1%), NYHA: class I ~49%, class III ~50%, class IV ~ 2%
- mean duration of HF 3.5 years (SD 4.2 years); primary cause of HF: ischemic 68%, non-ischemic 32%
- HTN 66.5%, MI 56%, DM 30.5%, stroke 8%, history of atrial fibrillation or flutter 8%
- **HF therapy at randomization:** ACEi/ARB ~93%, β-blocker 89.5%, diuretic 83.5%, antialdosterone agent (i.e. MRA) ~60%, digoxin ~22%, devices (CRT or ICD) 3.5%
- **Type of β-blocker & mean daily dosage:** 45% carvedilol (mean dose 25mg/day), 25.5% bisoprolol (mean dose 6.2mg/day), 14% metoprolol succinate (mean dose 90mg/day), 10% metoprolol tartrate (68mg/day), 3% nebivolol (5.9mg/day), 2% other
  - 26% at β-blocker target dose, 56% at ≥50% β-blocker target dose
  - reasons for not reaching target dose: 44.5% hypotension, 32% fatigue, 14% dyspnea, 12.5% dizziness, 10% bradycardia, 9.5% other
  - 11% were not on a β-blocker (reasons ~35% COPD, ~19% hypotension, 10.5% asthma, 8% cardiac decompensation, 6% dizziness or bradycardia, ~5% Raynaud or PAD, 12% other)

**RESULTS**

**TABLE 1: EFFICACY**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>IVABRADINE 7.5MG BID</th>
<th>PLACEBO</th>
<th>ARR/ARI HR (95% CI)</th>
<th>NNT/NNH /1.9 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
<td></td>
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</tr>
<tr>
<td>CV death or hospital admission for worsening of HF</td>
<td>24% (n=793)</td>
<td>29% (n=937)</td>
<td>↓5% 0.82 (0.75-0.90)</td>
<td>20</td>
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<tr>
<td><strong>SECONDARY ENDPOINTS</strong></td>
<td></td>
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</tr>
<tr>
<td>All-cause mortality</td>
<td>16% (n=503)</td>
<td>17% (n=552)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CV mortality</td>
<td>16% (n=449)</td>
<td>15% (n=491)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HF mortality</td>
<td>3% (n=113)</td>
<td>5% (n=151)</td>
<td>↓2% 0.74 (0.58-0.94)</td>
<td>50</td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>38% (n=1331)</td>
<td>42% (n=1356)</td>
<td>↓4% 0.89 (0.82-0.96)</td>
<td>25</td>
</tr>
<tr>
<td>Hospital admission for worsening HF</td>
<td>16% (n=514)</td>
<td>21% (n=672)</td>
<td>↓5% 0.74 (0.66-0.83)</td>
<td>20</td>
</tr>
<tr>
<td>Any CV hospital admission</td>
<td>30% (n=977)</td>
<td>34% (n=1122)</td>
<td>↓5% 0.85 (0.78-0.92)</td>
<td>25</td>
</tr>
<tr>
<td>CV death, hospital admission for worsening HF, or non-fatal MI</td>
<td>30% (n=825)</td>
<td>30% (n=979)</td>
<td>↓5% 0.82 (0.74-0.89)</td>
<td>20</td>
</tr>
<tr>
<td>Improvement in NYHA class</td>
<td>28% (n=867)</td>
<td>24% (n=776)</td>
<td>↑4%</td>
<td>25</td>
</tr>
<tr>
<td>Patient-reported Global Assessment Improvement</td>
<td>72% (n=2118)</td>
<td>68% (n=2017)</td>
<td>↑4%</td>
<td>25</td>
</tr>
<tr>
<td>Physician-reported Global Assessment Improvement</td>
<td>61% (n=1888)</td>
<td>57% (n=1772)</td>
<td>↑4%</td>
<td>25</td>
</tr>
<tr>
<td><strong>SUBGROUP ANALYSES – Primary Composite Endpoint (p-value for interaction = 0.029)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Baseline HR &lt;77bpm (n=3144)</td>
<td>21.4% (n=339)</td>
<td>22.8% (n=356)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Baseline HR ≥77bpm (n=3357)</td>
<td>27.4% (n=454)</td>
<td>34.2% (n=581)</td>
<td>↓6.8% 0.75 (0.67-0.85)</td>
<td>15</td>
</tr>
</tbody>
</table>

**COMMENTS**

- Primary composite endpoint driven by hospitalization
- non-statistically significant for those on ≥50% of their β-blocker target dose
- Kaplan-Meier curves separated within the 1st 3 months, & benefit was maintained
- HR net reduction:
  - Day 28: 10.9 bpm (95% CI 10.4-11.4)
  - 1 year: 9.1 bpm (95% CI 8.5-9.7)
- End of the study: 8.1 bpm (95% CI 7.5-8.7)
- mean dose 6.4mg (SD 1.6mg) at Day 28, 6.5mg (SD 1.6mg) at 1 year
- 1 year to end of study: 70% on target dose
- 49% were on at least 50% of their β-blocker target dose (was 56% at baseline)

**TABLE 2: SAFETY**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>IVABRADINE 7.5MG BID</th>
<th>PLACEBO</th>
<th>ARR/ARI HR (95% CI)</th>
<th>NNT/NNH /1.9 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation rates</td>
<td>21% (n=682)</td>
<td>19% (n=605)</td>
<td>↑2% 1.14 (1.02-1.27)</td>
<td>50</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>45% (n=1450)</td>
<td>48% (n=1553)</td>
<td>↓3%</td>
<td>34</td>
</tr>
<tr>
<td>HF adverse event</td>
<td>25% (n=804)</td>
<td>29% (n=937)</td>
<td>↓4%</td>
<td>25</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>5% (n=150)</td>
<td>1% (n=32)</td>
<td>↑4%</td>
<td>25</td>
</tr>
<tr>
<td>Discontinuation due to symptomatic bradycardia</td>
<td>1% (n=20)</td>
<td>&lt;1% (n=5)</td>
<td>↑0.5%</td>
<td>200</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6% (n=184)</td>
<td>1% (n=48)</td>
<td>↑5%</td>
<td>20</td>
</tr>
<tr>
<td>Discontinuation due to asymptomatic bradycardia</td>
<td>1% (n=28)</td>
<td>&lt;1% (n=5)</td>
<td>↑0.7%</td>
<td>143</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9% (n=306)</td>
<td>8% (n=251)</td>
<td>↑1%</td>
<td>100</td>
</tr>
<tr>
<td>Phosphates*</td>
<td>3% (n=89)</td>
<td>1% (n=17)</td>
<td>↑2%</td>
<td>50</td>
</tr>
</tbody>
</table>

*defined as transient enhanced brightness in a restricted area of the visual field

**STRENGTHS, LIMITATIONS, & UNCERTAINTIES**

**STRENGTHS:**
- clinically meaningful endpoints & clinically relevant subgroup analyses
- provided baseline information on type of β-blocker and mean daily β-blocker dose
- blinded adjudication of outcomes
- only 0.05% (n=3) of patients were lost to follow-up
**LIMITATIONS:**
- subgroup analysis suggests ivabradine’s benefits only apply to those with a baseline HR of ≥77 bpm
- while reflective of real world experience, only half of the patients were able to reach ≥50% of their target β-blocker dose
- the percentage of patients from Canada or North America was not reported

**UNCERTAINTIES:**
- the percentage of patients enrolled with devices (CRT, ICD) is lower than North American practice
- some patients required a reduction in their β-blocker dose during the study
- 49% were at least 50% of their target β-blocker dose (was 56% at baseline)
- efficacy & safety of ivabradine in patients with paroxysmal or persistent AF (permanent AF was an exclusion criteria, 8% of patients had a history of AF or Aflutter at baseline)
- efficacy & safety of ivabradine in older adults (mean age 60.4 years (SD 11.4yrs), 11% ≥75 years)
- no published trials have directly compared digoxin to ivabradine for HF-rEF
- unknown how many patients received the lowest ivabradine dose, & whether there was benefit

**REFERENCES**


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**REFERENCES**


