Ivabradine and Atrial Fibrillation: a Word of Caution? Comprehensive Meta-analysis of RCTs

Ivabradine

- Inhibits $I_f$ ion current, which is highly expressed in the SA node
- Mixed Na$^+$–K$^+$ inward current activated by hyperpolarization and modulated by the autonomic nervous system
- Reducing the SA node activity, allowing for improved diastolic filling
- Increased binding with higher HR vs lower HR

History

• 2005 - Approved by European Medicines Agency
  ◦ Stable angina with NSR who do not tolerate β-blocker therapy supported by Borer et al\textsuperscript{1}, INITIATIVE\textsuperscript{2}

• 2010
  ◦ Uncontrolled angina and a HR ≥60 bpm despite β-blocker therapy, following the results of BEAUTIFUL\textsuperscript{3}

\textsuperscript{2} Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005 Dec;26:2529-36
History

- 2012
  - Systolic CHF (NYHA II–IV) in patients in NSR and whose HR >75, in combination with standard therapy or when β -blockers are contraindicated or not tolerated, SHIFT\(^1\)

- 2015- Approved by US FDA
  - Stable patients with CHF and a HR of ≥70 on maximally tolerated β -blockers, SHIFT\(^1\)

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Aim

- Martin RI, et al suggested a 15% increased RR of atrial fibrillation associated with ivabradine¹
- Recently, SIGNIFY² published its study results with almost double the study population from the previous meta-analysis
- To update previous data and further investigate the increased risk of AF and use of ivabradine

¹ Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. Heart 2014; 100:1506-10
Study Selection

Database Search  
(n=88)

Inclusion Criteria
• Ivabradine
• Randomized Controlled Trial
• 4 week follow-up
• Reported AF data

Not relevant 50
Observational studies and registries 14
Duplicate 2
Post Hoc Analysis 10
AF data not available 5

PubMED Search Strategy

Ivabradine with filter of Randomized Controlled Trial

Total included  
(n=7)

1. BEAUTIFUL
2. SHIFT
3. Cappato
4. Dominguez-Rodriguez
5. Nerla
6. Villano
7. SIGNIFY
Meta-analysis Outcomes

- Primary outcome
  - Incidence of AF

- Secondary outcome
  - All cause mortality
  - Incidence of hospitalizations for HF
Statistical Review

- PRISMA-P-2015 (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015)
- Intention-to-treat analysis for primary and secondary outcomes
- Relative risks and their corresponding 95% confidence intervals were computed for each dichotomous outcomes using random effect
- Used $I^2$ statistic and p-value for heterogeneity (p for heterogeneity <0.1 was considered significant)
- To evaluate publication bias for primary outcome we utilized comparison adjusted funnel plot
- All p-values were 2-tailed, with statistical significance set at 0.05
Atrial Fibrillation

Control Worse  Ivabradine Worse
Results

- Seven trials published from 2008 to 2015 involving 36,622 patients
- Significantly higher incidence of atrial fibrillation in ivabradine group (4.2% vs. 3.4%, RR 1.24 (95% CI 1.08-1.43), p<0.002
- No evidence of significant heterogeneity (I²=21.7%, p=0.26) or publication bias (p=0.89) noted
- Number needed to harm was 127
Mortality

Control Worse  Ivabradine Worse
Heart Failure

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAUTIFUL</td>
<td>2008</td>
<td>0.99 (0.87, 1.13)</td>
<td>427/5479</td>
<td>426/5438</td>
<td>34.19</td>
</tr>
<tr>
<td>SHIFT</td>
<td>2010</td>
<td>0.77 (0.69, 0.85)</td>
<td>514/3241</td>
<td>672/3264</td>
<td>35.36</td>
</tr>
<tr>
<td>SIGNIFY</td>
<td>2014</td>
<td>1.19 (0.98, 1.45)</td>
<td>216/9550</td>
<td>181/9552</td>
<td>30.45</td>
</tr>
</tbody>
</table>

Overall: I-squared = 89.5%, p = 0.000

NOTE: Weights are from random effects analysis
Discussion

- Use of ivabradine was associated with an increased RR of 24% of AF, higher than noted as 15% by Martin RI\(^1\) with addition of SIGNIFY\(^2\)
- HCN4 gene coding for \(I_f\) channel; mutation also associated with AF\(^3\)

**Discussion**

- Bradycardia increases risk of AF; APC’s propagate AF\(^1\)
  - Pauses, short coupling cycles, short-long-short cycle

- **RR of AF**
  - SIGNIFY > SHIFT

<table>
<thead>
<tr>
<th></th>
<th>Mean LVEF (%)</th>
<th>Mean Age (Yrs)</th>
<th>HTN</th>
<th>Mean Dosage (mg BID)</th>
<th>BB Use (%)</th>
<th>Mean Baseline HR (bpm)</th>
<th>Mean Endpoint HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAUTIFUL</td>
<td>32.3</td>
<td>65.2</td>
<td>71.0</td>
<td>6.2</td>
<td>87.0</td>
<td>71.6</td>
<td>64.0</td>
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<tr>
<td>SHIFT</td>
<td>29.0</td>
<td>60.4</td>
<td>67.0</td>
<td>6.5</td>
<td>89.0</td>
<td>79.9</td>
<td>67.0</td>
</tr>
<tr>
<td>SIGNIFY</td>
<td>56.4</td>
<td>65.0</td>
<td>86.2</td>
<td>8.2</td>
<td>83.0</td>
<td>77.1</td>
<td>60.7</td>
</tr>
</tbody>
</table>

\(^1\) Lau C-P. Pacing for atrial fibrillation. Heart 2003;89:106–12.
Discussion

- Benefit of ivabradine vs harm (AF):
  - SHIFT
    - HF Hospitalization NNT 20
    - AF NNH 59
  - SIGNIFY
    - CV death/MI No benefit
    - AF NNH 141

- Benefit of ivabradine vs harm (HF):
  - SIGNIFY, 4 more hospitalizations would make it significant
    - No benefit, NNH 224
Conclusion

- Doubling the number of patients studied in RCTs comparing ivabradine with placebo made the higher incidence of atrial fibrillation in the ivabradine group quite noticeable.
- Further studies needed to identify patients more susceptible to atrial fibrillation who may benefit from ivabradine therapy.
Aknowledgements

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