Can **Ivabradine** be recommended in the management of acute heart failure complicating myocardial infarction?

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Conflicts of Interest

- NONE TO DECLARE
- NOT RECEIVED ANY GRANTS
Sinus Tachycardia is an independent predictor of mortality following acute myocardial infarction (MI).

Many situations, like acute heart failure complicating myocardial infarction demand rate control but beta blockers cannot be used, often due to low or borderline blood pressures.

This problem is further compounded by the use of ionotropes.
Ivabradine

- Selective $I_f$ antagonist
- Pure Sinus rate reduction
- Ivabradine has the potential advantage of reducing heart rate without lowering blood pressures in these acute situations
- Presently it is contraindicated in Acute MI and shock due to lack of data
- Contraindicated in Inferior wall MI
In our initial observational study, we had found that Ivabradine may have role in acute heart failure (Presented at ACC 2010)

- Reduced duration of ionotropic support
- Reduced recurrent symptoms of heart failure

In acute anterior wall MI also, it brought down the heart rate, without any appreciable side effects
Concept we proposed to Verify:

- Ivabradine is safe and beneficial in the management of
  - Acute heart failure with
  - Acute Anterior wall MI
Materials and Methods:

Inclusion Criteria:

- Patients with an acute anterior wall MI with:
  - a heart rate of more than 100/min
  - Systolic blood pressure $\leq 100$ mmHg including cardiogenic shock
  - one or more signs of Left ventricular failure
  - requiring ionotropcic support or having any other contraindications to beta-blockers

were given Ivabradine (5 to 7.5mg twice daily P.O.)

- Similar patients who did not receive Ivabradine formed the control group
The rest of the treatment was as per standard protocol in our intensive care unit for both groups.

We studied the hemodynamics in both groups and follow up was limited to index hospitalisation.
Exclusion Criteria:

- Mortality within 24 hours of admission
- Sustained ventricular or atrial arrhythmia
- AV blocks or sinus bradycardia at any time before randomization
- NSTEMI or NQMI (except LBBB)
Statistical analyses

- Data was entered onto MS Excel worksheet
- Analyzed using SPSS 12.0 software
- Statistical tests of significance was done using
  - Chi Square test for qualitative variables
  - Test of normality was done using Shapiro-Wilk test
  - Independent samples ‘t’ Test for normally distributed quantitative variables
  - Mann-Whitney U test (non-parametric) for quantitative variables not normally distributed.
Results:

- **Primary Efficacy End points:**
  - Mean Heart rate reduction
  - Duration of Ionotropic support required
  - Mean Troponin rise over first 24 hours

- **Secondary end points: (Safety)**
  - Recurrent angina and Re-infarction
  - Recurrent symptoms and signs of heart failure
  - All cause mortality
Results: (n = 390)

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n=187)</th>
<th>Control (n=203)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>56.42 years</td>
<td>56.6 years</td>
<td>NS</td>
</tr>
<tr>
<td>Symptoms to admission duration</td>
<td>10.58 hours</td>
<td>10.70 hours</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>116</td>
<td>134</td>
<td>NS</td>
</tr>
<tr>
<td>PCI</td>
<td>76</td>
<td>80</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Mean Age in years among the study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age in years</th>
<th>S.D</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56.46</td>
<td>12.95</td>
<td>54.67 – 58.25</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>56.42</td>
<td>12.78</td>
<td>54.57 – 58.26</td>
</tr>
</tbody>
</table>

p=0.975
Distribution of the study group based on sex

- **Male**: 50.4% Control, 49.6% Ivabradine
- **Female**: 56.3% Control, 43.7% Ivabradine
- **Total**: 52.1% Control, 47.9% Ivabradine

*p* value: 0.292
Mean Time in hours from symptom onset to admission

Control: 10.70 hours
Ivabradine: 10.58 hours

p=0.83
Thrombolysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Thrombolysis</th>
<th>No Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>62</td>
<td>38</td>
</tr>
</tbody>
</table>

p = 0.413
PCI (Both primary and rescue)

- Control: 39.4%
- Group: 60.6%
- Ivabradine: 59.4%

p=0.804  NS
Ventilator Requirement

Control: 26.6% (n=54)
Group: 73.4%
Ivabradine: 73.8% (n=49)

p=0.929  NS
Requirement of Ionotrope support

- Control: 84.7% (n=172), 15.3% (No Ionotrope)
- Ivabradine: 82.9% (n=155), 17.1% (No Ionotrope)

p=0.622, NS
Our Findings:

Mean heart rate reduction in beats per minute among study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean HR reduction in bpm</th>
<th>S.D</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.72</td>
<td>5.72</td>
<td>6.93 – 8.51</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>20.59</td>
<td>9.49</td>
<td>19.22 – 21.96</td>
</tr>
</tbody>
</table>

p=0.000, significant.
Mean heart rate reduction in beats per minute among study groups

Error bars showing 95% CI for mean heart rate reduction
<table>
<thead>
<tr>
<th>Group</th>
<th>Mean duration</th>
<th>S.D</th>
<th>95% C.I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34.71</td>
<td>14.41</td>
<td>32.54 – 36.88</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>17.52</td>
<td>9.12</td>
<td>16.07 – 18.96</td>
</tr>
</tbody>
</table>

p=0.000, significant
Mean Troponin I (ng/ml) rise in 24 hours among study groups

P <0.0001
Secondary End Points: Recurrent Angina and Reinfarction

- Control: Recurrent Angina/Reinfarction (27.1%) vs. No Recurrent Angina/Reinfarction (72.9%), n=55
- Group: Recurrent Angina/Reinfarction (13.9%) vs. No Recurrent Angina/Reinfarction (86.1%), n=26

p=0.001, significant
Secondary End Points: Recurrence of Heart Failure within index hospitalization

- Control: 19.2%, n=39
- Group: 80.8%
- Ivabradine: 92.5%, n=14

*p=0.001, significant*
Secondary End point: Mortality

- Control: 16.7% mortality with n=34
- Group: 83.3% mortality with n=19
- Ivabradine: 89.8% mortality with n=19

$p=0.058$ not significant
## Mortality Analysis:

<table>
<thead>
<tr>
<th>Event</th>
<th>Deaths in Control (n=34)</th>
<th>Deaths in Ivabradine (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Heart failure</td>
<td>1 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent Angina/Re-MI</td>
<td>18 (52.9%)</td>
<td>13 (68.4 %)</td>
</tr>
<tr>
<td>Recurrent HF + Re-MI</td>
<td>13 (37.9%)</td>
<td>04 (21.1%)</td>
</tr>
<tr>
<td>Sudden Cardiac death</td>
<td>2 (5.8%)</td>
<td>2 (10.5%)</td>
</tr>
</tbody>
</table>
## Combined end points:

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Control</th>
<th>Ivabradine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No death/Rec HF/Rec angina/MI</td>
<td>131</td>
<td>152</td>
<td>283</td>
</tr>
<tr>
<td>Rec HF only</td>
<td>14</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Rec angina/Reinfarction only</td>
<td>13</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Death only</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rec HF and Rec angina/Reinfarction only</td>
<td>11</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Rec HF and Death only</td>
<td>1</td>
<td>00</td>
<td>1</td>
</tr>
<tr>
<td>Rec angina/Reinfarction and Death only</td>
<td>18</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>Rec HF + Rec angina/Reinfarction + Death</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>187</td>
<td>390</td>
</tr>
</tbody>
</table>
Occurrence of Recurrent angina/MI, recurrent heart failure and death together

\[ p = 0.039 \text{ significant} \]

- Control: \( n = 13 \), Rec Angina/MI + Rec HF + Death: 6.4%
- Group: \( n = 4 \), No Rec Angina/MI + Rec HF + Death: 2.1%
- Ivabradine: \( n = 4 \), Rec Angina/MI + Rec HF + Death: 97.9%
Conclusions:

- In patients with Heart failure accompanying acute anterior wall MI, ivabradine:
  - Effectively controls the heart rate preventing excessive sinus tachycardia even with ionotropes
  - Reduces the infarct size probably secondary to control of heart rate
  - Reduces the duration of Ionotrope use
- Reduces recurrent heart failure symptoms
- Reduces a combined end point of death, recurrent angina/re-infarction, recurrent heart failure
- No significant reduction in mortality
CONCLUSION:

- In this interventional study, Ivabradine, by selectively controlling heart rate, seems to be a valuable addition in management of heart failure complicating Acute Myocardial infarction in reducing infarct size and in-hospital events in patients ineligible for beta-blocker therapy.

- It needs to be validated in further randomized studies.
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