Ottimizzazione della terapia medica anti-ischemica nel paziente con scarso controllo della frequenza cardiaca.

Fabio Barlocco
Cardiologia interventistica - Ospedale Civile di Legnano

CONVENTION DELLA CARDIOLOGIA LOMBARDIA
16 APRILE 2016
Humans are outliers relative to other mammals when comparing lifespan to heartbeat.
Resting heart rate and all-cause mortality in the Framingham Study.

$n=5070$; 30-year follow-up; ECG

- Men (35–64 years)
- Men (65–94 years)
- Women (35–64 years)
- Women (65–94 years)

$P<0.01$

Jeffrey S. Borer Eur Heart J Suppl 2008;10:F2-F6
Resting heart rate and mortality in the general population: epidemiological studies

$n=5713$ men; 23-year follow-up; ETT

Relative risk

- Non-sudden death from myocardial infarction; $P=0.02$
- Sudden death from myocardial infarction; $P<0.001$

<table>
<thead>
<tr>
<th>Resting heart rate (bpm)</th>
<th>Non-sudden death</th>
<th>Sudden death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>60–64</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>65–69</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>70–75</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>&gt;75</td>
<td>34</td>
<td>24</td>
</tr>
</tbody>
</table>

Jeffrey S. Borer Eur Heart J Suppl 2008;10:F2-F6

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Meccanismi sfavorevoli della frequenza cardiaca elevata
Relationship Between Resting Heart Rate Reduction and Reduced Mortality

Beta-Blocker Trials

Adapted from Kjekshus J. Eur Heart J. 1987;8(suppl L):115–122.
Effect of variations in RHR on cardiovascular mortality in several studies on heart failure.

Stéphane Cook et al. Eur Heart J 2006;27:2387-2393
Background beta-blocker treatment

Patients (%)

- BB at randomization: 89% (Ivabradine), 89% (Placebo)
- At least 50% target daily dose: 56% (Ivabradine), 56% (Placebo)
- Target daily dose: 26% (Ivabradine), 26% (Placebo)


www.shift-study.com
Ivabradine: Specific and Selective Inhibitor of the $I_f$ Ion Channel

Channel principally responsible for the SA Node Pacemaker Current

SINUS NODE INHIBITION:

Ivabradine selectively inhibits the “funny” current in the sinus node.

Slows HR independent of BB effect “less negative inotropy”

Implications for patients with impaired stroke volume.
Changes in heart rate at rest (A) and at peak exercise (B) in the different treatment groups during double-blind dose-ranging.


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Efficacy of ivabradine, a new selective \( I_f \) inhibitor, compared with atenolol in patients with chronic stable angina

Jean-Claude Tardif\(^1\)*, Ian Ford\(^2\), Michal Tendera\(^3\), Martial G. Bourassa\(^1\), and Kim Fox\(^4\) for the INITIATIVE Investigators

\(^1\)Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada; \(^2\)University of Glasgow, Scotland, UK; \(^3\)Slaska Akademia Medyczna, Katowice, Poland; and \(^4\)Royal Brompton Hospital, London, UK

Received 13 June 2005; revised 16 September 2005; accepted 22 September 2005; online publish-ahead-of-print 7 October 2005
**INITIATIVE**

Effects on total exercise duration at trough of drug activity.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>atenolol better</th>
<th>ivabradine better</th>
<th>E [95% CI]</th>
<th>P for non-inf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lva 5 mg bid</td>
<td>595</td>
<td></td>
<td></td>
<td>6.7 [-7.4; 20.8]</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>vs. ate 50 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lva 7.5 mg bid</td>
<td>300</td>
<td></td>
<td></td>
<td>10.3 [-8.3; 28.8]</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>vs. ate 100 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lva 10 mg bid</td>
<td>298</td>
<td></td>
<td></td>
<td>15.7 [-2.9; 34.3]</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>vs. ate 100 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jean-Claude Tardif et al. Eur Heart J 2005;26:2529-2536
INITIATIVE
Effects on time to 1 mm ST segment depression (TST) at trough of drug activity.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>atenolol better</th>
<th>ivabradine better</th>
<th>E [95% CI]</th>
<th>P for non-inf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iva 5 mg bid vs. ate 50 mg od at M1</td>
<td>594</td>
<td></td>
<td></td>
<td>4.9 [-11.9; 21.7]</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Iva 7.5 mg bid vs. ate 100 mg od at M4</td>
<td>297</td>
<td></td>
<td></td>
<td>4.3 [-16.8; 25.3]</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Iva 10 mg bid vs. ate 100 mg od at M4</td>
<td>297</td>
<td></td>
<td></td>
<td>-3.3 [-24.4; 17.8]</td>
<td>P = 0.021</td>
</tr>
</tbody>
</table>

Jean-Claude Tardif et al. Eur Heart J 2005;26:2529-2536
INITIATIVE: Summary

- Ivabradine 7.5 mg bid and 10 mg bid were noninferior to atenolol 100 mg as measured by
  - Total exercise duration
  - Time to limiting angina, angina onset, and 1 mm ST↓
- Most common adverse events were transient visual symptoms, mainly increased brightness in limited areas
- Sinus bradycardia occurred in 2.2% (ivabradine 7.5 mg), 5.4% (ivabradine 10 mg), and 4.3% (atenolol) of patients

I_{	ext{IR}} current inhibition may be as effective as β-blockade in treatment of stable angina

Efficacy of the $I_f$ current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial

Jean-Claude Tardif¹*, Piotr Ponikowski¹,²,³, and Thomas Kahan⁴ for the ASSOCIATE study Investigators

¹Montreal Heart Institute, Université de Montreal, 5000 Belanger Street, Montreal, Quebec, Canada H1T 1C8; ²Clinical Military Hospital, Wroclaw, Poland; ³Wroclaw Medical University (2nd Cardiology Department), Wroclaw, Poland; and ⁴Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden

Received 25 July 2008; revised 18 November 2008; accepted 27 November 2008; online publish-ahead-of-print 9 January 2009
Changes in exercise tolerance test criteria between baseline and M2 visit and between baseline and end of study (M4) in the full analysis set.

Coronary artery disease with and without ventricular systolic dysfunction
A step further in the management of stable coronary patients with ivabradine

Clinical objective
To examine the effects of ivabradine on cardiovascular events in coronary patients with left ventricular dysfunction

Pathophysiological objective
To examine the effects of elevated HR (≥70 bpm) on cardiovascular events in these coronary patients

Effect of ivabradine on primary endpoint (Overall population)

Hazard ratio = 1.00 (0.91 – 1.10)

P=0.94

Heart rate above 70 bpm increases risk of myocardial infarction by 46% 

Prospective data from the BEAUTIFUL placebo arm

Hazard ratio = 1.46 (1.11 – 1.91)  
P = 0.0066

Heart rate ≥70 bpm

Heart rate <70 bpm

% with coronary revascularization

Hazard ratio = 1.38 (1.02 – 1.86)  
P = 0.037

Heart rate ≥70 bpm

Heart rate <70 bpm

Ivabradine reduces the need for revascularization (HR ≥70 bpm)

Hazard ratio = 0.70 (0.52 – 0.93)  
P = 0.016

Placebo (HR ≥70 bpm)

RRR 30%

Ivabradine

Ivabradine reduces fatal and nonfatal myocardial infarction (HR ≥70 bpm)

Hazard ratio = 0.64 (0.49 – 0.84)  
P = 0.001

Placebo (HR ≥70 bpm)

RRR 36%

Ivabradine
Conclusions from the BEAUTIFUL Trial

- While there was no difference total cardiovascular mortality
- Ivabradine use appears to be a benefit in reducing readmissions due to coronary artery disease (when resting heart rate > 70)
  1. Acute Myocardial Infarction
  2. Coronary Revascularization
BEAUTIFUL

New Results
In angina patients

Summary of observed cardiovascular risk reduction in angina patients

<table>
<thead>
<tr>
<th>Predefined end point</th>
<th>Hazard ratio</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>0.76</td>
<td>24%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87</td>
<td>13%</td>
</tr>
<tr>
<td>CV death</td>
<td>0.88</td>
<td>12%</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.84</td>
<td>16%</td>
</tr>
<tr>
<td>Hospitalization for MI</td>
<td>0.58</td>
<td>42%</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0.70</td>
<td>30%</td>
</tr>
</tbody>
</table>

Ivabradine reduces myocardial infarction in patients with angina

Ivabradine reduces primary end point in angina patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>General considerations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>It is recommended to educate patients about the disease, risk factors and treatment strategy.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>It is indicated to review the patient’s response soon after starting therapy.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Angina/ischaemia relief</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting nitrates are recommended.</td>
<td>I</td>
<td>B</td>
<td>3,329</td>
</tr>
<tr>
<td>First-line treatment is indicated with B-blockers and/or calcium channel blockers to control heart rate and symptoms.</td>
<td>I</td>
<td>A</td>
<td>3,331</td>
</tr>
<tr>
<td>For second-line treatment it is recommended to add long-acting nitrates, ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.</td>
<td>IIA</td>
<td>B</td>
<td>177, 307, 3, 199, 284, 286, 308, 319, 321, 328, 364</td>
</tr>
<tr>
<td>For second-line treatment trimetazidine may be considered</td>
<td>IIIB</td>
<td>B</td>
<td>313, 315</td>
</tr>
</tbody>
</table>

According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.

<table>
<thead>
<tr>
<th>Event prevention</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose aspirin daily is recommended in all SCAD patients.</td>
<td>I</td>
<td>A</td>
<td>333, 334, 366</td>
</tr>
<tr>
<td>Clopidogrel is indicated as an alternative in case of aspirin intolerance.</td>
<td>I</td>
<td>B</td>
<td>335</td>
</tr>
<tr>
<td>Statins are recommended in all SCAD patients.</td>
<td>I</td>
<td>A</td>
<td>62</td>
</tr>
<tr>
<td>It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).</td>
<td>I</td>
<td>A</td>
<td>348, 349, 351, 352</td>
</tr>
</tbody>
</table>
Study end points

Primary composite end point
Cardiovascular death or nonfatal myocardial infarction

Secondary end points
All-cause death
Cardiovascular death
Coronary death
Nonfatal myocardial infarction
Coronary revascularization
Elective coronary revascularization
New-onset or worsening heart failure

Primary composite end point

Ivabradine n=654 (3.03% PY)  Placebo n=611 (2.82% PY)
HR = 1.08 [95% CI 0.96-1.20]  P=0.20

Cardiovascular death

Ivabradine n=329 (1.49% PY)  Placebo n=301 (1.36% PY)
HR = 1.10 [95% CI 0.94-1.28]  P=0.25
Components of primary composite end point (angina population: CCS class ≥II, n=12 049)

Cardiovascular death

Nonfatal myocardial infarction

Primary composite end point (angina population: CCS class ≥II, n=12 049)

Ivabradine n=469 (3.37% PY)  Placebo n=390 (2.86% PY)

HR = 1.18 [95% CI 1.03-1.35]  P=0.018

Conclusion

- Lowering heart rate with ivabradine in CAD patients without clinical heart failure does not reduce the risk of CV death or nonfatal MI.

- In the subgroup of patients with angina (CCS class ≥II), there appeared to be an increase in CV death or nonfatal MI.

- In the same subgroup there appeared to be improvement in symptoms and need for elective coronary revascularization.
**SHIFT Trial**
- Randomized, double-blinded, placebo controlled
- 6,500 subjects
  - Male (76%), Caucasian (89%)
  - Class II – IV heart failure, EF<35%, HR>70bpm
  - Admission for heart failure in the previous 2 months
- On optimal medical management
  - 90% on BB, 84% on ACE/ARBs, 60% Aldo antagonists
- Ivabradine vs placebo, followed for 3 years
- Primary endpoint: composite of CV death or hospital admission for heart failure.

**Cardiovascular Death**
- Ivabradine n=449 (7.5%PY) Placebo n=491 (8.3%PY)
- Cumulative frequency (%)
- HR = 0.91  p=0.128

**Hospitalization for heart failure**
- Ivabradine n=514 (9.4%PY) Placebo n=672 (12.7%PY)
- Cumulative frequency (%)
- HR = 0.74 [95% CI 0.66-0.83] p<0.0001

**Primary Composite Endpoint: CV Death + HF hospitalization**
- HR = 0.82 [95% CI 0.75-0.90]
- ARR = 4.2%  
  NNT = 24
Other treatments with less-certain benefits in patients with symptomatic (NYHA class II–IV) systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤ 40% and unable to tolerate an ACE inhibitor because of cough (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>A</td>
<td>108, 109</td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization in patients with an EF ≤ 40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA.</td>
<td>I</td>
<td>A</td>
<td>110, 111</td>
</tr>
<tr>
<td>Ivabradine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤ 35%, a heart rate remaining ≥ 70 b.p.m., and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIAa</td>
<td>B</td>
<td>112</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤ 35% and a heart rate ≥ 70 b.p.m. who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).*</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤ 45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate ≥ 70 b.p.m.). Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients with an EF ≤ 45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker,ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
</tbody>
</table>
Potential role of heart rate in cardiovascular disease.

Kim Fox Eur Heart J Suppl 2010;12:C16-C20

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In caso di rivascolarizzazione incompleta e/o angina residua con PCI e FC > 70 bpm utilizzate ivabradina?

83,8%

16,2%
Quale considerate l'indicazione principale all'uso di ivabradina?

- **Opzione A: Angina/Iscemia residua e FC > 70 bpm** 48,5%
- **Opzione B: Rivascolarizzazione incompleta e FC > 70 bpm** 5,1%
- **Opzione C: Disfunzione ventricolare sinistra** 2,0%
- **Opzione D: C+A+B** 43,4%
- **Opzione E: Alto rischio trombotico** 0,0%
- **Opzione F: Grave coronaropatia** 1,0%
Tartaruga: 6 bpm 150 anni di vita

“Chi va piano, va sano e va lontano”