Update on the Management of Chronic Stable Angina

Peter Collins
Professor of Clinical Cardiology, Faculty of Medicine,
Imperial College London
& Royal Brompton Hospital,
London, UK
Cardiovascular Disease in China

- “Report on Cardiovascular Disease in China 2011”
  - 230 million patients with CVD
  - 3 million cases of death of CVD each year accounting for 41% in total.
  - 23 million Chinese will develop angina which is difficult to control

Cardiovascular diseases in China: Current status and future perspectives
Li and Ge IJC Heart & Vasculature 6 (2015) 25–31
Question

A 72 year old fisherman has a DES 3 months ago and returns complaining of angina. This occurs in:

1) Less than 5% of patients per year
2) In 10% of patients per year
3) In 15% of patients per year
4) In over 25% of patients per year
Question

A 72 year old fisherman has a DES 3 months ago and returns complaining of angina. This occurs in:

1) Less than 5% of patients per year
2) In 10% of patients per year
3) In 15% of patients per year
4) **In over 25% of patients per year**
Freedom from angina over time as assessed with the Seattle angina questionnaire

Elements of OMT for stable CAD

- Anti-platelet therapy
- Lipid-lowering therapy
- Anti-ischaemic agents
- Nicotinic acid, fibrates
- ACE inhibitors
- Lifestyle measures

1. SIGN. Management of stable angina, February 2007
Two Primary Goals of Treatment in Stable CAD

1. To Improve Survival

2. To Improve Angina and Quality of Life (QOL)

These goals should govern the decision to revascularize
Extended Follow-up Study Cohort

PCI plus optimal medical therapy

Optimal medical therapy alone

Unadjusted hazard ratio for death, PCI plus medical therapy vs. medical therapy alone, 0.95 (95% CI, 0.79–1.13)  
P=0.53 by log-rank test

OMT vs OMT plus stenting in patients with stable angina and documented myocardial ischaemia (n = 5286)

PCI:

- reduces the incidence of angina.
- has not been demonstrated to improve survival in stable patients.
- may increase the short-term risk of MI.
- does not lower the long-term risk of MI.
Optimising medical therapy for stable angina: Other therapies?

Revascularisation should only be considered if symptoms are not satisfactorily controlled with optimal medical therapy.

1. NICE stable angina: Full guideline (July 2011).
Angina relief

1st line
Short-acting Nitrates, plus

- Beta-blockers or CCB-heart rate
- Consider CCB-DHP if low heart rate or intolerance/contraindications
- Consider Beta-blockers + CCB-DHP if CCS Angina > 2

May add or switch (1st line for some cases)

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine
Trimetazidine

2nd line

Event prevention

- Lifestyle management
- Control of risk factors

+ Educate the patient

- Aspirin
- Statins
- Consider ACEI or ARBs

+ Consider Angio → PCI –
Stenting or CABG
Angina guidelines – AHA/ACC 2014 – Medical Therapy

Class of recommendation I Level of evidence B

• 1. Beta blockers

• 2. Calcium channel blockers

• 3. Calcium channel blockers or long-acting nitrates, in combination with beta blockers

• 4. Sublingual nitroglycerin or nitroglycerin spray
Angina guidelines – AHA/ACC 2014 – Medical Therapy

Class of recommendation IIa

- Non dihydropyridine CCB (verapamil or diltiazem) instead of a beta blocker (B)
- Ranolazine in place of BB if SE (B)
- Ranolazine in combination with beta blockers (A)
## Ranolazine’s anti-anginal effect: comparison with other anti-anginal agents

<table>
<thead>
<tr>
<th>Anti-anginal drugs</th>
<th>Heart rate</th>
<th>Blood pressure</th>
<th>Anti-anginal effect</th>
</tr>
</thead>
</table>
| Ranolazine              | No significant effect $^{1,2}$ | No significant effect $^{1,2}$ | • Improved diastolic tone $^{1,2}$  
• Improved coronary blood flow $^1$  
• Potential antiarrhythmic effects $^{1,2}$ |
| Beta-blockers           | Decrease $^4$       | Decrease $^4$        | • Decrease $O_2$ demand, primarily slowing heart rate $^3$ |
| Calcium channel blockers|                     |                      | • Reduction in myocardial $O_2$ demand $^3$  
• Increase in $O_2$ supply $^3$  
• Relaxes systemic and coronary vascular smooth muscle $^3$ |
| • Dihydropyridine       | Increase $^4$       | Decrease $^4$        |                                                          |
| • Verapamil/diltiazem   | Decrease $^4$       | Decrease $^4$        |                                                          |
| Long-acting nitrate     | No effect $^4$      | Decrease $^4$        | • Relax vascular smooth muscle $^3$  
• Reduces myocardial wall tension and $O_2$ requirements $^3$ |
| Trimetazidine           | No significant effect $^5$ | No significant effect $^5$ | • Decreases fatty acid oxidation, stimulates glucose utilisation $^{3,5}$ |
| Ivabradine              | Decrease $^6$       | No significant effect $^6$ | • Decrease $O_2$ consumption $^6$ |

Table elaborated from:
Approved indication for Ranexa in Hong Kong

Ranexa is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists)
Unmet needs:

• An increasing number of patients are unsuitable for revascularisation because of complicating factors such as age, medical co-morbidities and unsuitable coronary anatomy

• Despite treatment with conventional agents or revascularisation, or both, many patients remain symptomatic one year after CABG or PCI

• Some patients may not tolerate the upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate

1. Hamm Eur Heart J 2004 (Suppl 1): i2-i2
3. Holubkov et al Am Heart J 2002: 144; 826
Ranolazine

- Unique mode of action
- Clinical trial data in chronic stable
- Clinical trial data in chronic stable in patients with diabetes
- Clinical trial data in acute coronary syndromes
The sodium current peaks at the onset of the action potential and continues throughout systole, with a so-called late component of late $I_{Na}$, which decays gradually.

Elaborated from:
The sodium channel

Diseases
(e.g. ischaemia, heart failure)

Pathological milieu
(Reactive O$_2$ species, ischaemic metabolites)

Toxins and drugs
(ATX-II, pyrethroid, DPI201-106, etc.)

APD: action potential duration; VT: ventricular tachycardia.

Elaborated from:
An increase in $I_{Na}$ impairs diastolic relaxation, increases MVO2 and reduces coronary O2 supply

- Increases MVO$_2$ (myoc. O2 consumption)
- Compresses intramural small vessels
- Reduces endocardial blood flow

Worsens ischaemia and angina

Ranolazine is proposed to mediate its antianginal effect by reducing the flow of the late sodium current in cardiac cells.

Adapted from Zerumsky K & McBride BF. *Am J Health Syst Pharm* 2006;63:2331–2338
Outline

• A review of clinical evidence on ranolazine’s efficacy and safety profile.
**Ranolazine: Main Clinical Studies**

- **MARISA**
  - N=191
  - Chronic angina
  - Ranexa vs placebo

- **CARISA**
  - N=823
  - Chronic angina
  - Ranexa vs placebo on top of standard therapy

- **ERICA**
  - N=565
  - Chronic angina
  - Ranexa vs placebo on top of amlodipine 10mg

- **MERLIN TIMI-36**
  - N=6560
  - Non-STE ACS
  - Ranexa vs placebo on top of standard care

- **TERISA**
  - N=949
  - CAD & DM II
  - Ranexa vs placebo on top of standard care

- **ROLE**
  - N=746
  - Chronic angina

References:
- J Am Coll Cardiol 2004;43:1375- 82
MARISA: efficacy on exercise parameters

$n=175$ pts who completed three of the four treatment periods.

**$p \leq 0.005$ vs. placebo ; ***$p<0.001$ vs. placebo

Note: in the European Union ranolazine is recommended, at a maximum dose of 750 mg bid, as add-on therapy for patients with stable angina.

Modified from:
ERICA: effect on angina frequency

Weekly angina frequency
Trimmed mean ± SE

Placebo + amlodipine 10 mg od (n=281)

Ranolazine 1,000 mg bid + amlodipine 10 mg od (n=277)

*\(p=0.028\)

Note: in the European Union ranolazine is recommended, at a maximum dose of 750 mg bid, as add-on therapy for patients with stable angina.

Adapted from:
Objectives

MERLIN-TIMI 36
Three major aims

1) ACUTE EFFICACY
   Acute Coronary Syndrome
   ↓ major CV events?

2) CHRONIC EFFICACY
   Chronic Management
   ↓ recurrent ischemia?

3) SAFETY

Morrow DA et al. JAMA 2007; 297: 1775-83
Angina and recurrent ischaemia in patients with a history of chronic angina, with an acute coronary syndrome

HR 0.77 (0.64-0.92)  
\( p=0.005 \)

HR 0.78 (0.67-0.91)  
\( p=0.002 \)

Adapted from: Figure 1 in: Wilson SR, et al. *Am Coll Cardiol* 2009;53:1510-6.
MERLIN-TIMI 36: ranolazine increased QoL and treatment satisfaction

SAQ quality of life and treatment satisfaction

- Placebo (n=3,281)
- Ranolazine (n=3,279) i.v. followed by 1,000 mg bid orally

Mean scores SAQ* at 12 months

QoL

- p=0.018

Treatment satisfaction

- p=0.019

*SAQ=Seattle Angina Questionnaire; scores ranging from 0 to 100, with higher scores indicating less disease burden.

### MERLIN-TIMI 36: significant lower incidence of arrhythmias

<table>
<thead>
<tr>
<th>Arrhythmias</th>
<th>Ranolazine (n)</th>
<th>Placebo (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset atrial fibrillation</td>
<td>55 (1.7)</td>
<td>75 (2.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Supraventricular tachycardia*</td>
<td>1,413 (44.7)</td>
<td>1,752 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pauses ≥ 3 sec</td>
<td>97 (3.1)</td>
<td>136 (4.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>VT ≥ 8 beats</td>
<td>166 (5.3)</td>
<td>265 (8.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous ECG (Holter) recording was performed for the first 7 days after randomisation

* ≥120 bpm lasting at least 4 beats

# Tolerability of Ranolazine

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine (n=3,268)</th>
<th>Placebo (n=3,273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>9%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Usually associated with higher doses in the studies

*Note: in the European Union ranolazine is recommended, at a maximum dose of 750 mg bid, as add-on therapy for patients with stable angina, but not for patients with acute coronary syndrome.*

Adapted from:
TERISA – Type 2 diabetes Evaluation of Ranolazine In Subjects with Angina pectoris

Kosiborod et al J Am Coll Cardiol 2013;61:2038–45
TERISA: Exploratory analysis among patients with diabetes – HbA$_{1c}$

<table>
<thead>
<tr>
<th>HbA$_{1c}$</th>
<th>Incidence Density Ratio*</th>
<th>$p$ for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6</td>
<td>0.8</td>
<td>0.046</td>
</tr>
<tr>
<td>≤ 6</td>
<td>0.9</td>
<td>0.047</td>
</tr>
<tr>
<td>&gt;6.5</td>
<td>0.9</td>
<td>0.047</td>
</tr>
<tr>
<td>≤ 6.5</td>
<td>1.1</td>
<td>0.022</td>
</tr>
<tr>
<td>&gt;7</td>
<td>1.1</td>
<td>0.022</td>
</tr>
<tr>
<td>≤ 7</td>
<td>1.2</td>
<td>0.041</td>
</tr>
<tr>
<td>&gt;7.5</td>
<td>1.2</td>
<td>0.041</td>
</tr>
<tr>
<td>≤ 7.5</td>
<td>1.2</td>
<td>0.038</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1.2</td>
<td>0.038</td>
</tr>
<tr>
<td>≤ 8</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

*Relative difference in the incidence rates

Figure 2: ETT outcomes (standardised mean difference)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>ETT – Total time</th>
<th>Time to ST depression</th>
<th>Time to angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB + CCB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB + BB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB/CCB + LAN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB/CCB + Ranolazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB/CCB + Trimetazidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB + Ivabradine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Belsey et al European Journal of Preventive Cardiology 2015; 22(7) 837–848
Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial

Giara Weisz, Philippe Généreux, Andres Iñiguez, Aleksander Zurakowski, Michael Shechter, Karen P Alexander, Ovidiu Dressler, Anna Osmukhina, Stefan James, E Magnus Ohman, Ori Ben-Yehuda, Ramin Farzaneh-Far, Gregg W Stone, for the RIVER-PCI investigators
primary endpoint was time to first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation
Possible reasons for null result

- 40% of events driven by lesion targeted for original PCI – restenosis/plaque rupture
- No test for ischaemia after enrollment
- Now have results of FAME 1/2
- Caution in interpreting post-hoc analyses
- Different patient population studied from MERLIN-TIMI 36
- Does not challenge efficacy of ranolazine on treatment of myocardial ischaemia
- No CV harm except in >75 yrs on MACE
Ranolazine: contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe renal impairment (creatinine clearance <30 ml/min)
- Moderate or severe hepatic impairment
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazol, posaconazol, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone)
- Concomitant administration of Class Ia (e.g. quinidine) or Class III (e.g. dofetilide, sotalol) antiarrhythmics other than amiodarone
Royal Brompton Hospital, London

Thank You!