How to successfully manage patients with ischemic heart disease
My conflicts of interest for this presentation:
I will receive honorarium from A. Menarini ...
Burden of chronic angina in the EU

- ~10 million European adults have chronic angina

- 53% of patients with angiographically proven coronary artery disease originally present with stable angina.\(^1\)

- 1 year after diagnosis, 22% have undergone PCI.\(^2\)

- 25% of patients experience angina up to five years post-PCI with optimal medical care.\(^3\)

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\(^1\) Euro Heart Survey on coronary revascularization. *Eur Heart J* **2005;26**:1169

\(^2\) Euro Heart Survey of stable angina. *Eur Heart J* **2006;27**:1298

\(^3\) *N Engl J Med* **2007;356**:1510
Prevalence of angina by sex and age in the UK in 2009

Estimates are based on records from a sample of general practices in each of the constituent countries of the UK.

British Heart Foundation: www.heartstats.org
Gender-related differences: background

- Angina pectoris is a more common manifestation of coronary heart disease in women (47%) than in men (26%)
- Older women and men curtail activity to avoid anginal episodes
- Women with coronary heart disease report consistently worse health-related quality-of-life outcomes than men
Prognostic implications of angina symptoms

Survival according to physical limitation due to angina (SAQ score)

- 75-100 (little or no limitation)
- 50-74 (mild limitation)
- 25-49 (moderate limitation)
- 0-24 (severe limitation)

$p<0.001$ for log/rank test for equality of survivor function

Am Heart J 2003;146:1015
Cellular pathophysiology of angina

- **Ischaemia**
  - \( \uparrow \text{Late } I_{Na} \)
  - \( \text{Na}^+ \) overload
  - \( \text{Ca}^{++} \) overload
- **Electrical dysfunction**
  - Arrhythmias
- **Mechanical dysfunction**
  - \( \uparrow \text{Diastolic tension} \)
  - \( \downarrow \text{Contractility} \)
- **O2 supply & demand**
  - \( \uparrow \text{ATP consumption} \)
  - \( \downarrow \text{ATP formation} \)

NCX: sodium-calcium exchanger

Clin Res Cardiol 2008;97:222
Cardiol Clin 2008;26:603
Medical therapy of ischaemia

**Oxygen supply**
- Vasospasm: NTG, Ca channel blocker
- Thrombus: ASA
- Atherosclerosis: Statin

**Oxygen demand**
- Afterload: Ca channel blocker
- Heart rate: β blocker
- Contractility: β blocker
- Preload (vascular): NTG

**Ischaemia**
- LV wall stiffness: ↑ LV preload
- Diastolic flow: ↓ myocardial blood flow
- LVEDP: ↑ diastolic tension

Adapted from Braunwald’s Heart Disease 7th Edition 2006
Anti-ischaemic strategies in stable coronary artery disease

**Initial therapy**

- **Drug therapy**
- **PCI**
- **CABG**

**Persistent/recurrent ischaemia**

- ↑ Anti-anginal drug therapy (uptitrate/add additional agents)
- Repeat revascularisation (if possible)
COURAGE: revascularisation versus optimal medication

Treatment strategies

PCI: percutaneous coronary intervention
OMT: optimal medical therapy

Angina-free (%) vs. Months

Baseline 1 3 6 12 24 36

PCI+OMT OMT

p

0.35

<0.001

<0.001

0.005

0.010

0.30

21 23 42 33 53 42 56 47 57 50 59 53 59 56

ESC stable angina guidelines: basic treatment/education

The initial management of the patient with stable angina should focus on all the following elements:

A. Anti-thrombotic and anti-anginal therapy
B. Blood pressure control
C. Cigarette smoking and cholesterol
D. Diet and diabetes
E. Education and exercise
Management of stable angina
new NICE guidelines 2011: SUMMARY

- Use either a beta-blocker or a calcium channel blocker as first-line treatment for stable angina.

- If symptoms are not satisfactorily controlled on a beta-blocker or a calcium channel blocker, consider using a combination of the two.

- For people on beta-blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta-blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:
  - A long-acting nitrate or
  - Ivabradine or
  - Nicorandil or
  - Ranolazine.

- Consider revascularisation (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.

Ranexa® is indicated 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.
The sodium channel

- Diseases (e.g. ischaemia, HF)
- Pathological milieu (Reactive O₂ species, ischaemic metabolites)
- Toxins and drugs (ATX-II, pyrethroid, DPI201-106, etc.)

Na⁺ channel (Gating mechanism malfunction)

- Increase ATP consumption
- Decrease ATP formation

Oxygen supply and demand

- Increase ATP consumption
- Decrease ATP formation

Electrical instability

- After potentials
- Beat-to-beat ΔAPD
- Arrhythmias (VT)

Mechanical dysfunction

- Abnormal contraction and relaxation
- ↑ Diastolic tension (↑LV wall stiffness)

Pathophysiology

Modified Eur Heart J 2004;6 (Suppl. I):13
Am J Hosp Pharm 2006;63:2331
**Ca**

**Overload**

**Diseases/conditions**
1. **Acquired**
   - Hypoxia/ROS
   - Ischaemia
   - Heart failure
   - CaMKII, AMPK

2. **Congenital (inherited)**
   - **Cardiac**: SCN5A (LQT3)
   - Sk Muscle: SCN4A (Myotonias)
   - CNS: SCN1A, 2A, 3A (seizures)
   - PNS: SCN9A (neuropathic pain)

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**Pathophysiology**

- Altered Na-channel gating leads to Ca²⁺ overload

- RANOLAZINE
Ranolazine Clinical Studies

A. Heart Rate

B. Arterial Blood Pressure

Treatment duration: 1 week; number of patients: 191
Therapeutic concentrations are ~750 - 4,000 ng/ml (~2 to 8 µM)
CARISA

On top of β-blockers or Ca-antagonist

Mean number of angina attacks/week at 12 weeks

Placebo + background therapy *

Ranolazine 750 mg b.i.d. + background therapy *

\[ p < 0.006 \]

-24% Reduction in Angina Frequency

\[ n = 258 \quad n = 272 \]

* Background therapy:
  - Atenolol 50 mg or
  - Diltiazem 180 mg or
  - Amlodipine 5 mg

JAMA 2004;291:309
On top of β-blockers or Ca-antagonist

Placebo + background therapy*
Ranolazine 750 mg b.i.d. + background therapy*

Mean nitroglycerin (NTG) doses/week at 12 weeks

-32% Reduction in NTG use

* Background therapy:
  - Atenolol 50 mg or
  - Diltiazem 180 mg or
  - Amlodipine 5 mg

n = 258
n = 272

JAMA 2004;291:309
CARISA

Mean increase in exercise time in ADD ON

- **Ivabradine**
  - 7.5 mg bid
  - On top of Amlodipine 10 mg
  - Mean increase: 7.50 seconds

- **Atenolol**
  - 50 mg
  - On top of Amlodipine 5 to 10 mg
  - Mean increase: 12.00 seconds

- **Ivabradine**
  - 5 to 7.5 mg bid
  - On top of Atenolol 50 mg
  - Mean increase: 16.30 seconds

- **B-blockers**
  - On top of Ca-antagonist
  - Mean increase: 17.00 seconds

- **Ca-antagonists**
  - On top of β-blockers
  - Mean increase: 23.00 seconds

- **Ranolazine**
  - 750 mg bid
  - On top of β-blockers or Ca-antagonist
  - Mean increase: 23.70 seconds

**Mean increase in exercise time in ADD ON**

**CARISA**

Ranolazine Clinical Studies
**Background therapy:**
- Atenolol 50 mg (43%) or Amlodipine 5 mg (31%) or Diltiazem 180 mg (26%)
- Antidiabetic drugs (100%)

Ranolazine Clinical Studies

In patients with diabetes

CARISA
Diabetes

Mean angina episodes/week at week 12 in diabetic patients

Mean NTG doses/week at week 12 in diabetic patients

Mean change from Baseline in HbA1c (%)

Placebo
(n=37)

Ranolazine
750 mg b.i.d.
(n=47)

-0.02%

-0.50%

0.48% reduction*

**P=0.008

JAMA 2004;291:309
MERLIN-TIMI 36: primary end-point in patients with ACS and prior history of angina

CV death, MI, or recurrent ischaemia (% at 12 months)

HR: 0.86; 95% CI: 0.75-0.97
p = 0.017

This is a randomised, double-blind, placebo-controlled study on 6560 patients with non-ST elevation-acute coronary syndromes on standard therapy, randomised to ranolazine (iv followed by oral 1000 mg twice daily) or placebo with a median follow-up of 348 day. Evaluation of the anti-anginal effects of ranolazine in the subgroup of patients with prior chronic angina (n = 3,565, 54%).

Ranolazine Clinical Studies
MERLIN-TIMI 36: anti-anginal effect of ranolazine

Angina and recurrent ischaemia in patients with a history of chronic angina, with an acute coronary syndrome

MERLIN-TIMI 36: a randomised, double-blind, placebo-controlled study on 6560 patients with non-ST elevation acute coronary syndromes on standard therapy, randomised to ranolazine (iv followed by oral 1000 mg twice daily) or placebo with a median follow-up of 348 day. Evaluation of the anti-anginal effects of ranolazine in the subgroup of patients with prior chronic angina (n =3,565, 54%).

J Am Coll Cardiol 2009;53:1510
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J Am Coll Cardiol 2009;53:1510
Baseline BNP and effect of ranolazine

Cumulative incidence of primary end-points stratified by BNP concentration

MERLIN-TIMI 36: a randomised, double-blind, placebo-controlled study on 6560 patients with non-ST elevation-acute coronary syndromes on standard therapy, randomised to ranolazine (i.v. followed by oral 1000 mg twice daily) or placebo with a median follow-up of 348 day. BNP elevation was defined as 80 pg/ml and has been evaluated in all available baseline samples (n=4,543).
Ranolazine:  
• Improved perfusion pattern and reduced severity of ischemia in 70% patients  
• Significantly increased treadmill exercise time by 32 seconds (p=0.017)  
• Reduced angina in 75% patients  
• Among the patients with reduced angina, 73% had an improvement in perfusion

Exploratory study in 20 patients with CAD and angina treated with Ranolazine

Ranolazine Clinical Studies

*PDS: perfusion defect size

During exercise  
Before RAN  
PDS* = 25% of LV  
Peak HR = 142 bpm  

During exercise  
After RAN (3-4 wks)  
PDS* = 11% of LV  
Peak HR = 142 bpm
## Treatment strategies

### Ranolazine 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<sup>1,2</sup> | No significant effect<sup>1,2</sup> | - Improved diastolic tone<sup>1,2</sup>  
- Improved coronary blood flow<sup>1</sup>  
- Potential antiarrhythmic effects<sup>1,2</sup> |
| **Beta-blockers**         | Decrease<sup>4</sup>            | Decrease<sup>4</sup>            | - Decrease O<sub>2</sub> demand, primarily slowing heart rate<sup>3</sup>          |
| **Calcium channel blockers** |                                 |                                 |                                                                                     |
| • Dihydropyridine         | Increase<sup>4</sup>            | Decrease<sup>4</sup>            | - Reduction in myocardial O<sub>2</sub> demand<sup>3</sup>                           |
| • Verapamil/diltiazem     | Decrease<sup>4</sup>            | Decrease<sup>4</sup>            | - Increase in O<sub>2</sub> supply<sup>3</sup>                                     |
|                           |                                 |                                 | - Relaxes systemic and coronary vascular smooth muscle<sup>3</sup>                  |
| **Long-acting nitrate**   | No effect<sup>4</sup>           | Decrease<sup>4</sup>            | - Relax vascular smooth muscle<sup>3</sup>                                         |
|                           |                                 |                                 | - Reduces myocardial wall tension and O<sub>2</sub> requirements<sup>3</sup>        |
| **Trimetazidine**         | No significant effect<sup>5</sup> | No significant effect<sup>5</sup> | - Decreases fatty acid oxidation, stimulates glucose utilisation<sup>3,5</sup>     |
| **Ivabradine**            | Decrease<sup>6</sup>            | No significant effect<sup>6</sup> | - Decrease O<sub>2</sub> consumption<sup>6</sup>                                 |

<sup>2</sup>. Revised June 2011.  
<sup>5</sup>. Am J Cardiol 2006; 98 (suppl):19J-24J.  
<sup>6</sup>. Ivabradine. SmPC.
SAFETY

(drug interactions)

- Careful dose titration is recommended with:
  - moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, erythromycin)
  - P-gp inhibitors (e.g. verapamil, cyclosporin)

- Do not administer Ranexa® together with:
  - potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, telithromycin, nefazodone)
  - class IA (e.g. quinidine) or class III (e.g. dofetilide, sotalol) anti-arrhythmics other than amiodarone

- There is a theoretical risk that concomitant treatment of ranolazine with other drugs known to prolong the QTc interval may give rise to a pharmacodynamic interaction and increase the possible risk of ventricular arrhythmias.
Impact on healthcare costs: ranolazine reduces healthcare costs

Data from a National Health Insurance Database (July 2005→ Feb 2008):
Frequency of hospitalisations, revascularisation and healthcare costs evaluated for 6 months post-anti-anginal medication changes in patients with angina and anti-anginal prescriptions.
CAD TRIAL

EFFICACY OF RANOLAZINE IN PATIENTS WITH CORONARY ARTERY DISEASE (CAD)

Double-blind, randomised, multicenter, international, parallel group versus placebo, phase IV study in patients with CAD

Code: MEIN/10/Ran-Cad/003

(EUDRA-CT number: 2011-001278-24)
STUDY POPULATION

1216 randomised patients with:

- CAD confirmed by angiography, prior MI, prior revascularization

AND

- exercise induced angina not controlled by the standard therapy
### SITES DISTRIBUTION

Table with site distribution:

<table>
<thead>
<tr>
<th>Country</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITALY</td>
<td>31</td>
</tr>
<tr>
<td>GREECE</td>
<td>5</td>
</tr>
<tr>
<td>AUSTRIA</td>
<td>3</td>
</tr>
<tr>
<td>SPAIN</td>
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<tr>
<td>ALBANIA</td>
<td>3</td>
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<tr>
<td>HOLLAND</td>
<td>3</td>
</tr>
</tbody>
</table>

**N° planned sites: 100**

1216 PATIENTS HAVE TO BE RANDOMISED
STUDY END-POINTS

PRIMARY:
- to verify whether ranolazine 750 mg b.i.d. is effective in increasing exercise capacity (exercise treadmill time at peak)

SECONDARY:
- to verify whether ranolazine is effective in reducing angina frequency and nitroglycerin consumption/week
- to assess safety (adverse events, laboratory findings and physical examination)
Ranolazine: algorithm for use

- Patients intolerant then CHANGE to next

Ranolazine

Treatment strategies

- Patients inadequately controlled then ADD next

Ranolazine
Thank you
Indepedently of comorbidities and previous treatment

<table>
<thead>
<tr>
<th>Stable Angina Patients with:</th>
<th>Add Ranexa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>√</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>√</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>√</td>
</tr>
<tr>
<td>Diabetes</td>
<td>√</td>
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<tr>
<td>Acute Coronary Syndrome</td>
<td>√</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>√</td>
</tr>
<tr>
<td>Prior MI</td>
<td>√</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>√</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients treated with:</th>
<th>Add Ranexa</th>
</tr>
</thead>
<tbody>
<tr>
<td>β- blockers</td>
<td>√</td>
</tr>
<tr>
<td>Calcium Channel blockers</td>
<td>√</td>
</tr>
<tr>
<td>Long acting nitrates</td>
<td>√</td>
</tr>
</tbody>
</table>
The recommended initial dose of Ranolazine is 375 mg twice daily. After 2–4 weeks, the dose should be titrated to 500 mg twice daily and, according to the patient’s response, further titrated to a recommended maximum dose of 750 mg twice daily.

If a patient experiences treatment-related adverse events (e.g. dizziness, nausea, or vomiting), down titration of Ranolazine to 500 mg or 375 mg twice daily may be required. If symptoms do not resolve after dose reduction, treatment should be discontinued.
Burden of chronic angina in the EU

- Coronary heart disease (CHD) is the most common cause of death in EU, accounting for over 740,000 deaths per year

- The cost of CHD in the EU is estimated to be over €49 billion per year

- Angina pectoris is estimated to affect 20,000-40,000 individuals per million in most European countries

- There is a need for new anti-anginal agents given that despite receiving “optimal” anti-anginal therapy, a proportion of patients will continue to experience angina

Drugs 2008;68:2483