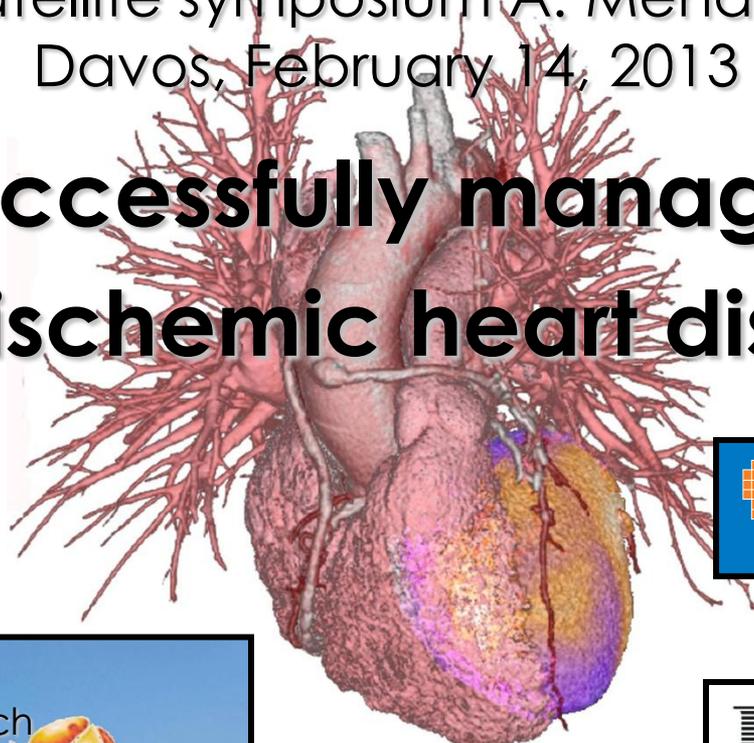


Cardiology Update 2013  
Satellite symposium A. Menarini  
Davos, February 14, 2013

# How to successfully manage patients with ischemic heart disease



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A composite image featuring a background of the Jet d'Eau fountain in Geneva, with a 3D anatomical model of a heart and its coronary arteries overlaid on the right side. The text is positioned in the upper left quadrant of the image.

**My conflicts of interest for this presentation:**

**I will receive honorarium from A. Menarini ...**

## **Burden of chronic angina in the EU**

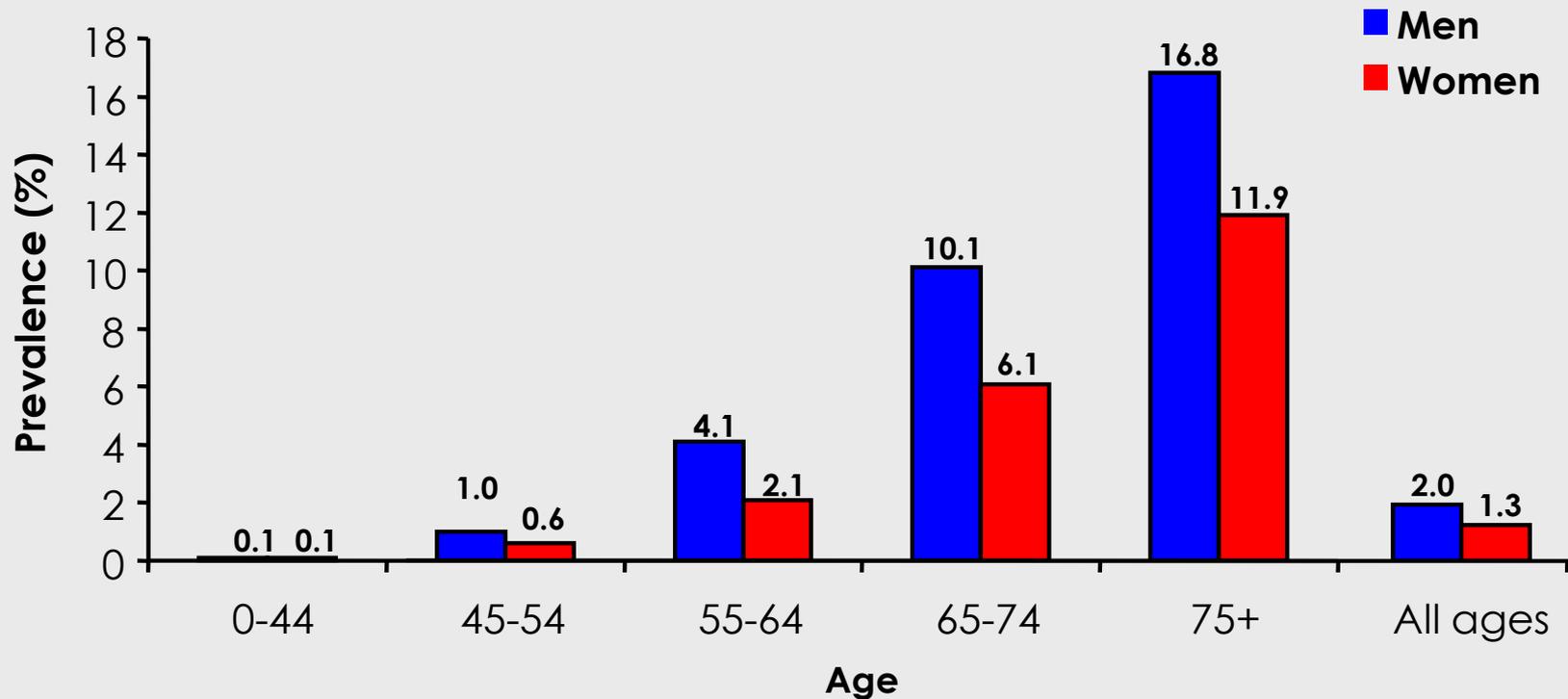
- ~ 10 million European adults have chronic angina
- 53% of patients with angiographically proven coronary artery disease originally present with stable angina<sup>1</sup>
- 1 year after diagnosis, 22% have undergone PCI<sup>2</sup>
- 25% of patients experience angina up to five years post-PCI with optimal medical care<sup>3</sup>

<sup>1</sup> Euro Heart Survey on coronary revascularization. *Eur Heart J* 2005;26:1169

<sup>2</sup> Euro Heart Survey of stable angina. *Eur Heart J* 2006;27:1298

<sup>3</sup> *N Engl J Med* 2007;356:1510

## Prevalence of angina by sex and age in the UK in 2009



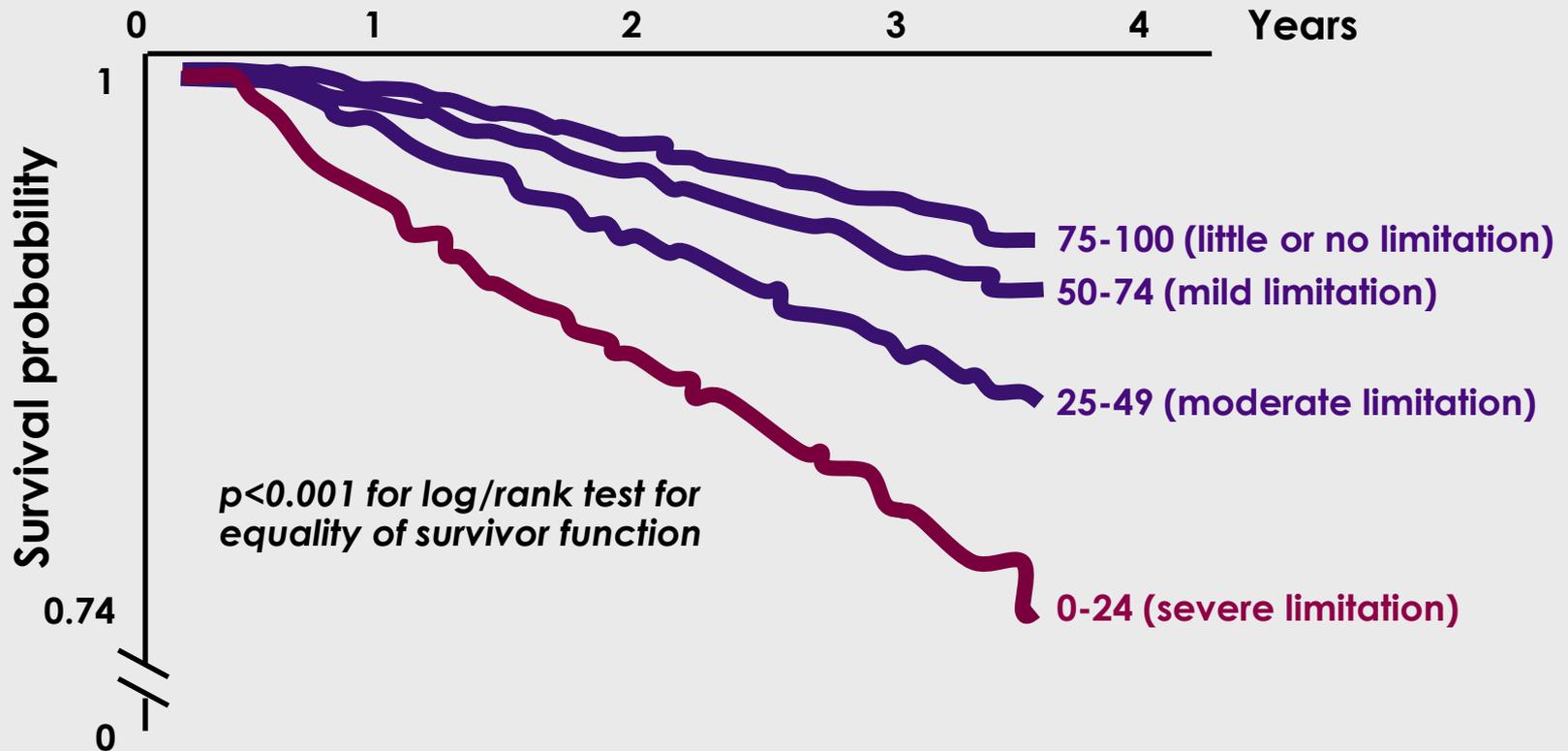
Estimates are based on records from a sample of general practices in each of the constituent countries of the UK.

## **Gender-related differences: background**

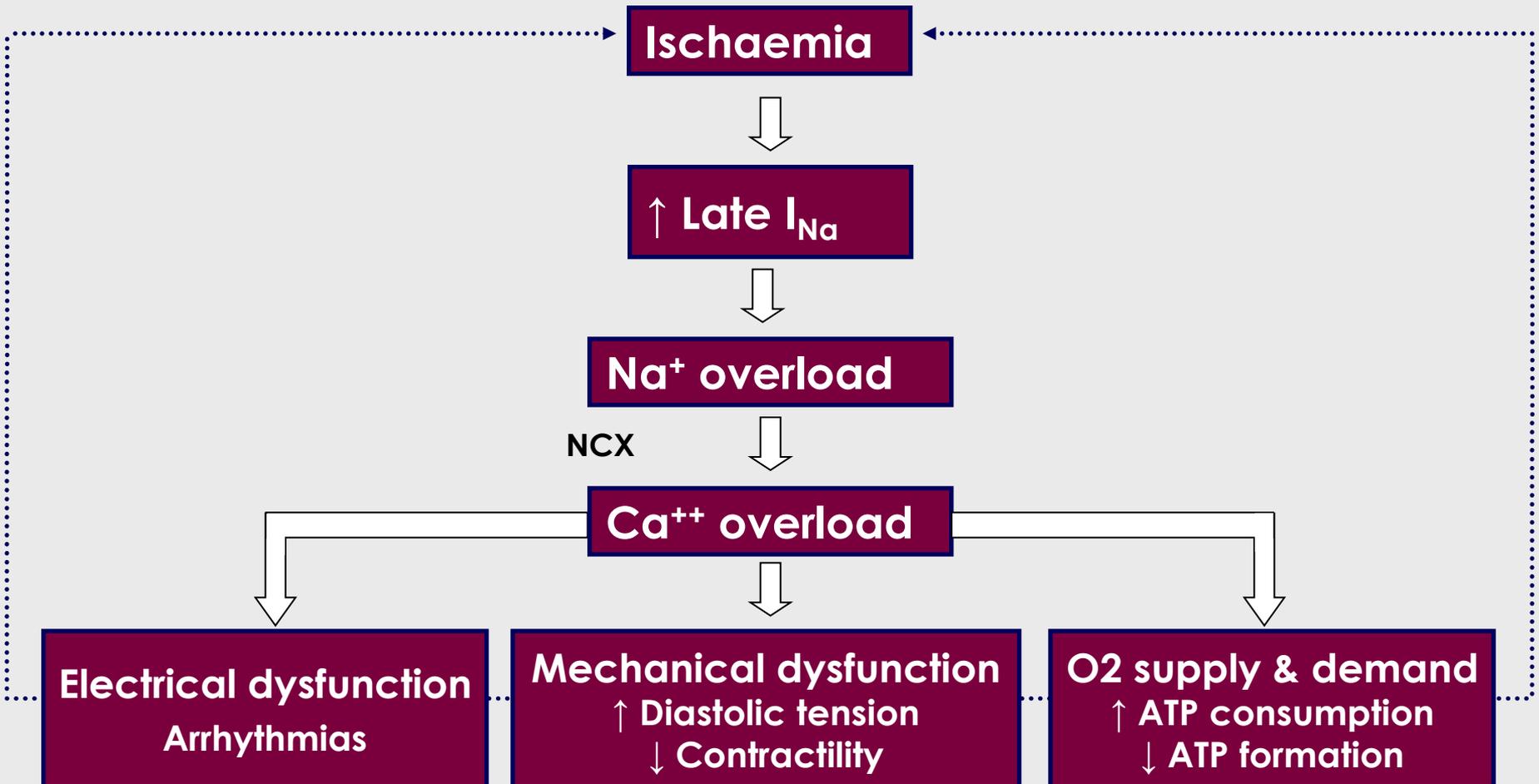
- Angina pectoris is a more common manifestation of coronary heart disease in women (47%) than in men (26%)
- Older women and men curtail activity to avoid anginal episodes
- Women with coronary heart disease report consistently worse health-related quality-of-life outcomes than men

## Prognostic implications of angina symptoms

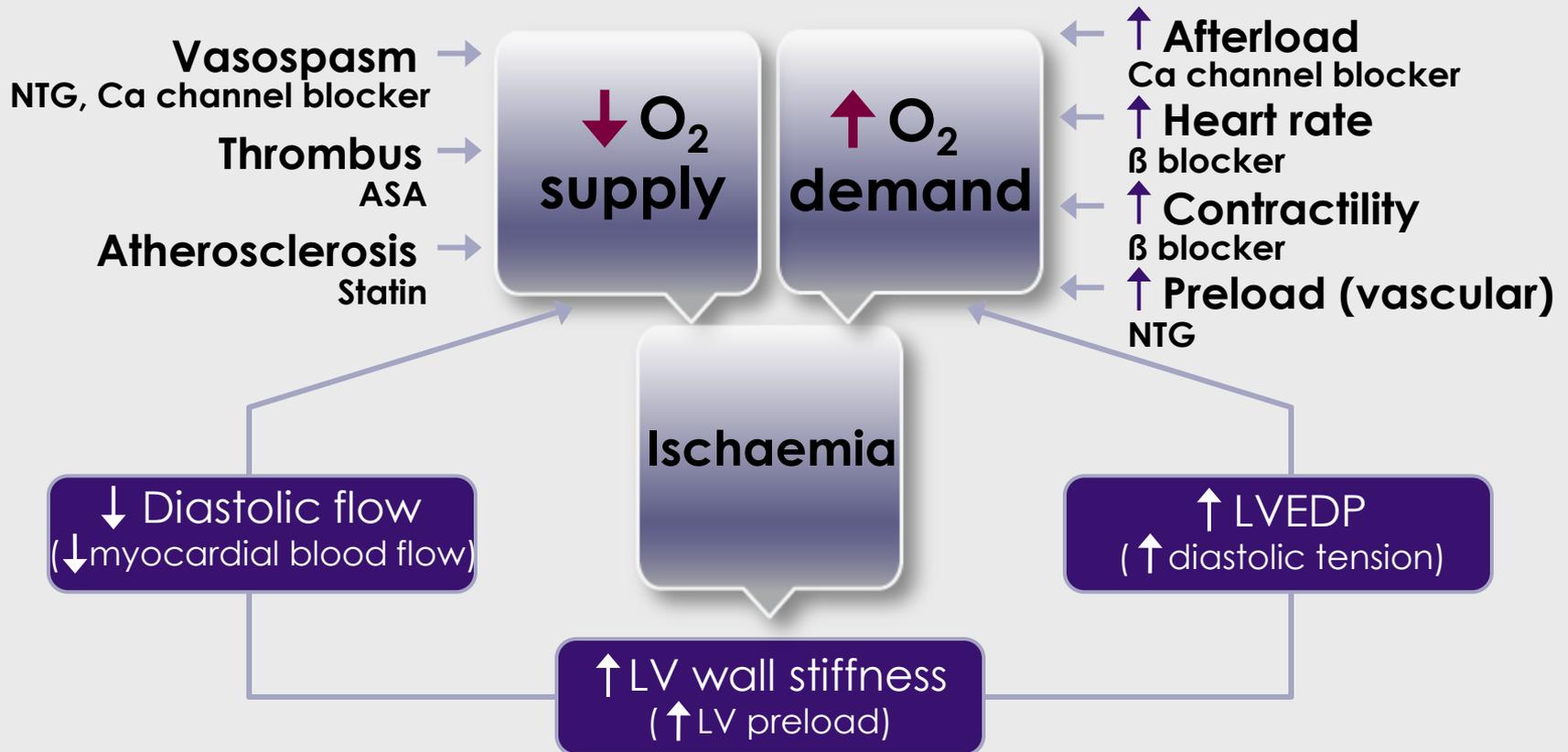
Survival according to physical limitation due to angina (SAQ score)



## Cellular pathophysiology of angina



## Medical therapy of ischaemia



***Anti-ischaemic strategies in stable  
coronary artery disease***

**Initial therapy**

**Drug therapy**

**PCI**

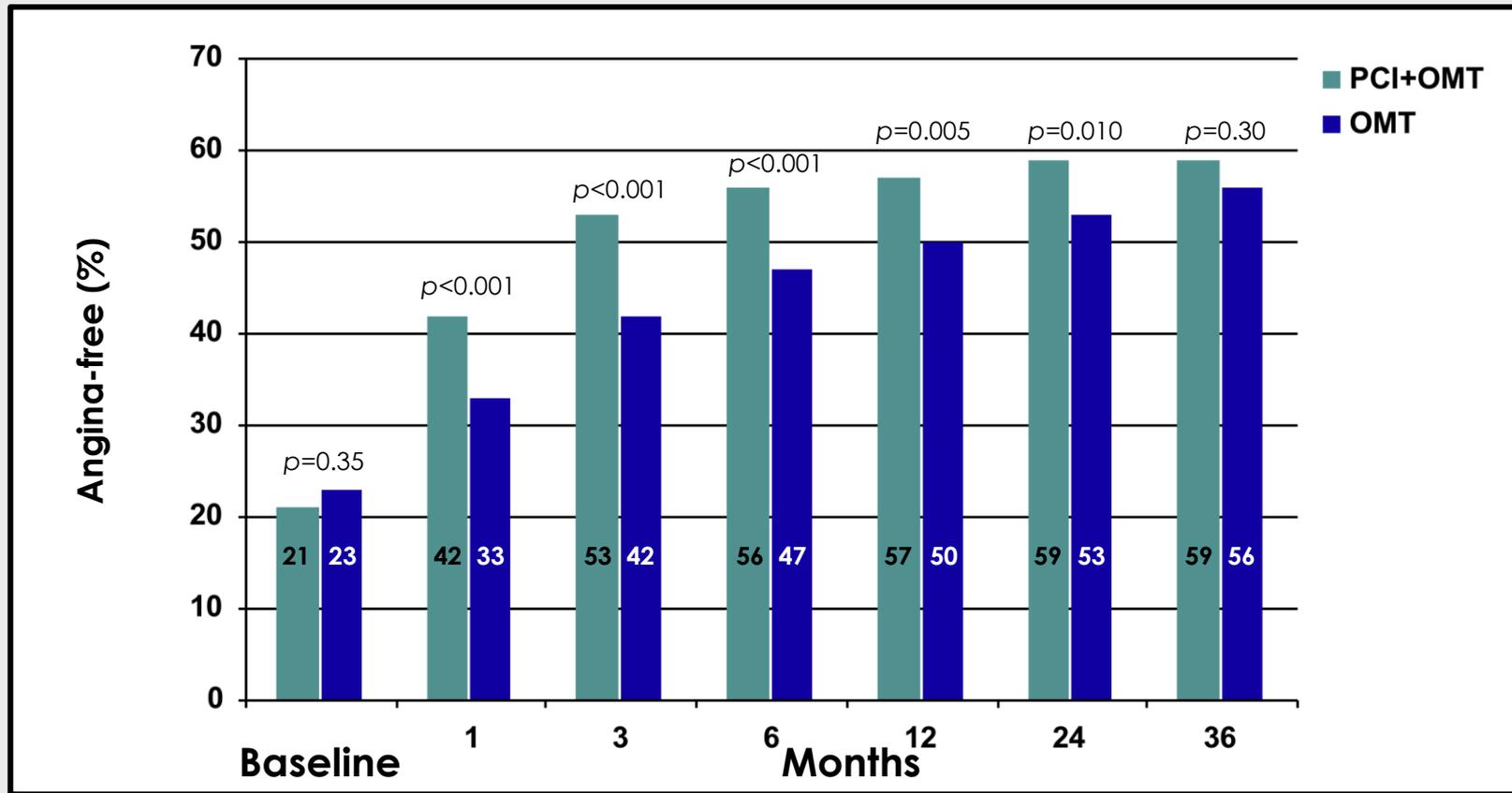
**CABG**

**Persistent/recurrent ischaemia**

**↑ Anti-anginal drug therapy  
(up-titrate/add additional agents)**

**Repeat revascularisation  
(if possible)**

## ***COURAGE: revascularisation versus optimal medication***



PCI: percutaneous coronary intervention  
 OMT: optimal medical therapy

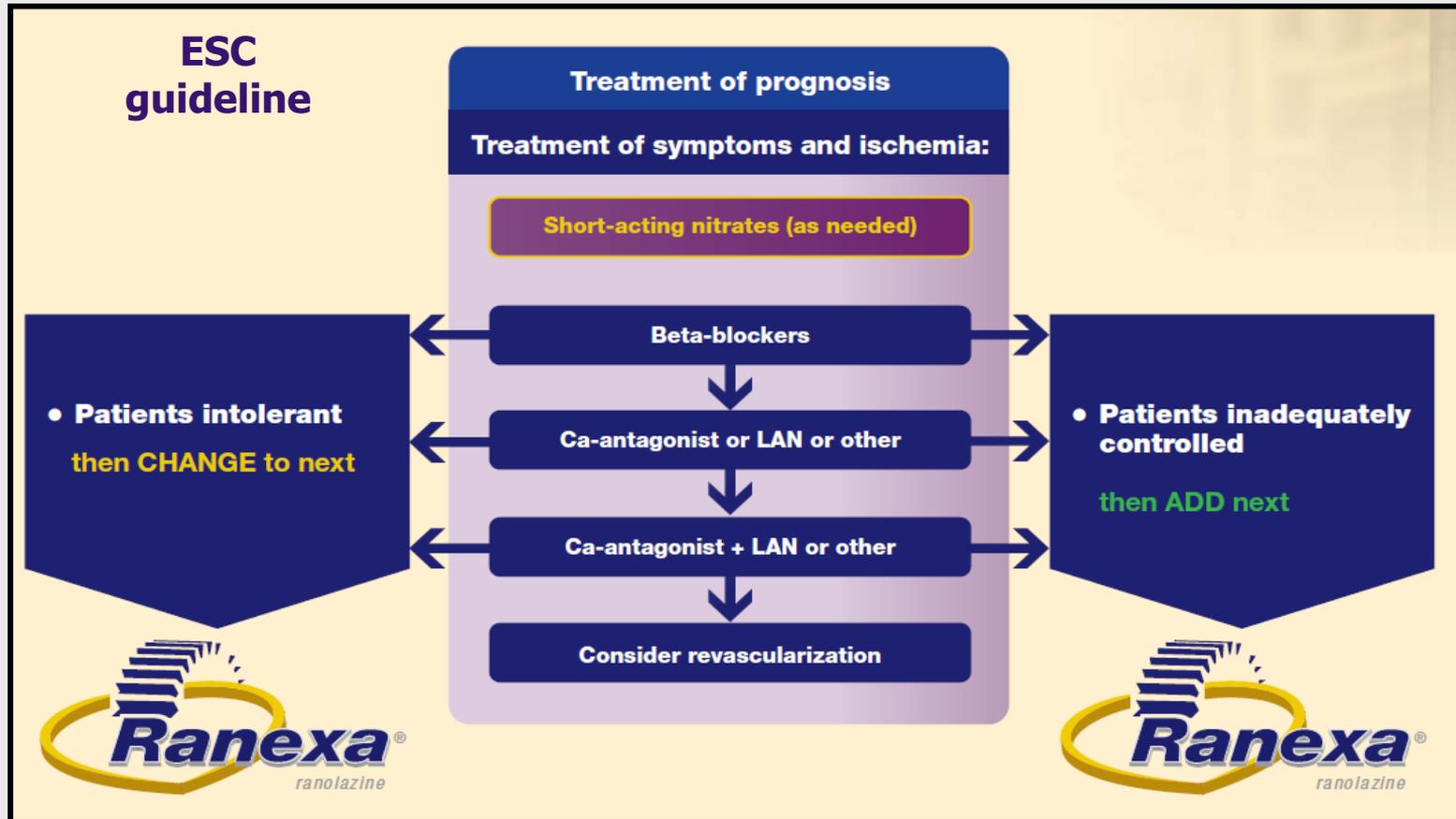
***ESC stable angina guidelines: basic treatment/education***

**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

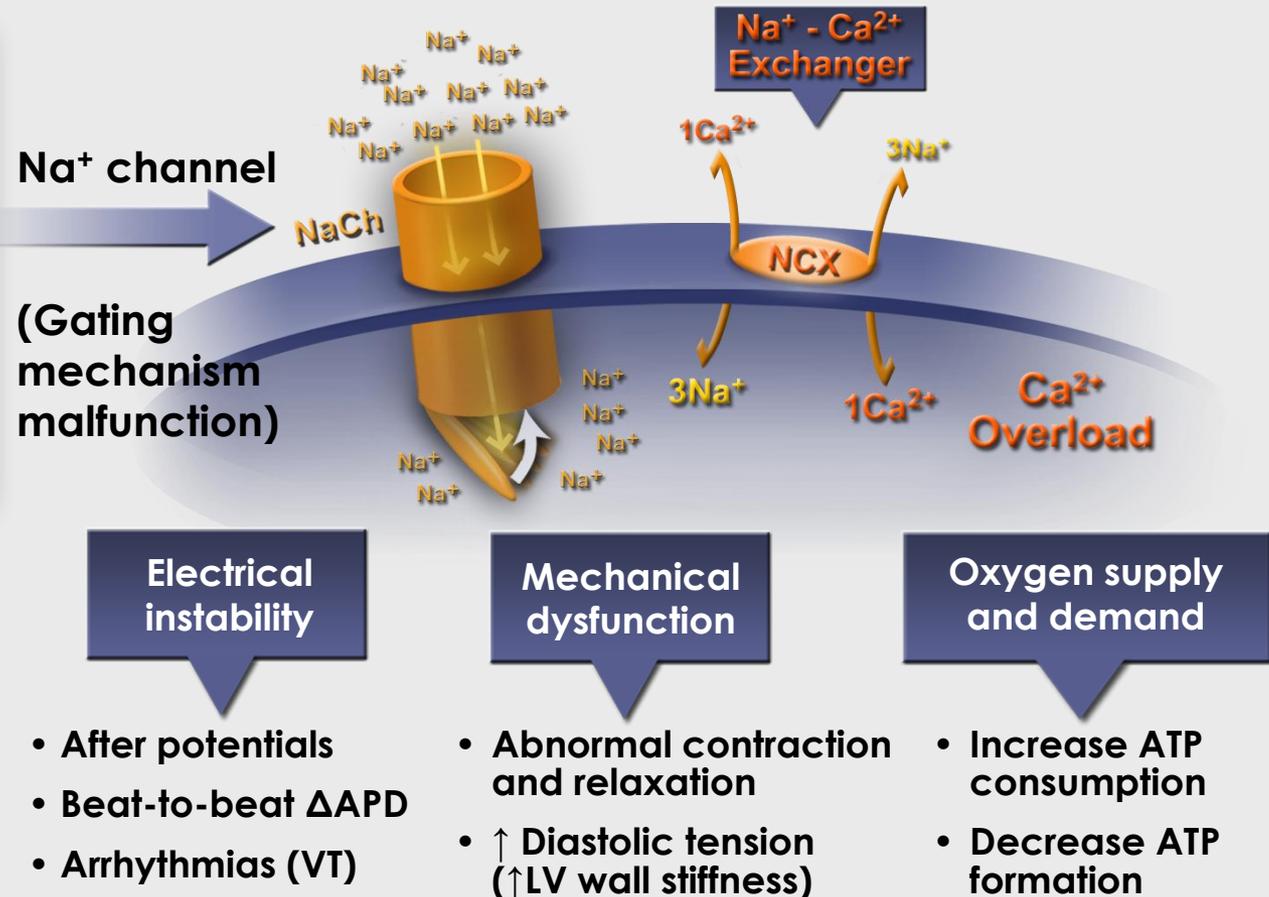
- Use either a beta-blocker or a calcium channel blocker as **first-line** treatment for stable angina
- If symptoms are not satisfactorily controlled on a beta-blocker or a calcium channel blocker, consider using a **combination of the two**
- For people on **beta-blocker or calcium channel blocker 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 O<sub>2</sub> species, ischaemic metabolites)
- **Toxins and drugs**  
(ATX-II, pyrethroid, DPI201-106, etc.)



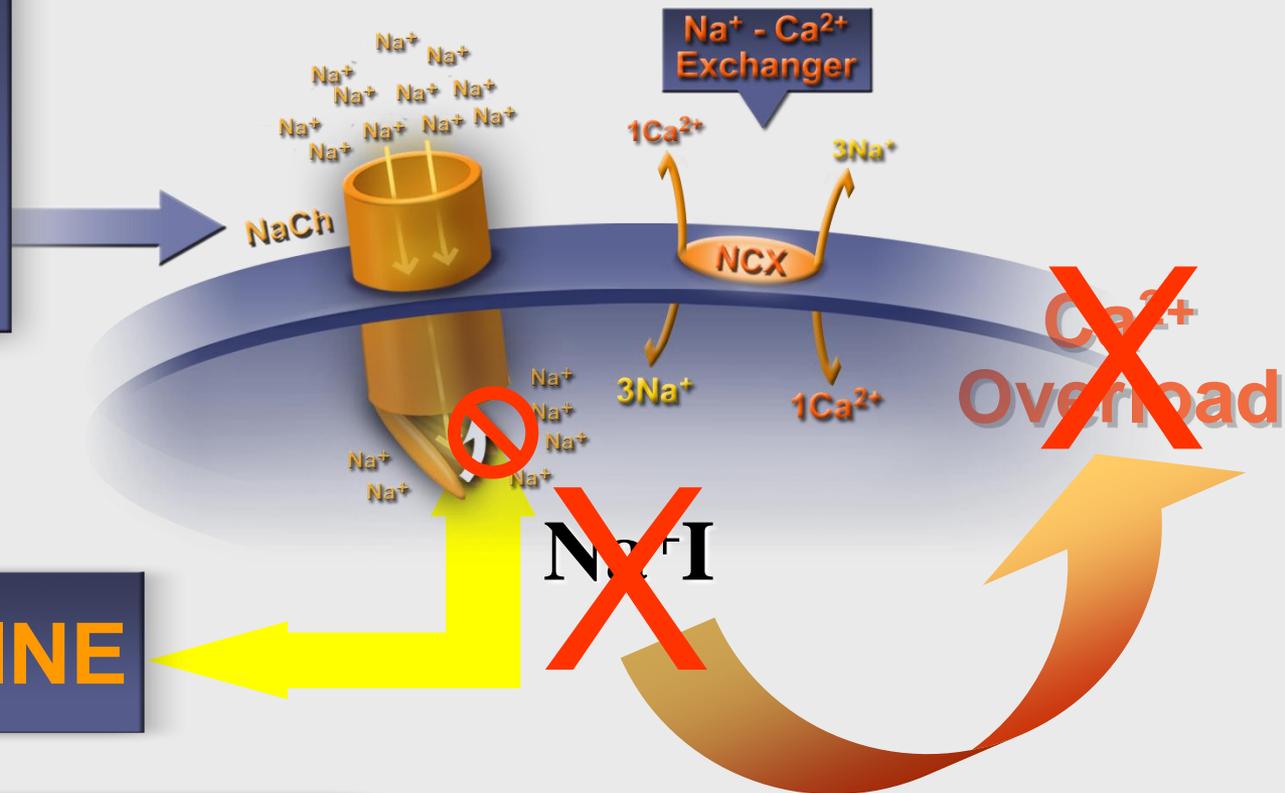
## Diseases/conditions

### 1. Acquired

- Hypoxia/ROS
- Ischaemia
- Heart failure
- CaMKII, AMPK

### 2. Congenital (inherited)

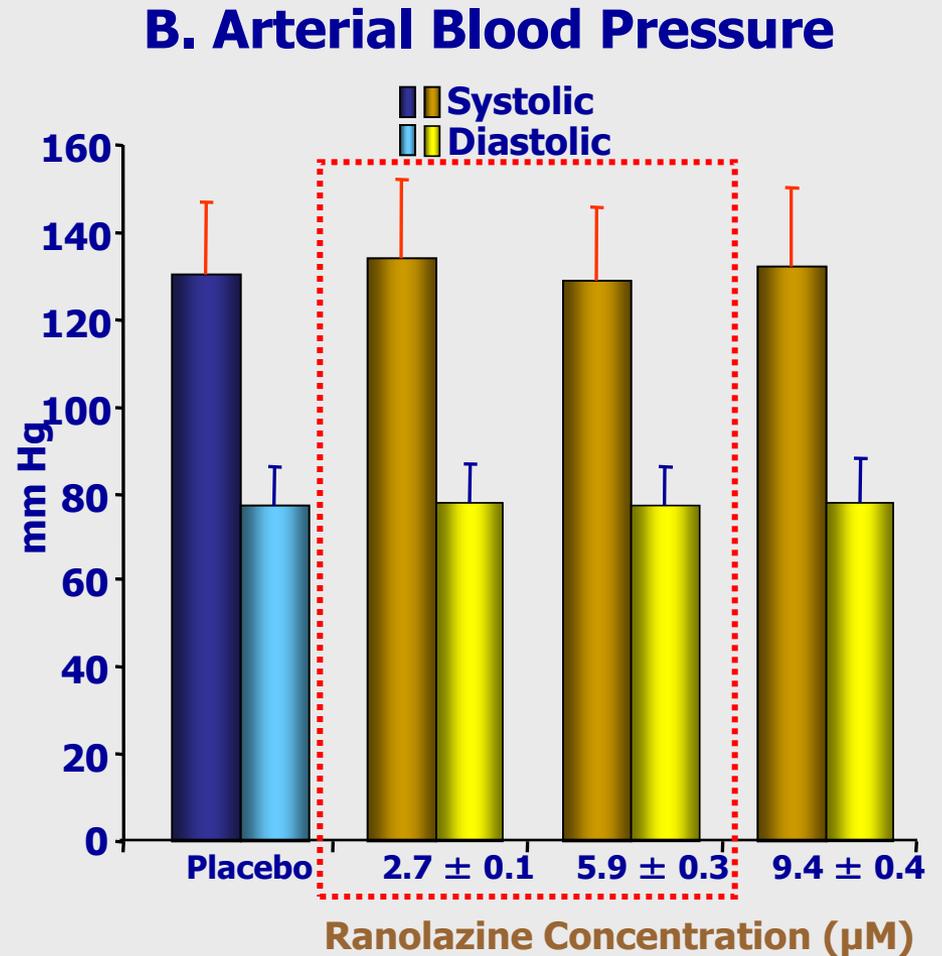
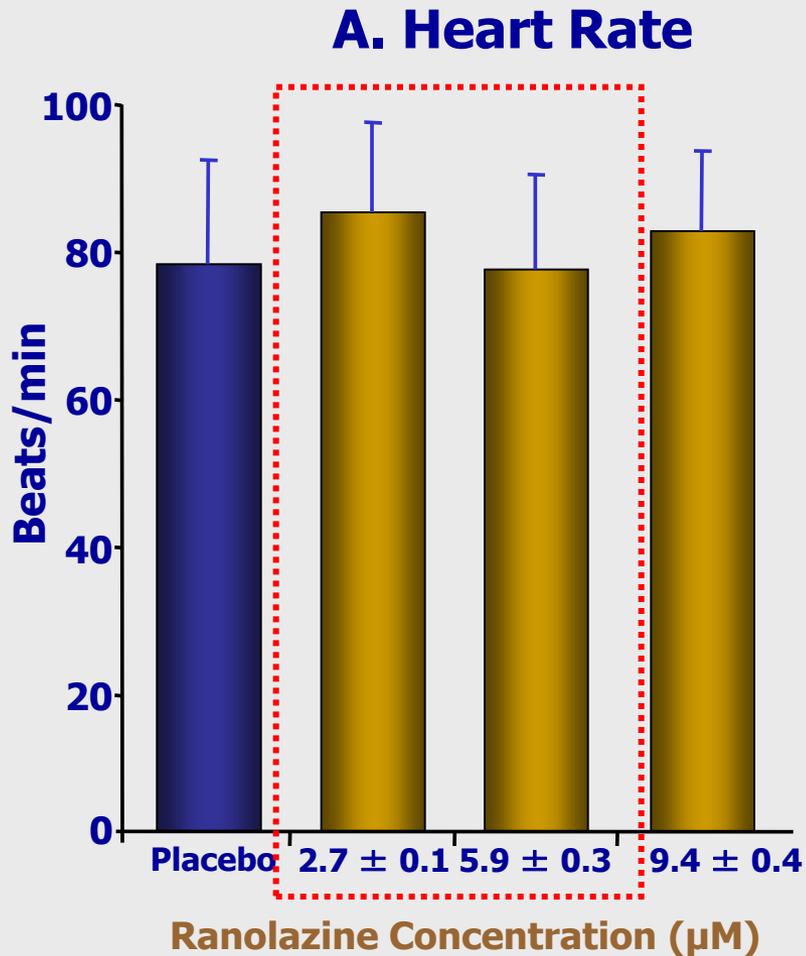
- **Cardiac: SCN5A (LQT3)**
- Sk Muscle: SCN4A (Myotonias)
- CNS: SCN1A, 2A, 3A (seizures)
- PNS: SCN9A (neuropathic pain)



**RANOLAZINE**

Altered Na-channel gating  
leads to  $\text{Ca}^{2+}$ - overload

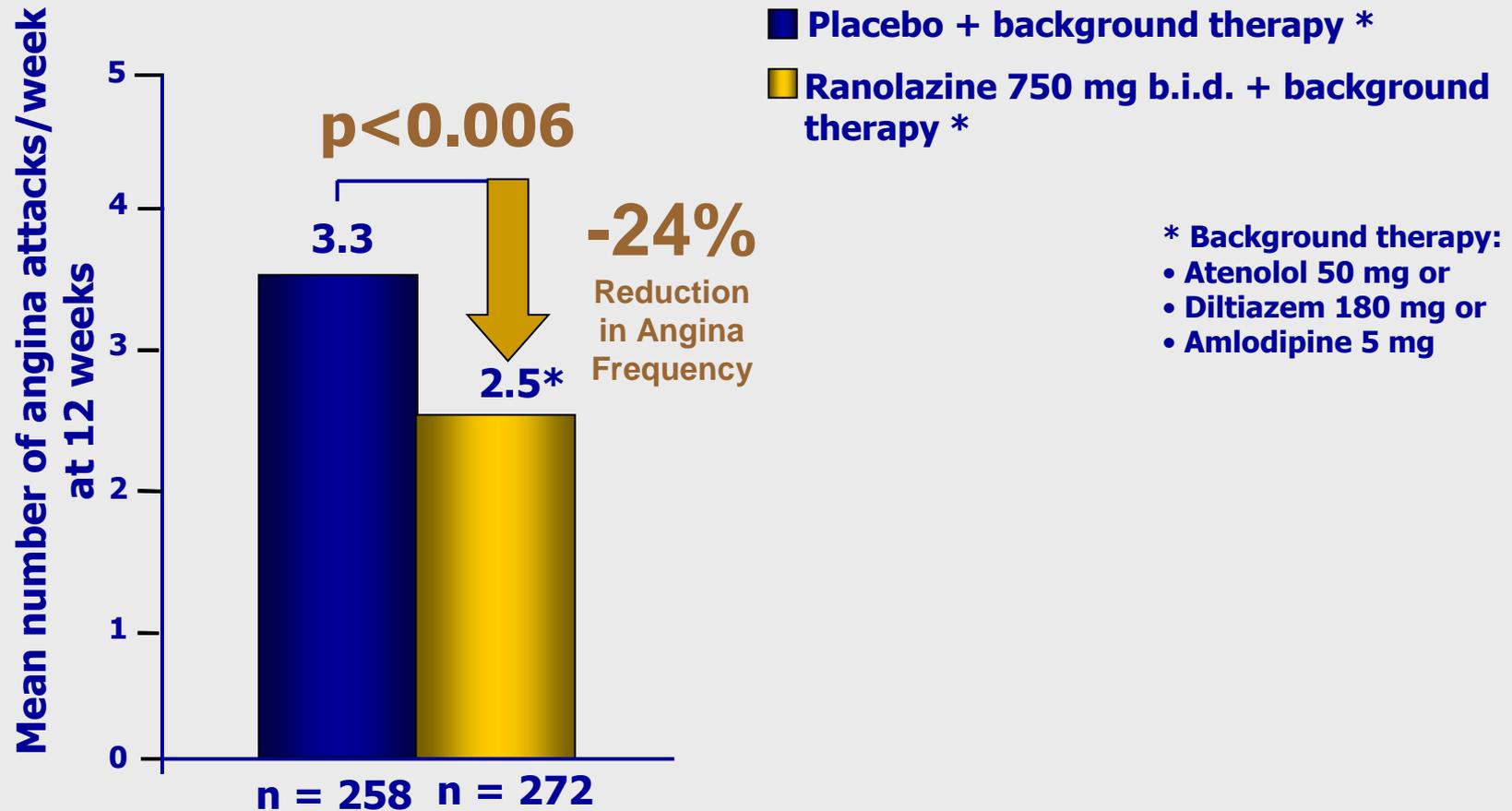
# Ranolazine Clinical Studies



Treatment duration: 1 week; number of patients: 191  
Therapeutic concentrations are  $\sim 750 - 4,000$  ng/ml ( $\sim 2$  to  $8$   $\mu\text{M}$ )

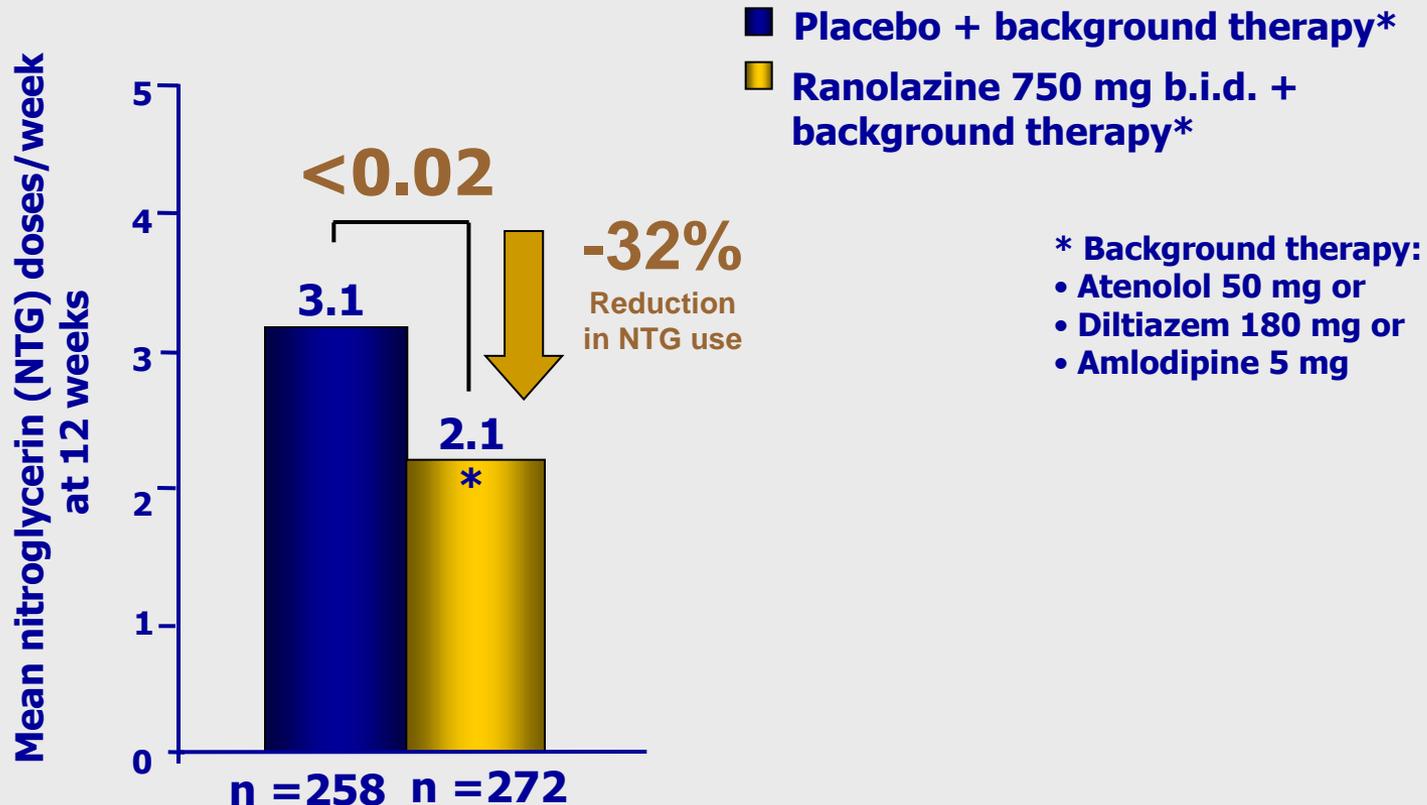
On top of  $\beta$ -blockers or Ca-antagonist

## CARISA



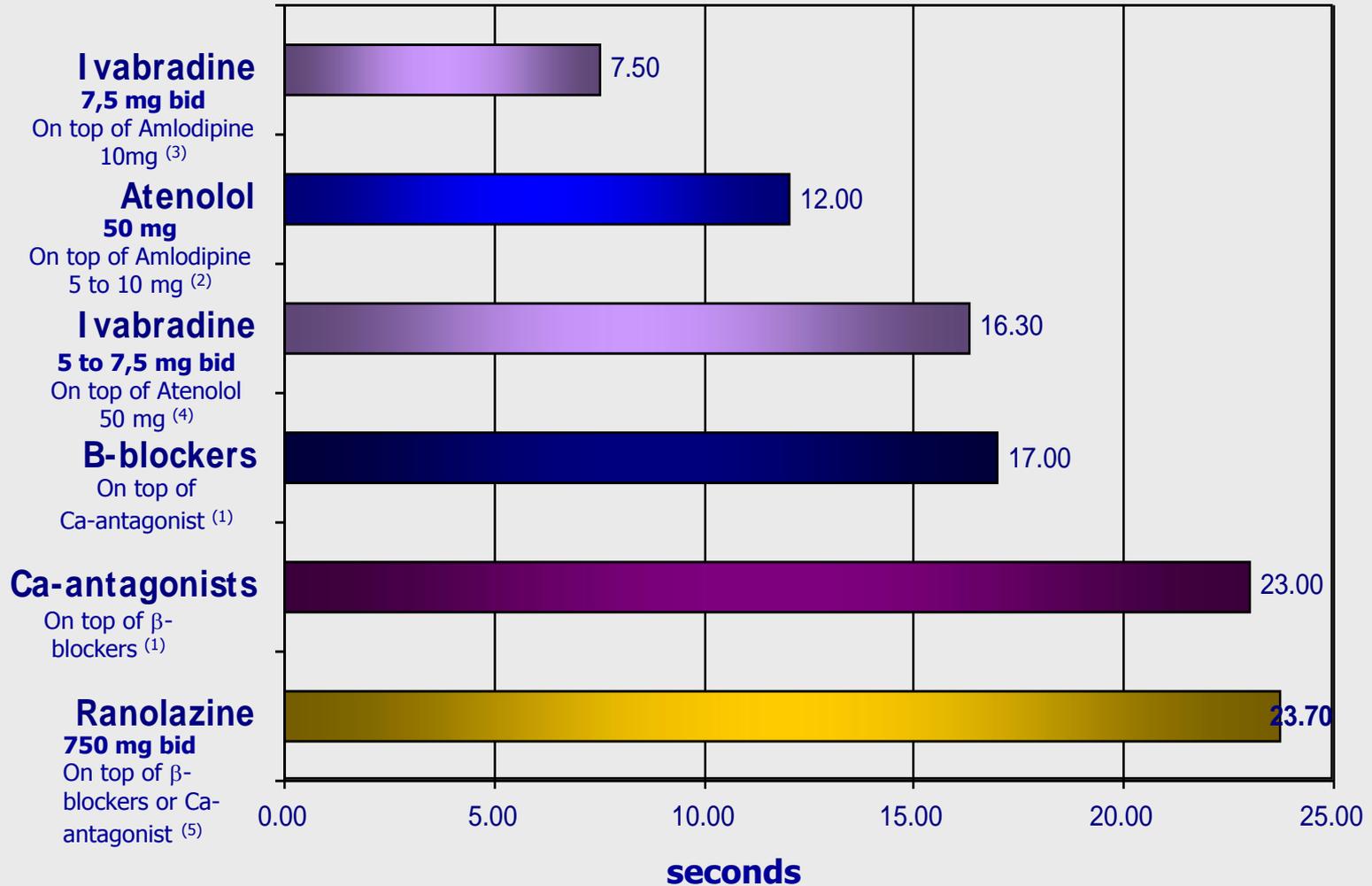
## On top of $\beta$ -blockers or Ca-antagonist

### CARISA



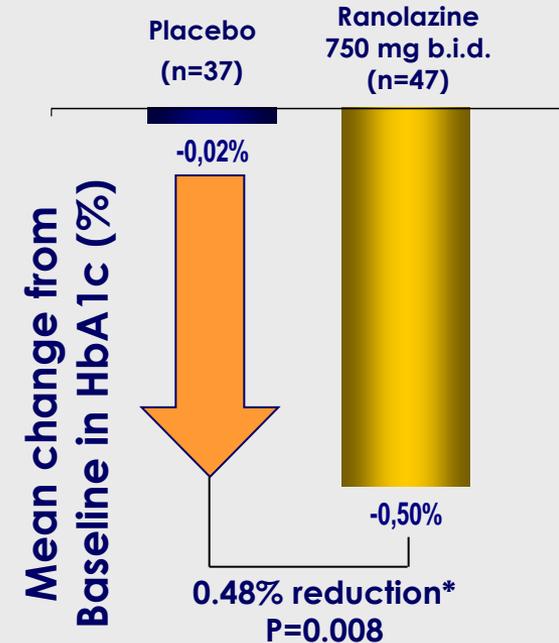
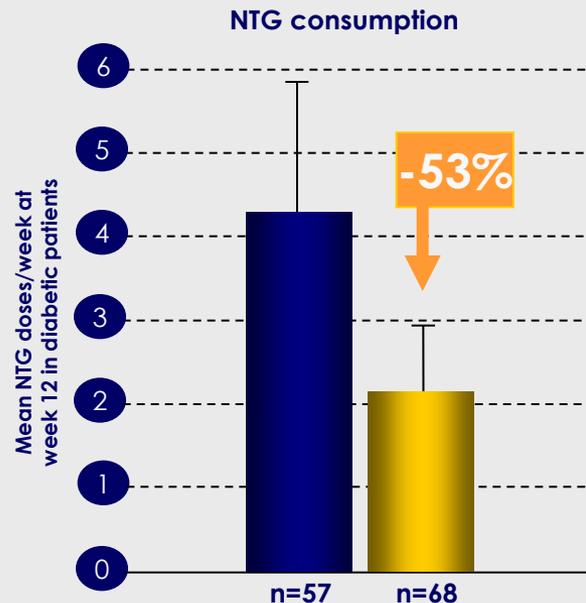
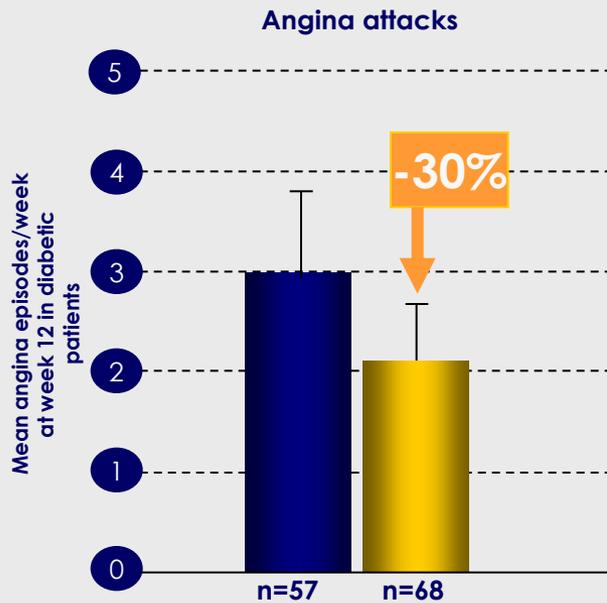
## CARISA

### Mean increase in exercise time in ADD ON



## In patients with diabetes

### CARISA Diabetes



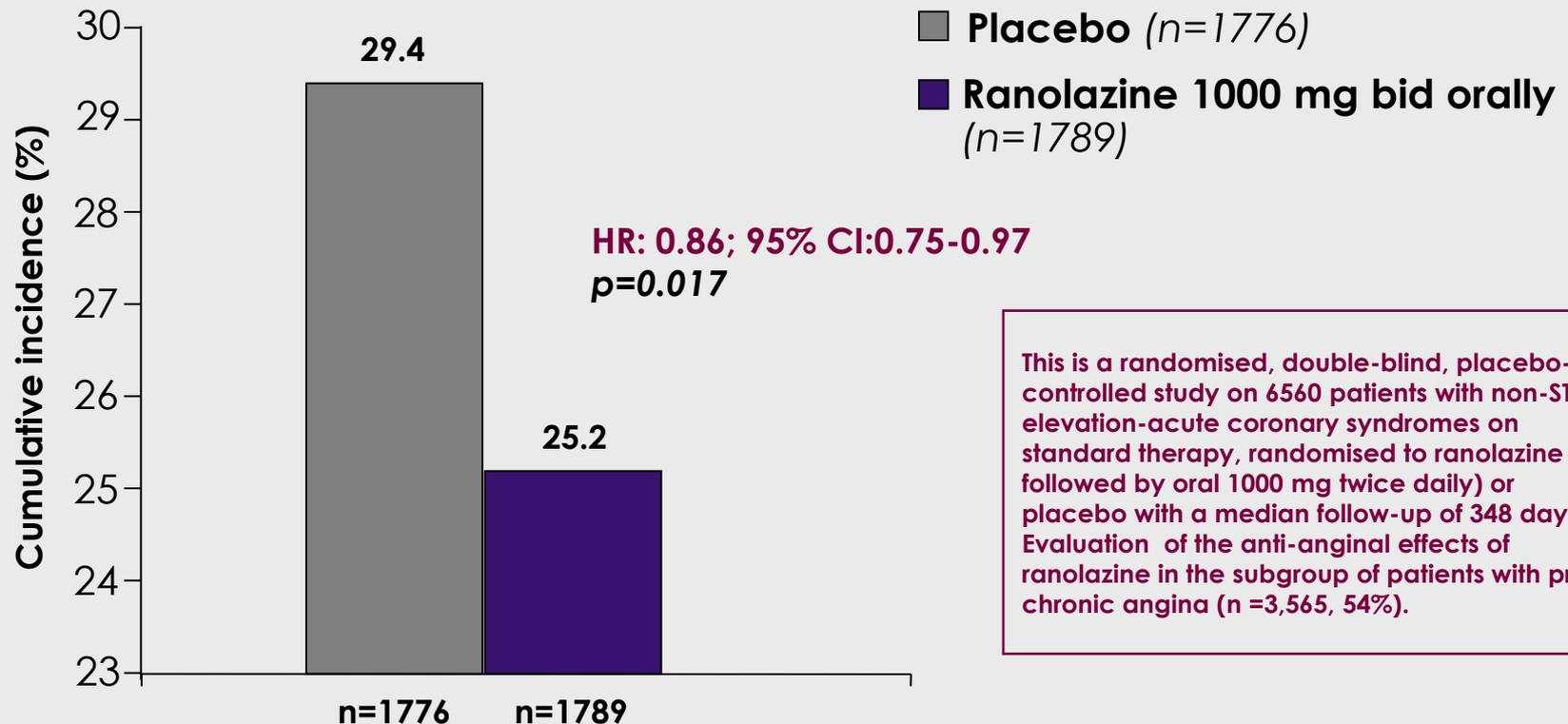
■ Placebo + background therapy od\*\*  
■ Ranexa® 750 mg bid + background therapy od\*\*

**\*\*Background therapy:**

- Atenolol 50 mg (43%) or Amlodipine 5 mg (31%) or Diltiazem 180 mg (26%)
- Antidiabetic drugs (100%)

## MERLIN-TIMI 36: primary end-point in patients with ACS and prior history of angina

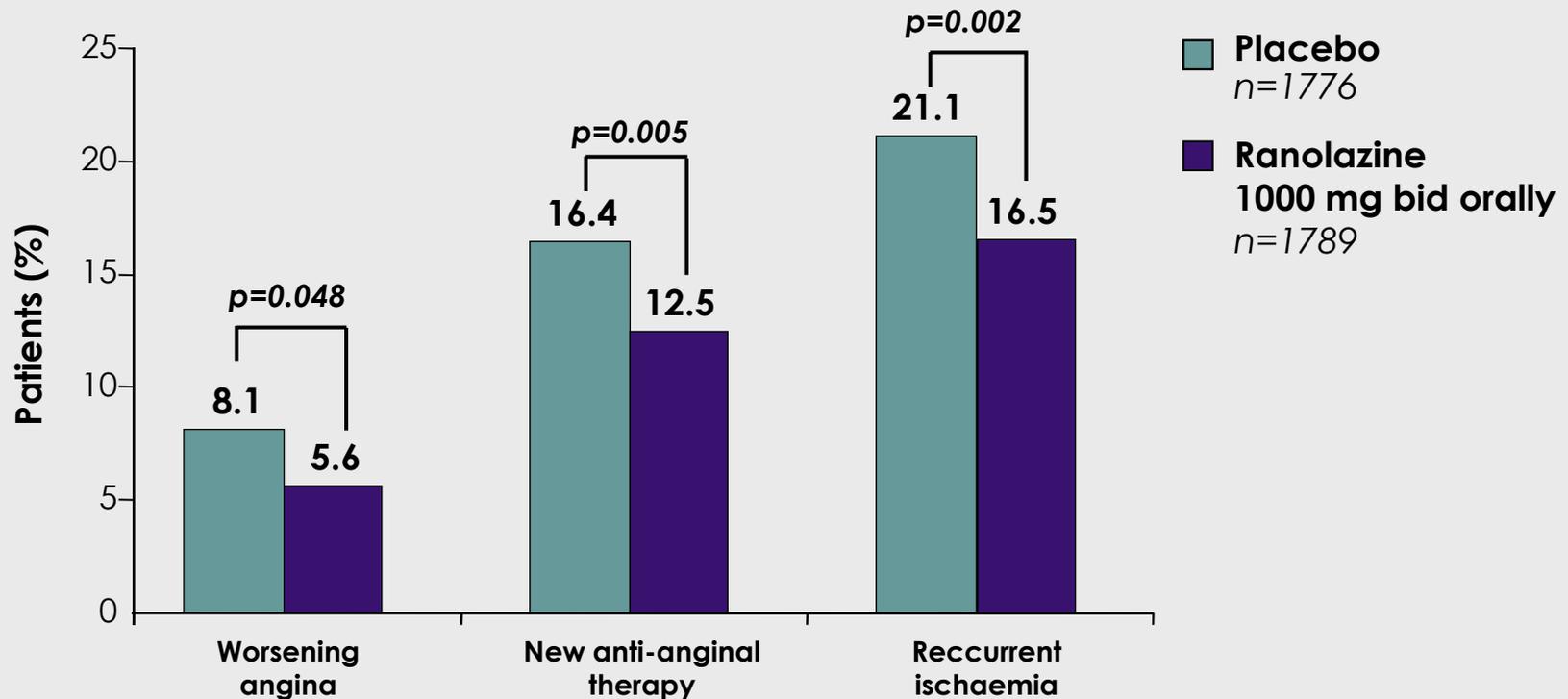
CV death, MI, or recurrent ischaemia (% at 12 months)



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%).

## MERLIN-TIMI 36: anti-anginal effect of ranolazine

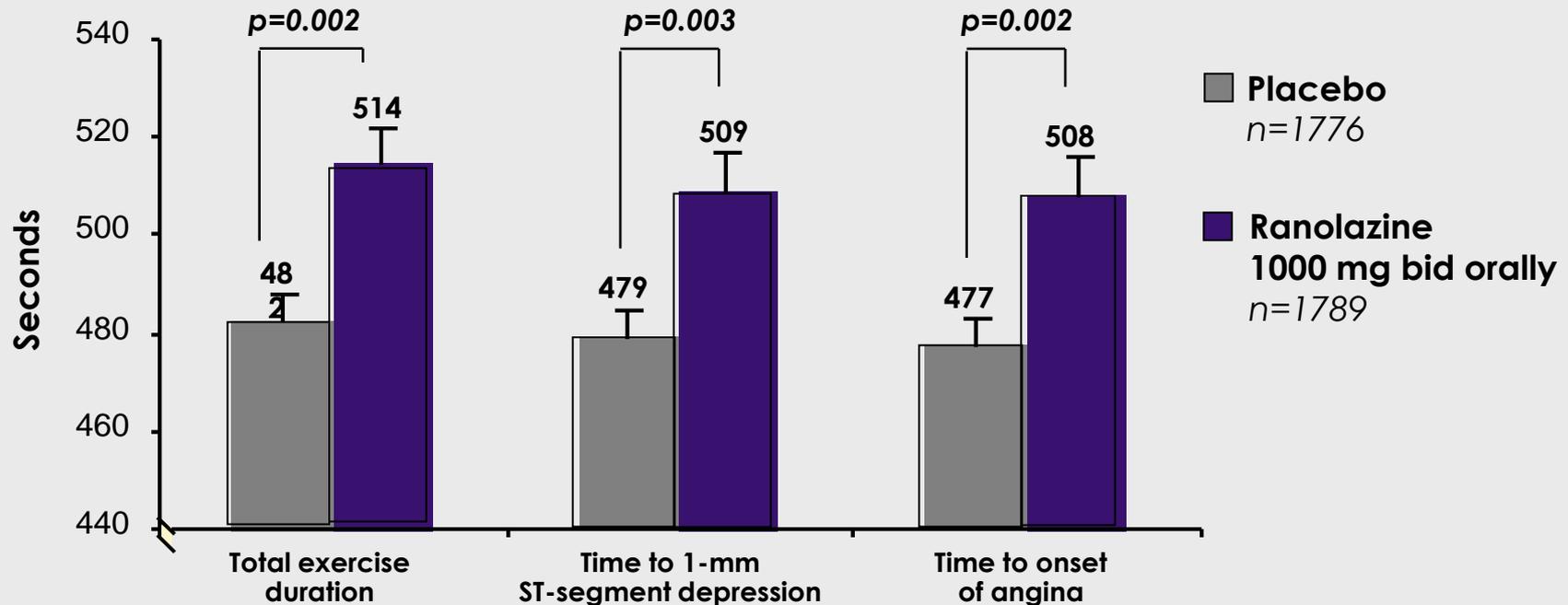
Angina and recurrent ischaemia in patients with a history of chronic angina, with an acute coronary syndrome



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%).

## MERLIN-TIMI 36: exercise performance in patients with ACS and prior history of angina

ETT performance at 8 months

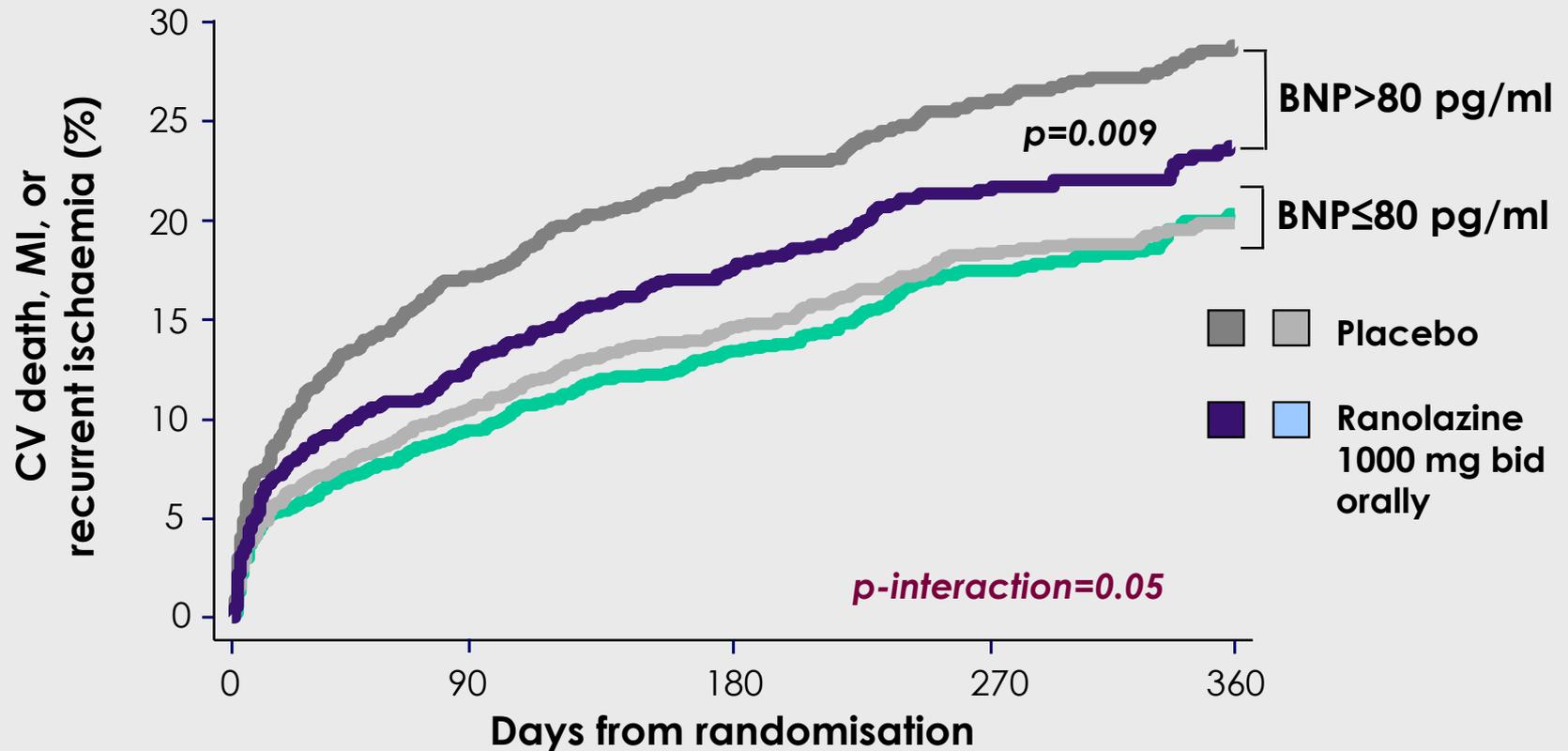


ETT: exercise treadmill test

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%).

## Baseline BNP and effect of ranolazine

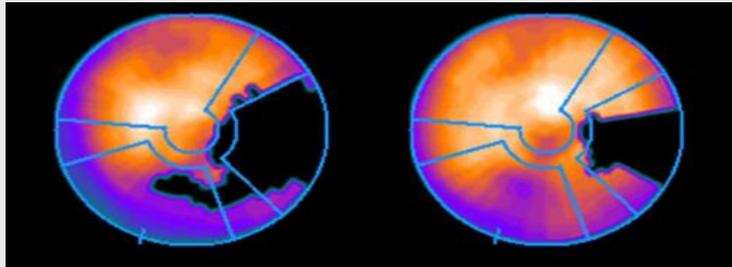
Cumulative incidence of primary end-points stratified by BNP concentration



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).

## with CAD and chronic angina treated with Ranolazine

### *Exploratory study in 20 patients with CAD and angina*



*\*PDS: perfusion defect size*

<b>During exercise Before RAN</b>	<b>During exercise After RAN (3-4 wks)</b>
<b>PDS* = 25% of LV</b>	<b>PDS* = 11% of LV</b>
<b>Peak HR = 142 bpm</b>	<b>Peak HR = 142 bpm</b>

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**

## Ranolazine anti-anginal effect: comparison with other anti-anginal agents

Anti-anginal drugs	Heart rate	Blood pressure	Anti-anginal effect
<b>Ranolazine</b>	No significant effect <sup>1,2</sup>	No significant effect <sup>1,2</sup>	<ul style="list-style-type: none"> <li>Improved diastolic tone <sup>1,2</sup></li> <li>Improved coronary blood flow <sup>1</sup></li> <li>Potential antiarrhythmic effects <sup>1,2</sup></li> </ul>
<b>Beta-blockers</b>	Decrease <sup>4</sup>	Decrease <sup>4</sup>	<ul style="list-style-type: none"> <li>Decrease O<sub>2</sub> demand, primarily slowing heart rate <sup>3</sup></li> </ul>
<b>Calcium channel blockers</b> <ul style="list-style-type: none"> <li>Dihydropyridine</li> <li>Verapamil/diltiazem</li> </ul>	Increase <sup>4</sup> Decrease <sup>4</sup>	Decrease <sup>4</sup> Decrease <sup>4</sup>	<ul style="list-style-type: none"> <li>Reduction in myocardial O<sub>2</sub> demand<sup>3</sup></li> <li>Increase in O<sub>2</sub> supply <sup>3</sup></li> <li>Relaxes systemic and coronary vascular smooth muscle <sup>3</sup></li> </ul>
<b>Long-acting nitrate</b>	No effect <sup>4</sup>	Decrease <sup>4</sup>	<ul style="list-style-type: none"> <li>Relax vascular smooth muscle <sup>3</sup></li> <li>Reduces myocardial wall tension and O<sub>2</sub> requirements <sup>3</sup></li> </ul>
<b>Trimetazidine</b>	No significant effect <sup>5</sup>	No significant effect <sup>5</sup>	<ul style="list-style-type: none"> <li>Decreases fatty acid oxidation, stimulates glucose utilisation <sup>3,5</sup></li> </ul>
<b>Ivabradine</b>	Decrease <sup>6</sup>	No significant effect <sup>6</sup>	<ul style="list-style-type: none"> <li>Decrease O<sub>2</sub> consumption <sup>6</sup></li> </ul>

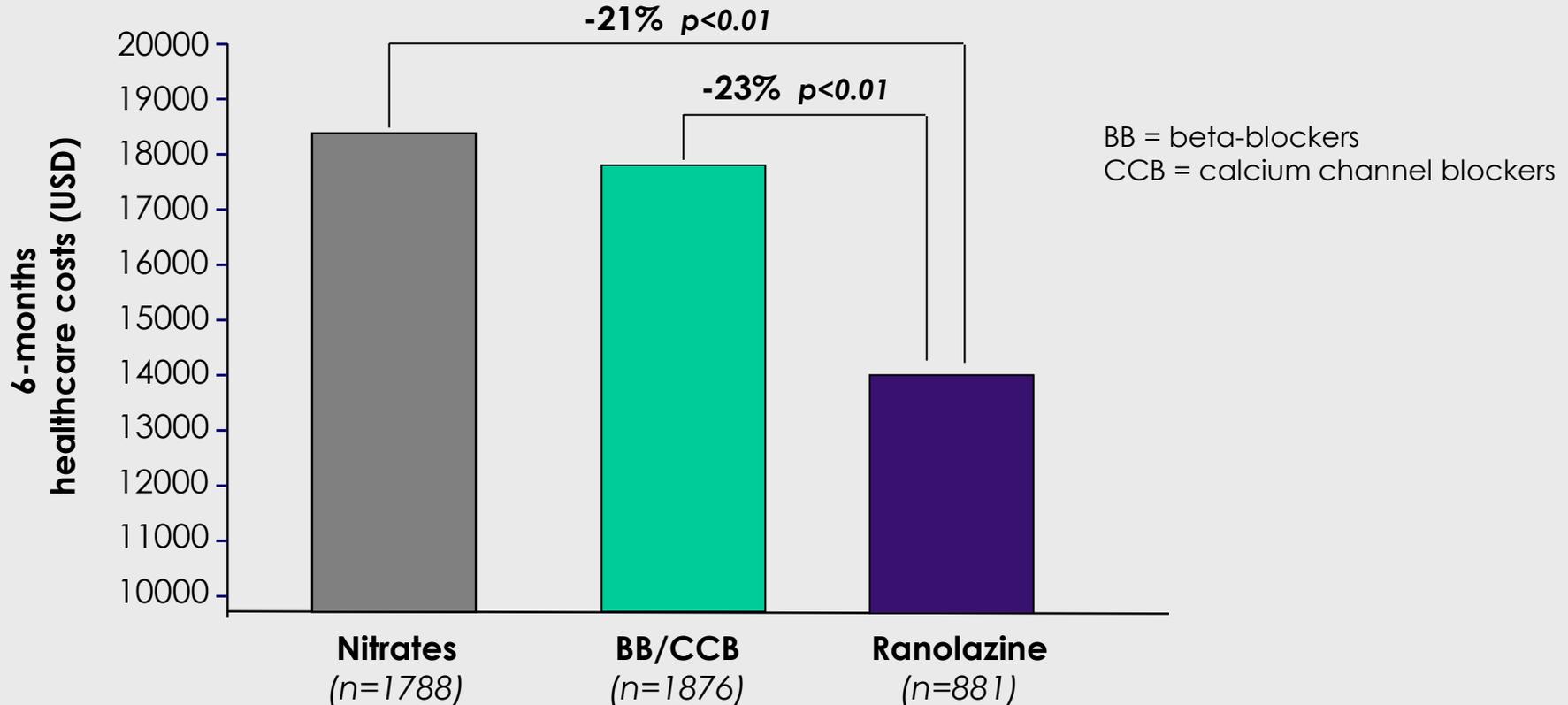
1. *Clin Res Cardiol* 2008;97(4):222-6. 2. Revised June 2011. 3. *Braunwald's Heart Disease - A Textbook of Cardiovascular Medicine*. Eighth edition 4. *Scardiol lin* 2008;26:603-14 5. *Am J Cardiol* 2006; 98 (suppl):19J-24J. 6. *Ivabradine*. *SmPC*.

## 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<sup>®</sup> 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

N° planned sites: 100

**ITALY: 31 sites**

**GREECE: 5 sites**

**AUSTRIA: 3 sites**

**SPAIN: 27 sites**

**GERMANY: 10 sites**

**SWITZERLAND: 3 sites**

**IRELAND: 7 sites**

**UK: 8 sites**

**ALBANIA: 3 sites**

**HOLLAND: 3 sites**

**1216 PATIENTS HAVE TO BE RANDOMISED**

# STUDY END-POINTS

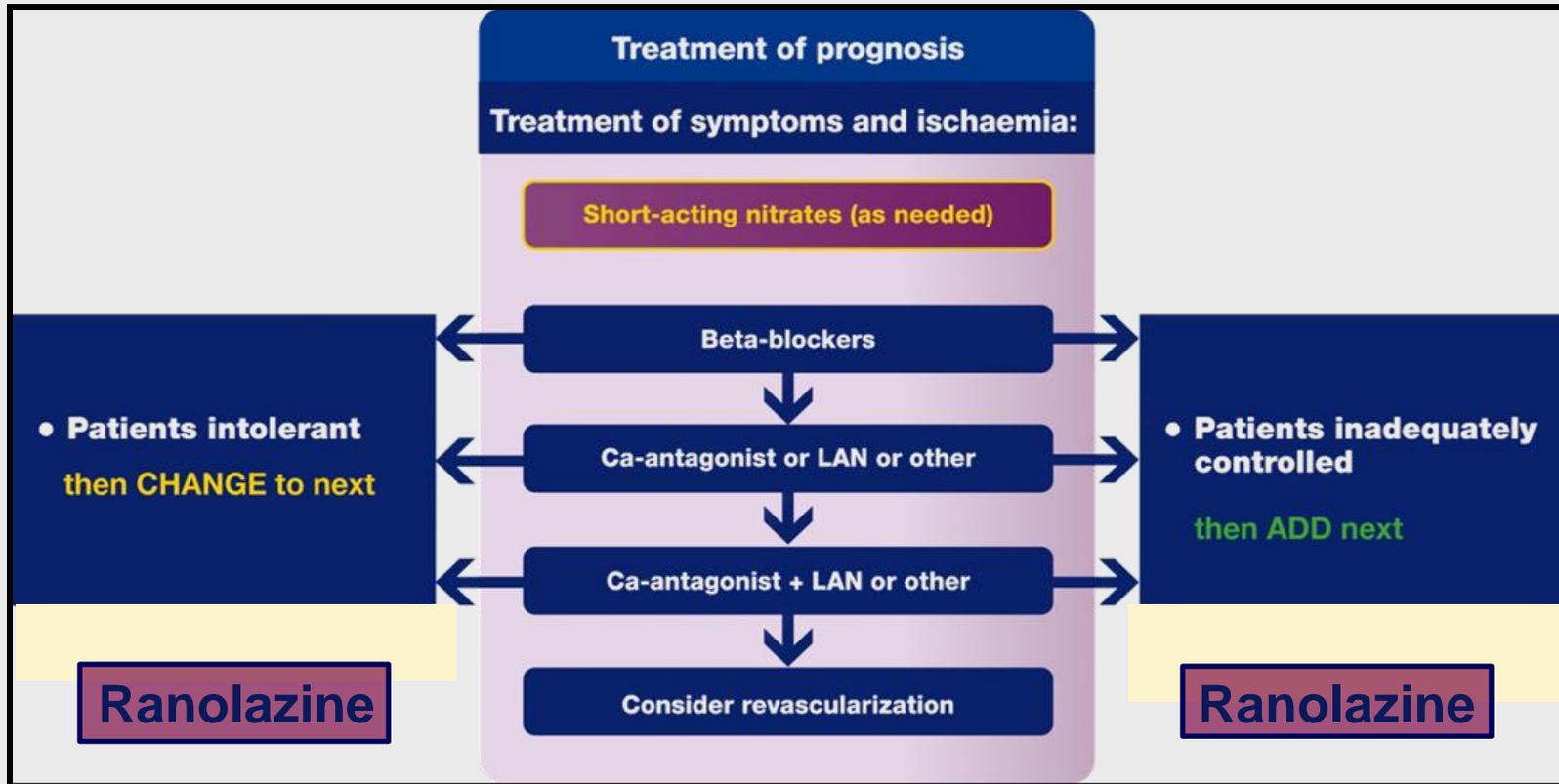
## PRIMARY:

- 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





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## Independently of comorbidities and previous treatment

Stable Angina Patients with:	Add Ranexa
Hypertension	√
Myocardial infarction	√
Heart Failure	√
Diabetes	√
Acute Coronary Syndrome	√
Prior CABG	√
Prior MI	√
Dyslipidaemia	√
Patients treated with:	Add Ranexa
β- blockers	√
Calcium Channel blockers	√
Long acting nitrates	√

## Posology

- 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