Manejo clínico del paciente con cardiopatía isquémica crónica y comorbilidades asociadas

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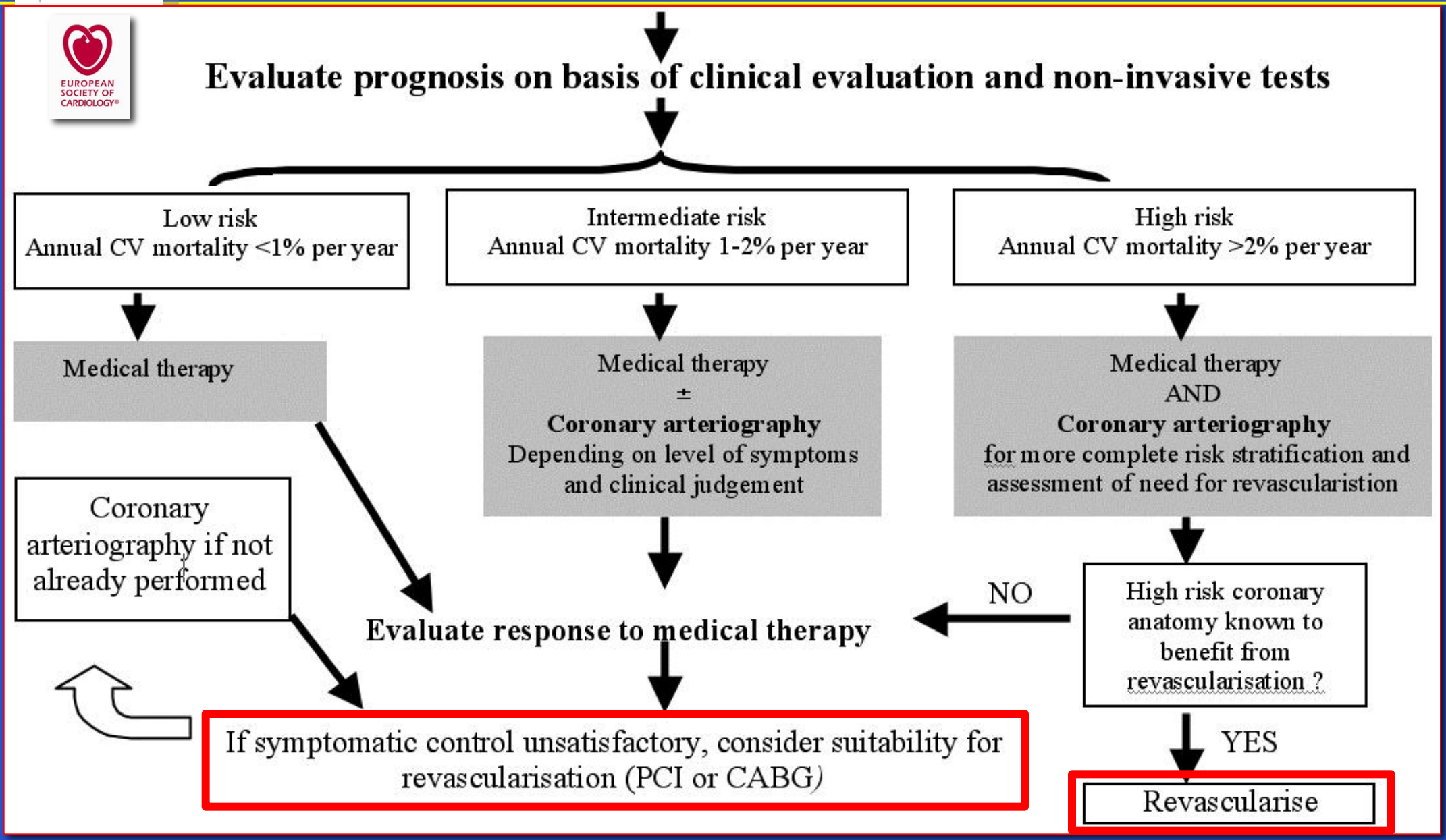
Starting Point

Chronic ischemic heart disease and comorbidities



ESC Stable Angina Guidelines Eur Heart J 2006;27:1341

Treatments aimed at Improving Prognosis

Aspirin 75-150 mg od → **Contraindications** → **Clopidogrel**

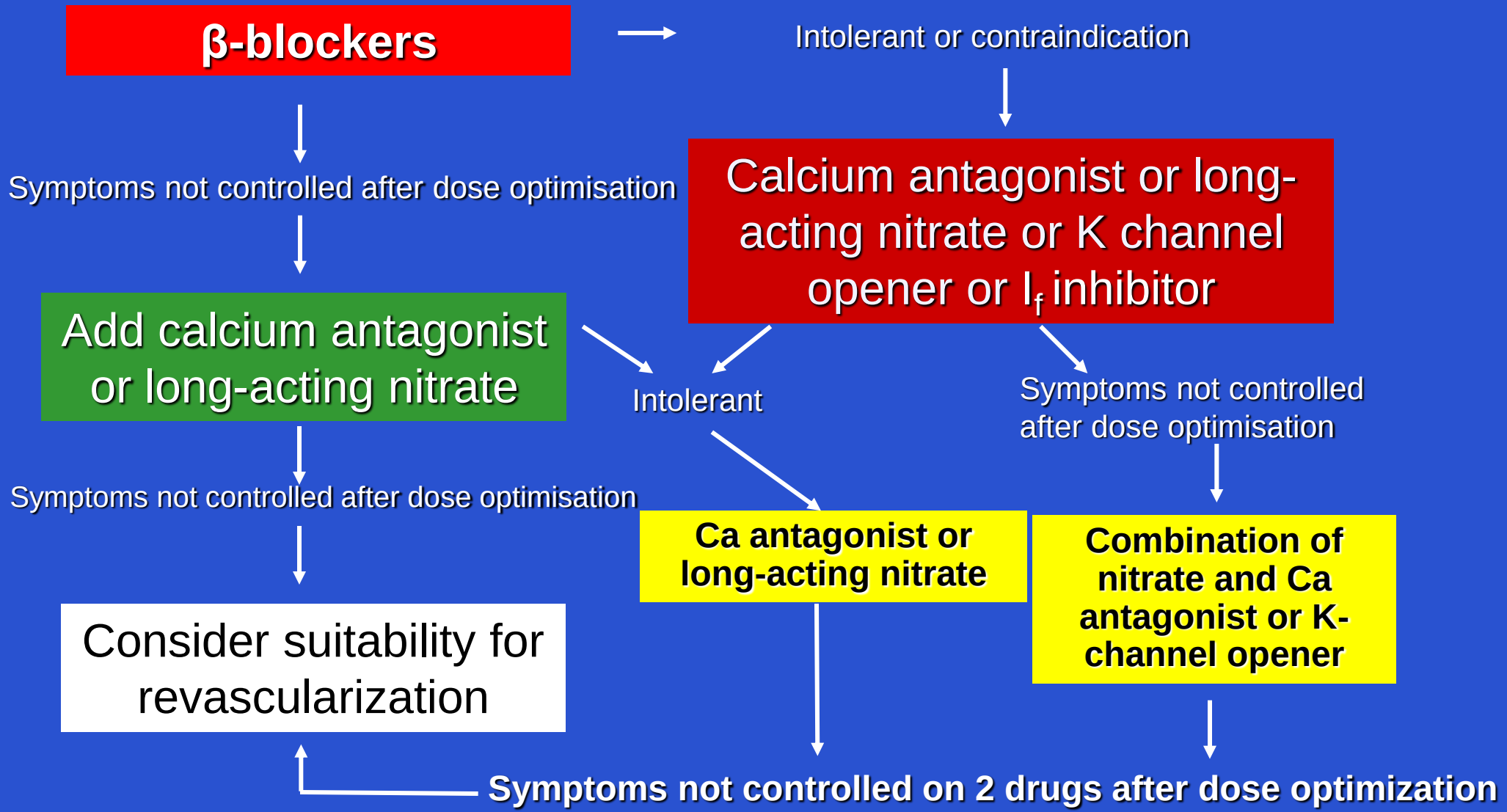
Statin → **Intolerant / contraindications** → **Lower dose / alternative agent**

ACEI in proven CVD

β-blocker in post MI

ESC Guidelines Stable Angina Eur Heart J. 2006; 27:1341

Treatments aimed at Symptom / Ischemia Relief



ESC Guidelines Stable Angina Eur Heart J. 2006; 27:1341

The problem of Comorbidities

Comorbidities in Chronic Ischemic Heart Disease

CLARIFY	All	Angina (22%)	No angina
Hypertension, %	70.9	78.4	68.8
Diabetes, %	29.3	28.9	29.4
Dyslipidemia, %	74.9	78.6	73.9
PAD, %	9.8	12.9	8.9
History of stroke, %	4.0	5.3	3.6
History of TIA, %	3.1	4.9	2.5
HF	14.9	39.7	7.8
History of atrial fibrillation/flutter	7.0	7.4	6.9
Asthma, COPD, %	7.4	9.2	6.9

Steg G, ECC 2011

Common problems related with comorbidities

- Worse prognosis
- Diagnosis more difficult
- Need of specific treatment
- Worse compliance
- Limitation of effective antiischemic treatments

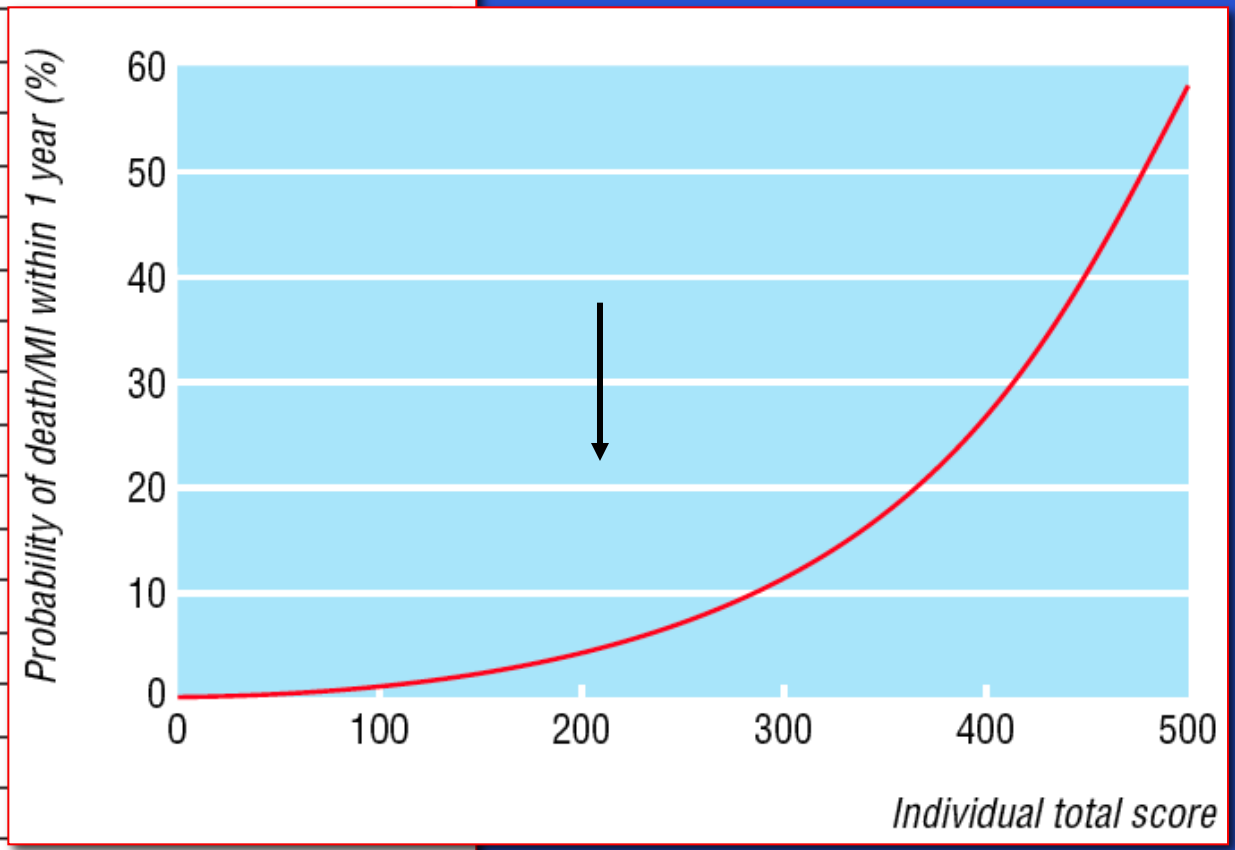
Chronic ischemic heart disease and comorbidities

EHS Stable angina

BMJ 2006;332:262

Table 6 Score sheet to calculate risk score for patients presenting with stable angina

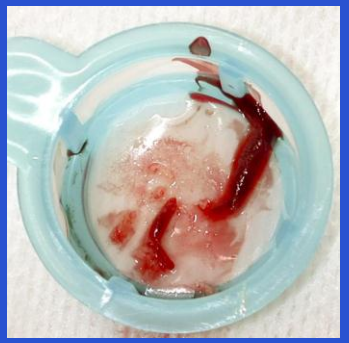
Risk factor	Score contribution	Individual's score
Comorbidity*		
No	0	
Yes	86	
Diabetes		
No	0	
Yes	57	
Angina score		
Class I	0	
Class II	54	
Class III	91	
Duration of symptoms		
≥6months	0	
<6 months	80	
Abnormal ventricular function		
No	0	
Yes	114	
ST depression or T wave inversion on resting electrocardiogram		
No	0	
Yes	34	
		Total=



EUROPEAN SOCIETY OF CARDIOLOGY®

BICA Study
Bacterial Infection in Culprit Artery in STEMI

- 101 STE-MI <24h in 2 Finnish hospitals
- Thrombus aspiration and DNA analysis to identify bacteria
  - 78% common dental bacteria in 78%
    - 98% viridans (mitis-group) streptococci
  - 0% Bacteriemia
- Ortopantomography
  - 47% Periapical lesions
  - 50% vertical bone pockets



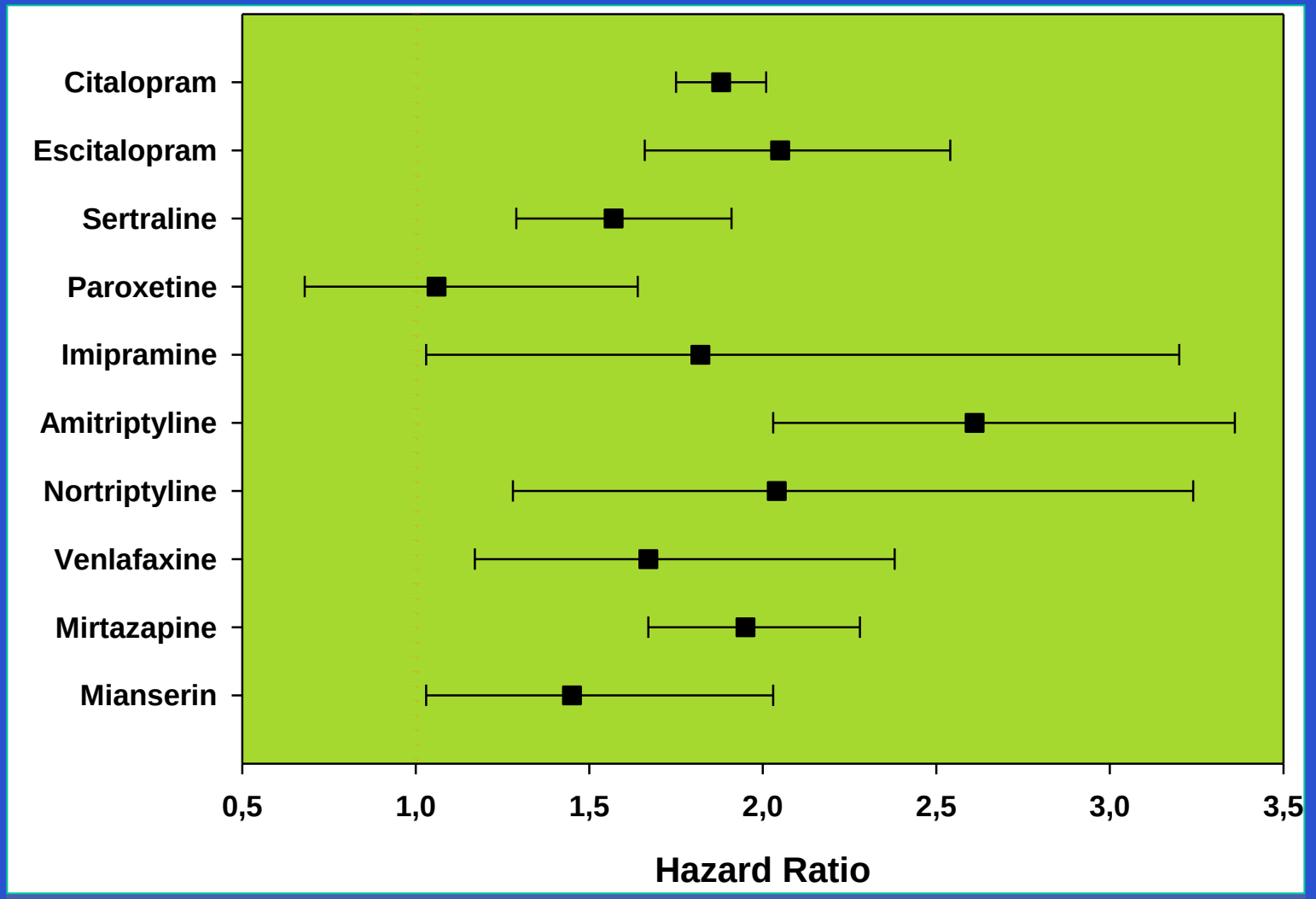
J Mikkelsson, FI, P-5688

Antidepressive Drugs after AMI

Denmark
1997-2006
1st AMI
N=60,131

Anti-depressants
15.9%

FU: 4 y



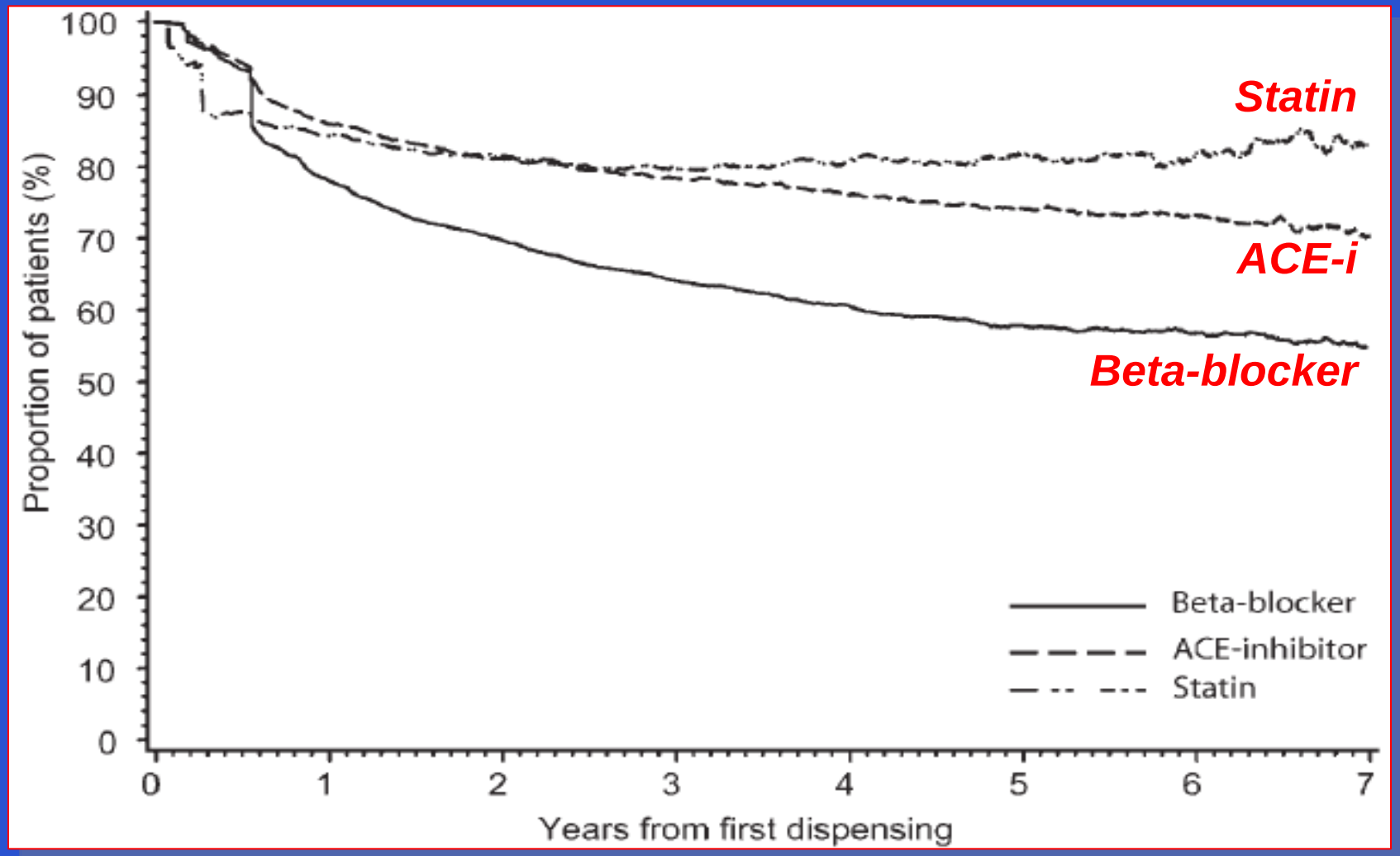
JK Jensen, DK, P-4204

Comorbidities	Importance
Bronchial disease	BB Contraindicated
Peripheral vasc disease	BB Contraindicated
Diabetes, hypercholesterolemia	Prognosis, target for treatment
Heart failure	Veramapil, Diltiazem contraindicated
Atrial Fib	Antithrombotics, Bleeding
Renal failure	Pharmacokinetics
Hypertension	J curve response
Hypotension	Most antiischemic drugs contraindicated
Bradicardia	BB, verapamil, diltiazem contraindicated
Anemia	Antithrombotics, Bleeding
Stroke	Antithrombotics
Infections	Physiopathology
Cancer	Compliance, prognosis, bleeding
Dementia, cognitive disorders	Compliance
Genotype	Individual response to treatment
Constipation	Ca antagonsts contraindicated
Depression	Antidepresive drugs increase mortality

Chronic ischemic heart disease and comorbidities

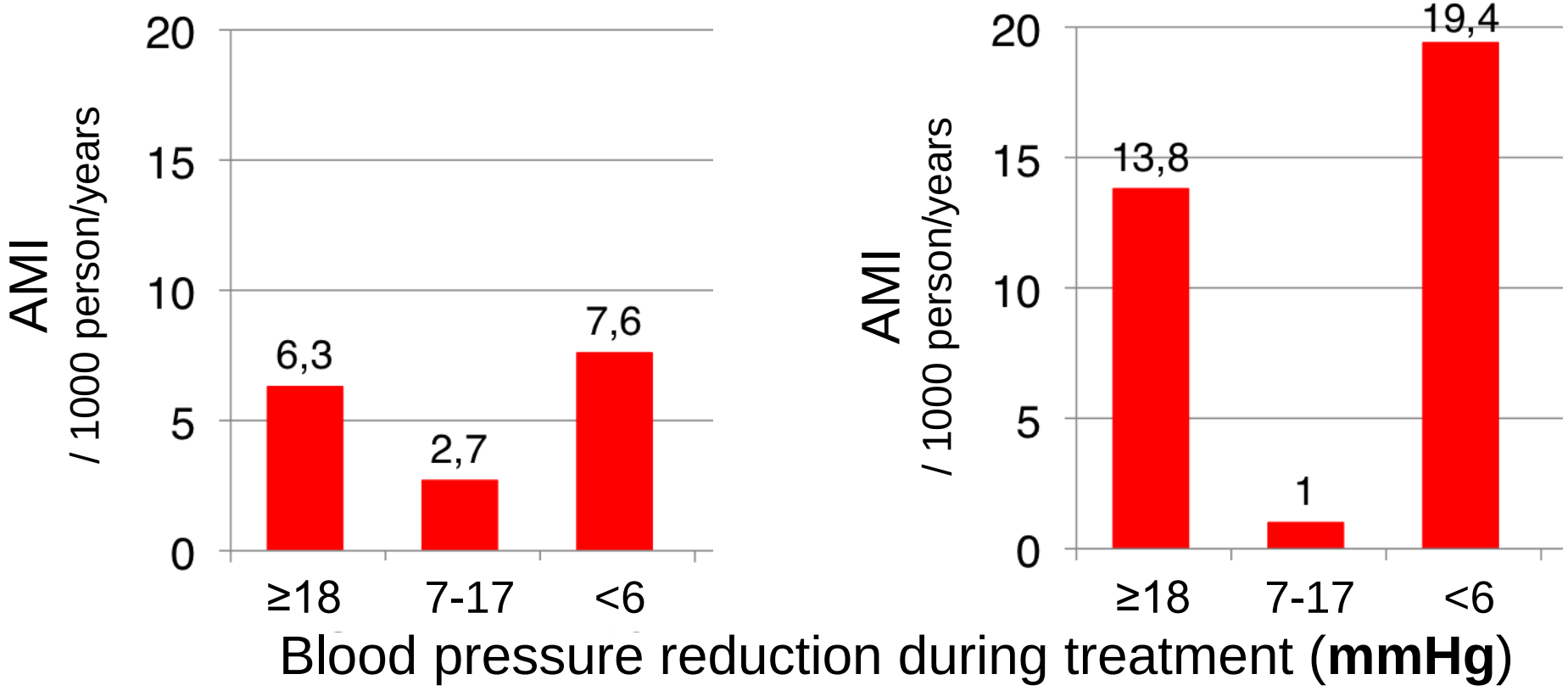
Comorbidities	Importance
Bronchial disease	BB Contraindicated
Heart failure	Veramapil, Diltiazem contraindicated
Hypotension	Most antiischemic drugs contraindicated
Bradicardia	BB, verapamil, diltiazem contraindicated

Discontinuation of treatment



Gislason G. Eur Heart J. 2006;27:1153-1158.

Change in Systolic Blood pressure and Incidence of AMI

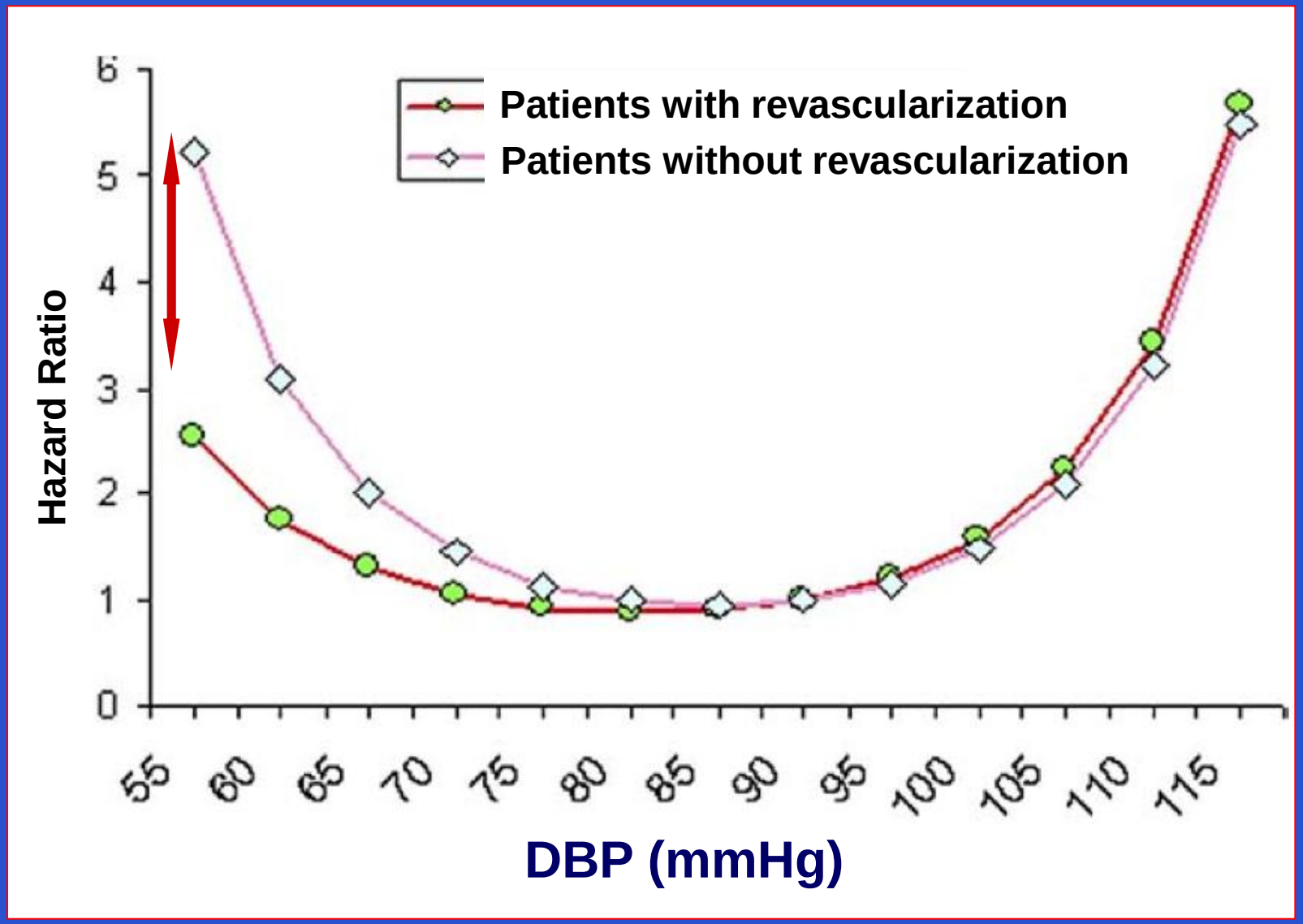


Alderman et al JAMA 1989;261:920 *N= 1765* *BP ≥ 160/85* *Follow-up 4,2y*

Chronic ischemic heart disease and comorbidities

"J curve" between Blood Pressure and Coronary Artery Disease

INVEST
22.500 pts
3y F-up

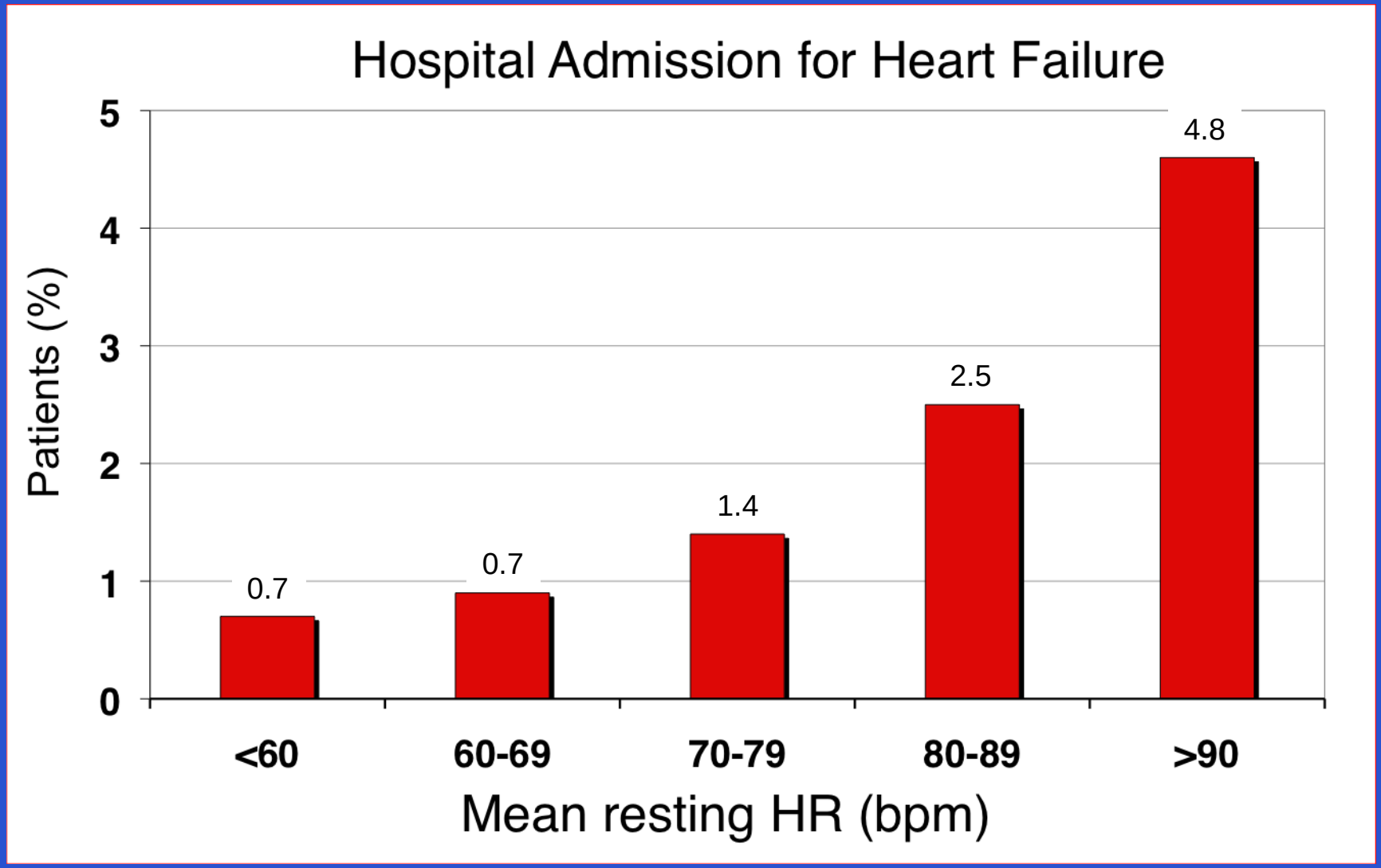


JACC 2009; 54:1827

JAMA 2003;290:2805

Hospitalization for Heart Failure in Stable Angina

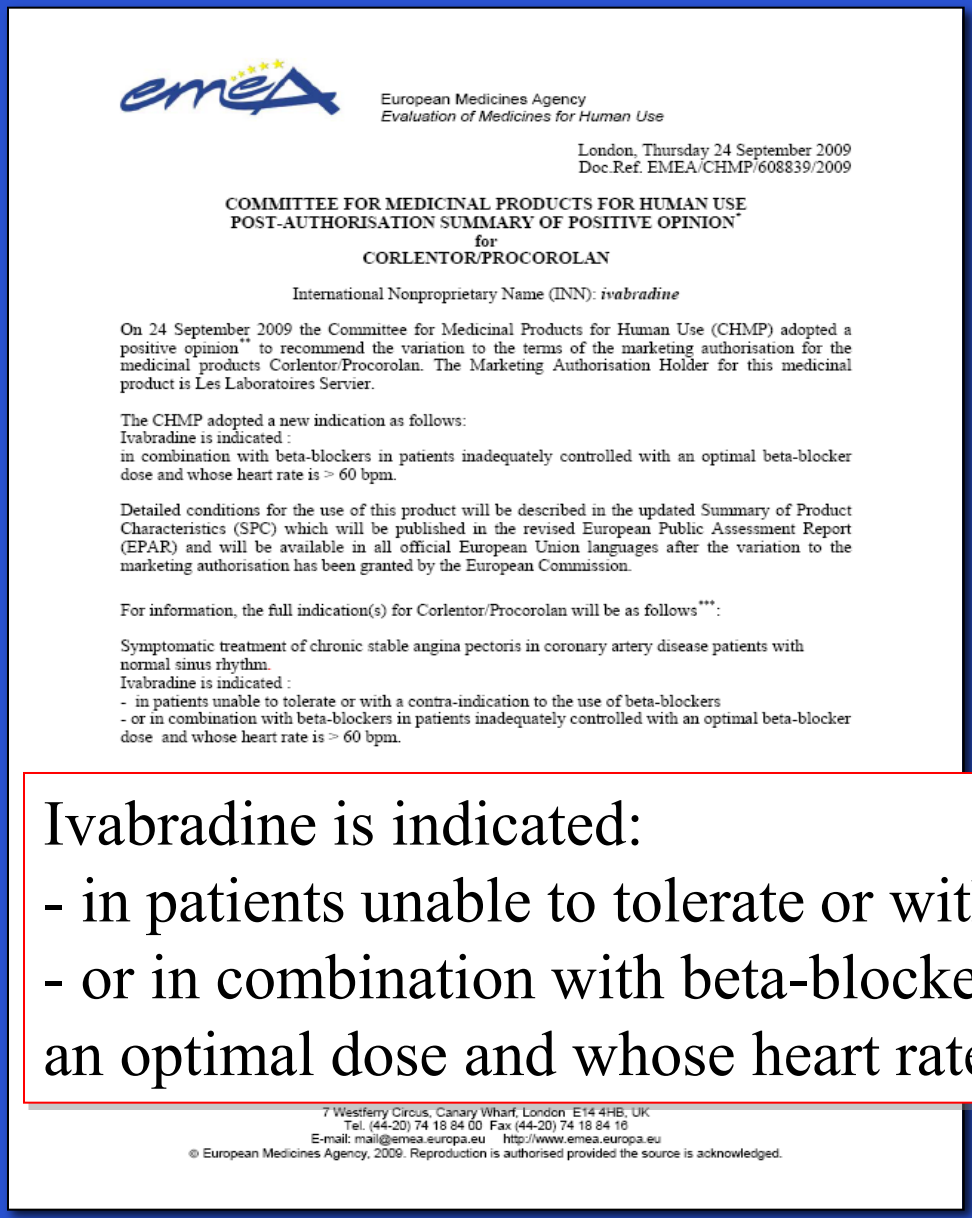
1y F-up



Euro Heart Survey Stable Angina C Daly et al. Postgrad Med J 2010;86212

New Drugs

Ivabradine in combination with Beta-Blockers



European Medicines Agency
Evaluation of Medicines for Human Use

London, Thursday 24 September 2009
Doc.Ref. EMEA/CHMP/608839/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
POST-AUTHORISATION SUMMARY OF POSITIVE OPINION*
for
CORLENTOR/PROCOROLAN

International Nonproprietary Name (INN): ***ivabradine***

On 24 September 2009 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion** to recommend the variation to the terms of the marketing authorisation for the medicinal products Corlentor/Procorolan. The Marketing Authorisation Holder for this medicinal product is Les Laboratoires Servier.

The CHMP adopted a new indication as follows:
Ivabradine is indicated :
in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.

Detailed conditions for the use of this product will be described in the updated Summary of Product Characteristics (SPC) which will be published in the revised European Public Assessment Report (EPAR) and will be available in all official European Union languages after the variation to the marketing authorisation has been granted by the European Commission.

For information, the full indication(s) for Corlentor/Procorolan will be as follows***:

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients with normal sinus rhythm.
Ivabradine is indicated :
- in patients unable to tolerate or with a contra-indication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.

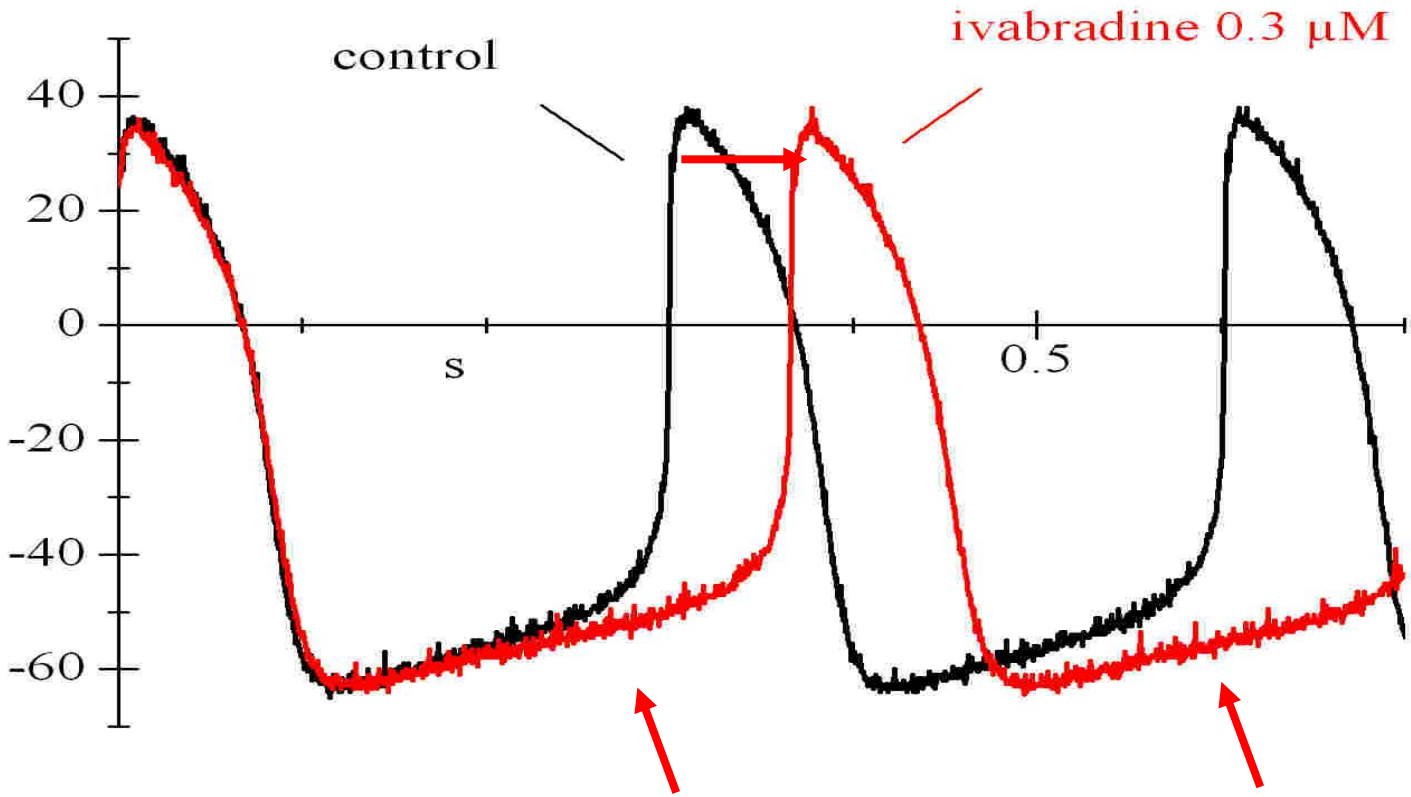
7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

New indication

HR > 60 lpm

Ivabradine is indicated:
- in patients unable to tolerate or with a contraindication to beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal dose and whose heart rate is > 60

Ivabradine's mechanism of action
Effects on sinus node diastolic depolarisation

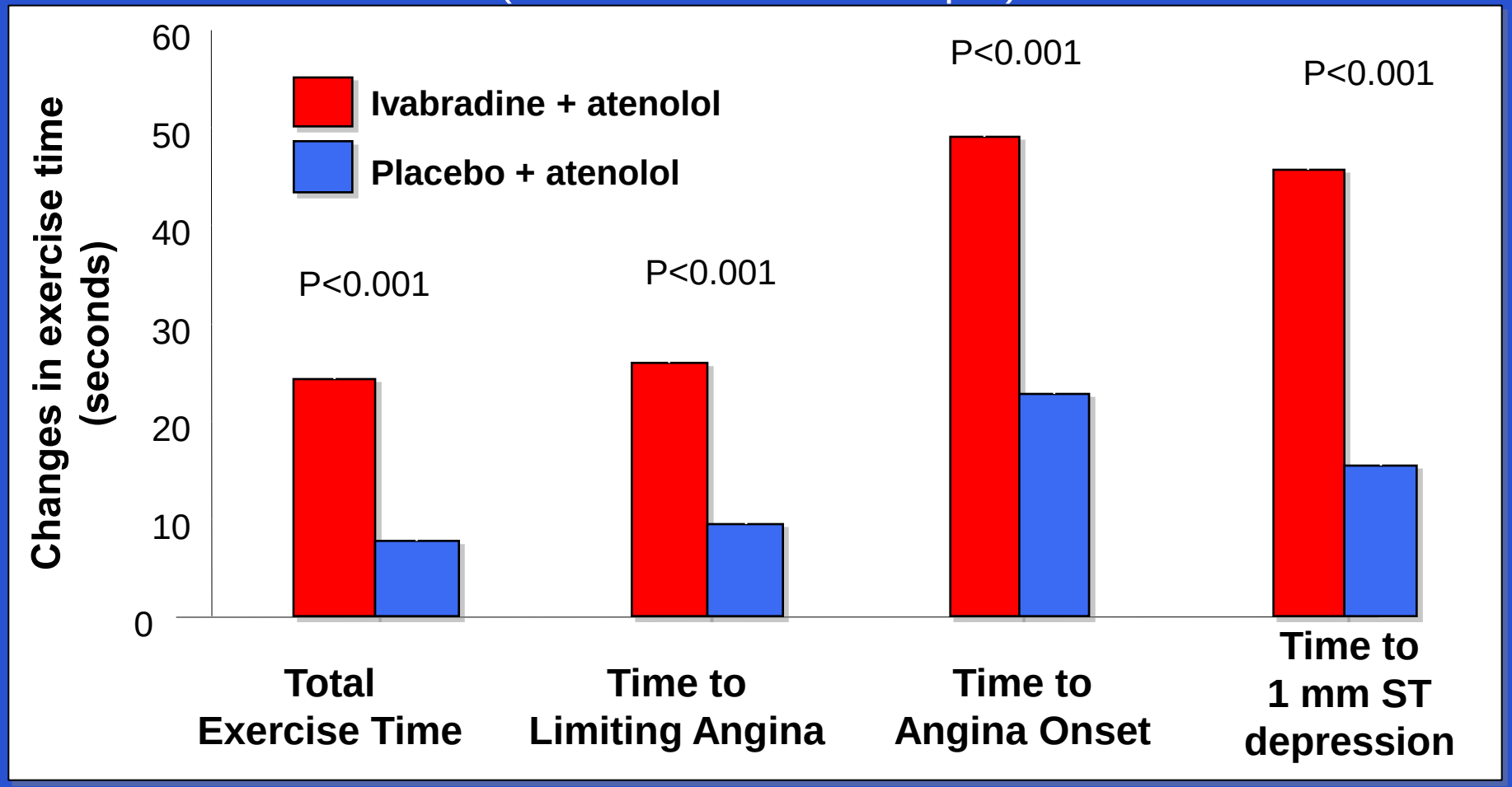


Delay of diastolic depolarisation in the sinus node

DiFrancesco and Camm, Drugs 64: 1757-1765, 2004

Ivabradine associated with beta-blockers

Heart Rate > 60 bpm
(Basal Heart Rate 67 bpm)

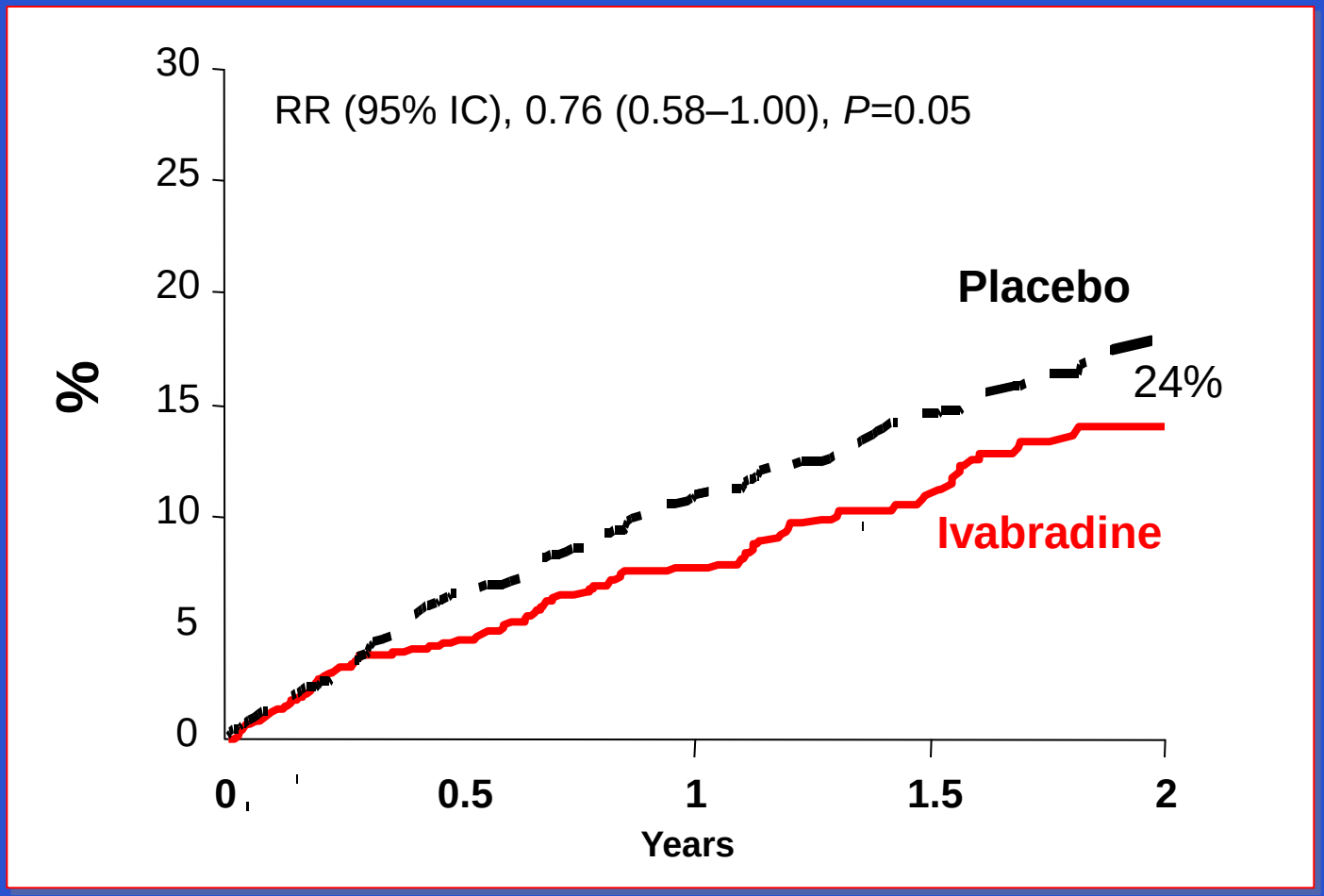


ASSOCIATE
Evaluation of the Anti-anginal efficacy and Safety of the asSociation Of the I_f Current inhibitor IvabrAdine with a beTa-blockEr

Tardif, et al. Eur Heart J 2009;30:540

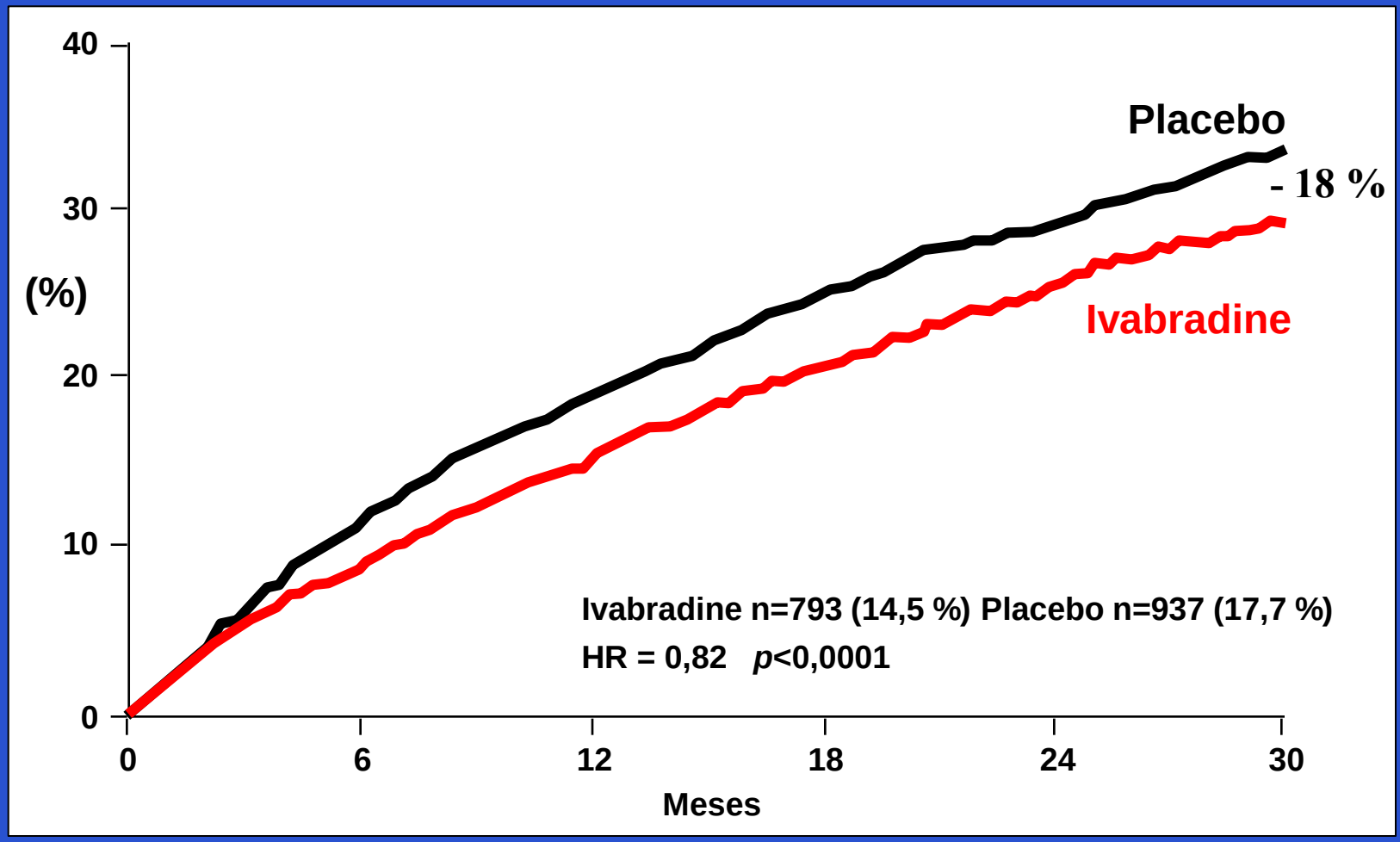
BEAUTIFUL Patients with angina (HR > 60 bpm)

CV Death, hospitalization for MI or heart failure



Fox K, et al. Eur Heart J. 2009;30:2337

CV Death or Hospitalization for worsening HF



Lancet. Online 29-08-2010

European Medicines Agency

Authorisation valid through the European Union 9 July, 2008 2008

EMEA/H/C/805

Ranexa[1]
ranolazine

EPAR summary for the public

This document is a summary of the European Public Assessment Report (EPAR). It explains how

ranolazine is released slowly from the tablet over a few hours.

What is Ranexa used for?
Ranexa is used to treat the symptoms of stable angina pectoris (chest pain caused by reduced blood flow to the heart). It is used as an add-on to existing treatment in patients whose disease is not adequately controlled by other medicines for angina pectoris, such as beta-blockers or calcium antagonists, or in patients who cannot take these medicines.
The medicine can only be obtained with a prescription.

How is Ranexa used?
The recommended starting dose of Ranexa is 375 mg twice a day. After two to four weeks, the dose should be increased to 500 mg twice a day, and then to 750 mg twice a day, depending on the patient's response. The maximum dose is 750 mg twice a day. Doses may need to be lower in patients who have certain side effects. Dose increases should be carried out carefully in the elderly, in patients who weigh less than 60 kg, and in patients who have problems with their kidneys, liver or heart. Ranexa

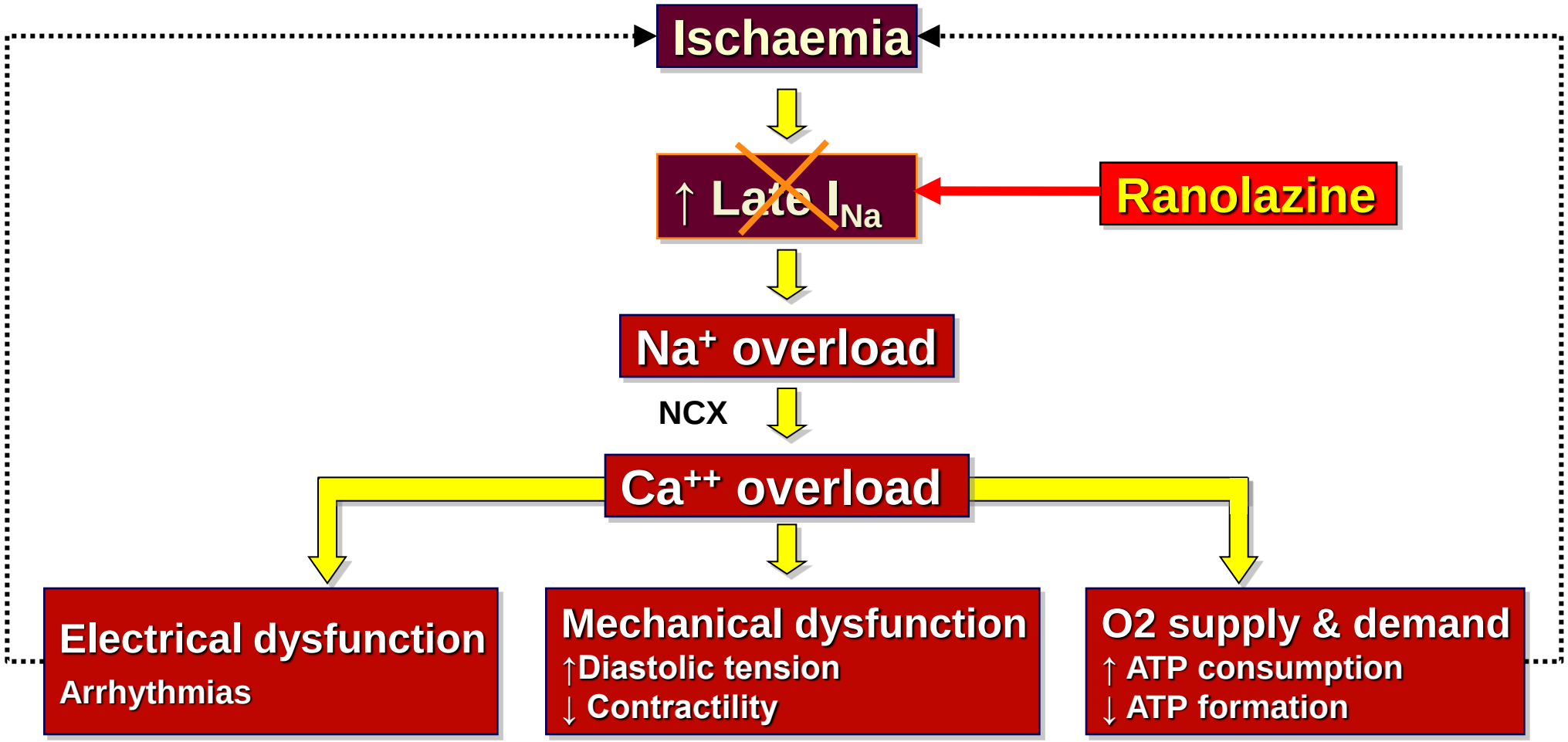
Ranolazine
Na channel inhibitor

4.1 Therapeutic indications

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 (such as betablockers and/or calcium antagonists).

Chronic ischemic heart disease and comorbidities

Ranolazine: mechanism of action

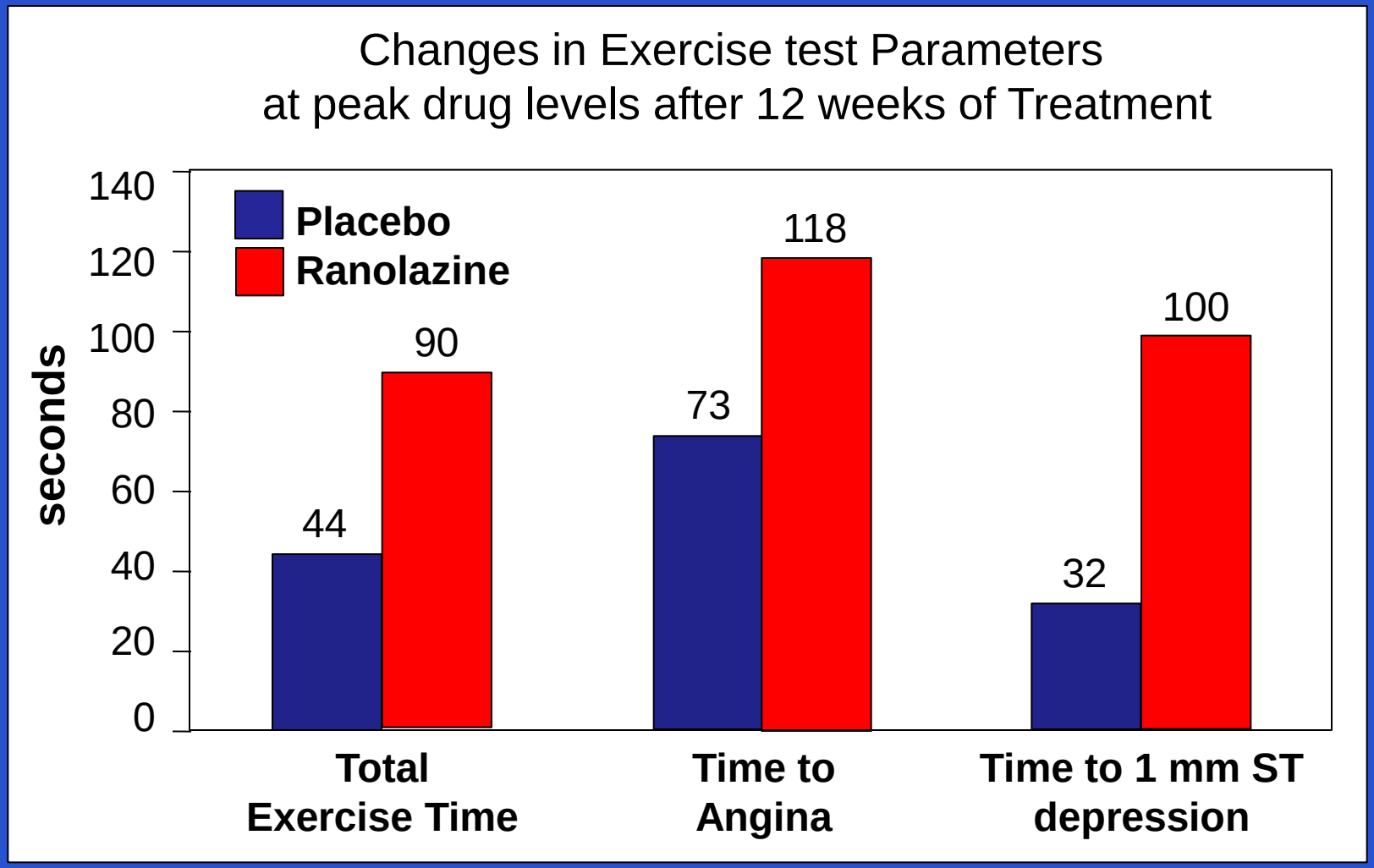


Hasenfuss G, et al Clin Res Cardiol 2008;97:22
Maier LS. Cardiol Clin 2008;26:603

NCX: sodium-calcium exchanger

Ranolazine vs Placebo

in patients with maximal tolerated BB and Ca Channel blockers

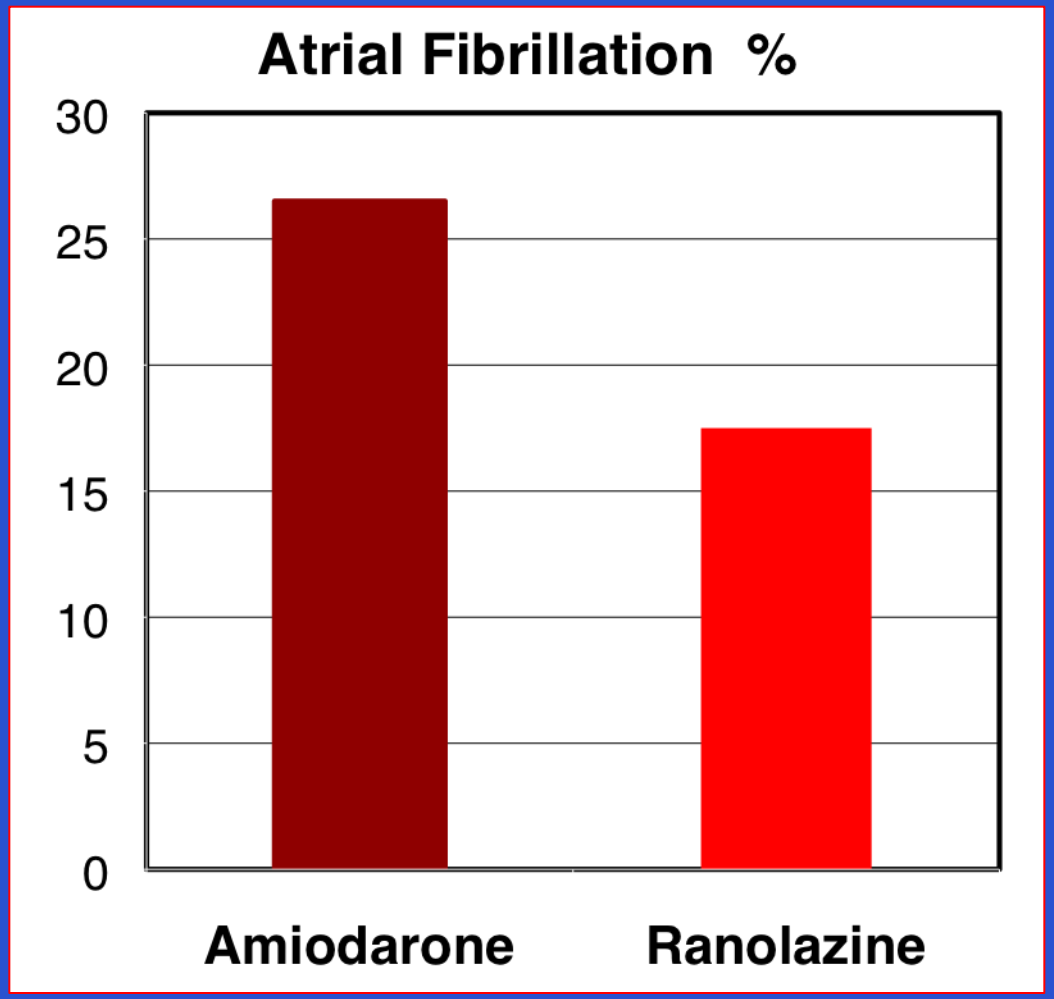


CARISA
subgroup in press

Ranolazine versus Amiodarone for AF Prophylaxis After CABG

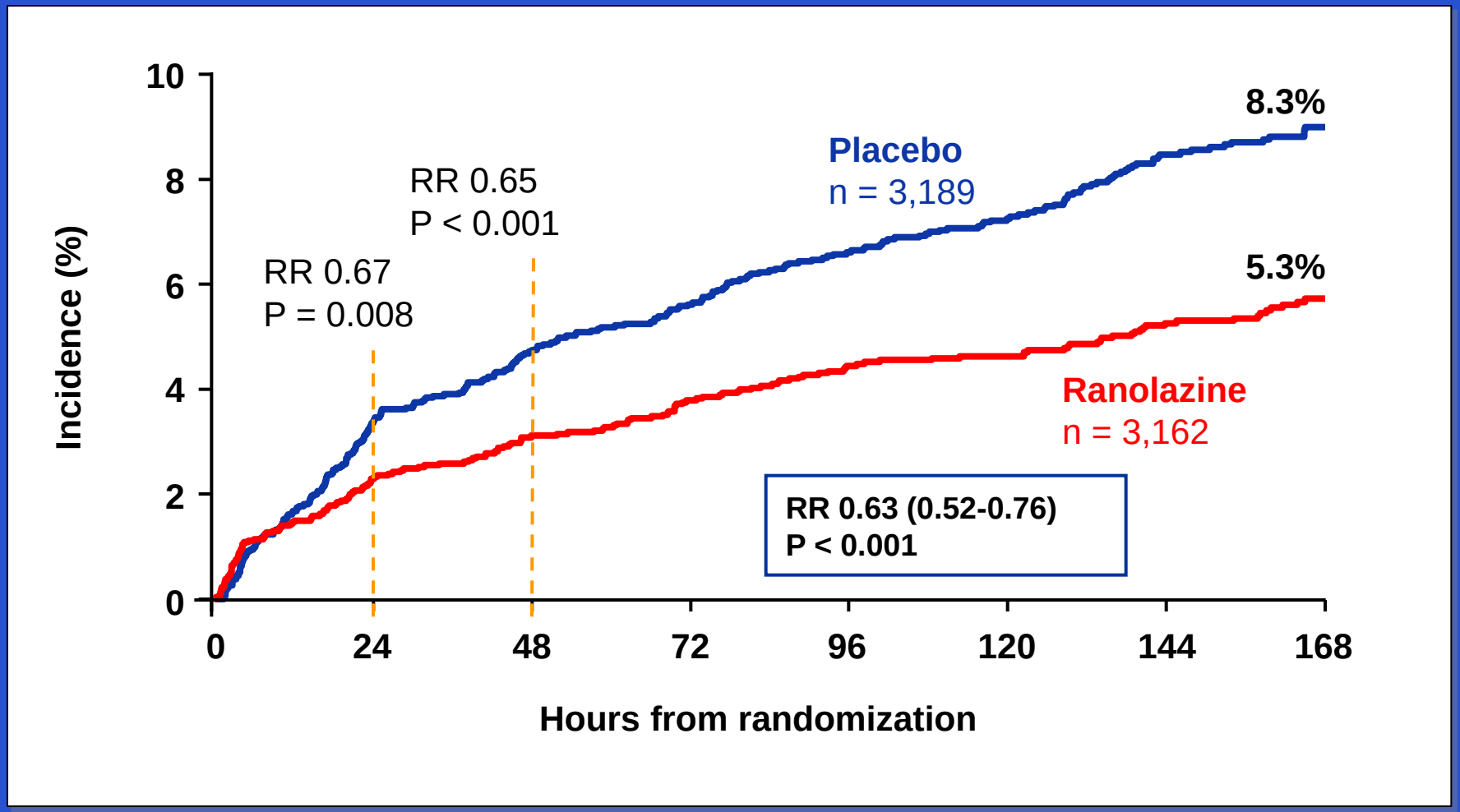
Ranolazine associated independently with a reduction of post –op AF

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10-14 days)
- Ranolazine (1500 mg preoperative followed by 1000 mg twice daily for 10-14 days)
- Mean age 65 ± 10 years, 72% men



Murdock D, et al. ACC 2011

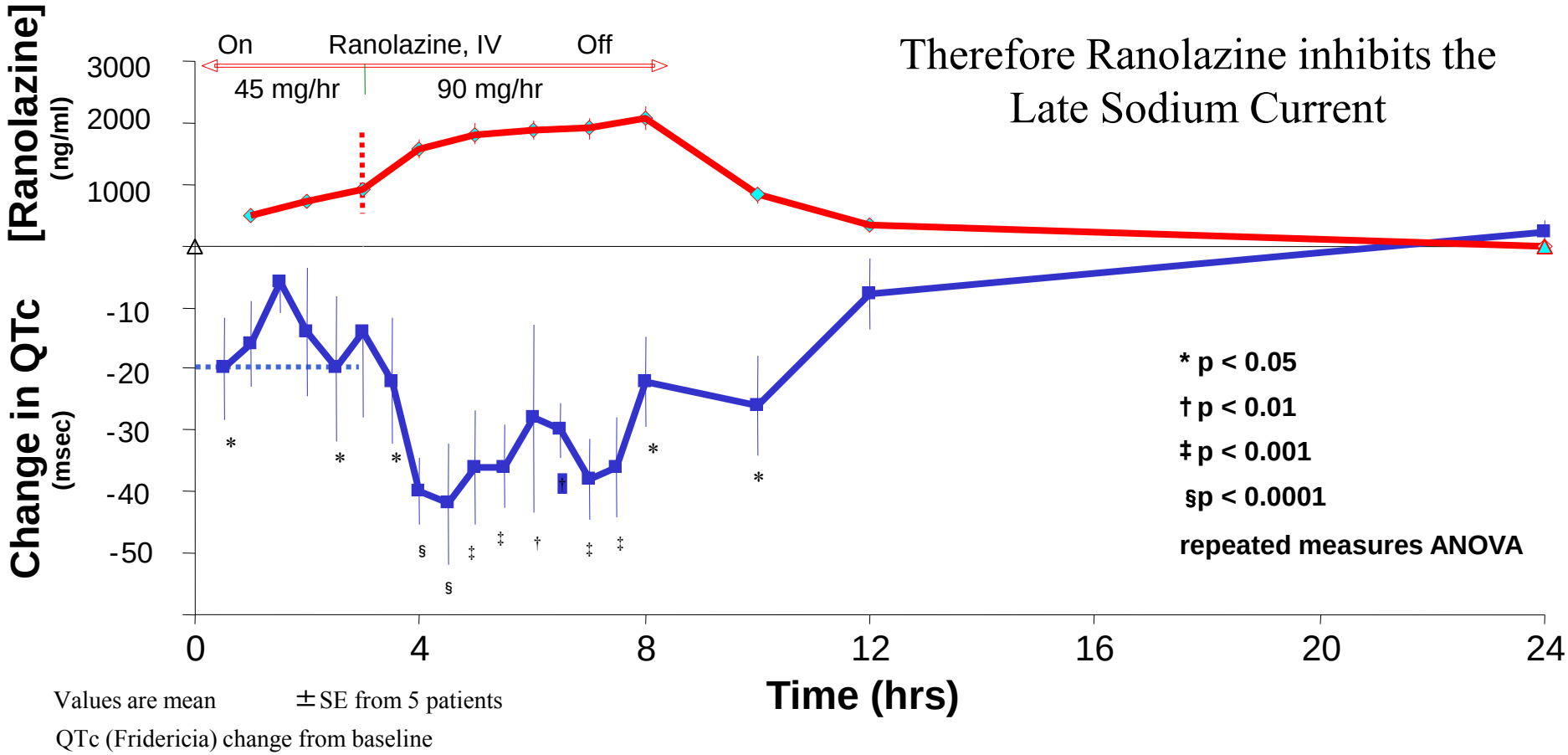
MERLIN-TIMI 36: Reduction in VT lasting ≥8 beats



Scirica BM et al. Circulation. 2007;116: 1647-1652

Effect of Ranolazine on QTc interval in LQT3

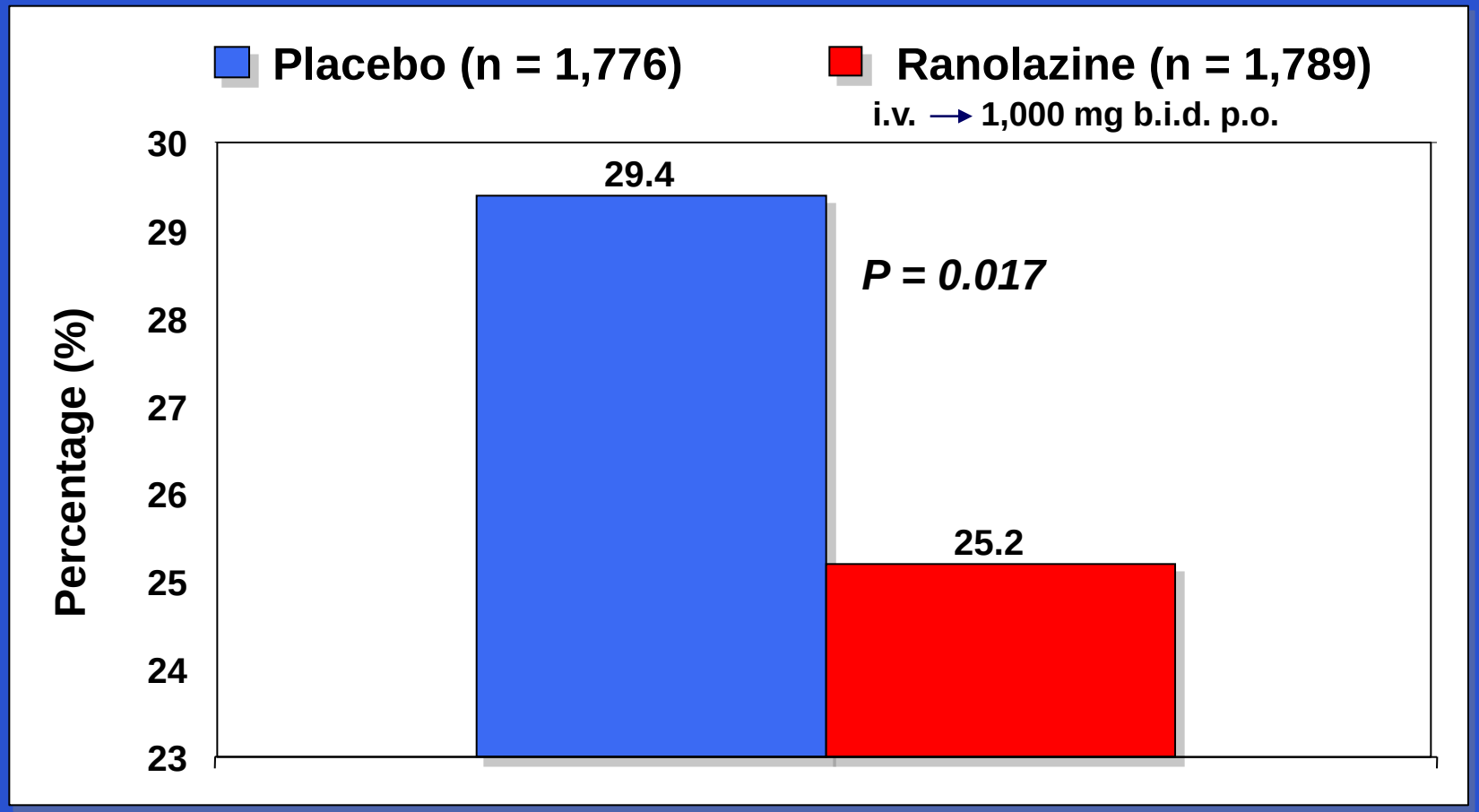
LQT3 due to KPQ mutation leading to increased SCN5A – activation of Late Na current



ΔQTc vs. [RAN] plasma r = 0.7 ± 0.22
slope = 24.1 msec/1,000 ng/ml (P = 0.008)

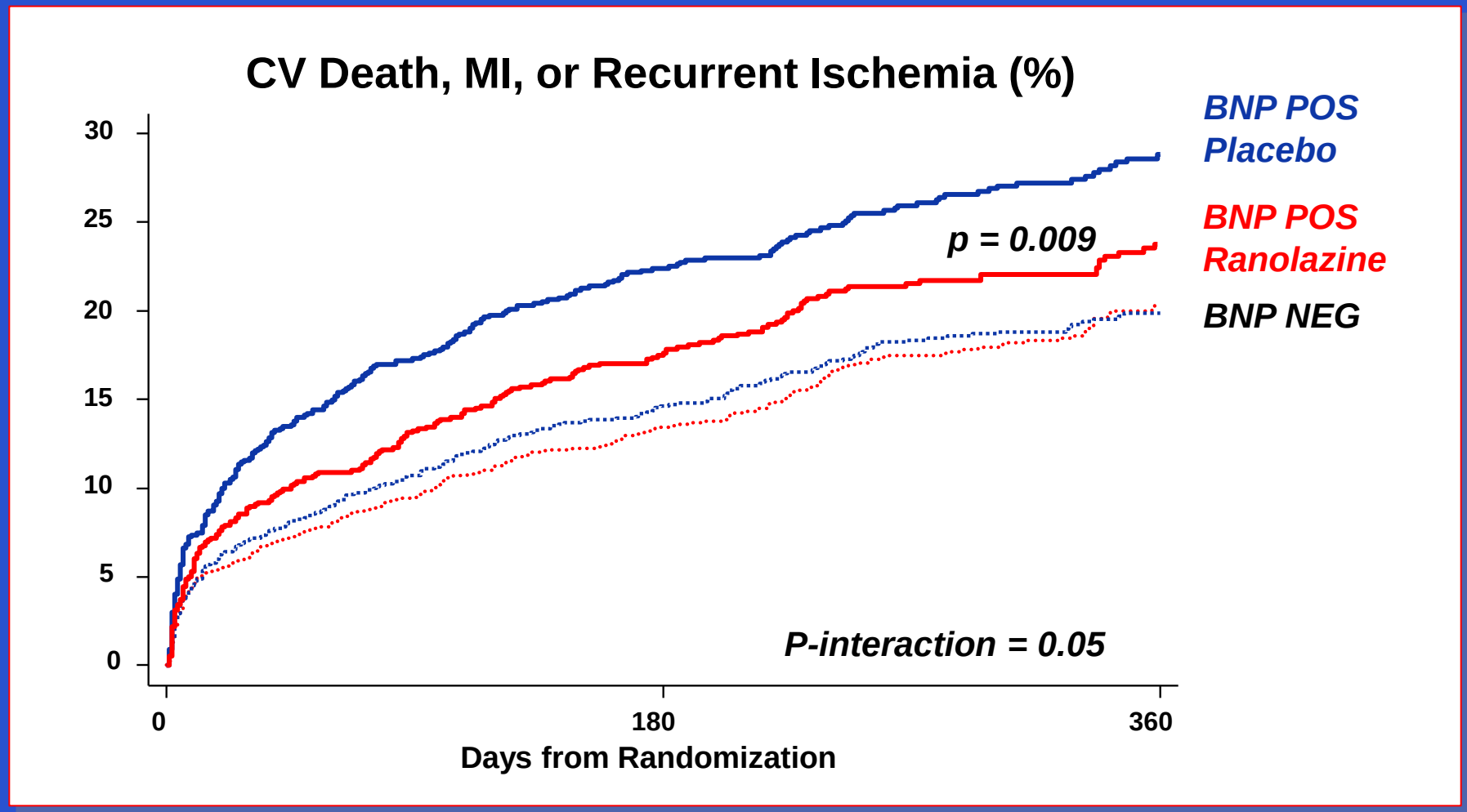
Moss A, et al. J Cardiovasc Electrophysiol 2008;19:1289-93

Merlin: Patients with prior angina
CV death, MI or recurrent Ischemia



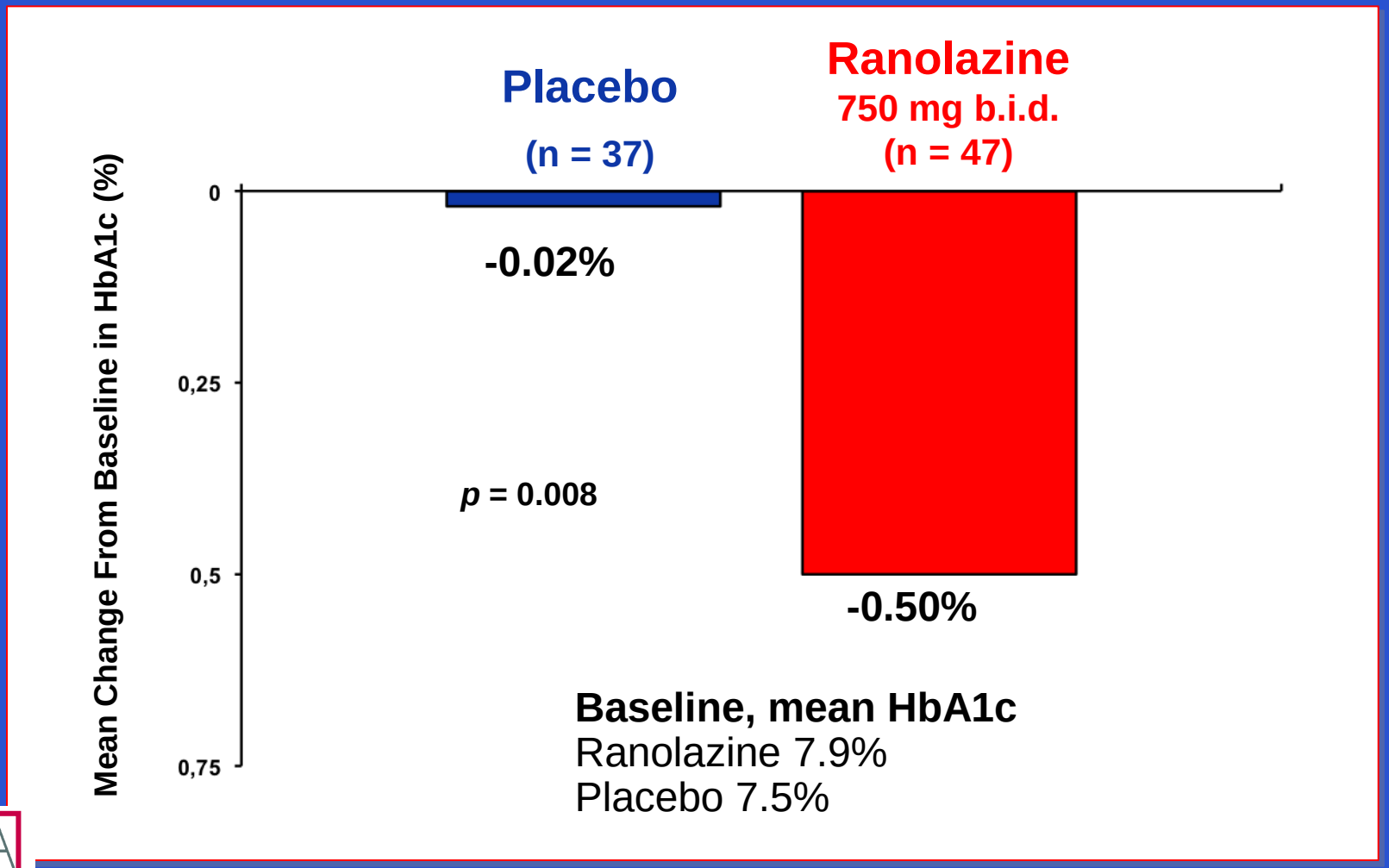
Wilson S.R. et al. JACC 2009;53:1510

Baseline BNP and Effect of Ranolazine on Primary Endpoint



Morrow DA et al. AHA 2007, Orlando, FL

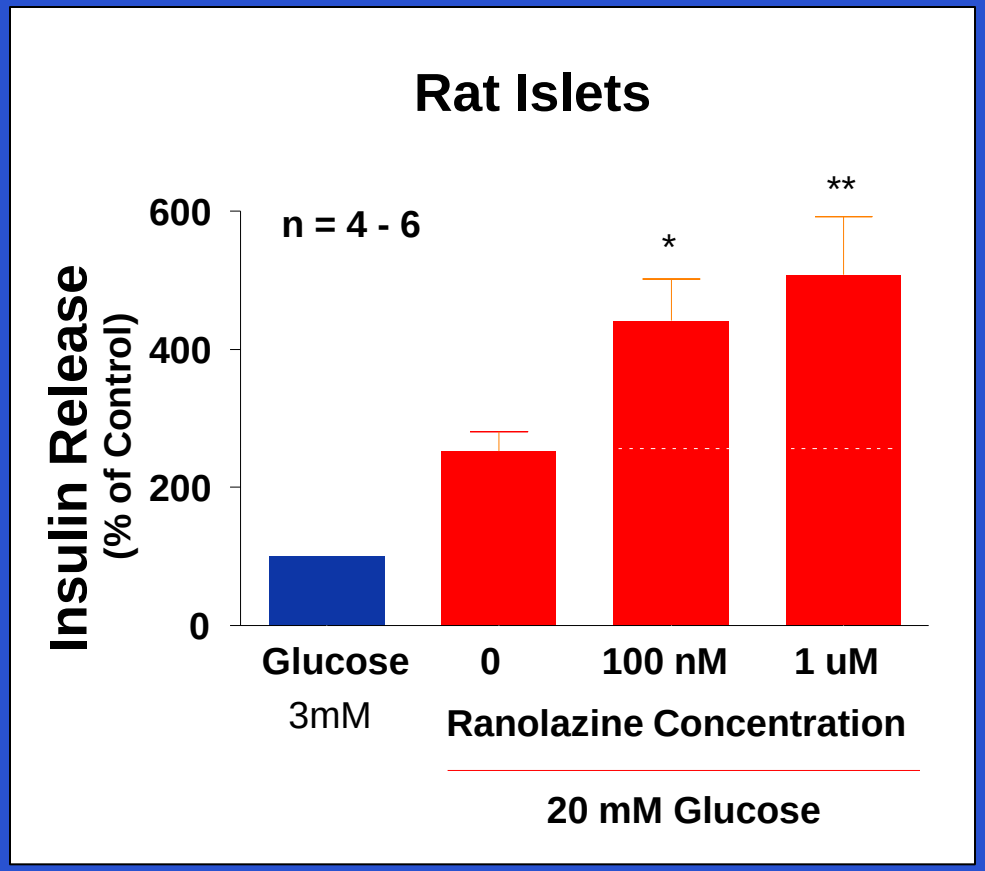
Ranolazine in Patients With Diabetes and CAD
Absolute Reduction in HbA1c From Baseline to Week 12

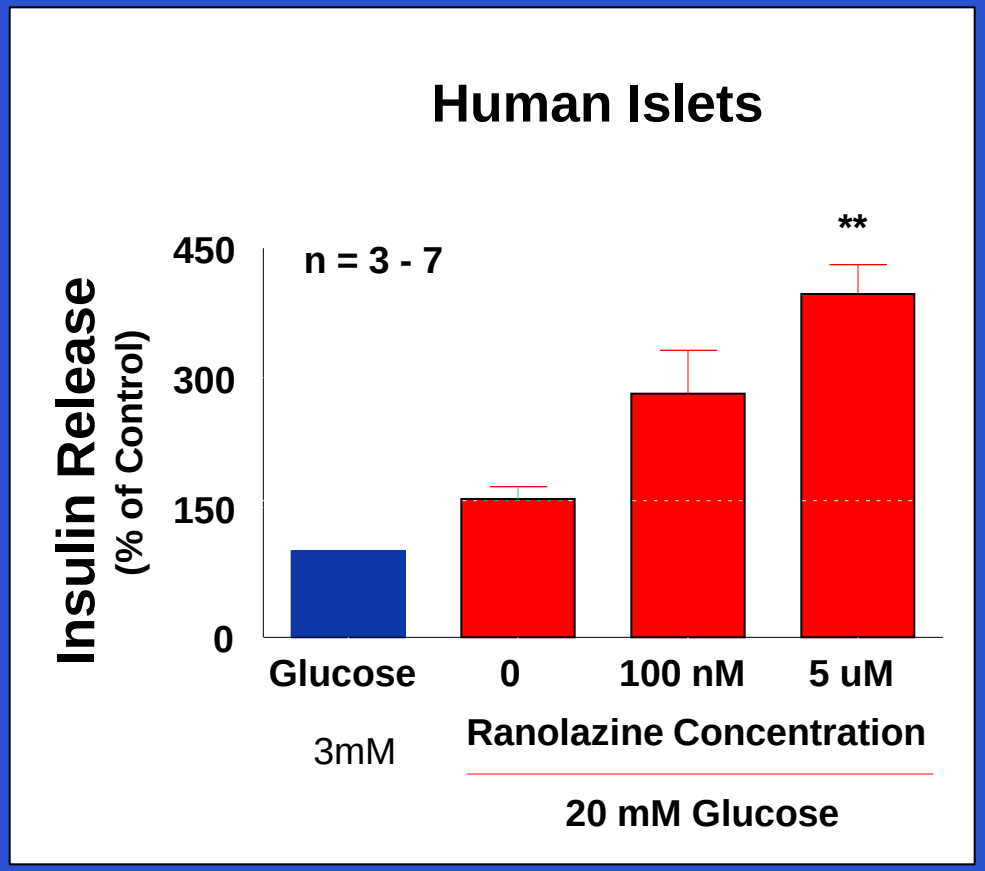


CARISA COMBINATION ASSESSMENT OF RANOLAZINE IN STABLE ANGINA

Timmis AD, et al. Eur Heart J. 2006;27:42

Effect of Ranolazine on Glucose Stimulated Insulin Secretion (GSIS) in Pancreatic Islets





* p<0.05, ** P <0.01

Ranolazine for Angina with Non-obstructive CAD in Women

- Pilot randomized, double-blind, placebo-controlled, crossover trial
- 20 women with angina, no obstructive CAD, and 10% ischemic myocardium
- Ranolazine 1000 mg bid or placebo for 4 weeks / 2-week washout
- The Seattle Angina Questionnaire was evaluated after each treatment

SAQ scores on ranolazine versus placebo

	Ranolazine	Placebo	Treatment Effect (p Value)
Physical functioning	91.7 (79.2, 97.9)	83.3 (66.6, 97.2)	**0.046**
Angina stability	75.0 (50.0, 100.0)	50.0 (25.0, 75.0)	**0.008**
Angina frequency	80.0 (50.0, 100.0)	75.0 (60.0, 87.5)	0.197
Treatment satisfaction	87.5 (75.0, 100.0)	93.8 (75.0, 100.0)	0.058
Quality of life	75.0 (60.4, 83.3)	66.7 (58.3, 75.0)	**0.021**

Mehta PK, et al. JACC Cardiovasc Imaging 2011;4:514-22a

Treatments aimed at Symptom Relief

Betablockers, 1st line treatment

Insuficient control of angina / ischaemia	Contraindication or intolerant
Add	Other option

Ca antagonists:

Amlodipine: Low heart rate, HT

Diltiacem, verapamil: Tach, HT

Ivabradine: → Heart rate > 60 b/m

Nitrate / Nicorandil: → General option

Ranolazine: → General option (diabetes, HF, arrhythmias)

Treatment of Myocardial Ischemia and Comorbidities

	B-Blockers	Ca Ch Block	Nitrates	Ivabradine	Ranolazine
General	1st Line	2nd Line	2nd Line Current Efficacy Unknown	2nd Line HR > 60	2nd Line
Heart Failure	OK	Contraindicated	OK	OK	OK
Atrial Fib	OK	OK	OK	No effect	OK
Hypotension	Limited	Limitado	Limited	OK	OK
AV-Block	Contraindicated	D & V contraindicated	OK	OK	OK
Bradicardia	Limited	Limited	Limited	Limited	OK
COPD/Asthma	Limited	OK	OK	OK	OK
Diabetes	Difficult control	OK	OK	OK	OK

Conclusions

1- Follow Guidelines

2- Identify and treat comorbidities

3- Ivabradine and Ranolazine new drugs for treatment of ischemia

4- Revasc complementary to meds