Unmet Needs in the Management of Chronic Stable Angina

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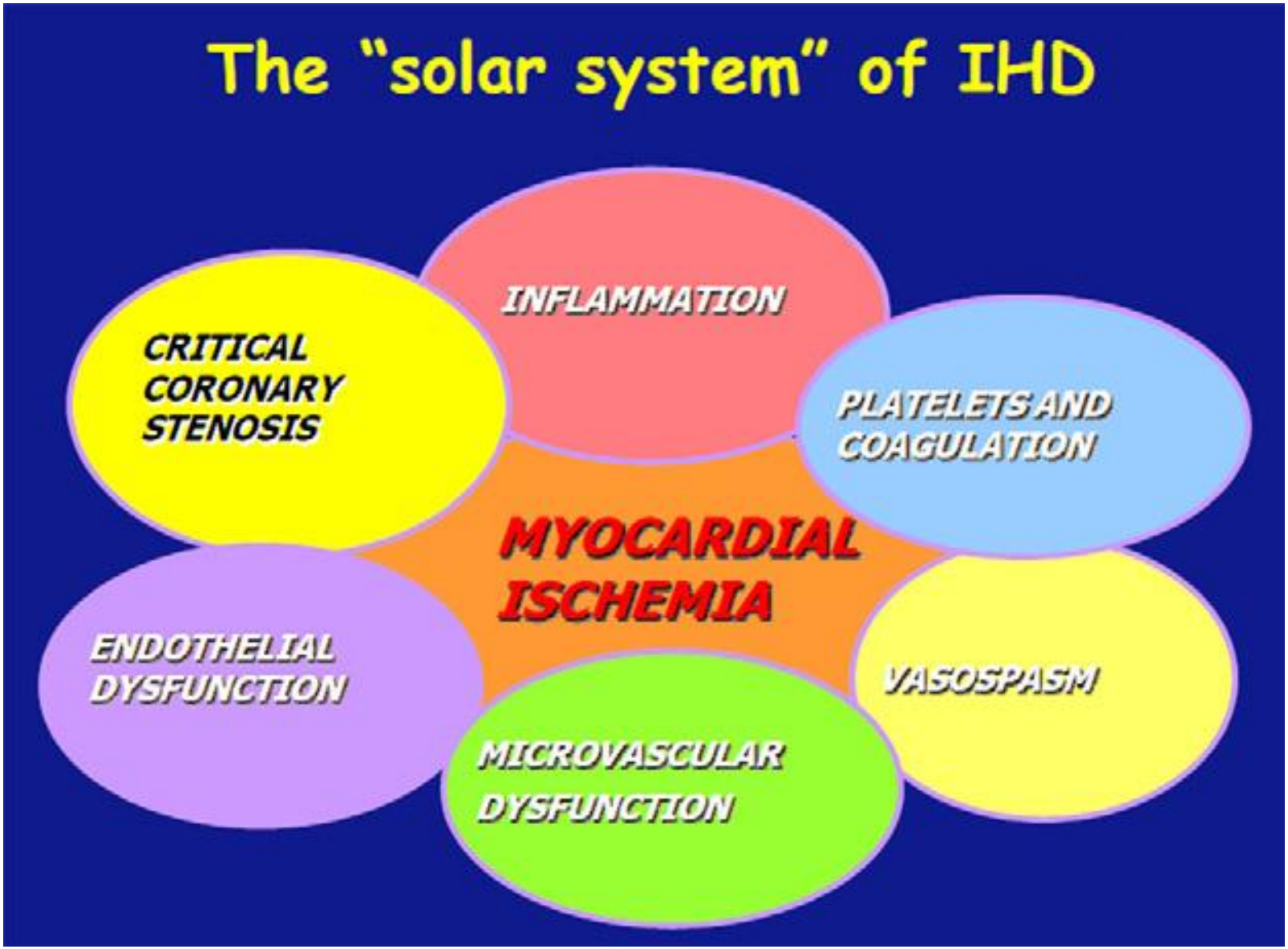
London, UK

Declaration of Interests

Speaking honoraria from
Menarini, Astra Zenica, Bayer, Itamar Medical,
Abbott, Ferring Pharmaceuticals

SCHD



Marzilli et al J Am Coll Cardiol 2012;60:951

Question

A 62 year old man has a DES 12 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 62 year old man has a DES 12 months ago and returns complaining of angina. This occurs in:

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2) In 10% of patients per year
3) In 15% of patients per year
4) **In over 25% of patients per year**

How common?

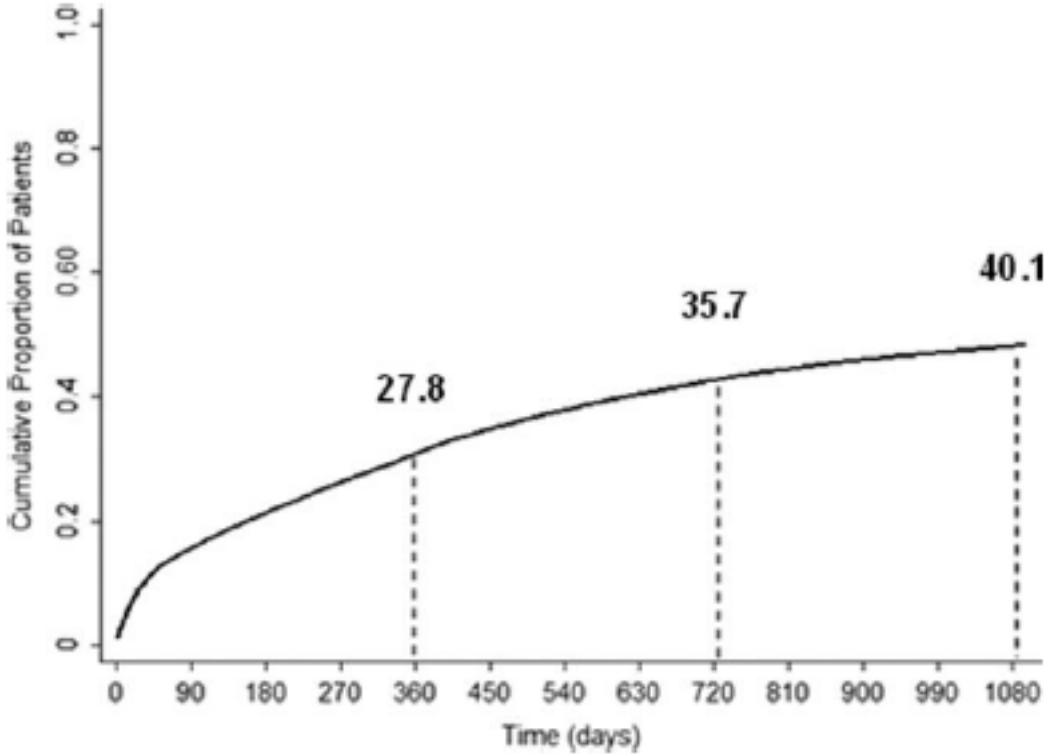


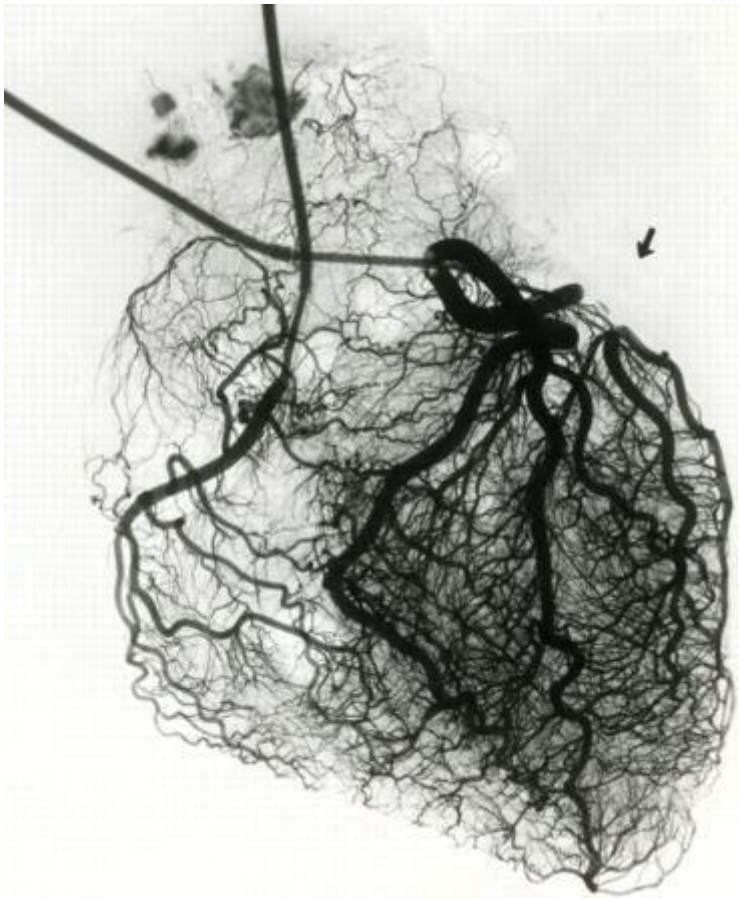
Fig. 1. Cumulative prevalence of angina or chest pain during 3 years post-PCI.

Ben-Yehuda et al Catheter Cardiovasc Interv 2016; 88:1017

Coronary Microvascular Dysfunction

“Chest pain with normal coronary arteries” or “cardiac syndrome X” has puzzled physicians over the years and continues to represent an unsolved “mystery” for many in clinical practice.

The coronary microcirculation has remained elusive to conventional imaging techniques



Hermann J, Kaski JC, Lerman A. Eur Heart J. 2012

Medical management of patients with SCAD

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

2nd line

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

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine[a]
Trimetazidine[a]

+ Consider angio → PCI - stenting *or* CABG

Event prevention

- Lifestyle management
- Control of risk factors

+ Educate the patient

- Aspirin[b]
- Statin
- Consider ACEI or ARBs

ACEI = angiotensin converting enzyme inhibitors;
ARB = angiotensin receptor blocker;
CABG = coronary artery bypass graft;
CCB = calcium channel blockers;
CCS = Canadian Cardiovascular Society;
DHP = dihydropyridines;
PCI = percutaneous coronary intervention.
[a]Data for diabetics.
[b]If intolerance, consider clopidogrel.

This slide corresponds to Figure 4 in the full text.

Eur Heart J 2013;34:2949–3003. doi:10.1093/eurheartj/eht296

The continuing burden of stable angina

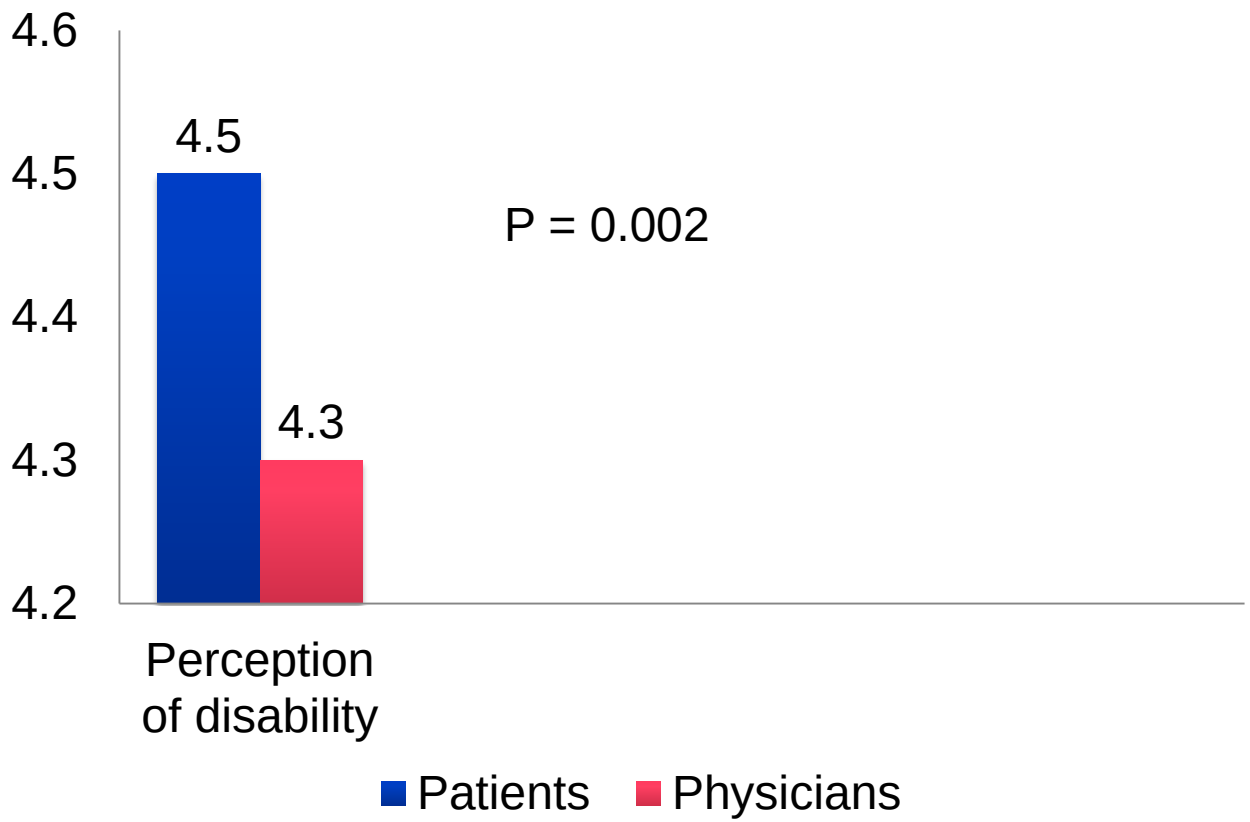
- 2039 stable angina patients (73% male, age 68)
- 419 cardiologists in 2 years
- 66% prior re-vascularisation
- Stable angina recurred in 59%.

  Despite:

  - Beta blockers - 78%
  - LAN - 53%
  - CCB - 40%
  - Ivabradine - 11%
  - Trimetazidine - 7%,
  - 50% of 2024 remained symptomatic and 30% ↓ QoL

Borras et al. The AVANCE registry, Rev. Esp. Cardiol. 2012; 65: 734

QoL assessments



Borras et al. The AVANCE registry, Rev. Esp. Cardiol. 2012; 65: 734

Unmet needs:

- An increasing number of patients are unsuitable for revascularisation because of complicating factors such as age, medical co-morbities and unsuitable coronary anatomy[1]

- Despite treatment with conventional agents or revascularisation, or both, many patients remain symptomatic one year after CABG or PCI[2.3]

- Some patients may not tolerate the upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate[4]

- A very recent RCT (ORBITA - the very first!) seriously questions the efficacy of PCI in SCAD[5]

1. Hamm Eur Heart J 2004 (Suppl 1): i2. 2. Serrys et al N Engl J Med 2001: 344; 1117. 3. Holubkov et al Am Heart J 2002: 144; 826. 4. Chaitman et al JAMA 2004: 291; 309. 5. Al-Lamee et al Lancet 2018; 391: 31

First and second line treatment for SCHD

	Mortality	Symptom relief		
		Symptoms	ESC	ACC/AHA
Beta-blockers	No	Yes	IA	IB
DHPs	No	Yes	IA	IB
Non-DHPs	No	Yes	IA	IIaB
LAN	No	Yes	IIaB	IB
Ivabradine	No	Yes	IIaB	–
Ranolazine	No	Yes	IIaB	IIaA
Nicorandil	No	Yes	IIaB	–
Trimetazidine	No	Yes	IIbB	–

DHPs: Dihydropyridines, LAN: long acting nitrates

Explanation of the recommendations

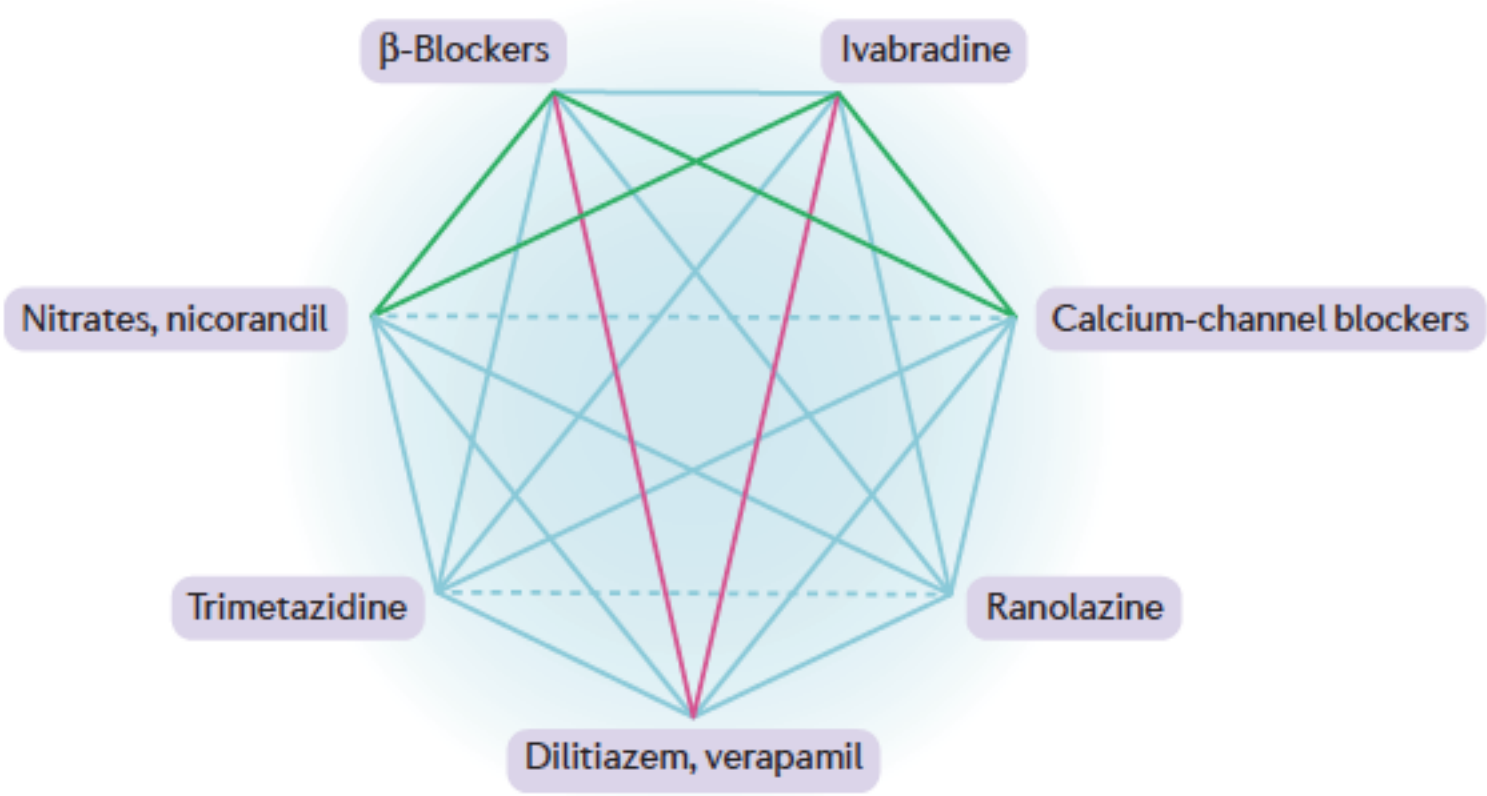
- Authors of the current ESC guidelines concede that they recommend older drugs as first line treatment because they are cheap, effective, and available everywhere

Regarding novel antianginal drugs:

- Stated in the guidelines that there is roughly the same level of evidence as with the 1st line drugs

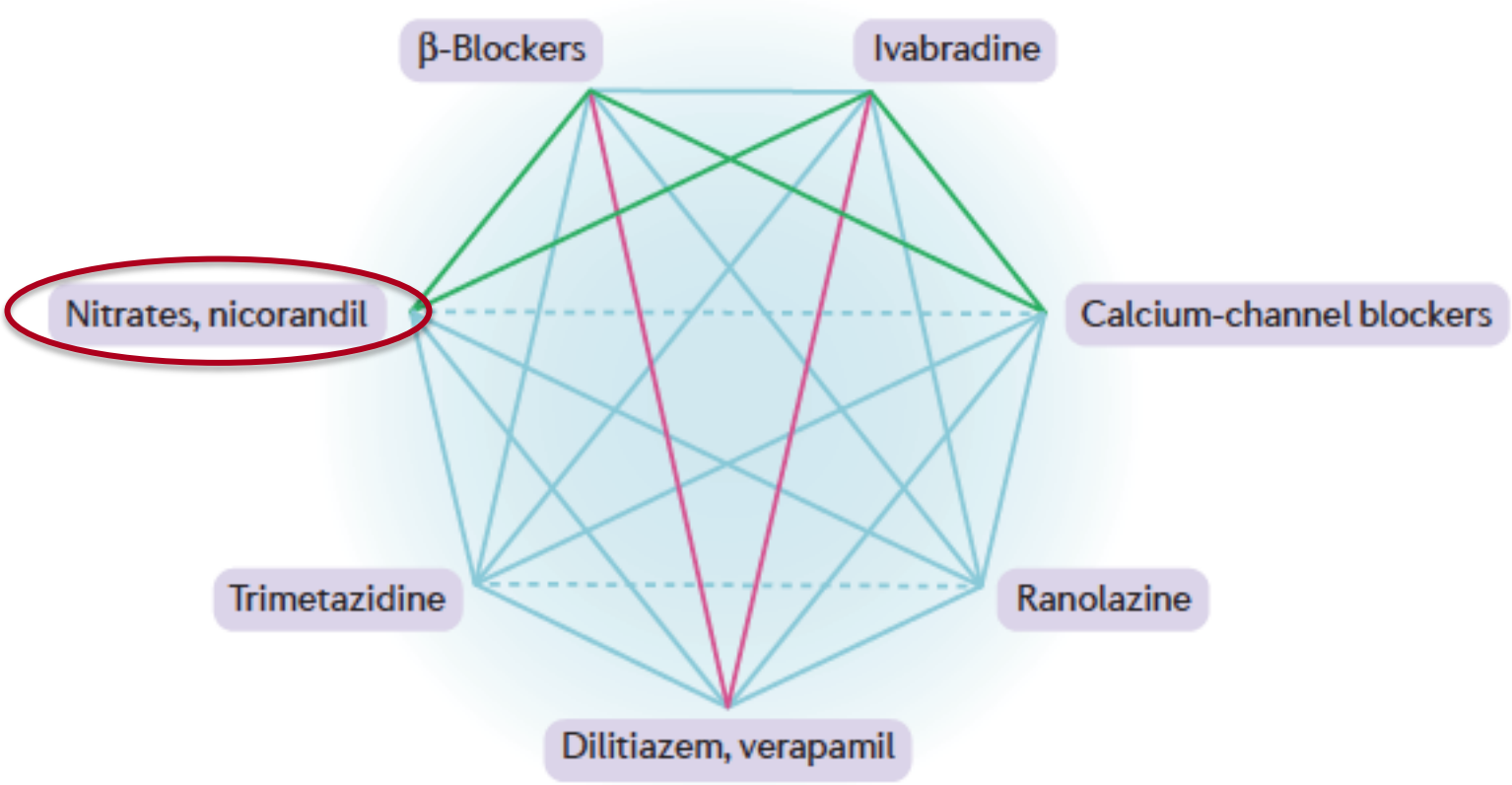
Taylor, New ESC guidelines published on stable coronary artery disease, Eur. Heart J. 34 (2013) 2927

Possible combinations of different classes of antianginal drugs



Ferrari et al Nat Rev Cardiol 2018; 15; 120-132

Possible combinations of different classes of antianginal drugs

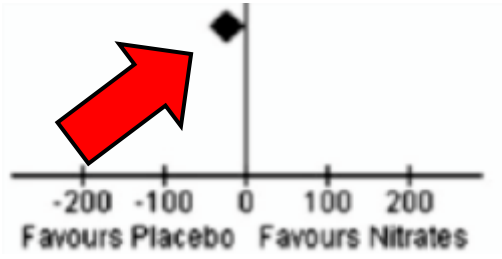


Ferrari et al Nat Rev Cardiol 2018; 15; 120-132

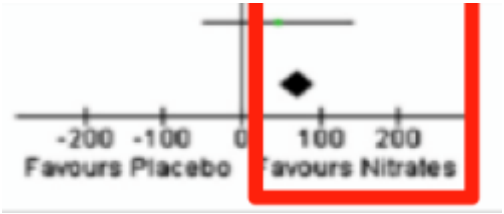
Data for long acting nitrates

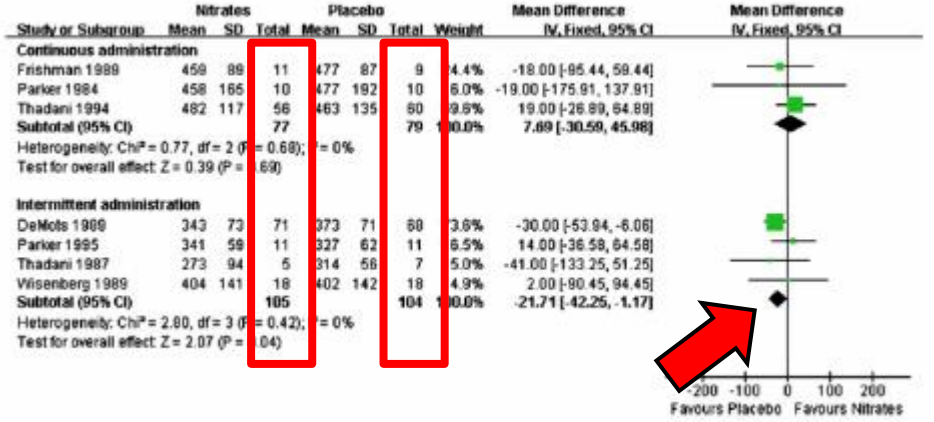
- No effect
- Our assumption: just because the spray works, the longer-acting pill works is incorrect

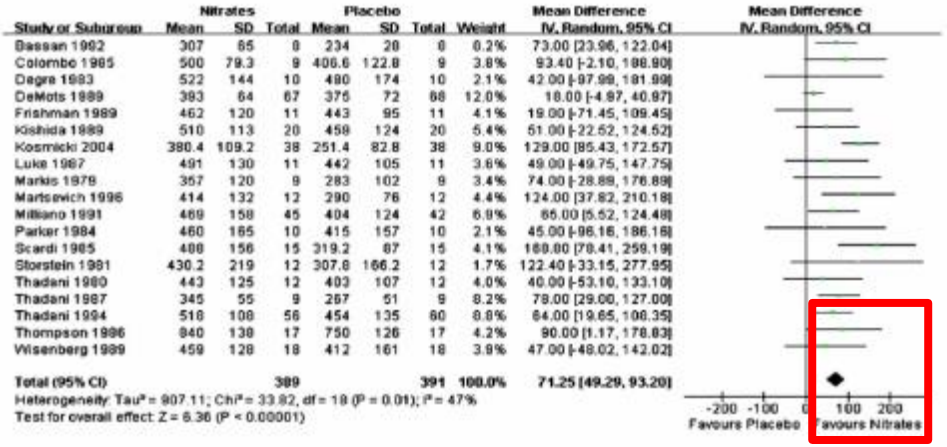
- Long acting Nitrates



- Short acting Nitrates







Wei et al. International Journal of Cardiology 2011

Data for long acting nitrates

Arguments against long acting nitrates

- Induces endothelial dysfunction in vitro and in animal models

Once Daily Therapy With Isosorbide-5-Mononitrate Causes Endothelial Dysfunction in Humans

Evidence of a Free-Radical–Mediated Mechanism

George R. Thomas, PHD,* Jonathan M. DiFabio, MSC,* Tommaso Gori, MD, PHD,† John D. Parker, MD, FACC*

Toronto, Canada; and Siena, Italy

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doi:10.1016/j.jacc.2008.04.019

VIEWPOINT

Nitrate-Induced Toxicity and Preconditioning

A Rationale for Reconsidering the Use of These Drugs

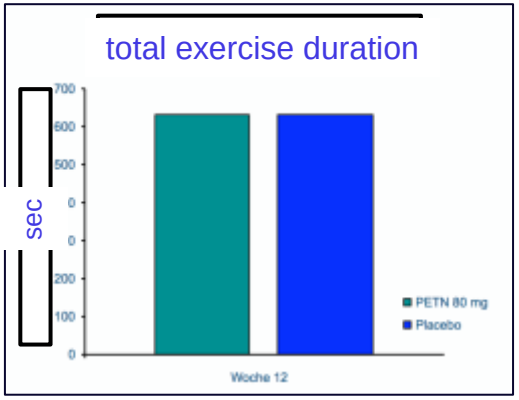
- No symptomatic data

European Heart Journal (2014) 35, 895–903
doi:10.1093/eurheartj/eht084

CLINICAL RESEARCH
Coronary artery disease

Efficacy of the long-acting nitro vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial

Thomas Münzel[1]*, Thomas Meinertz[2], Ulrich Tebbe[3], Heinrich Theodor Schneider[4], Dirk Stalleicken[5], Manfred Wargenau[6], Tommaso Gori[7†], and Ingrid Klingmann[7†], for the CLEOPATRA Study Investigators

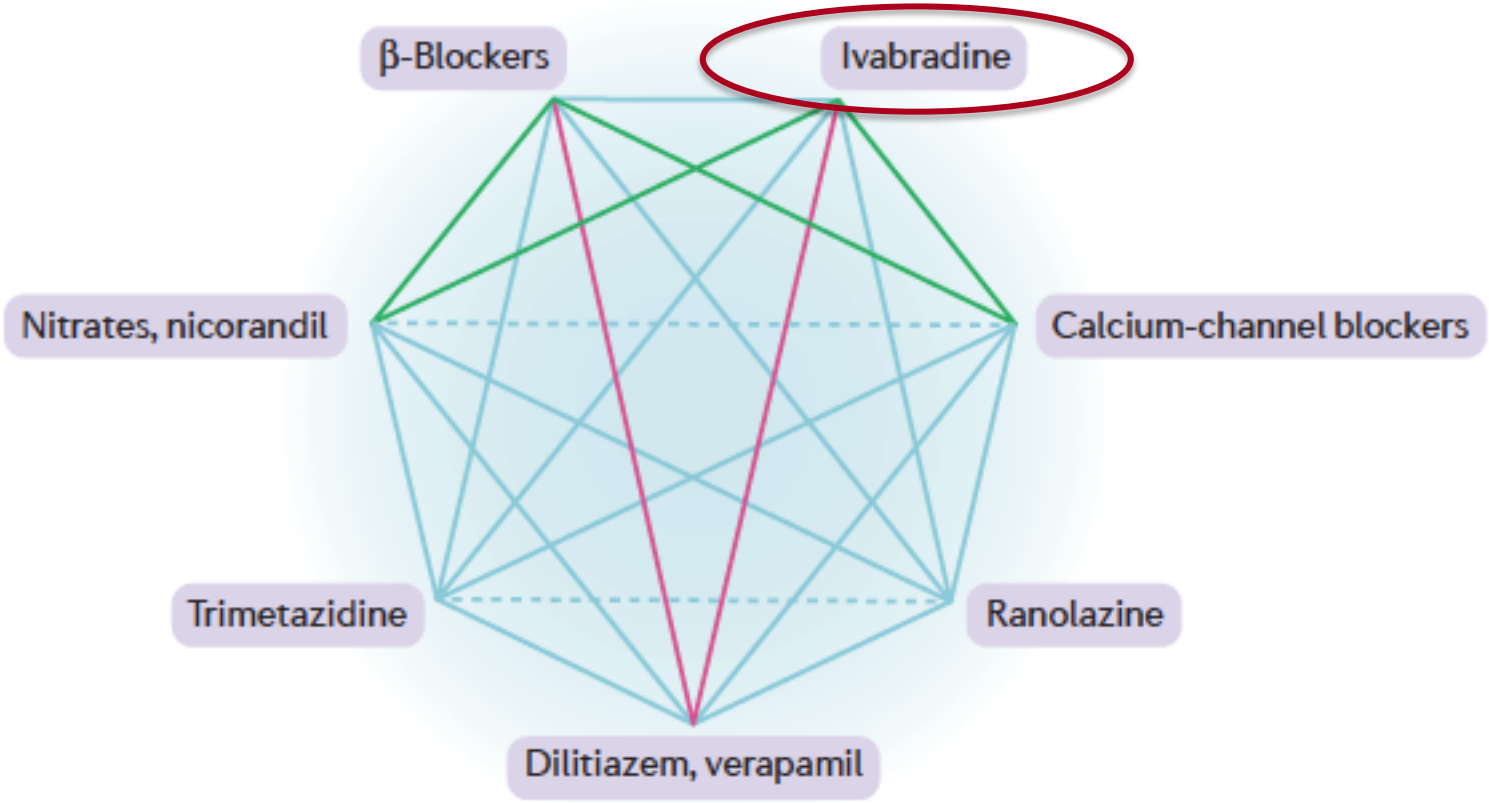


Warning

Nicorandil (Ikorel®): Advice on the Risk of Serious Ulcerations or Related Events

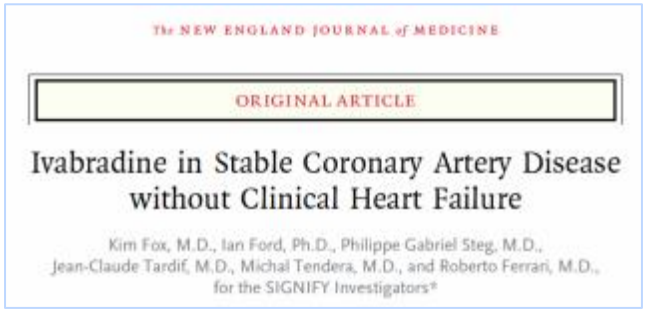
Ikorel Tablets 10mg PA 540/102/1 and Ikorel Tablets 20mg PA 540/102/2

Possible combinations of different classes of antianginal drugs



Ferrari et al Nat Rev Cardiol 2018; 15; 120-132

Increased risk of ivabradine



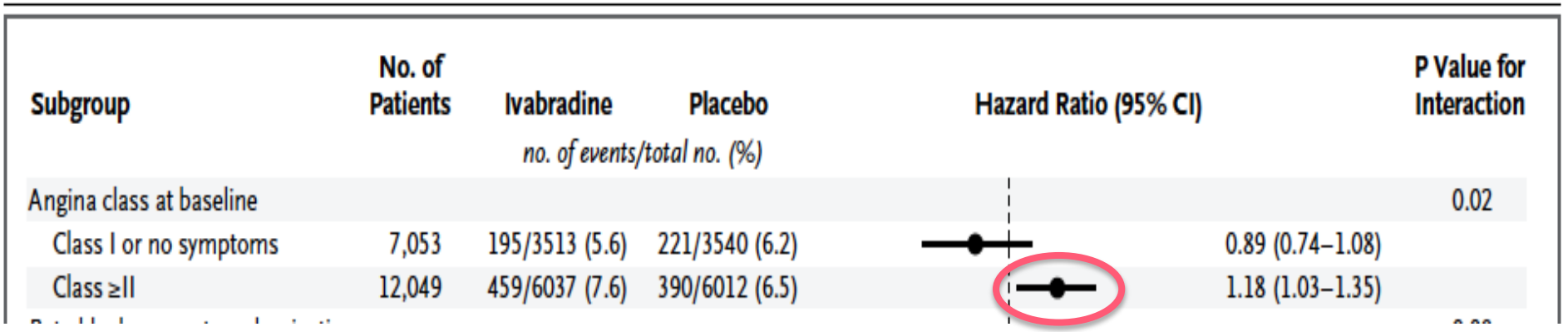
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

Kim Fox, M.D., Ian Ford, Ph.D., Philippe Gabriel Steg, M.D., Jean-Claude Tardif, M.D., Michal Tendera, M.D., and Roberto Ferrari, M.D., for the SIGNIFY Investigators*

- Prognostic relevance in heart failure
- Good antiangianal potential
- Tested in >17000 patients with CAD
- Not safe

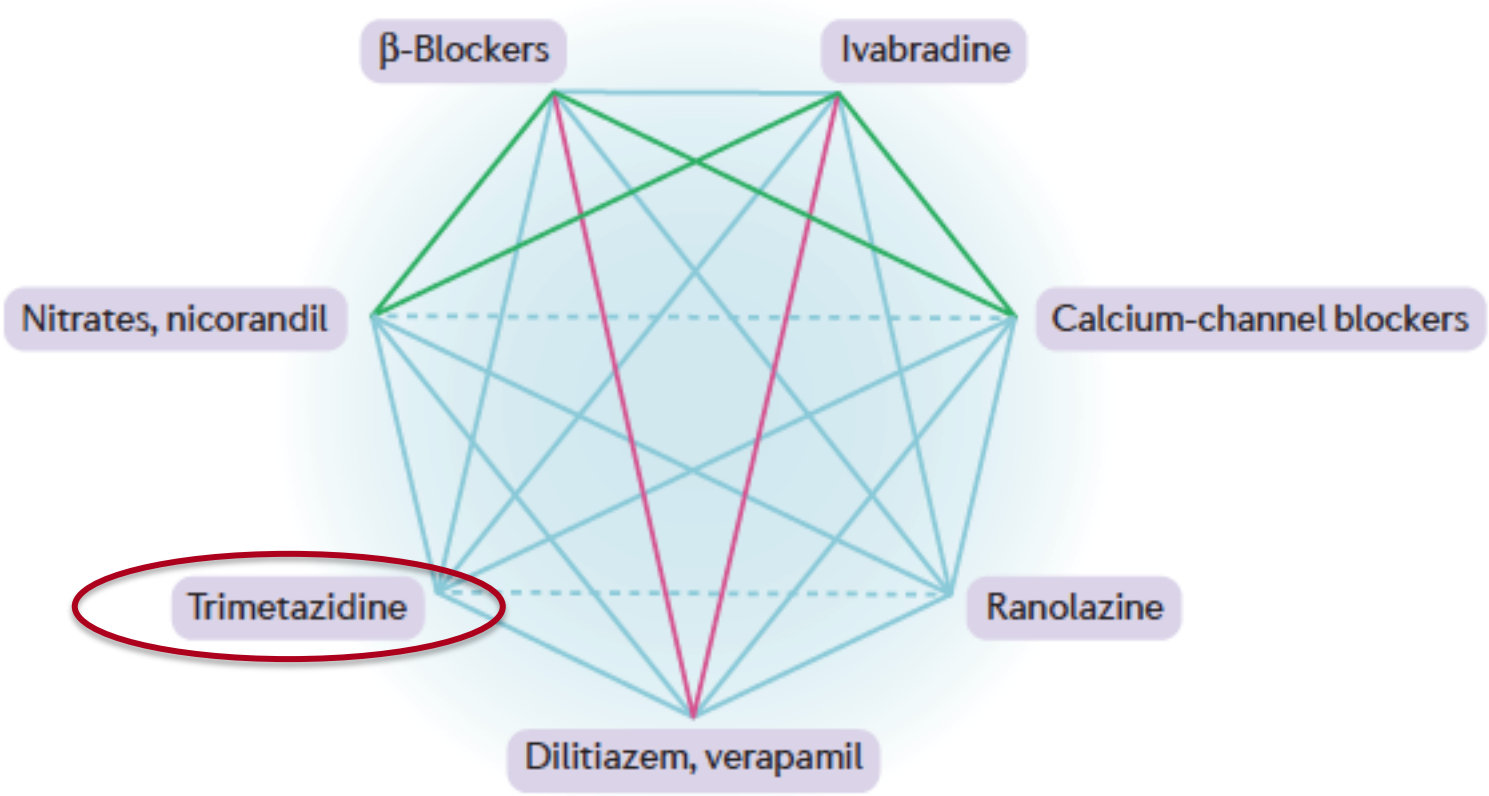


Subgroup	No. of Patients	Ivabradine	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Angina class at baseline					0.02
Class I or no symptoms	7,053	195/3513 (5.6)	221/3540 (6.2)	0.89 (0.74–1.08)	
Class ≥II	12,049	459/6037 (7.6)	390/6012 (6.5)	1.18 (1.03–1.35)	

Significant increase in the primary endpoint – death from cardiovascular causes or nonfatal myocardial infarction.

Fox et al N Engl J Med. 2014; 371: 1091-9

Possible combinations of different classes of antianginal drugs



Ferrari et al Nat Rev Cardiol 2018; 15; 120-132

Cochrane Library

Cochrane Database of Systematic Reviews

Trimetazidine for stable angina (Review)

Ciapponi A, Pizarro R, Harrison J

Trimetazidine for stable angina

Agustín Ciapponi[1], Rudolf Pizarro[2], Jeff Harrison[3]

Trimetazidine

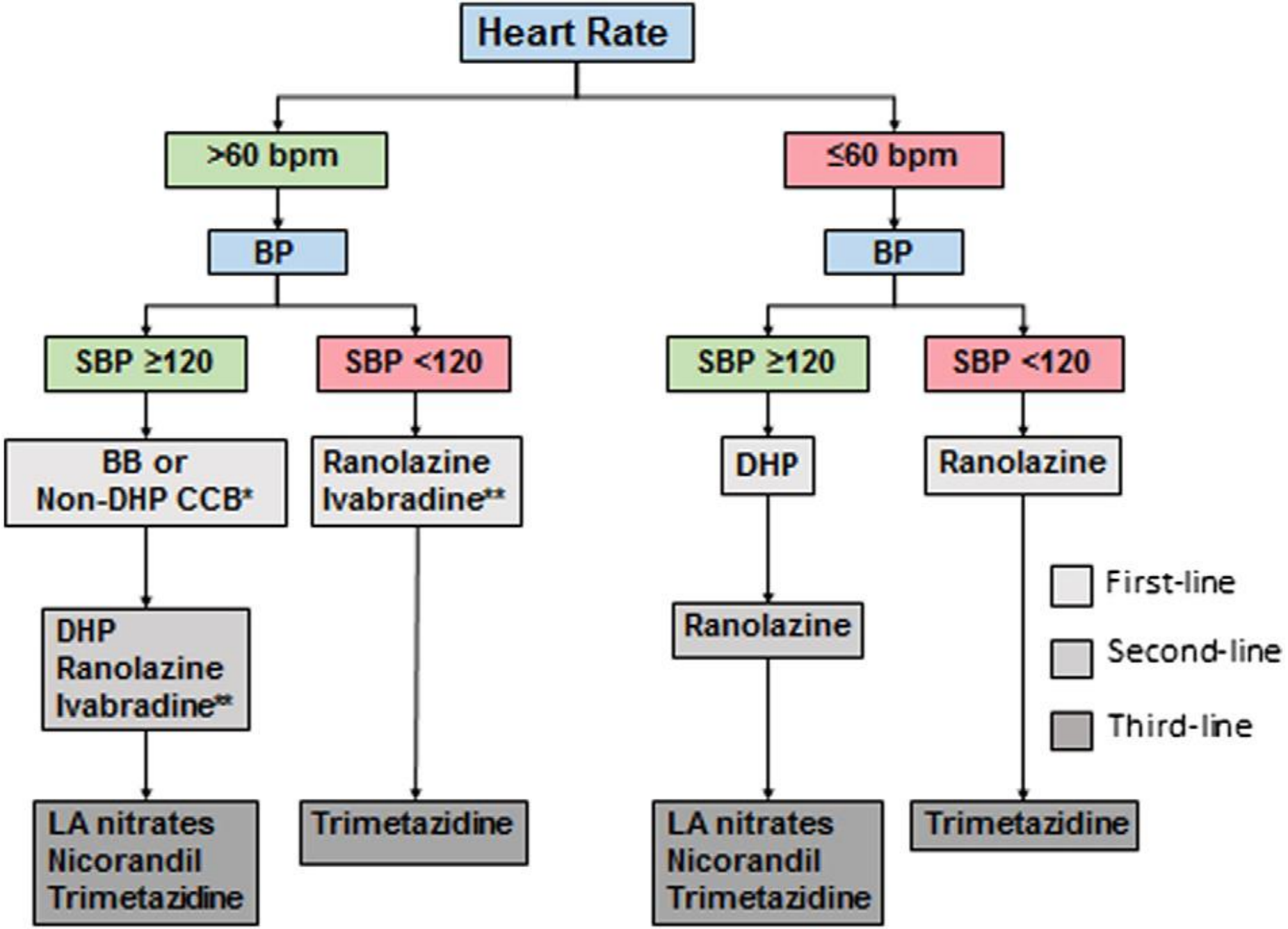
- **1300 subjects in randomised clinical trials**

- A U T H O R S ’ C O N C L U S I O N S
- Implications for practice:
- This meta-analysis confirms the modest efficacy of trimetazidine in the treatment of stable angina, compared with placebo. The data available are too sparse to make recommendations for use of trimetazidine both as monotherapy, or in a combination with conventional anti-anginal agents. Trimetazidine may result in fewer withdrawals due to adverse events than placebo or other anti-anginal agents but robust data are lacking

- Proven poor efficacy

Preferred drugs (listed alphabetically)

Intolerance to initial therapy	**DHP's, Ivabradine, LA Nitrates, Nicorandil, Ranolazine, Trimetazidine.**
Low HR	**DHP's, LA Nitrates, Nicorandil, Ranolazine, Trimetazidine**
Low BP	**Ivabradine, Ranolazine, Trimetazidine**
AF	**β-blockers (rate control), Non-DHP's (rate control), Ranolazine**
CHF	**β-blockers, Ivabradine, possibly Nitrates**
Microvascular ischaemia	**β-blocker, CCB, Nicorandil, Ranolazine**
Diabetes Mellitus	**Ranolazine, Trimetazidine, Vasodilating β-blockers**
COPD	**β-blockers (cardio-selective), DHP's, Ivabradine, LA Nitrates, Nicorandil, Ranolazine, Trimetazidine**



Manolis et al Int J Cardiol 220 (2016) 445–453

A new drug class:

A late sodium current inhibitor

New Drug Class

Ranolazine for chronic stable angina

David T Nash, Stephen D Nash

Lancet 2008; 372: 1335–41

Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

Ranolazine: Augmenting the Antianginal Armamentarium*

John A. Cairns, MD, FRCPC, FACC
Vancouver, Canada

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
Long Term Safety

Morrow DA, et al. JAMA. 2007;297:1775-1783

J Am Coll Cardiol 2004;43:1375- 82

Chaitman BR, et al. JAMA. 2004;291:309-316

Stone PH, et al. J Am Coll Cardiol 2006;48:566-575.

N=9,834

Reference on CCB's in the American Guidelines

852. Frishman WH, Sica DA. Calcium Channel Blockers. In: Frishman WH, Sonnenblick EH, Sica DA, editors. Cardiovascular Pharmacoherapeutics. New York: McGraw-Hill; 2003.
853. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. N Engl J Med. 1999;341:1447–57.
854. Ezekowitz MD, Hossack K, Mehta JL, et al. Amlodipine in chronic stable angina: results of a multicenter double-blind crossover trial. Am Heart J. 1995;129:527–35.
855. Boman K, Saetre H, Karlsson LG, et al. Antianginal effect of conventional and controlled release diltiazem in stable angina pectoris. Eur J Clin Pharmacol. 1995;49:27–30.
856. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. Drugs. 1996;51:792–819.
861. Parmley WW, Nesto RW, Singh BN, et al. Attenuation of the circadian patterns of myocardial ischemia with nifedipine GITS in patients with chronic stable angina. N-CAP Study Group. J Am Coll Cardiol. 1992;19:1380–9.

Review

Review

n=103; 2 arms of treatment; 77 days on treatment. Holter

n=41; 2 arms of treatment; ? Days on treatment. Holter, QoL

Review

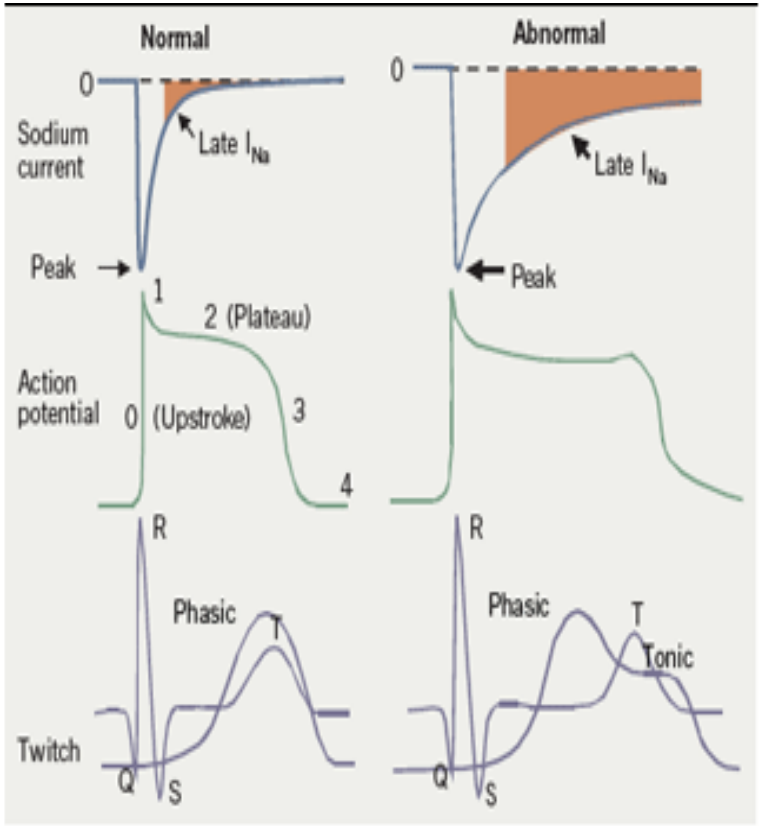
n=207; 2 arms of treatment; 70 days on treatment. Holter

N=251

The sodium current

- 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.

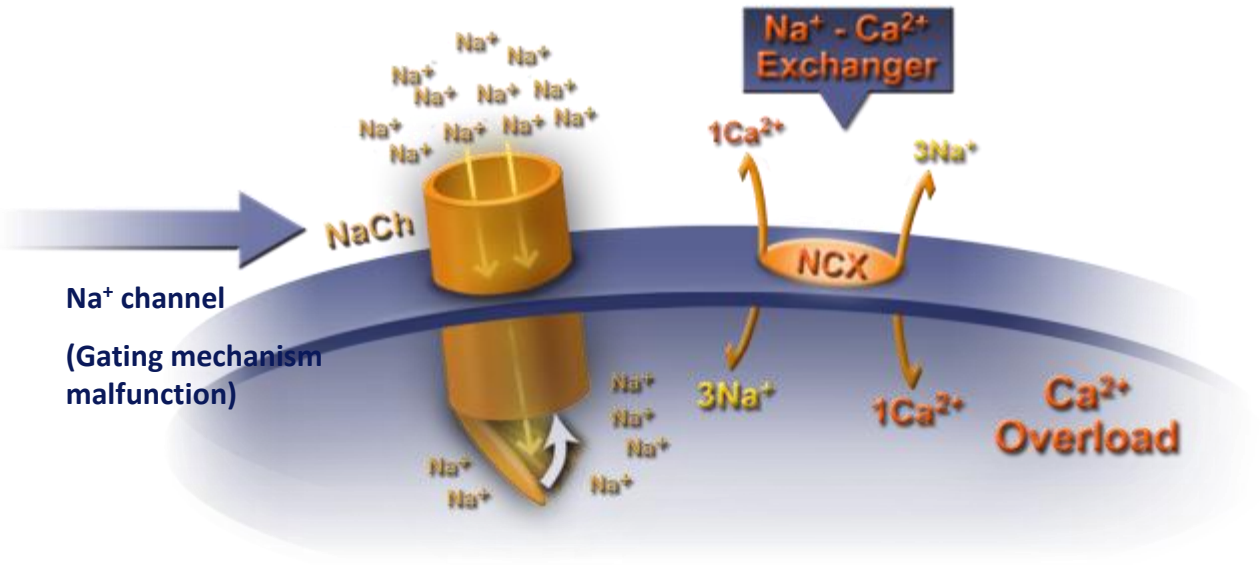
The cardiac sodium channel current.



Elaborated from:
Camm J. Br J Cardiol 2008;15(Suppl 1):S5-S7.

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.)



Electrical instability

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

Mechanical dysfunction

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

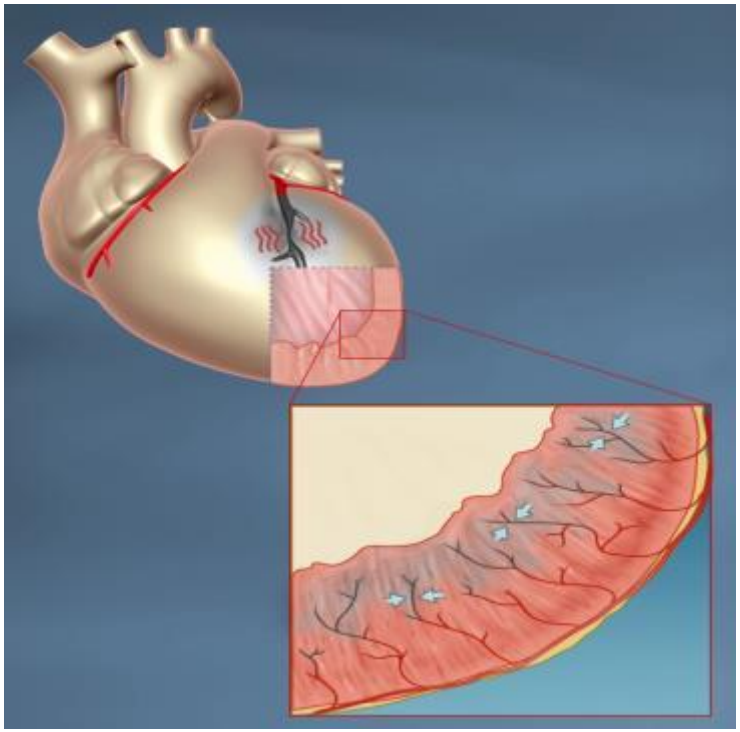
Oxygen supply and demand

- **Increased ATP consumption**
- **Decreased ATP formation**

APD: action potential duration; VT: ventricular tachycardia.

Elaborated from:
1. Saint DA. *Br J Pharmacol* 2008;153(6):1133-42;
2. Belardinelli L, et al. *Heart* 2006;92(Suppl IV):iv6-14.

An increase in INa impairs diastolic relaxation, increases MVO2 and reduces coronary O2 supply



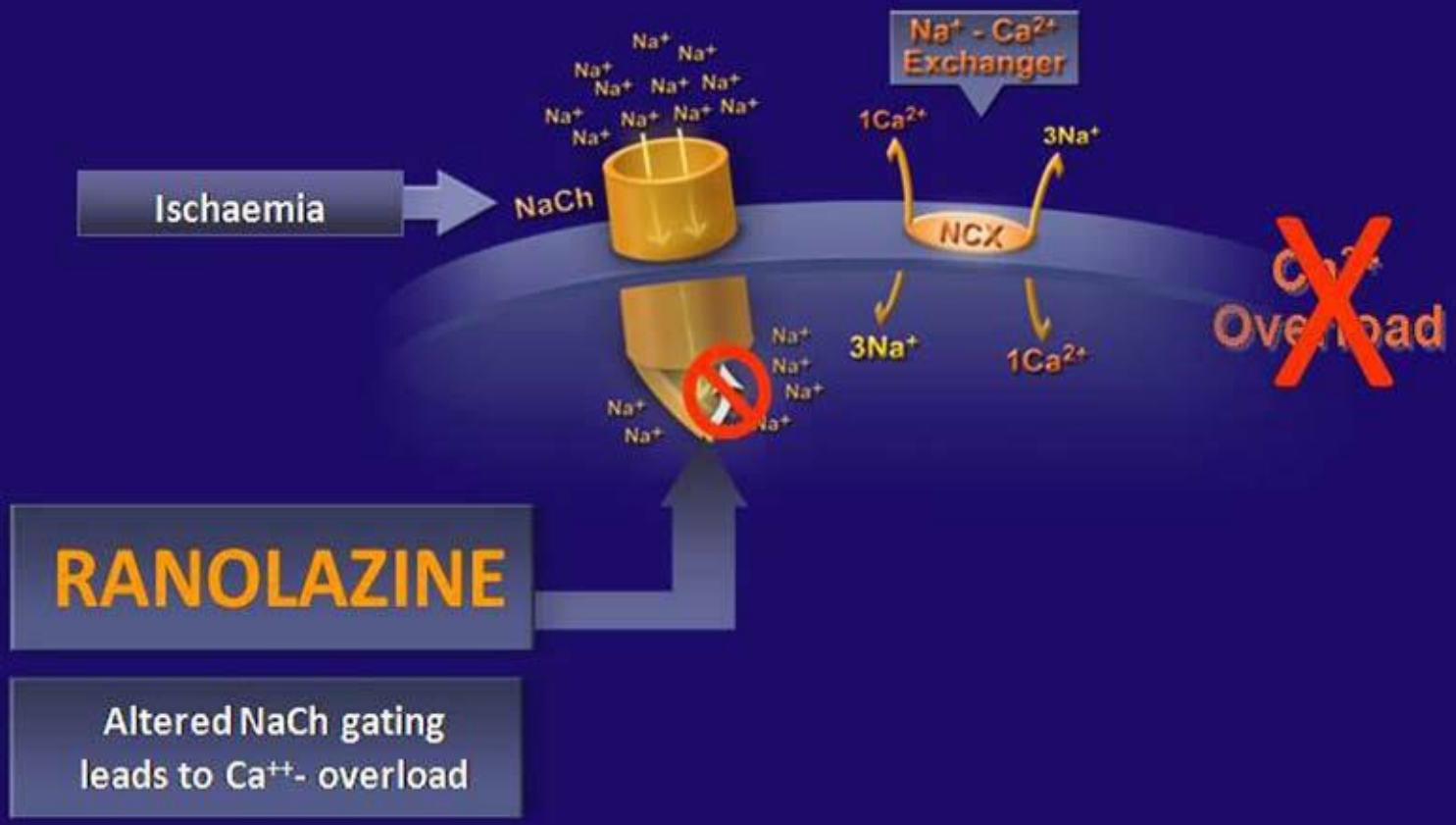
Na^+ and Ca^{++} overload Increased diastolic wall tension:

- Increases MVO_2 (myoc. O2 consumption)
- Compresses intramural small vessels
- Reduces endocardial blood flow

Worsens ischaemia and angina

1. Saint DA. *Br J Pharmacol* 2008;153(6):1133-42
2. Hasenfuss G, et al. *Clin Res Cardiol* 2008;97:222-6.
3. Shryock JC, et al. *Br J Pharmacol* 2008:153;1128-32.

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



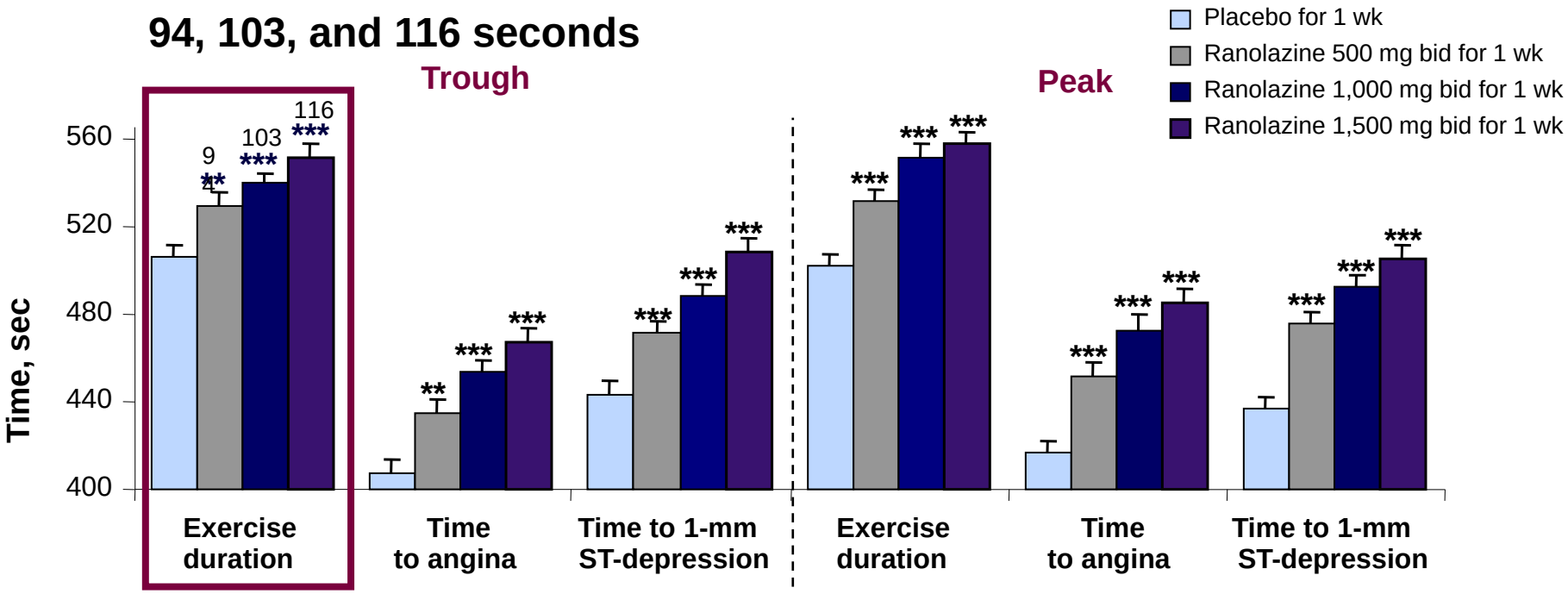
Adapted from Zerumsky K & McBride BF. *Am J Health Syst Pharm* 2006;63:2331–2338

What is clinically relevant

- What parameters/endpoints are important when assessing clinical trials in angina?
  - Exercise time
  - Time to ischaemia
  - Angina frequency
  - GTN usage
  - QoL

1. Borer et al Circulation 2003; 107: 817; 2. Chaitman et al JAm Coll Cardiol 2004; 43: 75

MARISA: efficacy on exercise parameters

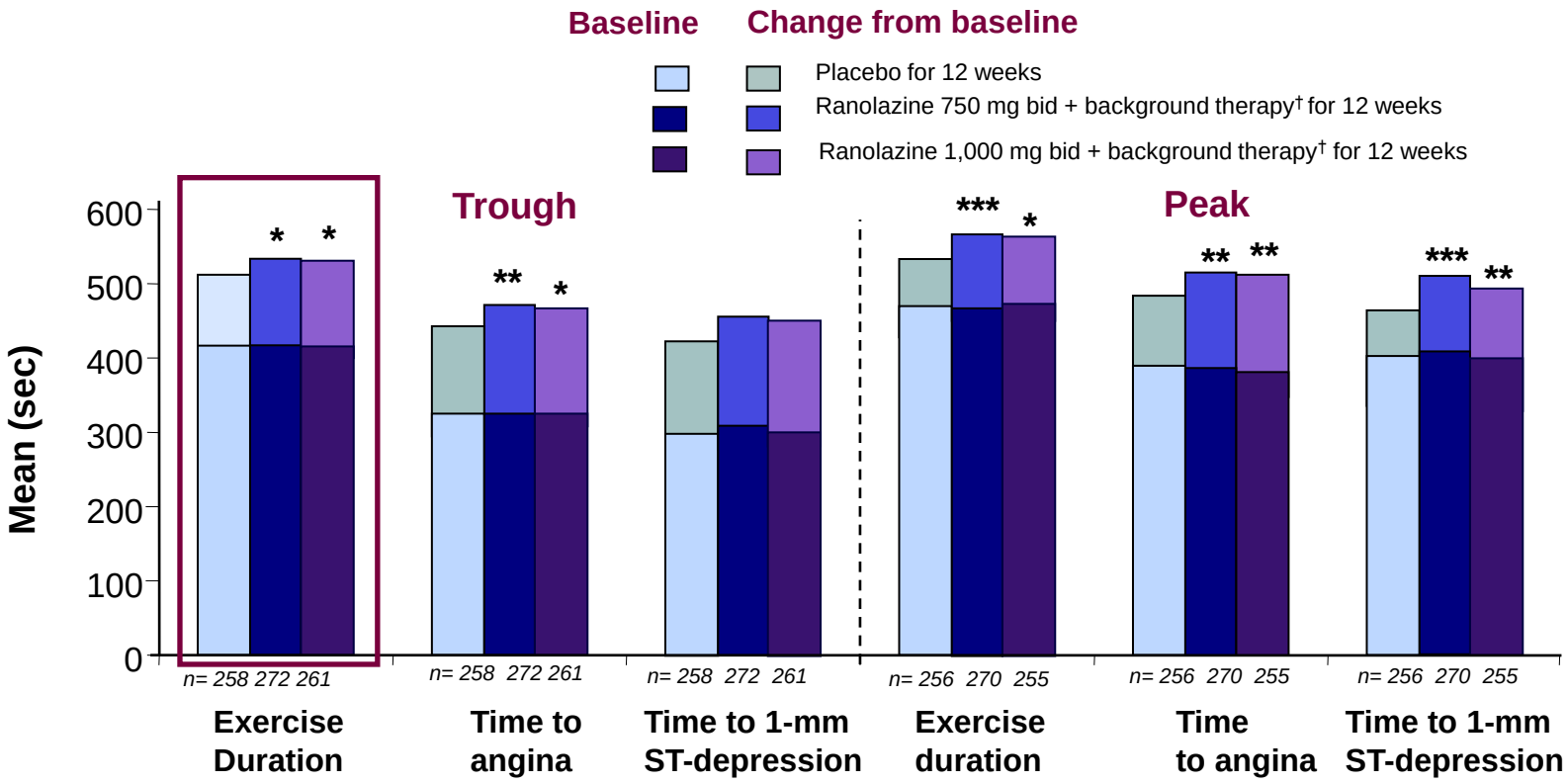


n=175 pts who completed three of the four treatment periods.
***p≤0.005 vs. placebo ; ***p<0.001 vs. placebo*

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:
Chaitman BR, et al. *J Am Coll Cardiol* 2004;43:1375-82 (from Tab II).

CARISA: efficacy on exercise treadmill parameters after 12 weeks of treatment



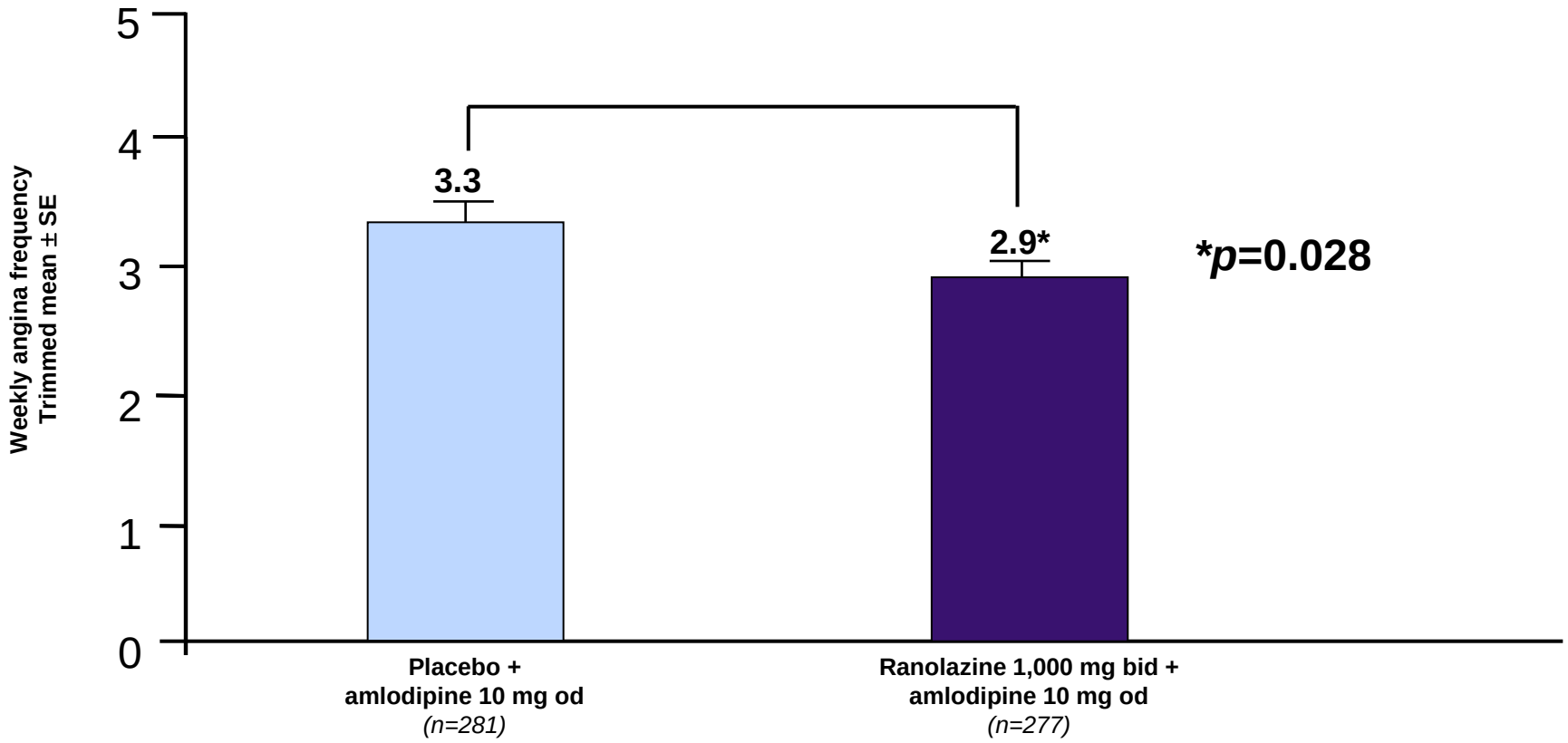
*Change from baseline: *p<0.05; **p≤0.01 ***p≤0.001 vs. placebo n=791, ITT/LOCF; LS means ± SE.*

†Background therapy: atenolol 50 mg od or amlodipine 5 mg od or diltiazem 180 mg od.

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:
Chaitman BR, et al. *JAMA*. 2004;21;291(3):309-16. (from Tab II).

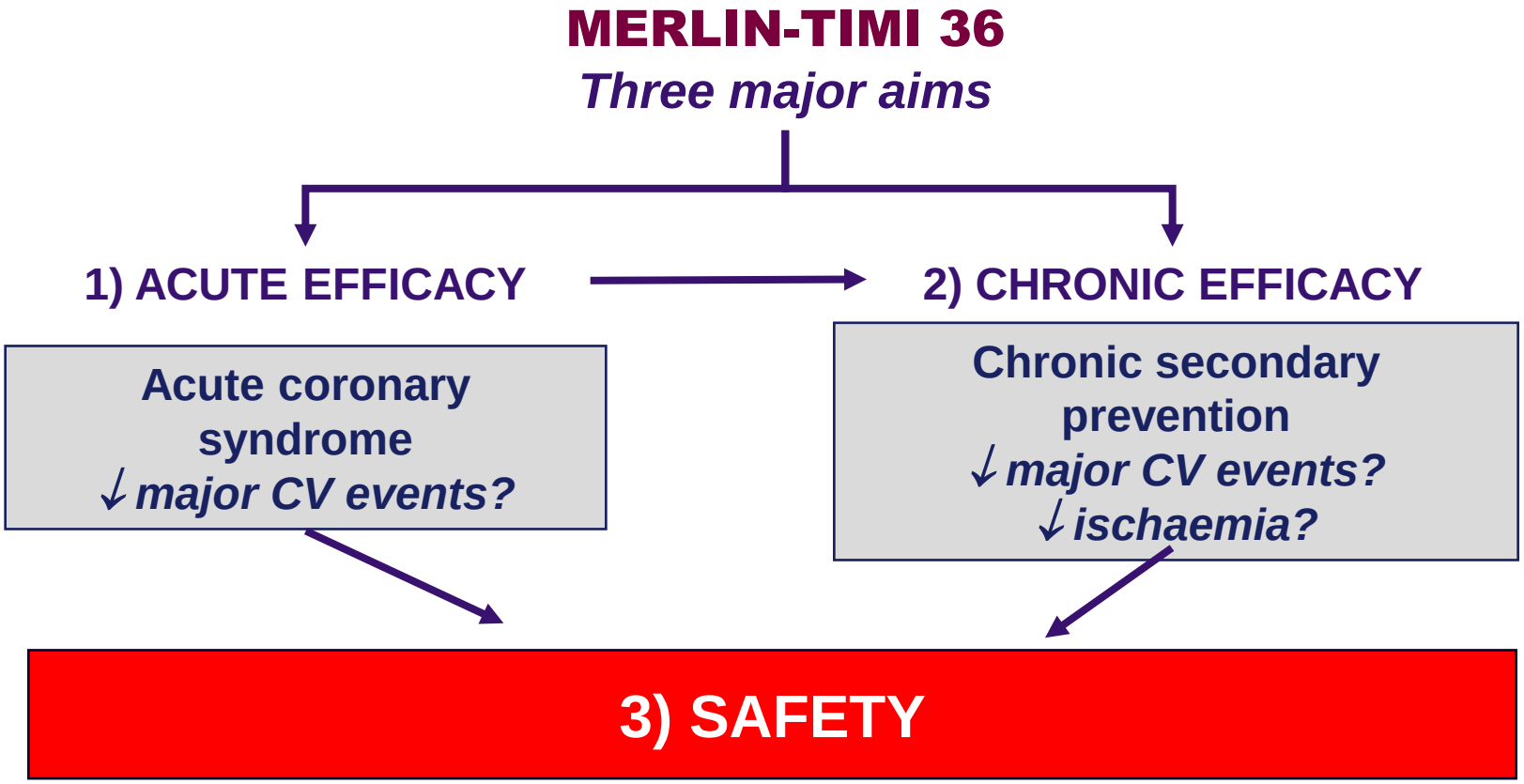
ERICA: effect on angina frequency



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.

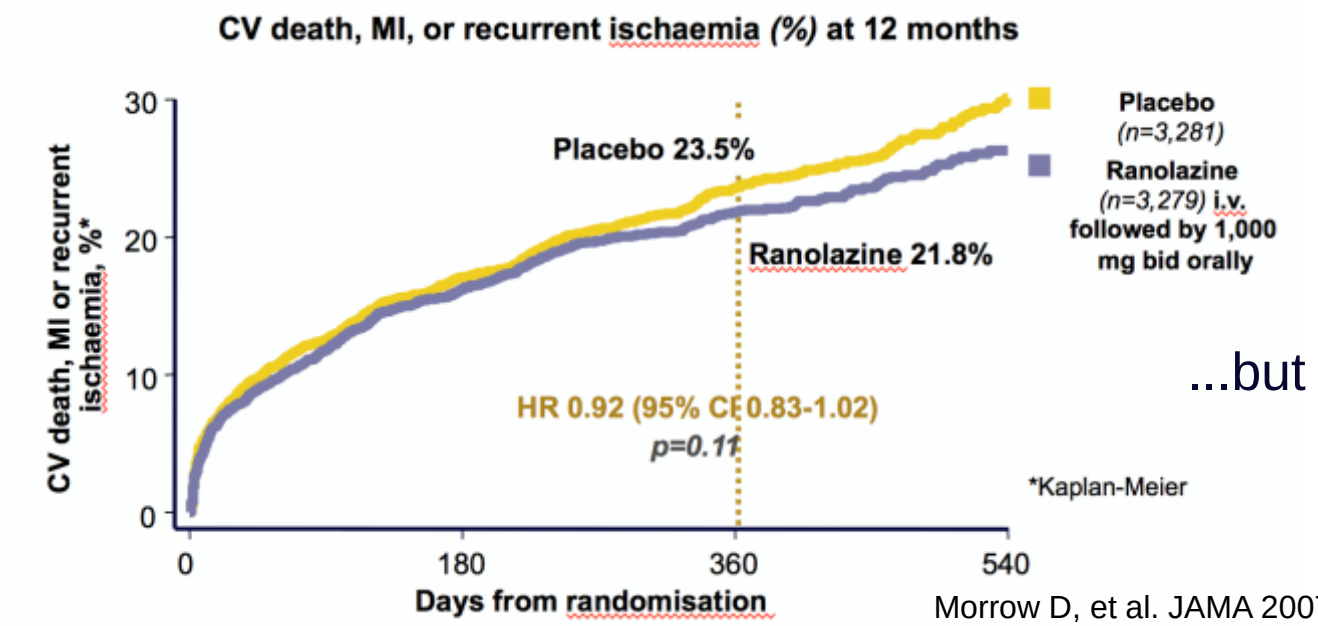
Adapted from:
Stone PH, et al. *J Am Coll Cardiol.* 2006;48(3):566-75

At the request of the FDA
safety in acute coronary syndrome
MERLIN-TIMI 36



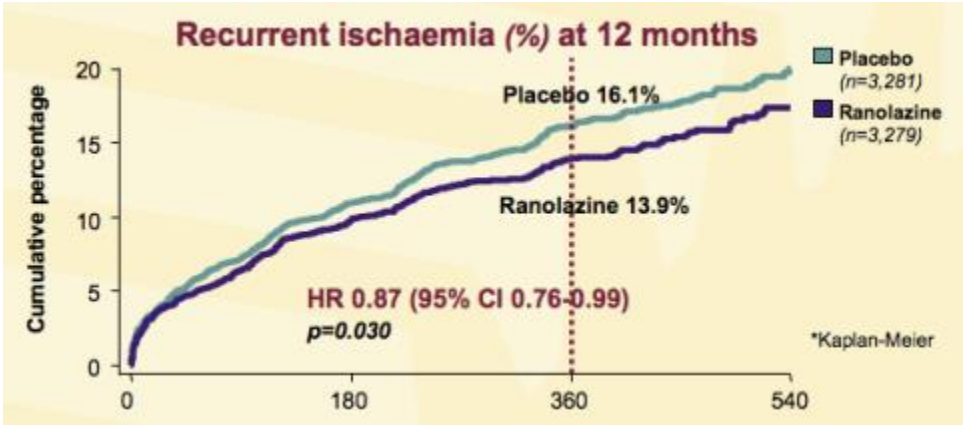
Morrow D, et al. JAMA 2007;297:1775-83.

MERLIN-TIMI 36: primary efficacy end-point

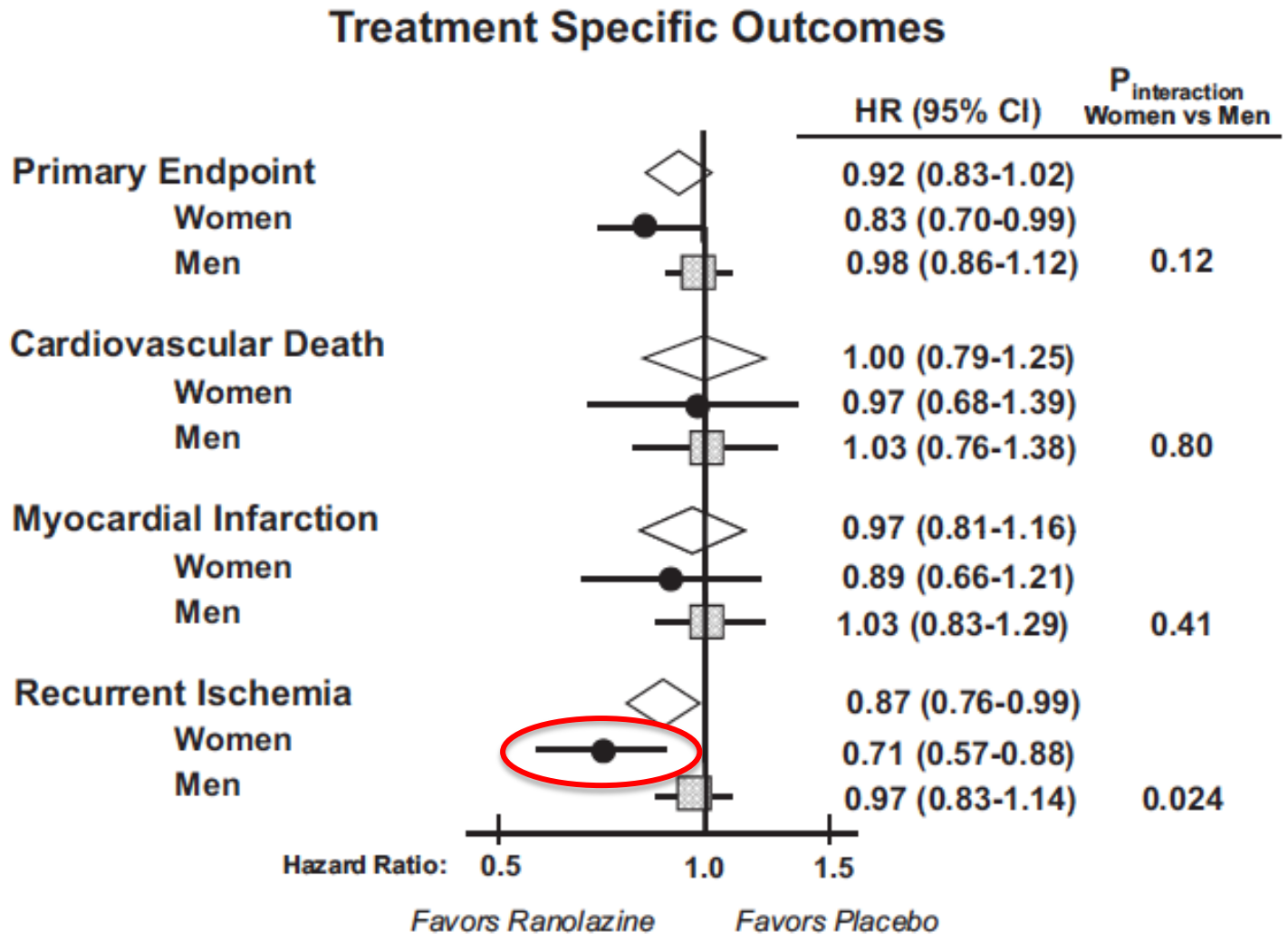


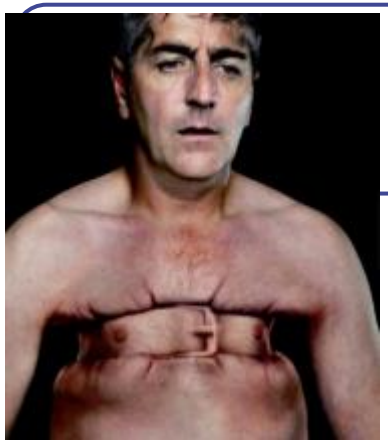
...but .....

Morrow D, et al. JAMA 2007;297:1775-83.



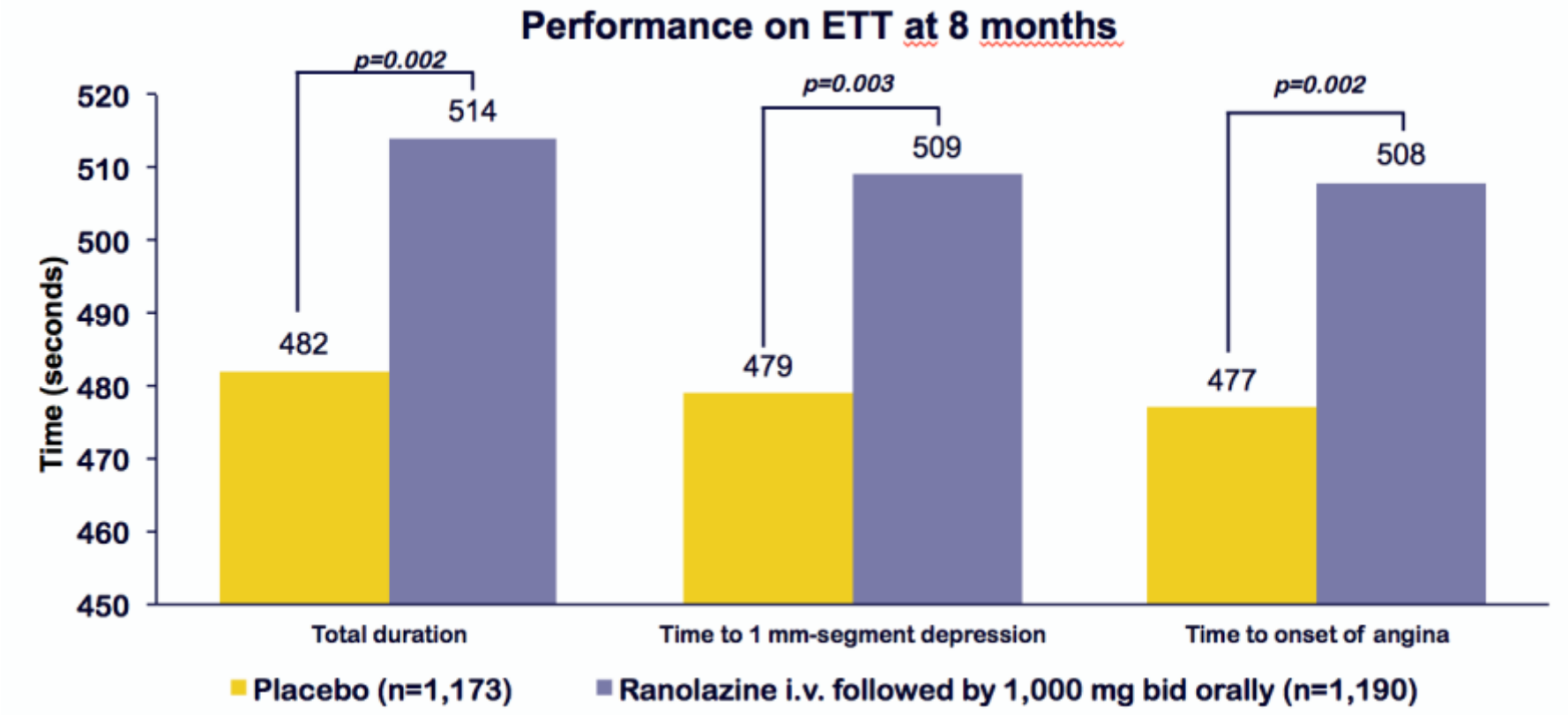
MERLIN-TIMI 36





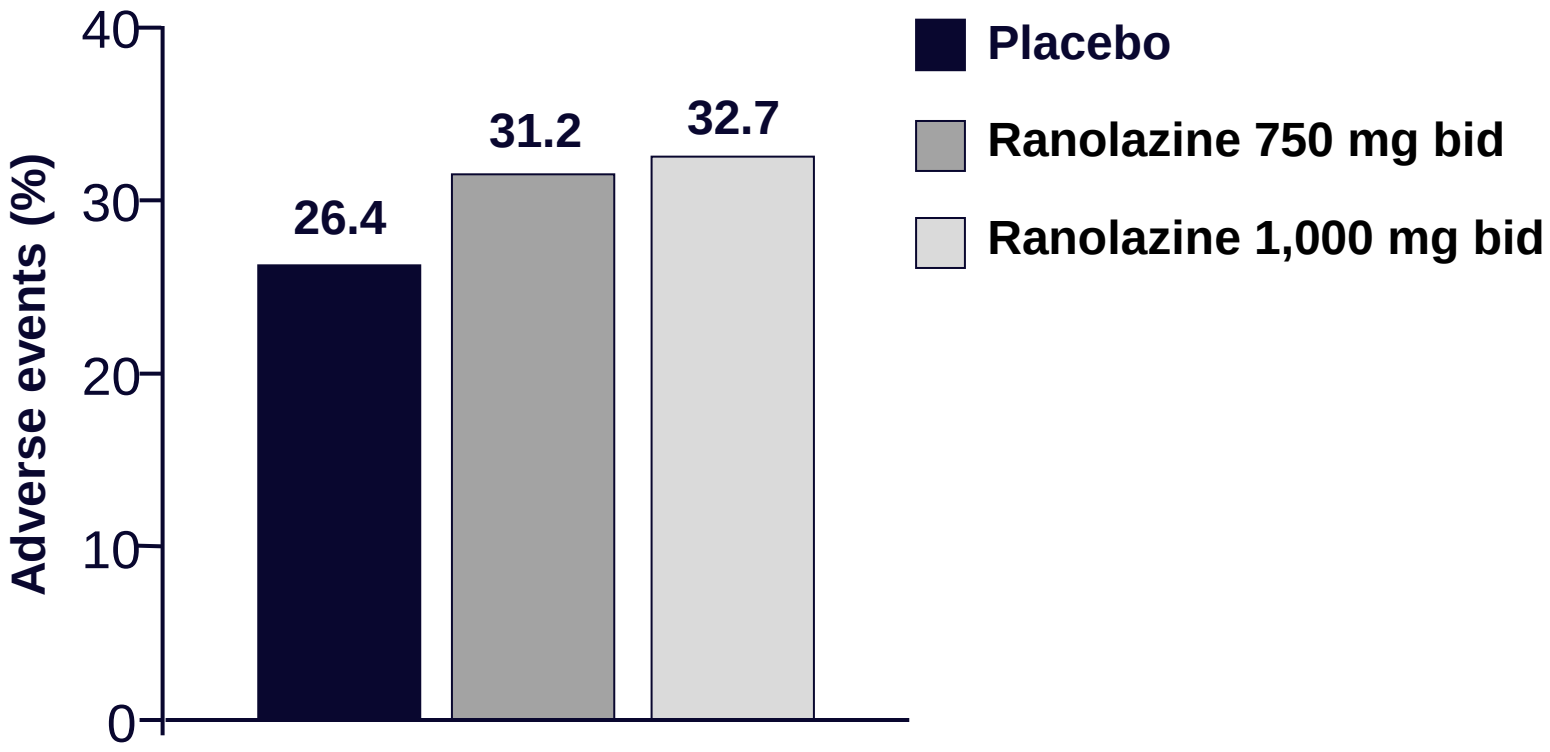
MERLIN-TIMI 36: subgroup analysis

patients with ACS and chronic angina



Wilson SR, et al. J Am Coll Cardiol 2009;53(17):1510-6.

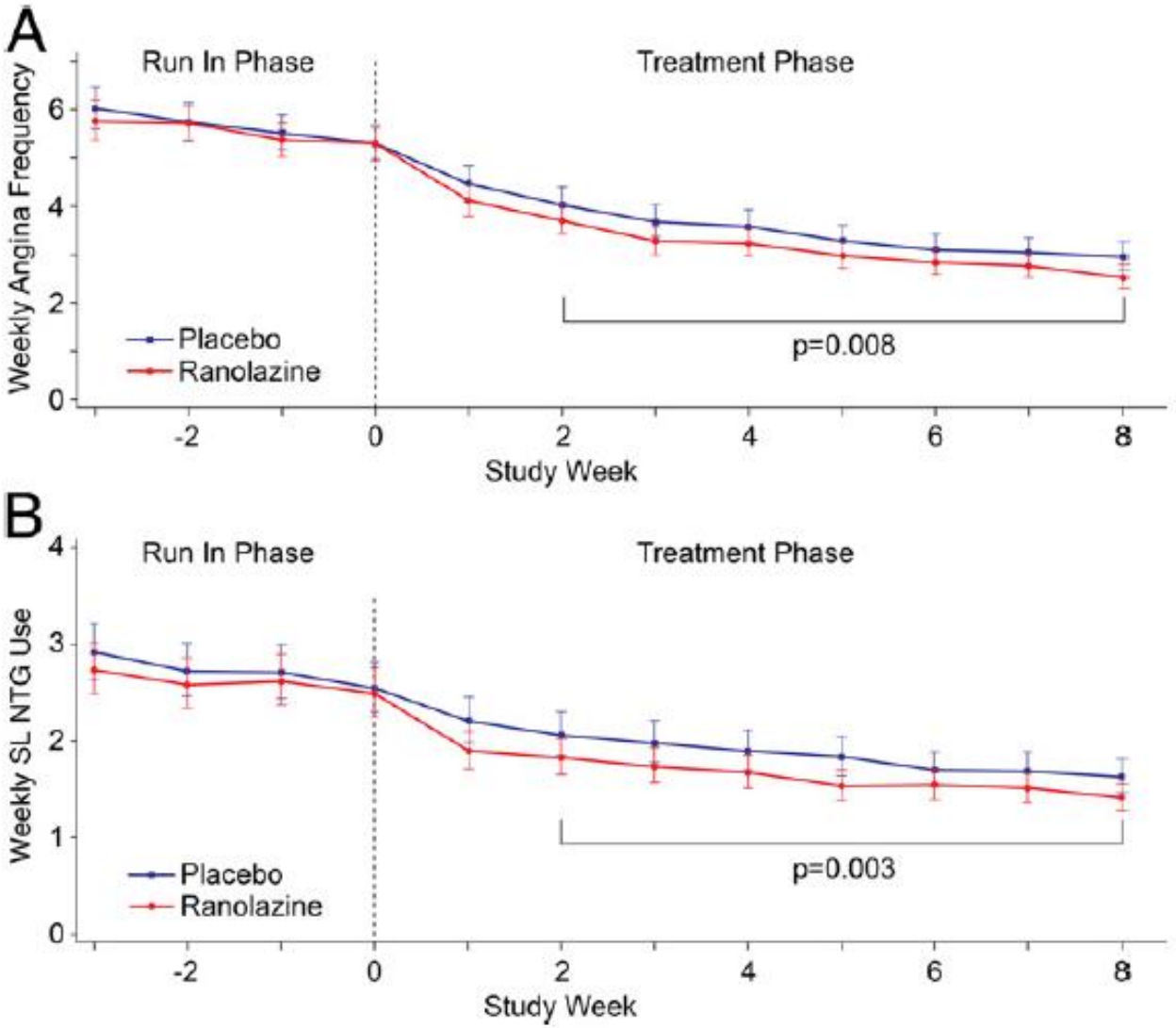
Very few adverse events



The most common dose-related adverse events were constipation, dizziness, nausea, asthenia.

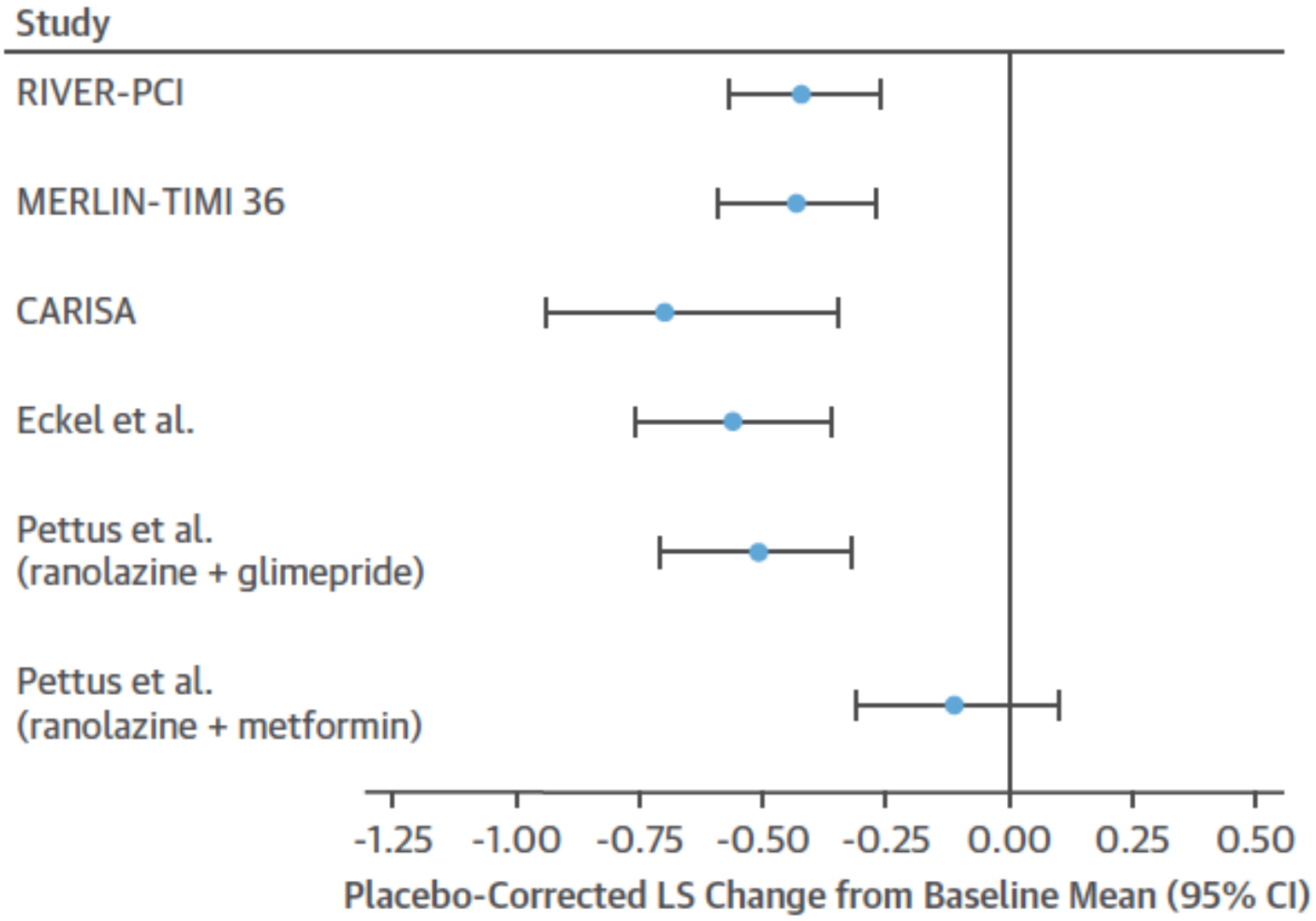
Modified from: Chaitman BR, et al. JAMA 2004;291:309-16.

TERISA – **T**ype 2 diabetes **E**valuation of **R**anolazine **I**n **S**ubjects with **A**ngina pectoris



Kosiborod et al J Am Coll Cardiol 2013;61:2038–45

Effect of Ranolazine on HbA1C in Patients with DM



Beneficial effect of Ranolazine in patients with microvascular angina (MVA)

The results of four trials show that, among patients with MVA, those with reduced CFR and evidence of exercise-induced myocardial ischaemia may have appreciable benefits from ranolazine administration

Crea and Lanza EHJ 2016 37, 1514

- Mehta et JACC Cardiovasc Imaging 2011; 4:514–522 (n=20; 20F)
- Villano et al Am J Cardiol 2013; 112:8-13 (n=15; 3M, 12F)
- Tagliamonte et al Echocardiography 2015; 32:516–251 (n=58; 39M, 19F)
- Bairey Merz et al Eur Heart J 2016; 37:1504 – 1513 (n=128; 6M,122F)

Dosing regimen - Ranolazine

Start: 375 mg twice daily

2-4 weeks 500 mg twice daily

2-4 weeks 750 mg twice daily

Which patient groups for Ranolazine ?

Continuing angina despite first line therapy with beta blockers and/or CCB's – proven highly effective ADD ON (no vascular effects)

Chronic angina high risk revascularisation or after successful revascularisation

Diabetes with successful revascularisation or with non-obstructive CAD and diabetic microvascular dysfunction

Angina in the presence of CAD and AF

Angina normal coronary arteries (MVA) – highly effective

Elderly with chronic ischaemia multiple risk factors and/or intolerant to or ineffective therapy

Angina with contraindication to other anti-anginals

Key takeaway messages

- Ranolazine is a first in class drug
- Novel mode of action: ischemia treatment at the cardiomyocyte
- Suitable for all causes of ischemia (not only coronary artery disease)
- Large database (N>9,500) in well conducted RCT's
- Well tolerated
- Safe (positive in subgroups: Angina pectoris, Diabetes)
- Very solid and strong symptomatic data
  - Anti-ischemia
  - Anti-Angina: less Angina, increase in exercise capacity
- Effective in monotherapy or in combination with beta-Blocker or CCB
- Positive metabolic profile: reduction of HbA1c
- No effect on heart rate or blood pressure

Conclusions

- Despite best efforts with OMT and revascularization about 30% of patients with SCAD continue to have symptoms independent of treatment, resulting in decreased QoL
- Guidelines give guidance
- There is the potential for management improvement
- Co-morbidities plus simple clinical assessment of heart rate and systolic BP may enable better choice of therapy
- Inadequate control of symptoms increases healthcare costs
- The use of the new novel non-vascular anti-ischaemic therapy, Ranolazine increases the possibility of optimal anginal symptomatic control

Royal Brompton Hospital, London

Thank You!

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

Ranolazine European SmPC. Revised April 2014.

Conclusions

- Despite best efforts with OMT and revascularization about 30% of patients with SCAD continue to have symptoms independent of treatment, resulting in decreased QoL
- Guidelines give guidance
- There is the potential for management improvement
- Routine clinical practice should include regular assessment of the adequacy of stable angina control (? STAR chart)
- The use of a simple checklist would facilitate assessment of disease burden
- Inadequate control of symptoms increases healthcare costs
- The use of the new novel non-vascular anti-ischaemic therapy, Ranolazine increases the possibility of optimal anginal symptomatic control