Update on the Management of Chronic Stable Angina

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Disclaimer and Declaration of Competing Interests

- None

The continuing burden of stable angina: Insight from ADVANCE Registry

- 2,039 stable angina patients (73% male, age 68)
- 419 cardiologists in 2 years
- 66% prior re-vascularization
- Stable angina recurred in 59%

- Despite:
  - Beta blockers - 78%
  - CCB - 40%
  - Long acting nitrates - 53%
  - Ivabradine - 11%
  - Trimetazidine - 7%,
- 50% of 2,024 remained symptomatic and -30% QoL

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

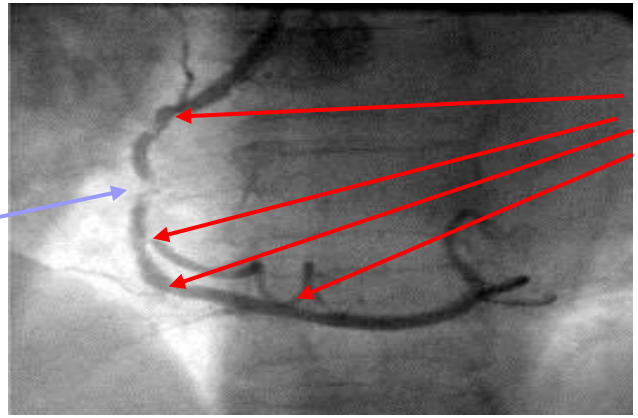
A paradigm that suggests why randomized trials have not demonstrated a survival benefit for revascularization in SIHD

Stable IHD

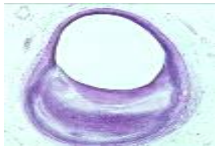
ACS

Severe Obstruction (angina, no rupture) vs Moderate Obstruction (no angina, likely to rupture)

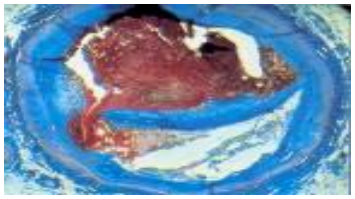
Severe fibrotic plaque
- **Severe obstruction**
- **No /minimal lipid**
- **Fibrosis, Ca^{2+}**



Vulnerable plaque
- **Moderate (to severe) obstruction**
- **Eccentric plaque**
- **Lipid pool**
- **Thin cap**



Plaque rupture
- **Acute MI**
- **Unstable angina**
- **Sudden death**



Exertional angina
- **(+) ETT**

Revascularization
Anti-anginal Rx

Angina +/-
Pharmacologic stabilization
Thrombolytic / Urgent PCI
Early identification of high-risk?

Modified from courtesy of PH Stone, MD

International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA)

Maron DJ et al, New Eng J Med 2020, 382;15:1395-1407

ISCHEMIA – Study Flow

Enrolled (8518)

Screen Failure (3339)
Major Reasons:
- Insufficient ischemia (N = 1350)
- No obstructive CAD (N = 1218)
- Unprotected LMD (N =434)

Randomized (5179)
Study CCTA in 73% of randomized participants

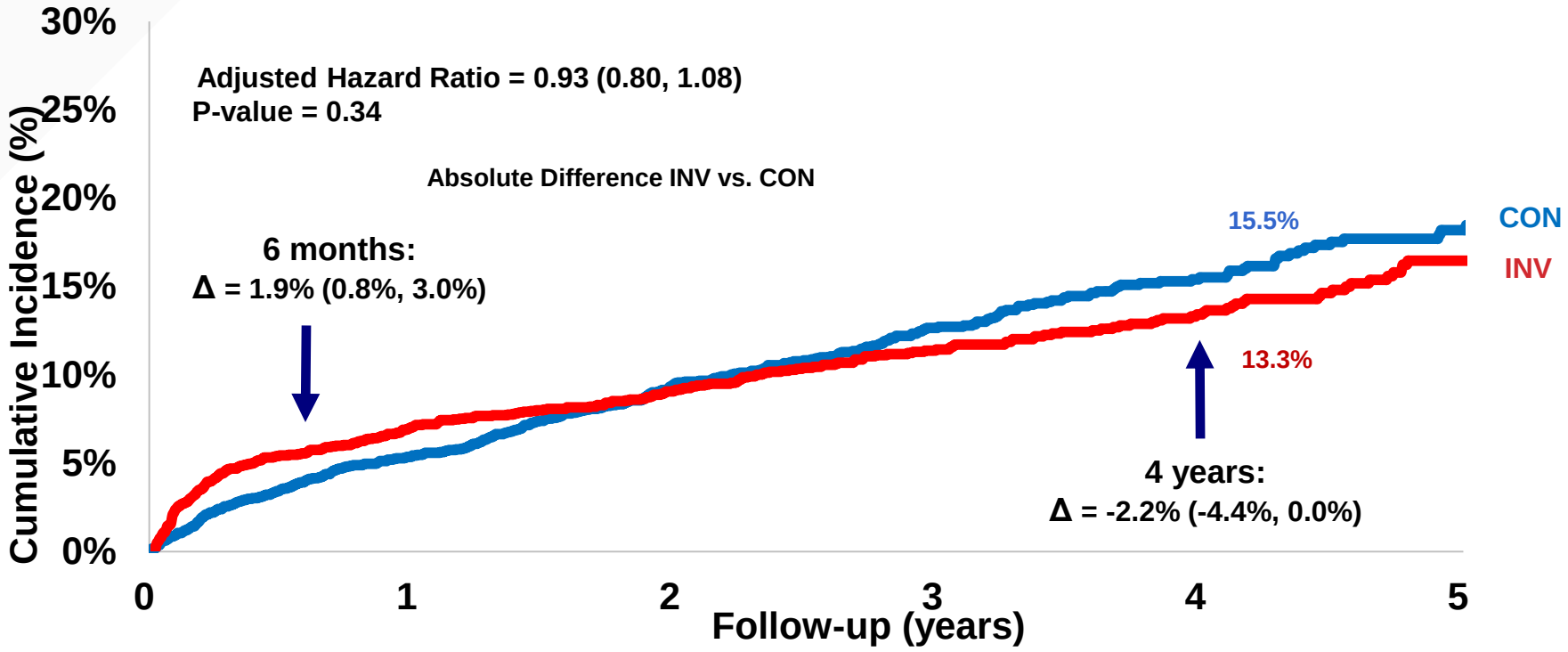
Randomized to INV (2588)

Median follow-up for survivors 3.3 years
(IQR 2.2 to 4.3 years)
Proportion of follow-up completed: 99.4%

Randomized to CON (2591)

Median follow-up for survivors 3.3 years
(IQR 2.2 to 4.4 years)
Proportion of follow-up completed: 99.7%

Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

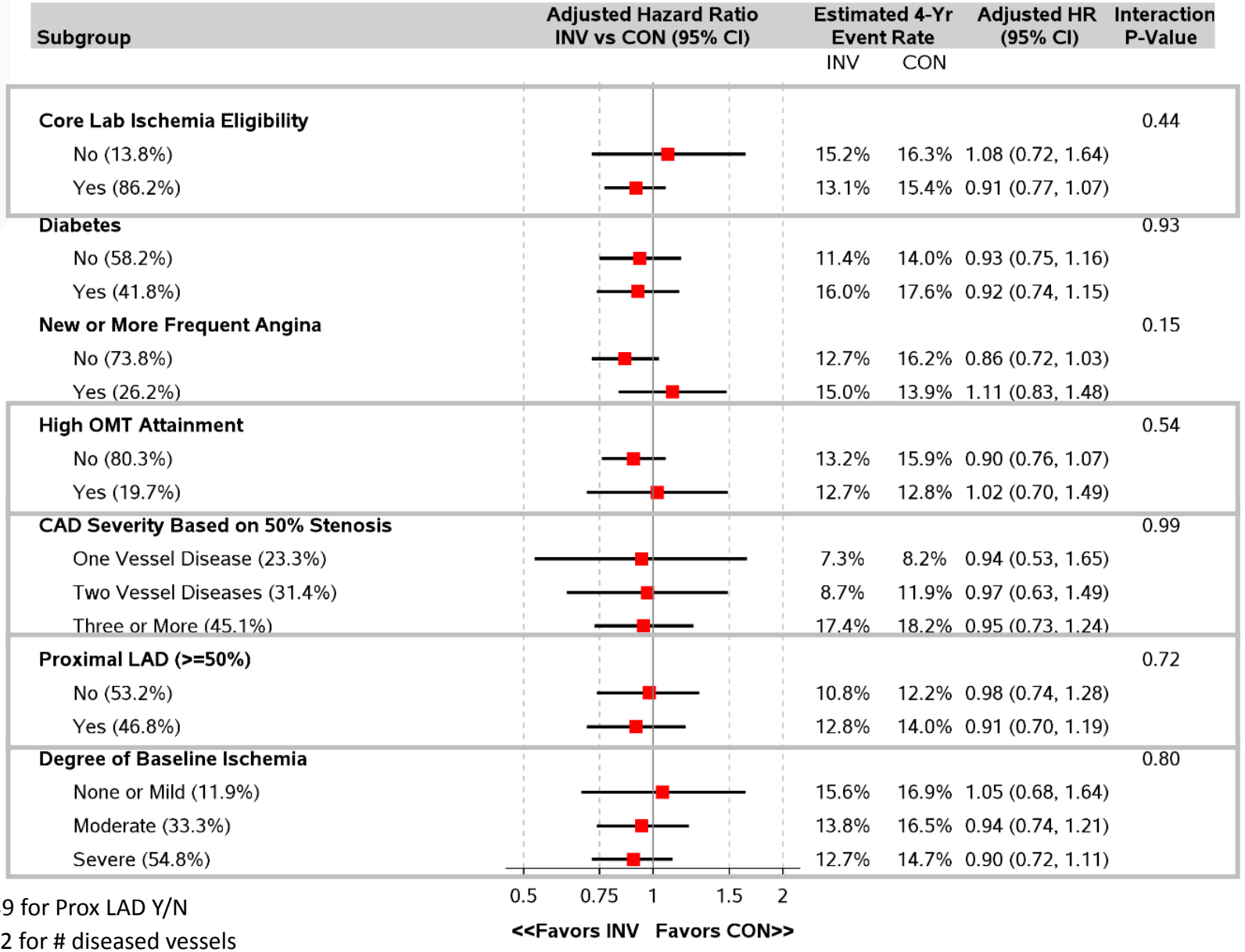


Subjects at Risk

CON	2591	2431	1907	1300	733	293
INV	2588	2364	1908	1291	730	271

Maron DJ et al, New Eng J Med 2020, 382;15:1395-1407

Primary endpoint : Pre-specified Important Subgroups : There was no heterogeneity of treatment effect



N=3739 for Prox LAD Y/N

N=2982 for # diseased vessels

Conclusions from ISCHEMIA trial

- ISCHEMIA is the largest trial of an invasive vs conservative strategy for patients with SIHD
- Overall, an initial INV strategy as compared with an initial CON strategy did not demonstrate a reduced risk over median 3.3 years for
  - Primary endpoint - CV death, MI, hospitalization for UA, HF, RCA
  - Major Secondary endpoint - CV death or MI
- The probability of at least a 10% benefit of INV on all-cause mortality was <10%, based on pre-specified Bayesian analysis

Maron DJ et al, New Eng J Med 2020, 382;15:1395-1407

ESC
European Society of Cardiology
European Heart Journal (2019) **00**, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Juhani Knuuti* (Finland) (Chairperson), William Wijns* (Ireland) (Chairperson), Antti Saraste (Finland), Davide Capodanno (Italy), Emanuele Barbato (Italy), Christian Funck-Brentano (France), Eva Prescott (Denmark), Robert F. Storey (United Kingdom), Christi Deaton (United Kingdom), Thomas Cuisset (France), Stefan Agewall (Norway), Kenneth Dickstein (Norway), Thor Edvardsen (Norway), Javier Escaned (Spain), Bernard J. Gersh (United States of America), Pavel Svitil (Czech Republic), Martine Gilard (France), David Hasdai (Israel), Robert Hatala (Slovak Republic), Felix Mahfoud (Germany), Josep Masip (Spain), Claudio Muneretto (Italy), Marco Valgimigli (Switzerland), Stephan Achenbach (Germany), Jeroen J. Bax (Netherlands)

What is new in the ESC 2019 Guidelines? New/revised concepts

- The Guidelines have been revised to focus on CCS instead of stable CAD. (CCS= Chronic Coronary Syndromes)

- This change emphasizes the fact that the clinical presentations of CAD can be categorized as either ACS or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation that can be modified by lifestyle, pharmacological therapies, and revascularization, which result in disease stabilization or regression.

- CAD is chronic, most often progressive, and hence serious, even in clinically apparently silent periods.

- In the current Guidelines on CCS, six clinical scenarios most frequently encountered in patients are identified.

SIX most frequently encountered CCS scenarios

The Guidelines have been revised to focus on CCS instead of stable CAD.

This change emphasizes the fact that the clinical presentations of CAD can be categorized as either ACS or CCS.

CCS are defined by the different evolutionary phases of CAD, excluding situations in which an acute coronary artery thrombosis dominates the clinical presentation.

The most frequently encountered clinic scenarios in patients with suspected or established CCS.

Patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea

Patients with new onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD

Asymptomatic subjects in whom CAD is detected at screening

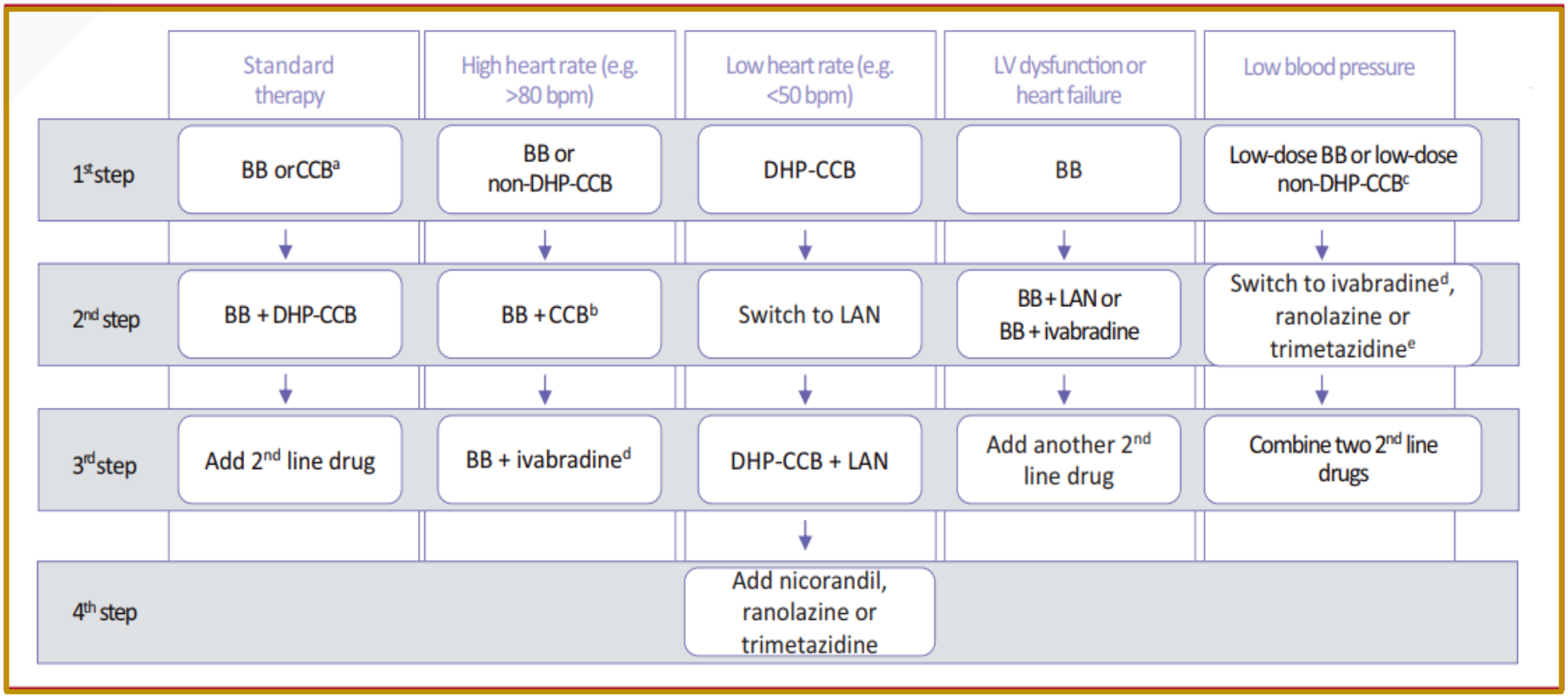
Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization

Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization

Patients with angina and suspected vasospastic or microvascular disease

All of these scenarios are classified as a CCS but involve different risks for future cardiovascular events and the risk may change over time

Suggested stepwise strategy for long term anti-ischaemic drug therapy



Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient' s characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB = non-dihydropyridine calcium channel blocker. a Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step; b The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure; c Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure; d Ivabradine should not be combined with non-DHP-CCB; e Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged

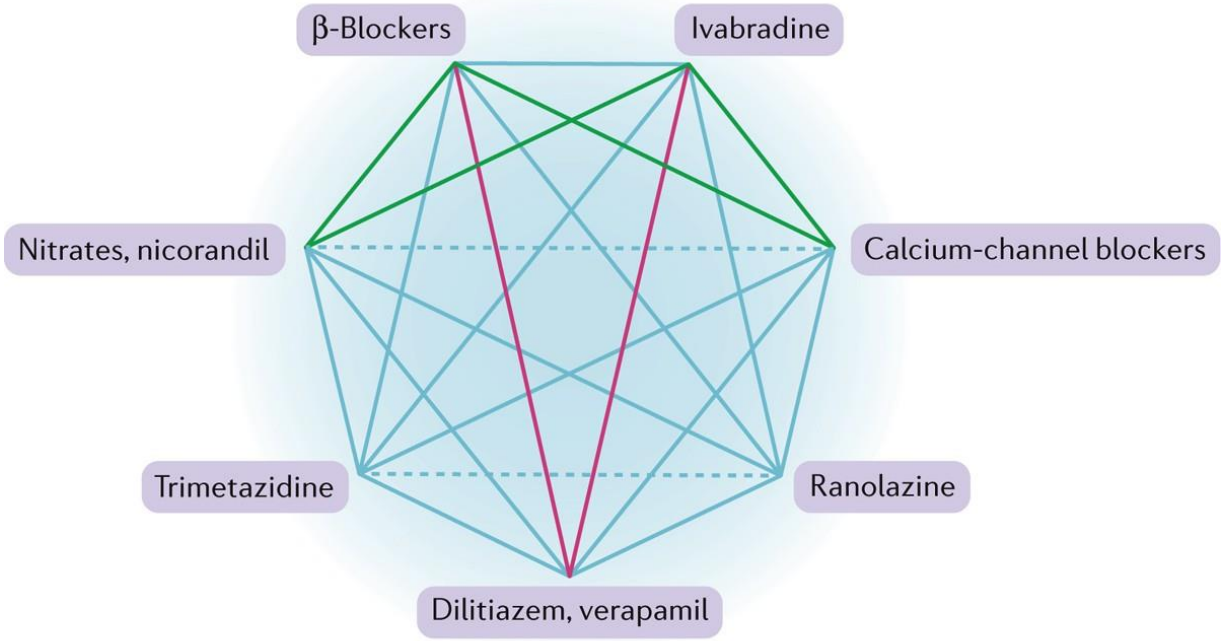
Traditional antianginals

- Blood pressure limitations
- Pulse rate limitations
- Effectiveness limited
- Side effects – headaches with nitrates, fatigue/erectile dysfunction with beta-blockers

EXPERT CONSENSUS DOCUMENT

A 'diamond' approach to personalized treatment of angina

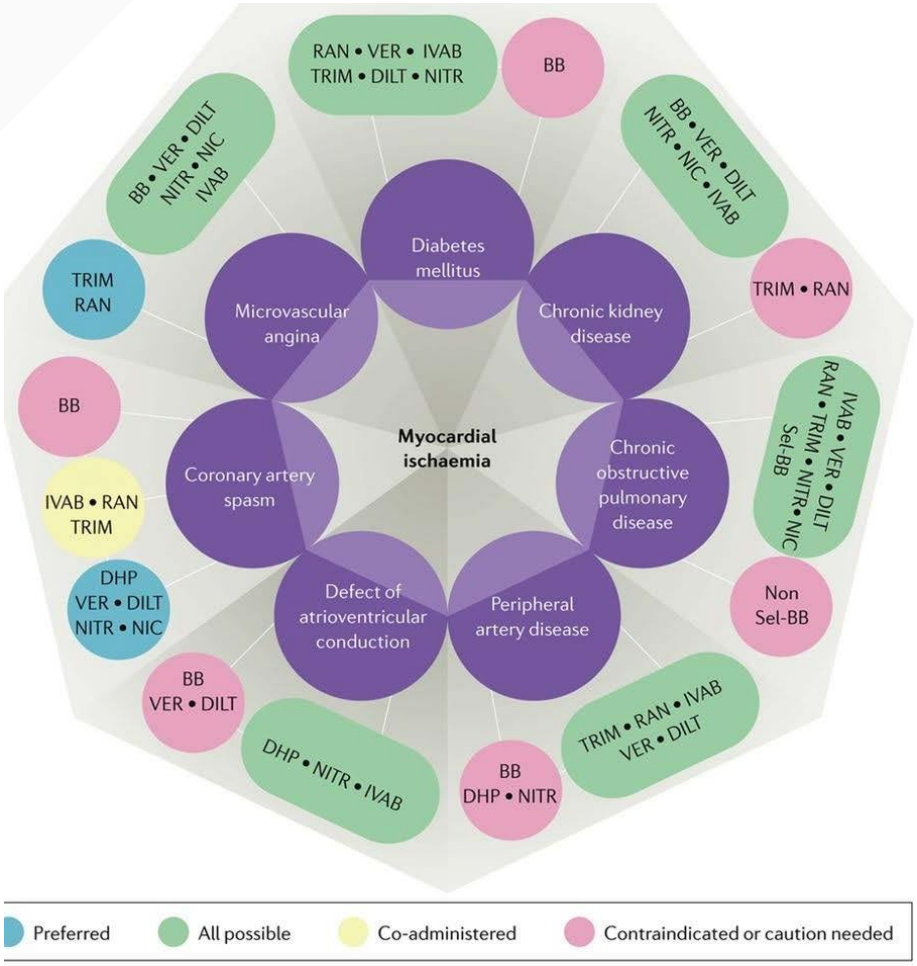
Roberto Ferrari[1,2], Paolo G. Camici[3], Filippo Crea[4], Nicolas Danchin[5], Kim Fox[6], Aldo P. Maggioni[7], Athanasios J. Manolis[8], Mario Marzilli[9,10], Giuseppe M. C. Rosano[11,12] and José L. Lopez-Sendon[13]



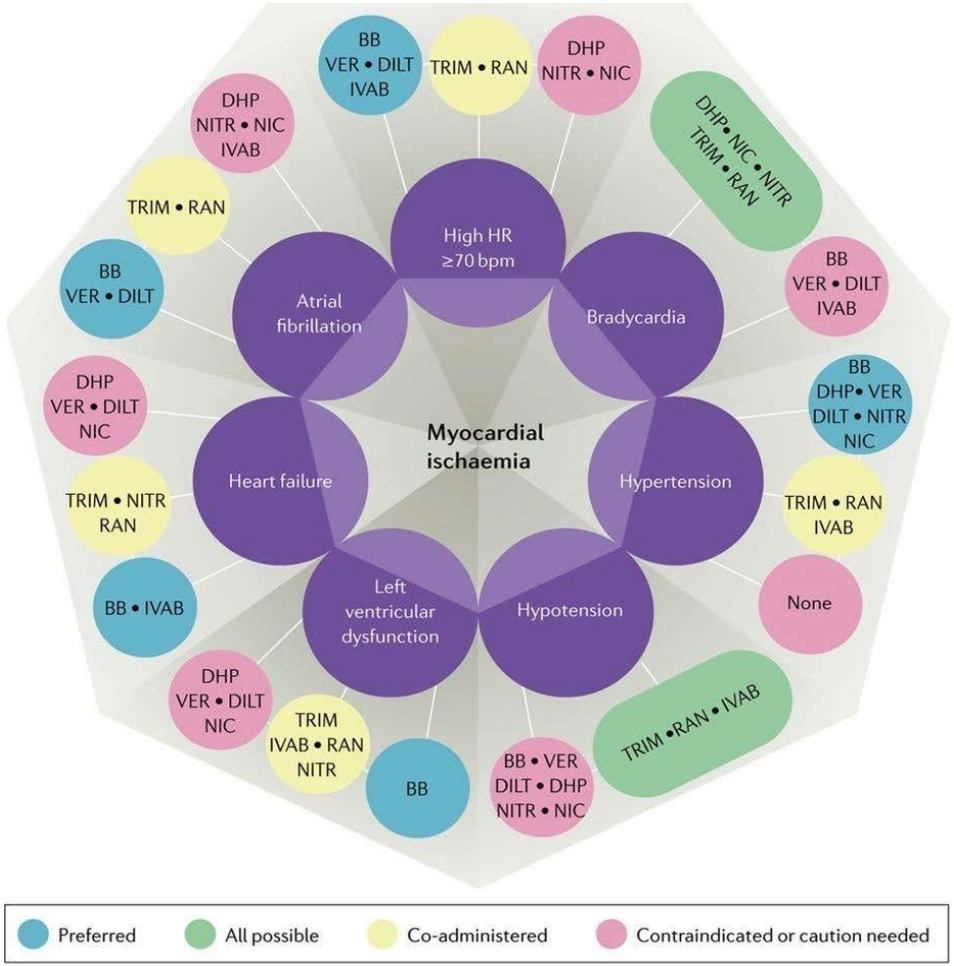
Nature Reviews | Cardiology

Possible combinations of different classes of antianginal drugs. The schematic shows useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (blue solid lines), and drugs with similar actions (blue dashed lines).

Possible combinations of classes of antianginal drugs according to different comorbidities



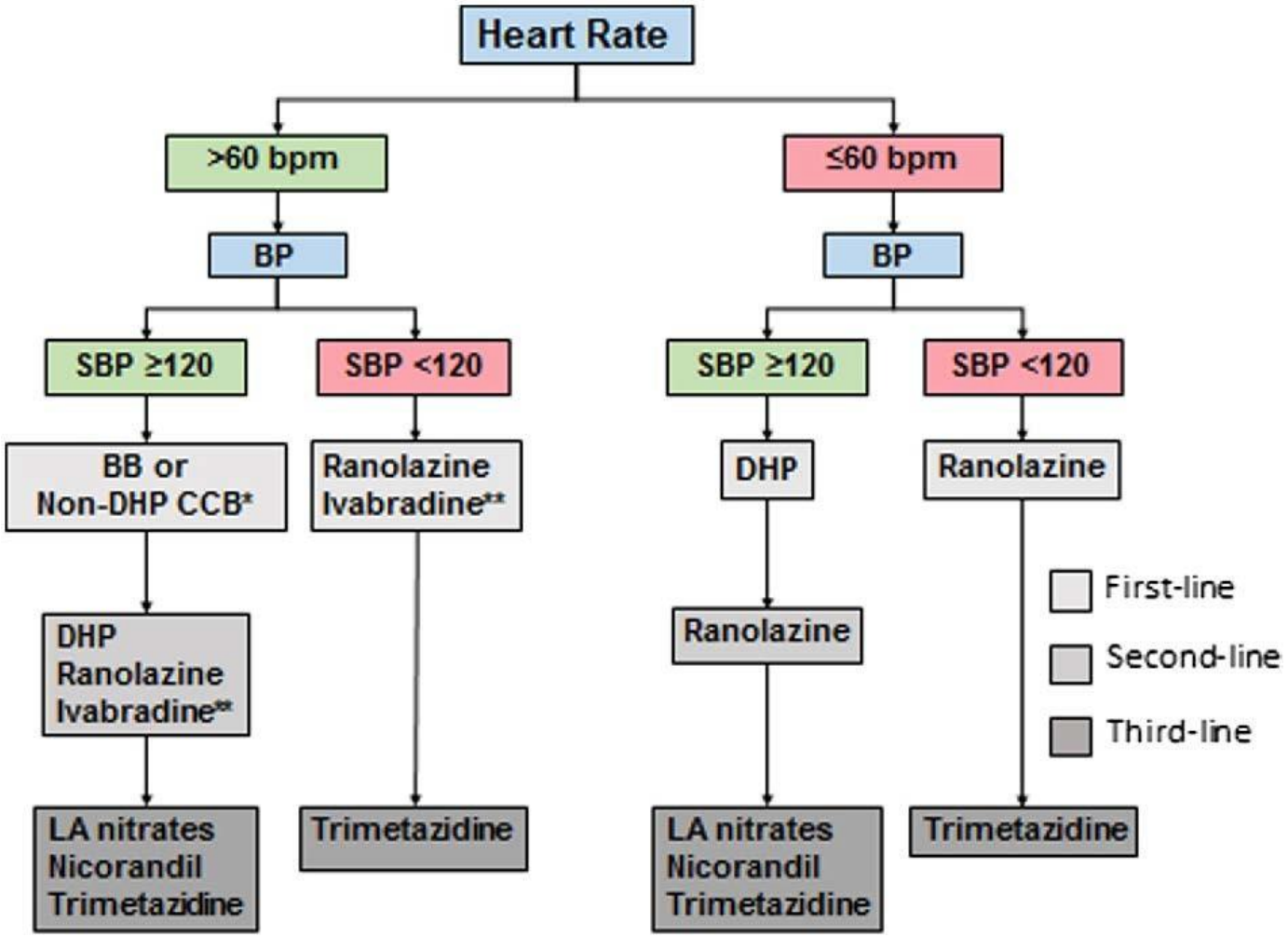
Nature Reviews | Cardiology



Nature Reviews | Cardiology

Ferrari, R. *et al.* (2017) A 'diamond' approach to personalized treatment of angina. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.131

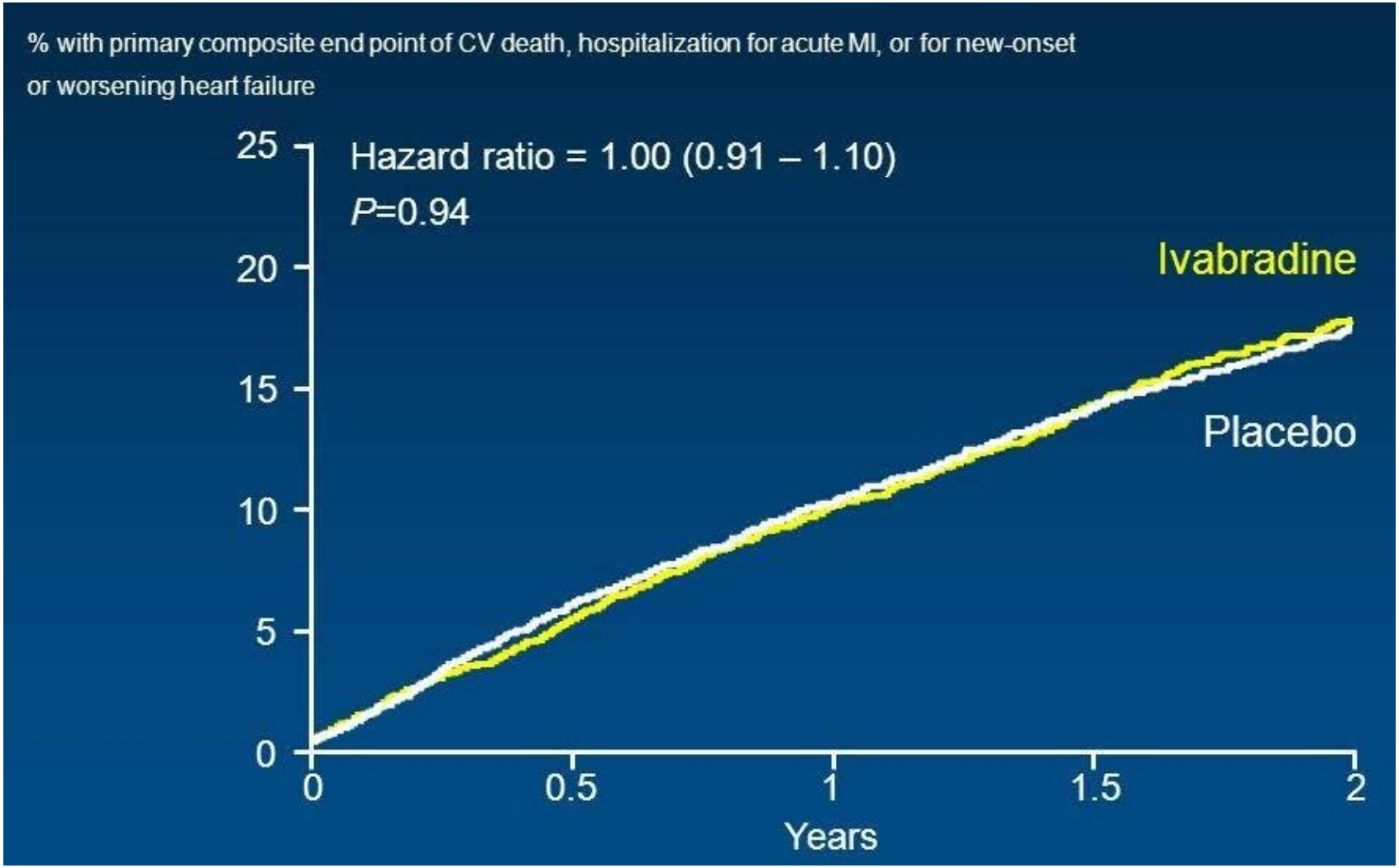
Choice of Antianginal Agent According to Haemodynamic Criteria



https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Stable-angina-pectoris-which-_drugs-or-combinations-to-use-in-which-patients

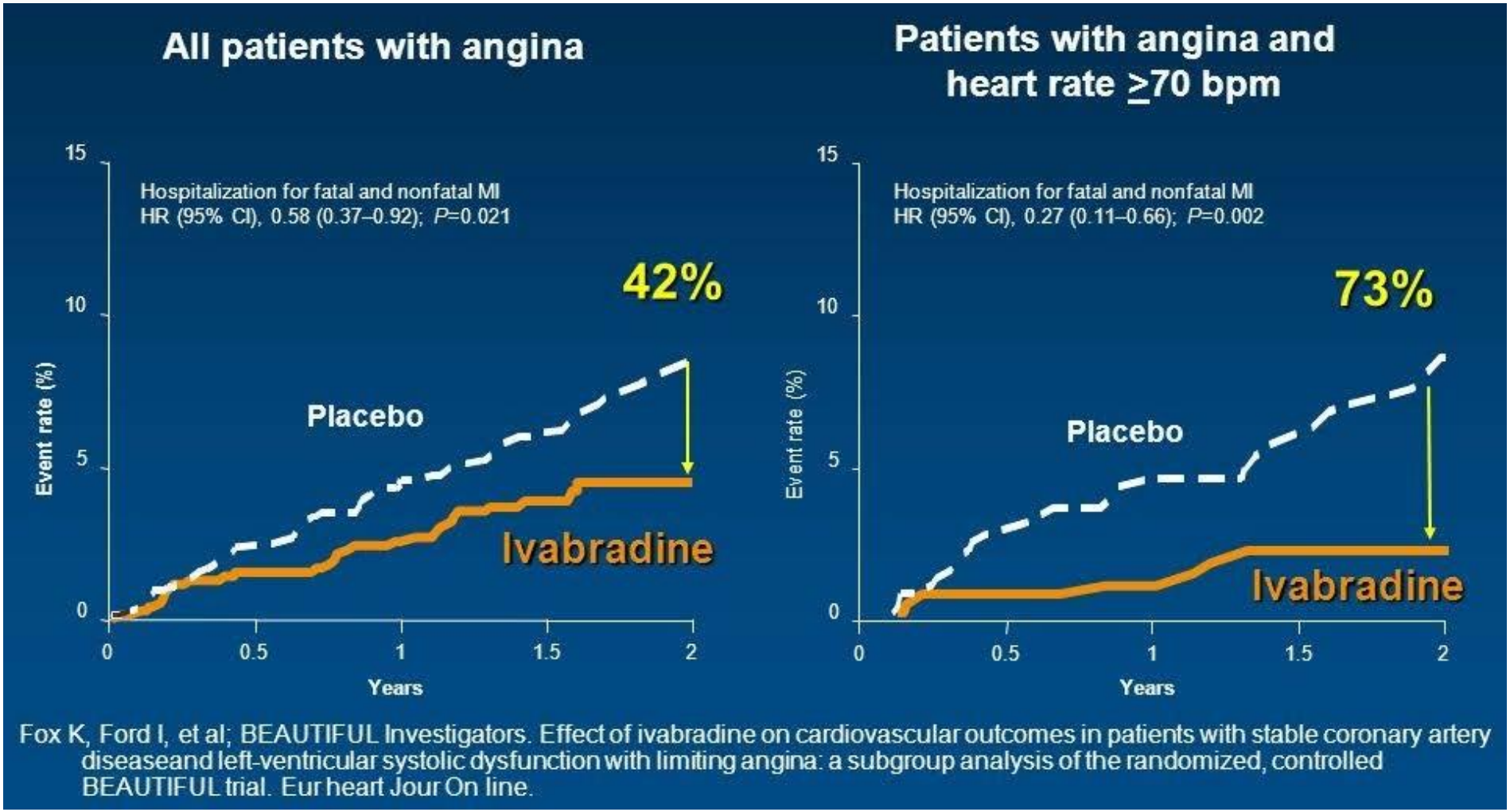
Ivabradine

BEAUTIFUL: Ivabradine reduces Myocardial infarction in patients with Angina



Fok K et al, Lancet 2008;372:807-16

BEAUTIFUL: Effect of Ivabradine on Primary Endpoint (Overall population)

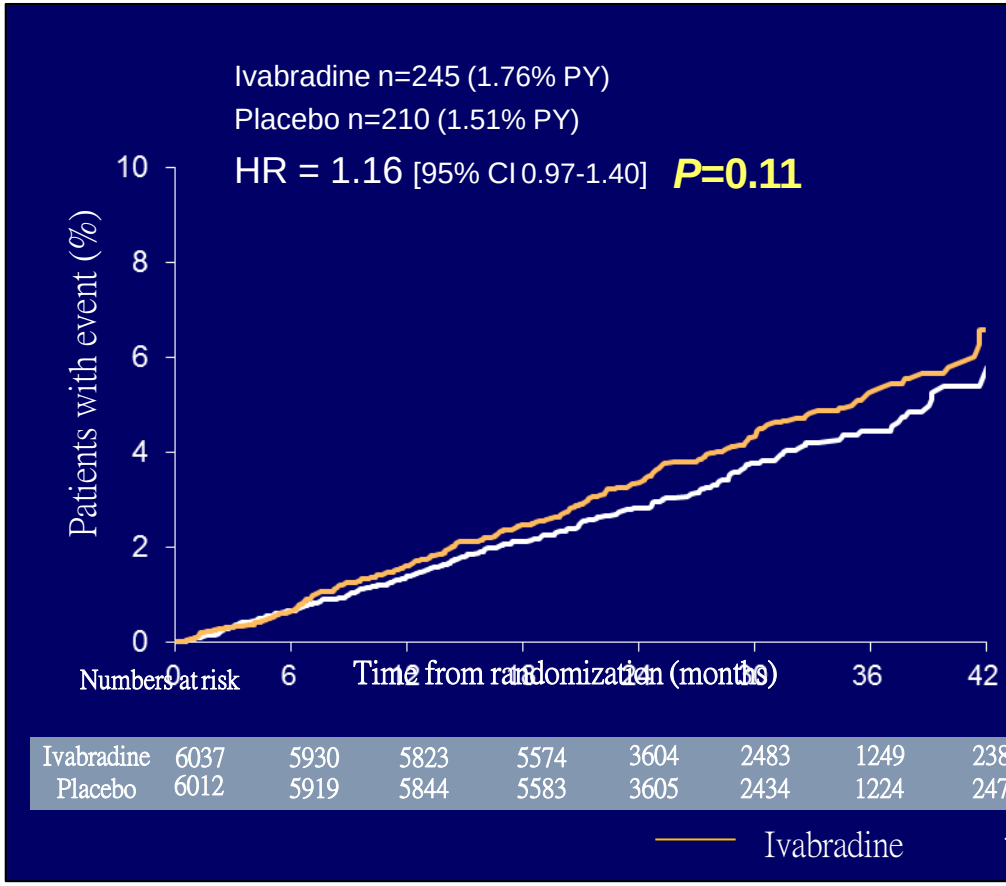


Fox K, Ford I, et al; BEAUTIFUL Investigators. Effect of ivabradine on cardiovascular outcomes in patients with stable coronary artery diseaseand left-ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur heart Jour On line.

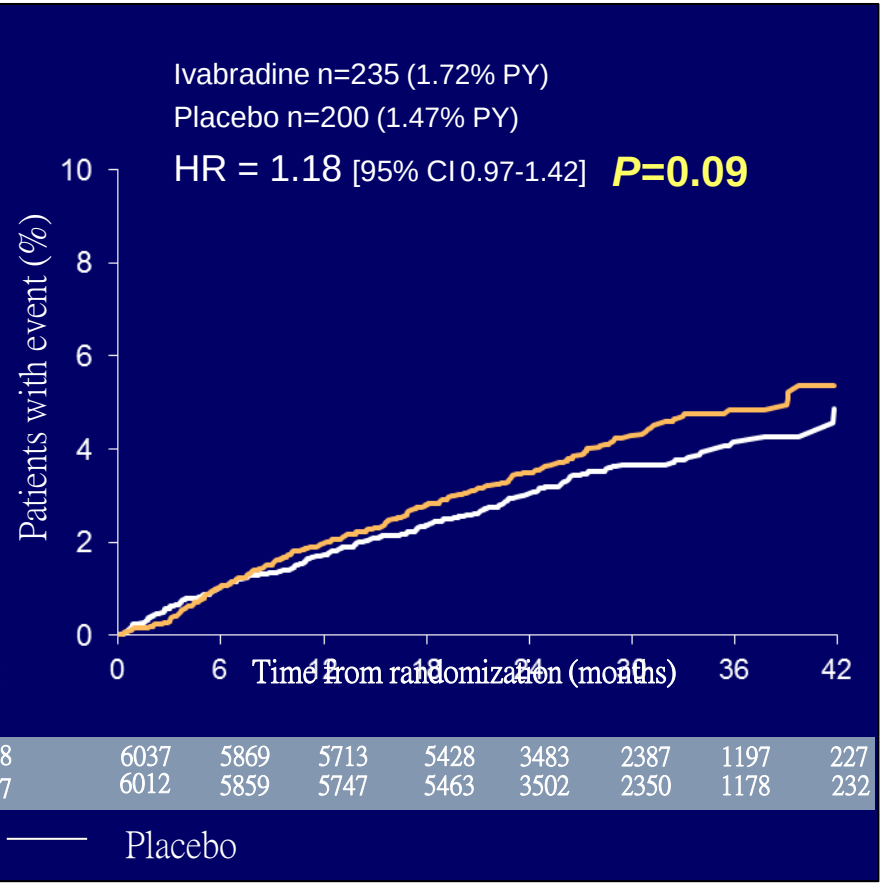
Fok K et al, Lancet 2008;372:807-16

SIGNIfY: Components of Primary composite endpoint (Angina population, CCS class ≥II, N=12049)

Cardiovascular death



Non-fatal myocardial infarction



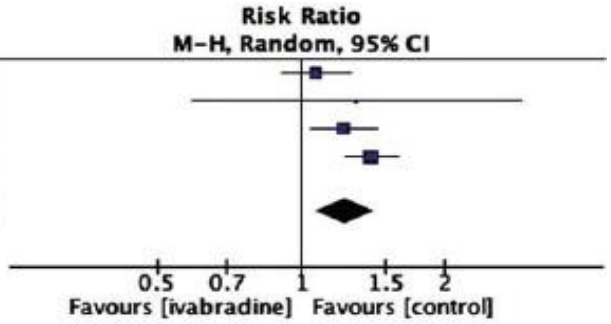
Fox K, ET ALN Eng J Med. 2014 August 31. DOI:10.1056/NEJMoa1406430.

The Risk of AF with Ivabradine Treatment : A Meta-analysis of more than 40,000 Patients

(A)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
beautiful	286	5477	264	5430	30.5%	1.07 [0.91, 1.26]
EMA-OOSS	26	2811	8	1125	2.9%	1.30 [0.59, 2.86]
shift	306	3232	251	3260	31.0%	1.23 [1.05, 1.44]
signify	508	9550	362	9552	35.6%	1.40 [1.23, 1.60]
Total (95% CI)		**21070**		**19367**	**100.0%**	**1.24 [1.08, 1.42]**
Total events	1126		885			

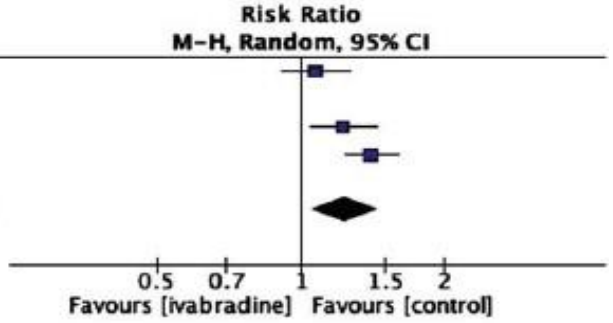
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.35$, df = 3 (P = 0.10); $I^2 = 53\%$
Test for overall effect: Z = 3.01 (P = 0.003)



(B)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
beautiful	286	5477	264	5430	31.7%	1.07 [0.91, 1.26]
EMA-OOSS	26	2811	8	1125	0.0%	1.30 [0.59, 2.86]
shift	306	3232	251	3260	32.2%	1.23 [1.05, 1.44]
signify	508	9550	362	9552	36.1%	1.40 [1.23, 1.60]
Total (95% CI)		**18259**		**18242**	**100.0%**	**1.24 [1.06, 1.44]**
Total events	1100		877			

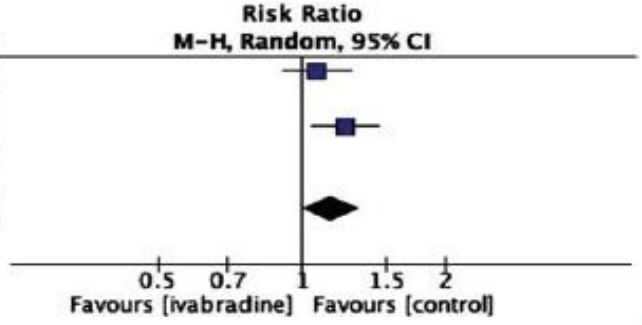
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.34$, df = 2 (P = 0.04); $I^2 = 68\%$
Test for overall effect: Z = 2.67 (P = 0.008)



(C)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
beautiful	286	5477	264	5430	49.2%	1.07 [0.91, 1.26]
EMA-OOSS	26	2811	8	1125	0.0%	1.30 [0.59, 2.86]
shift	306	3232	251	3260	50.8%	1.23 [1.05, 1.44]
signify	508	9550	362	9552	0.0%	1.40 [1.23, 1.60]
Total (95% CI)		**8709**		**8690**	**100.0%**	**1.15 [1.01, 1.31]**
Total events	592		515			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, df = 1 (P = 0.24); $I^2 = 26\%$
Test for overall effect: Z = 2.07 (P = 0.04)



Tanboga I et al. Clin Cardiol 2016

Trimetazidine

TRIMPOL II trial – TMZ + Metoprolol

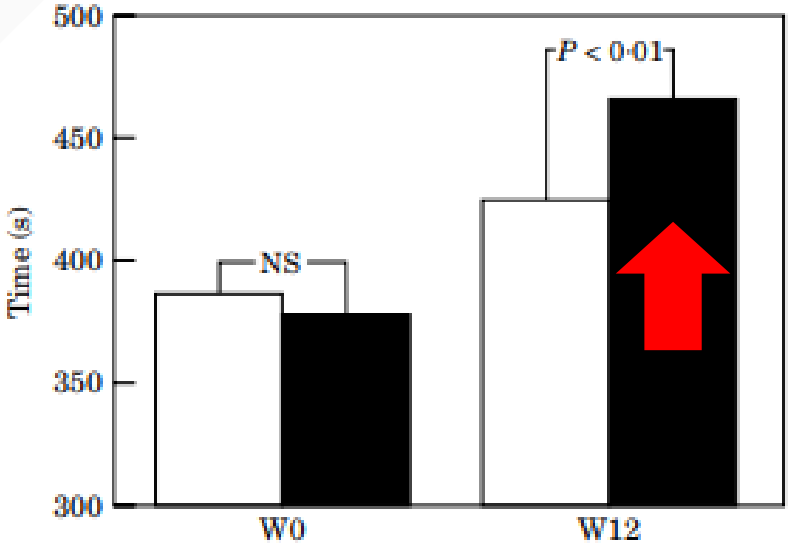


Figure 4 Time to onset of angina. □=PL; ■=TMZ.

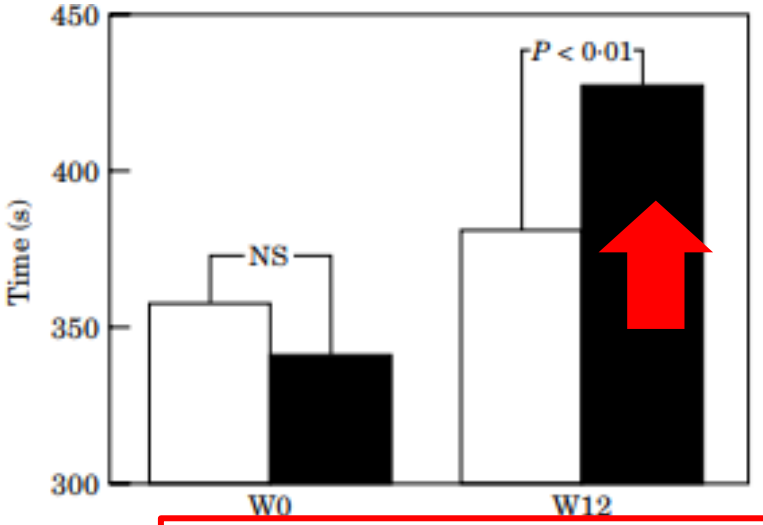


Figure 3 Time to 1 mm ST segment depression. □=PL; ■=TMZ.

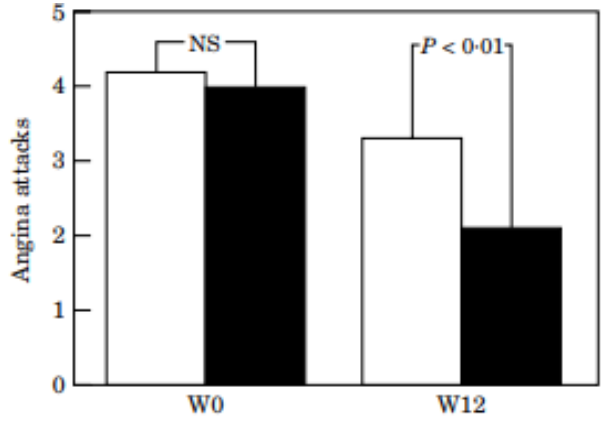


Figure 5 Mean number of angina attacks per week. □=PL; ■=TMZ.

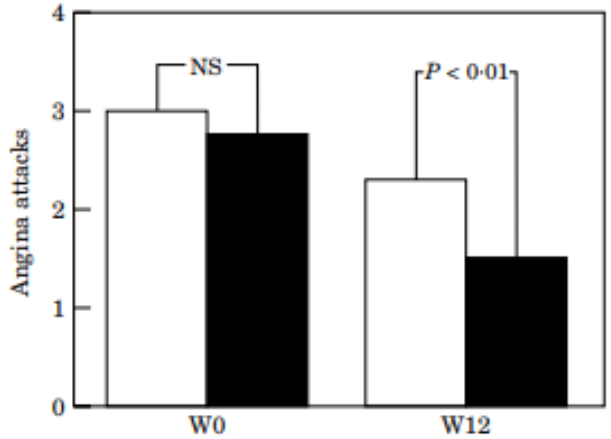


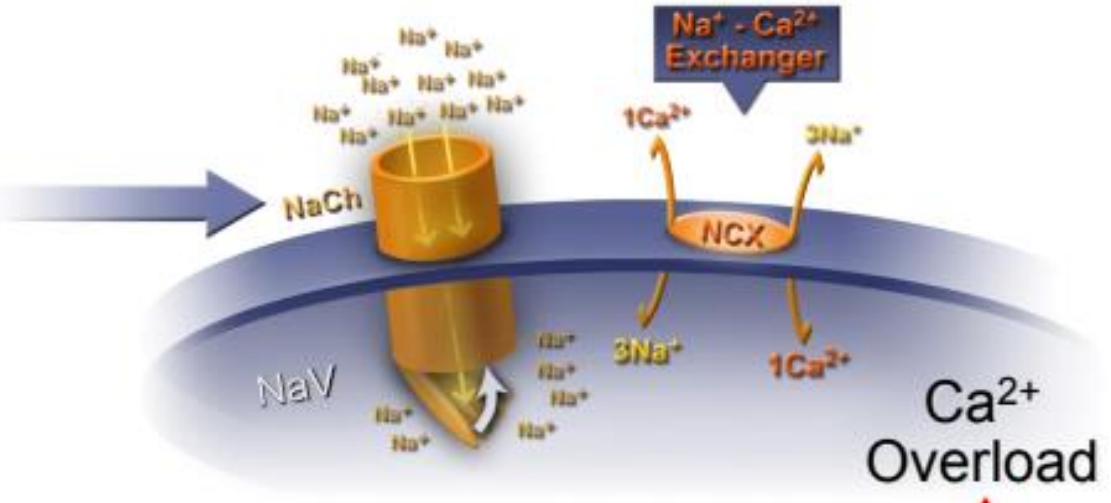
Figure 6 Mean nitrate consumption per week. □=PL; ■=TMZ.

Ranolazine

Mechanism of Action of Ranolazine

Diseases/Conditions

1. **Acquired**
   - Hypoxia/ROS
   - Ischaemia
   - Heart failure
   - Atrial fibrillation
2. **Congenital (inherited)**
   - Cardiac: SCN5A (LQT3)



Defective Na Channel gating leads to Ca^{++}-overload

Na Ch inactivation failure

↓

Enhanced late I_{Na}

Ranolazine is a piperazine derivative that seems to exert its anti-ischemic effects through antagonism of the late phase of the inward sodium current (late I_{Na}) that is increased in myocardial ischemia and contributes to detrimental cellular sodium and calcium overload. Ranolazine exerts anti-ischemic actions without a clinically significant effect on heart rate or blood pressure

Drugs for angina: pharmacology, symptom relief, outcomes benefits, and guideline recommendations

Table 1 | **Drugs for angina: pharmacology, symptom relief, outcomes benefits, and guideline recommendations**

Antianginal drug	HR	SBP	DBP	PVR	CC	CV	Symptom relief	Outcomes benefit	ESC*	ACC/AHA*
Nitrates										
Short-acting	↑–	↓↓	↓↓	↓–	–	↑↑↑	Yes	No	IB	IB
Long-acting	↑–	↓	↓	↓–	–	↑↑	Yes	No	IIB	IB
β-Blockers										
Noncardioselective	↓↓↓	↓↓	↓↓	↑–	↓↓	–	Yes	No	IA	IB
Cardioselective (preserved EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	No	IA	IB
Cardioselective (reduced EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	Yes	IB	IB
With vasodilatation (preserved EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	No	IB	IB
With vasodilatation (reduced EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	Yes	IA	IA
Calcium-channel blockers										
Dihydropyridines	↑–	↓↓↓	↓↓↓	↓↓↓	↑–	↑↑↑	Yes	No	IA	IB
Nondihydropyridines	↓↓	↓↓	↓↓	↓↓	↓↓	↑↑	Yes	No	IA	IIB
Other (considered second-choice treatment in guidelines)										
Ivabradine	↓↓	↓–	↓–	–	–	–	Yes	No	II_aB	NA
Nicorandil	↑	↓↓	↓↓	↓–	–	↑↑↑	Yes	Yes	II_aB	NA
Ranolazine	–	–	–	–	–	–	Yes	No	II_aB	IIA
Trimetazidine	–	–	–	–	–	–	Yes	No	II_bB	NA

*Guideline classification of benefit: class I = benefit >>> risk; class II_a = benefit >> risk; class II_b = benefit > risk. Level of evidence: A = one or two large, randomized trials; B = one randomized trial or small meta-analysis. CC, cardiac contractility; CV, coronary vasodilatation; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; NA, not available; PVR, peripheral vascular resistance; SBP, systolic blood pressure.

Ferrari R, et al. Nat Rev Cardiol. 2018;15:120-132

Ranolazine Meta-analysis
Chronic Stable Angina

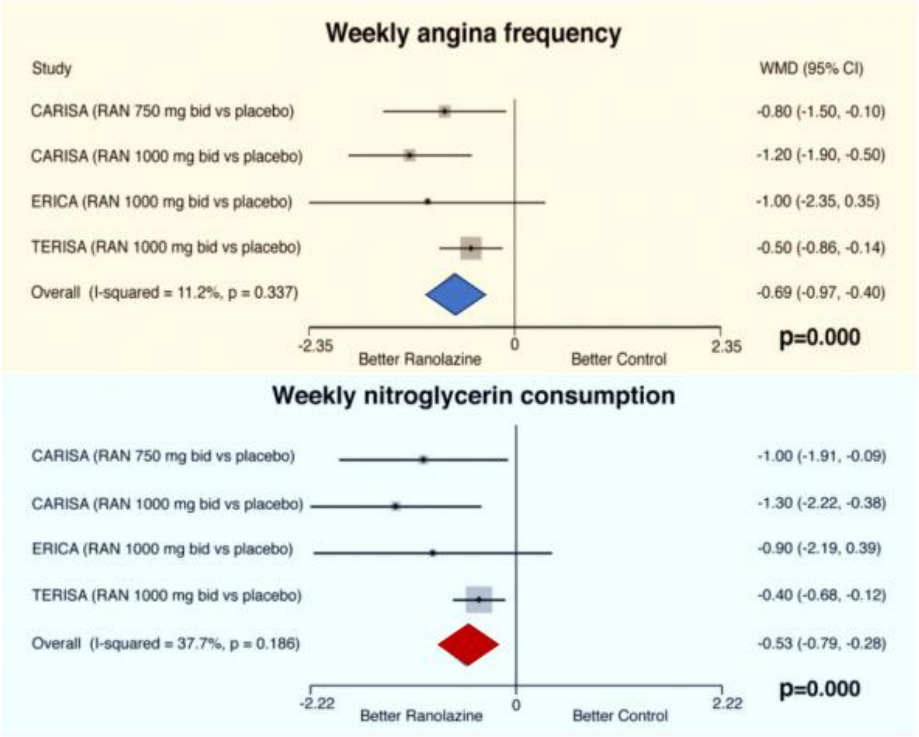
Six trials enrolling 9,223 patients

In symptomatic patients with chronic CAD,
Ranolazine, added to conventional therapy, effectively:

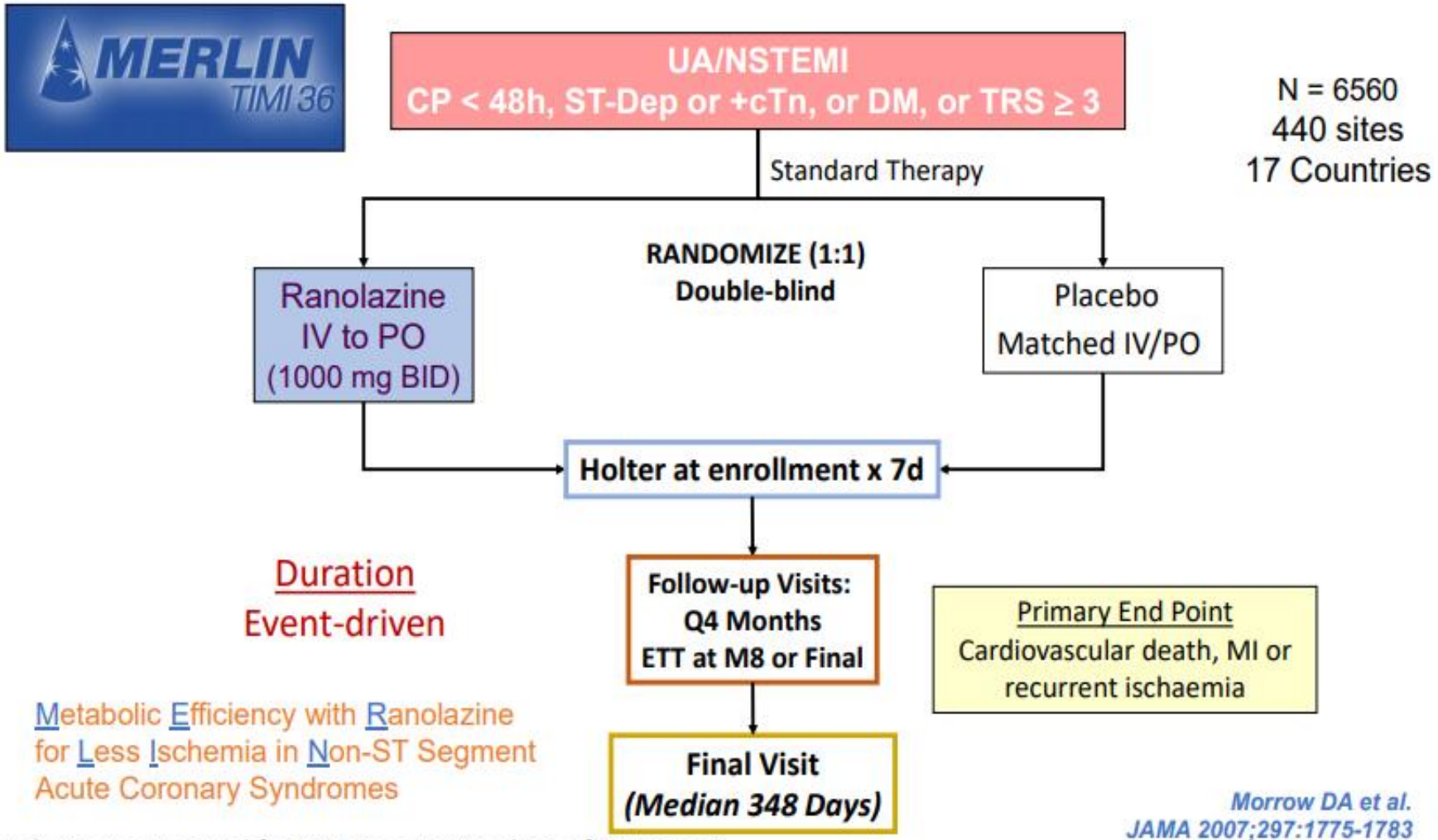
1) reduces angina frequency and sublingual nitroglycerin consumption

2) while prolonging exercise duration as well as time to onset of ischemia and to onset of angina

3) with no substantial effects on blood pressure and heart rate



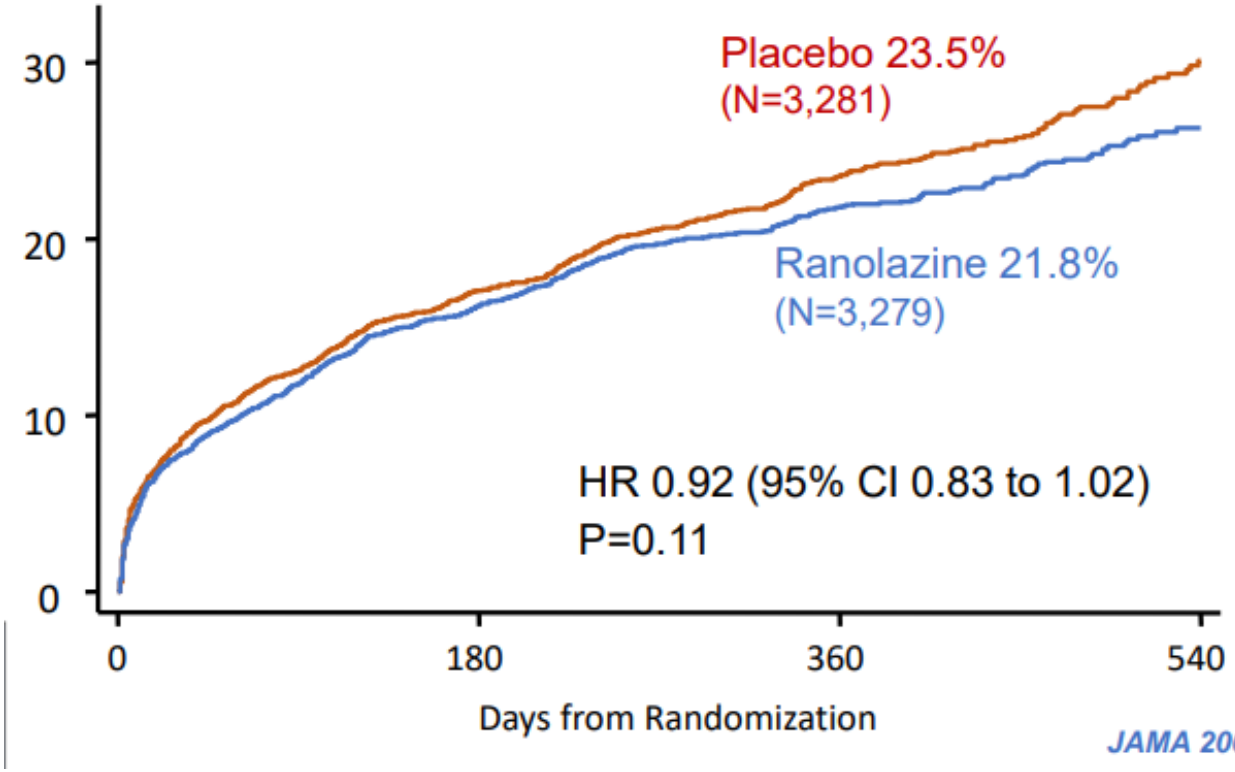
Savarese G, et al. Int J Cardiol. 2013 Nov 15;169(4):262-70



Ranolazine is approved for CSA at a starting dose of 375mg BD

Primary Endpoint

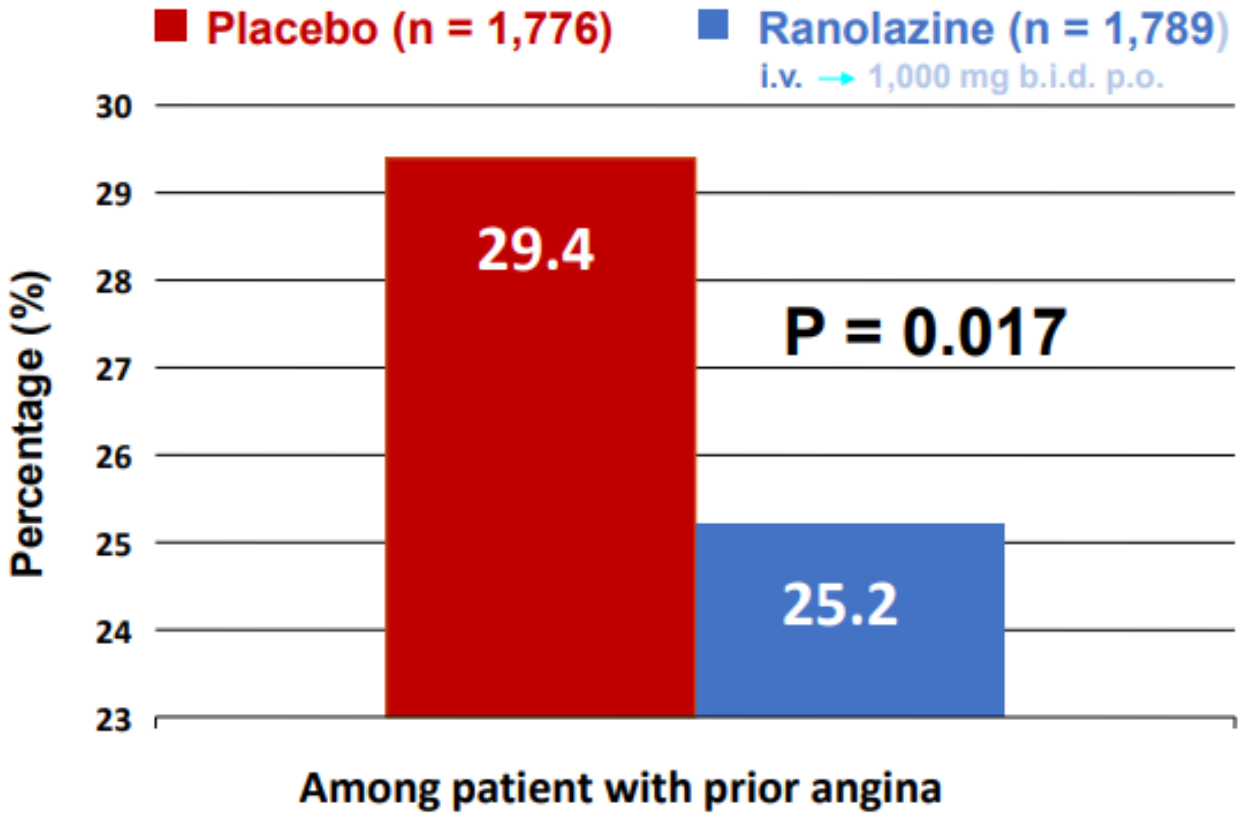
CV Death, MI, or Recurrent Ischaemia (% at 12M)



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

MERLIN: Chronic Angina Patients

Primary Endpoint: CV death, MI or Recurrent Ischaemia



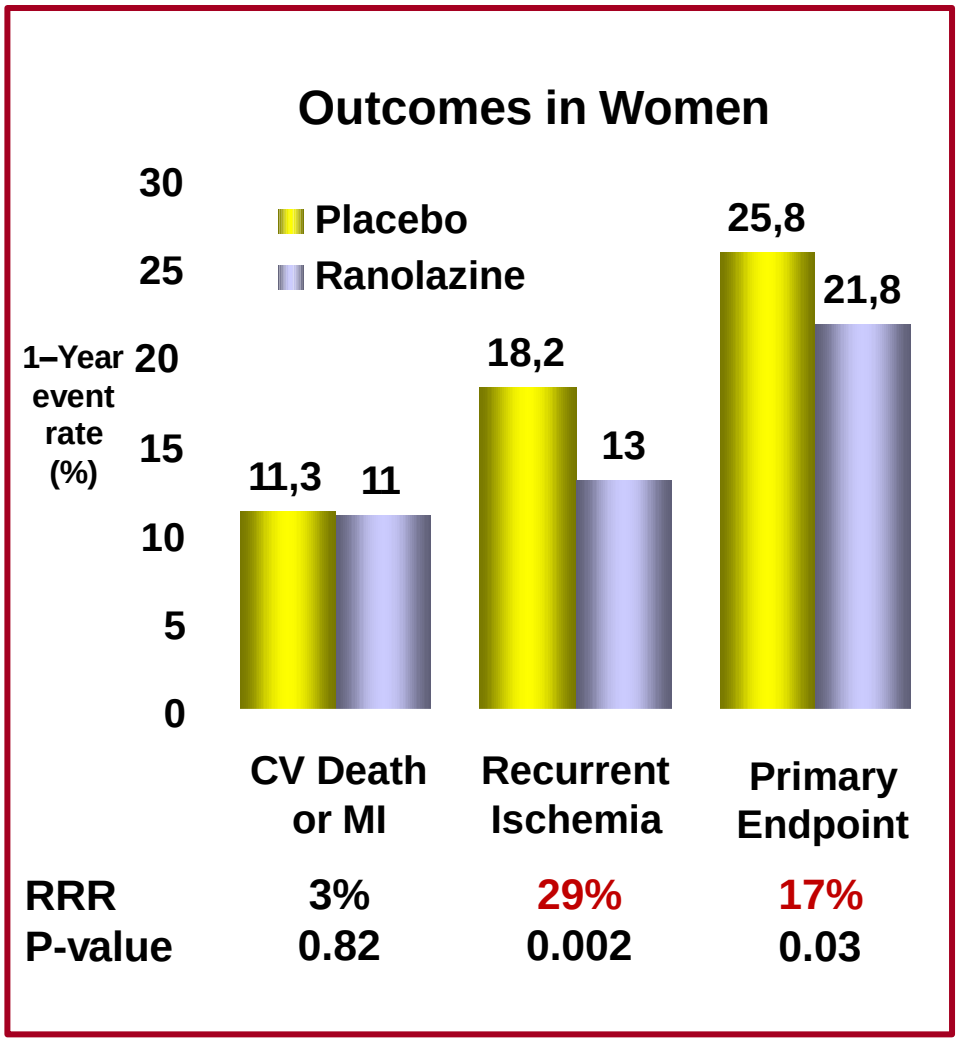
Wilson S.R. et al.: J Am Coll Cardiol 2009; 53 (17): 1510-1516

Ranolazine is Particularly Effective in Women: MERLIN-TIMI 36 Trial

Women (n = 2291) vs men (n = 4269)

- Older, with higher rates of
  - DM, HT
  - HF
  - Prior angina
  - ST↓
  - ↑BNP
- However, lower rates of
  - Stenosis >50%
  - ↑Troponin
- Greater burden of ischemia on Holter monitoring and Seattle Angina Questionnaire

P < 0.001 for all comparisons



Mega JL et al. Circulation

MERLIN-TIMI 36:
Significantly lower incidence of arrhythmias

Arrhythmias	Ranolazine *(n)* %	Placebo *(n)* %	*p*-value
New-onset atrial fibrillation	55 (1.7)	75 (2.4)	0.08
Supraventricular tachycardia*	1,413 (44.7)	1,752 (55)	<0.001
Pauses ≥3 sec	97 (3.1)	136 (4.3)	0.01
VT ≥8 beats	166 (5.3)	265 (8.3)	<0.001

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

** ≥120 bpm lasting at least 4 beats*

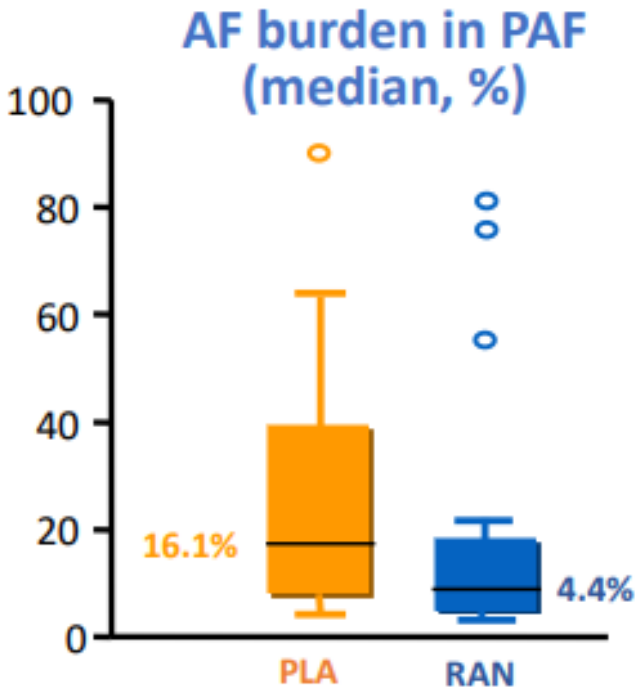
Randomised, double-blind, placebo-controlled study. Patients (n= 6,560) with non-ST elevation-acute coronary syndromes on standard therapy were randomised to ranolazine (iv followed by oral 1,000 mg twice daily, n=3,279) or placebo (n=3,281) with a median follow-up of 348 days.(1). Continuous ECG (Holter) recording was performed for the first 7 days after randomisation. Analysis on 6,351 patients (97%) who had evaluable continuous ECG recordings.(2)

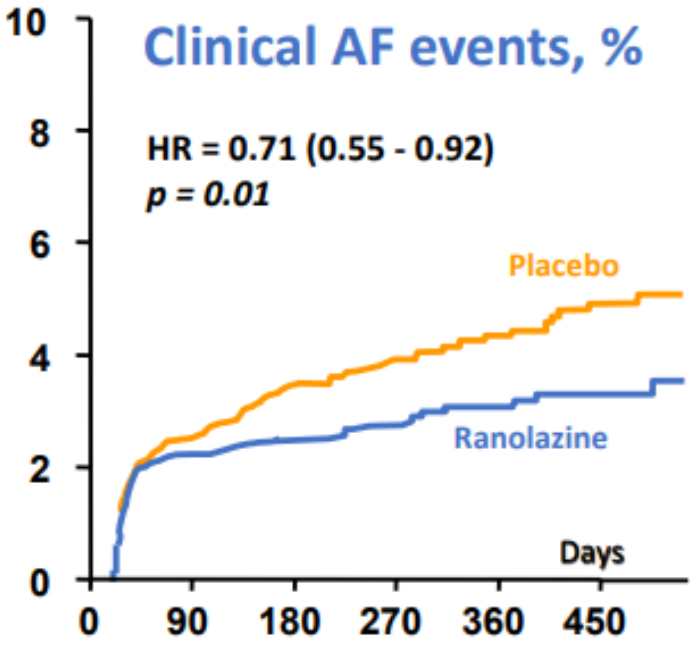
Morrow D, et al. JAMA 2007;297:1775-83. 2. Elaborated from Scirica BM, et al. Circulation. 2007;116:1647-52

Ranolazine in ACS: MERLIN-TIMI-36

- N = 6560 with NSTEMI ACS
- 6,351 (97%) with 7-day LR
- Follow-up: 1 year
- Clinical AF during F-Up was based on AE reporting

Patients treated with ranolazine tended to have fewer AF episodes during the first 7 days vs placebo: 55 (1.7%) vs 75 (2.4%), p = 0.08





Scirica BM, et al. Europace 2015;17:32-7

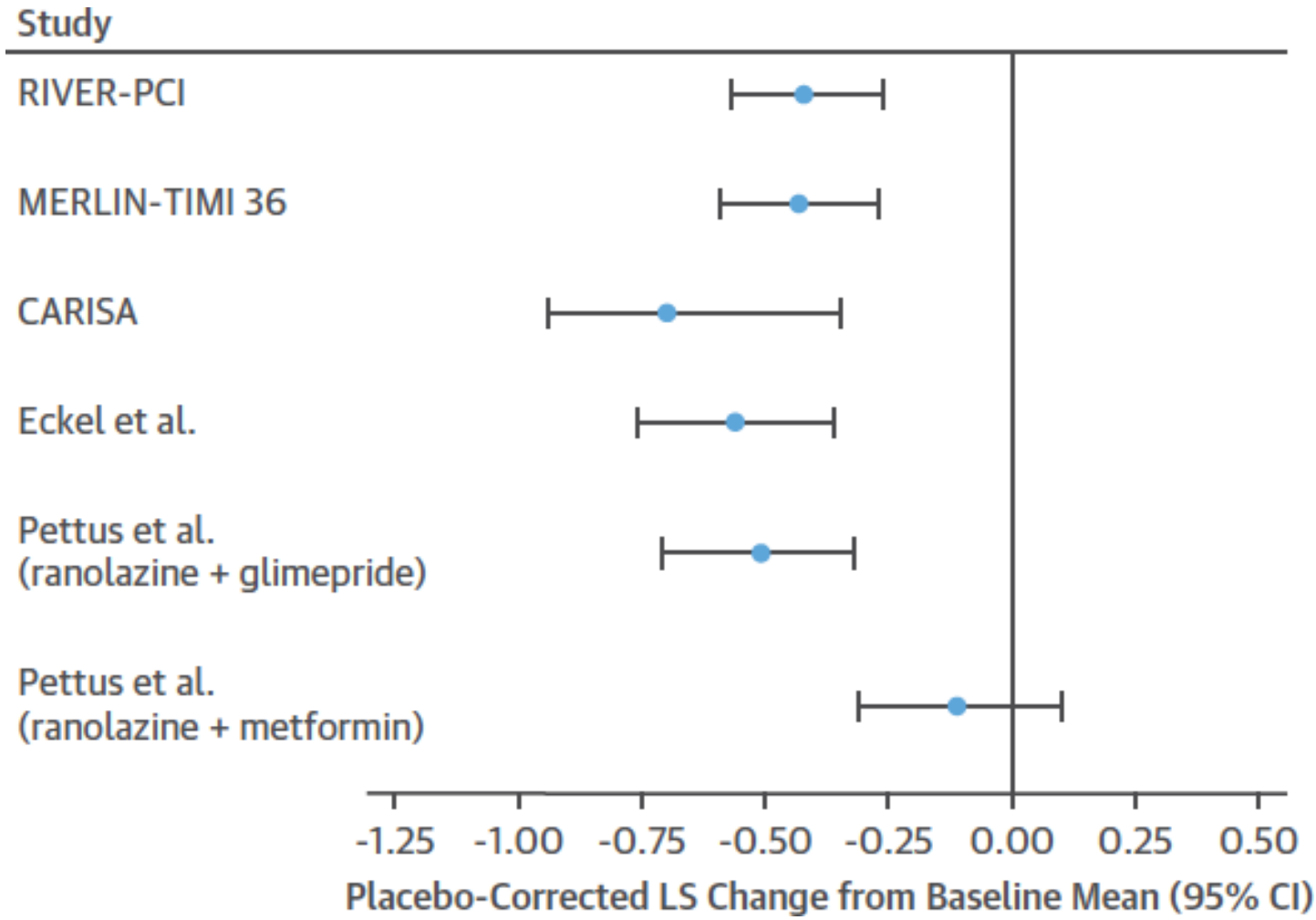
Microvascular Angina

Possible Role of Ranolazine

MVA: Pathogenetic Factors	Action of Ranolazine
Conceivably an ischemic disease	Anti-ischaemic drug
Microvascular dysfunction	Reduces mechanical dysfunction
Endothelial dysfunction	Anti-inflammatory or antioxidant effects. May improve endothelial function
Glucose intolerance	Improves glyco-metabolic control

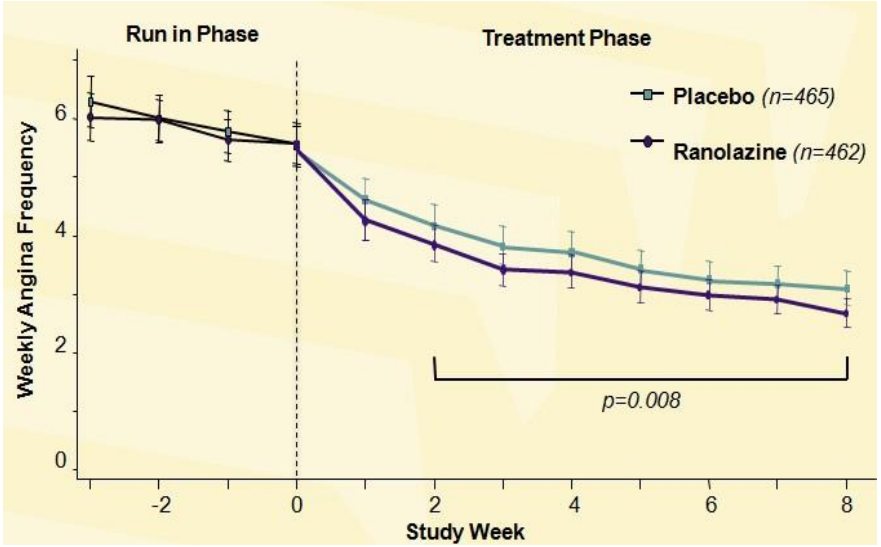
Cattaneo M, et al. International Journal of Cardiology 181 (2015) 376–381

Effect of Ranolazine on HbA1C in CSA Patients with DM in Published Clinical Trials

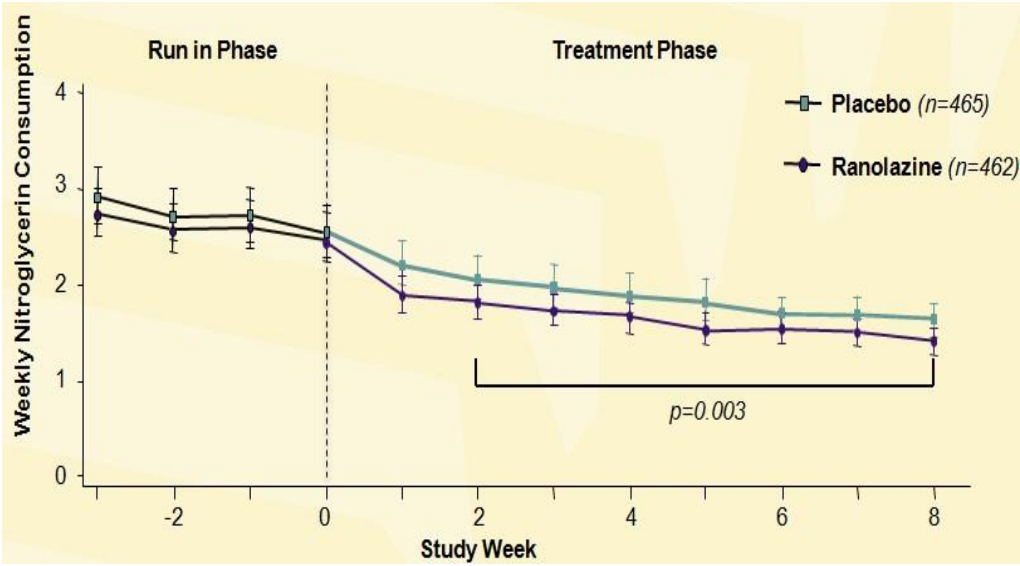


TERISA: Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina

Primary endpoint : Weekly Angina Frequency



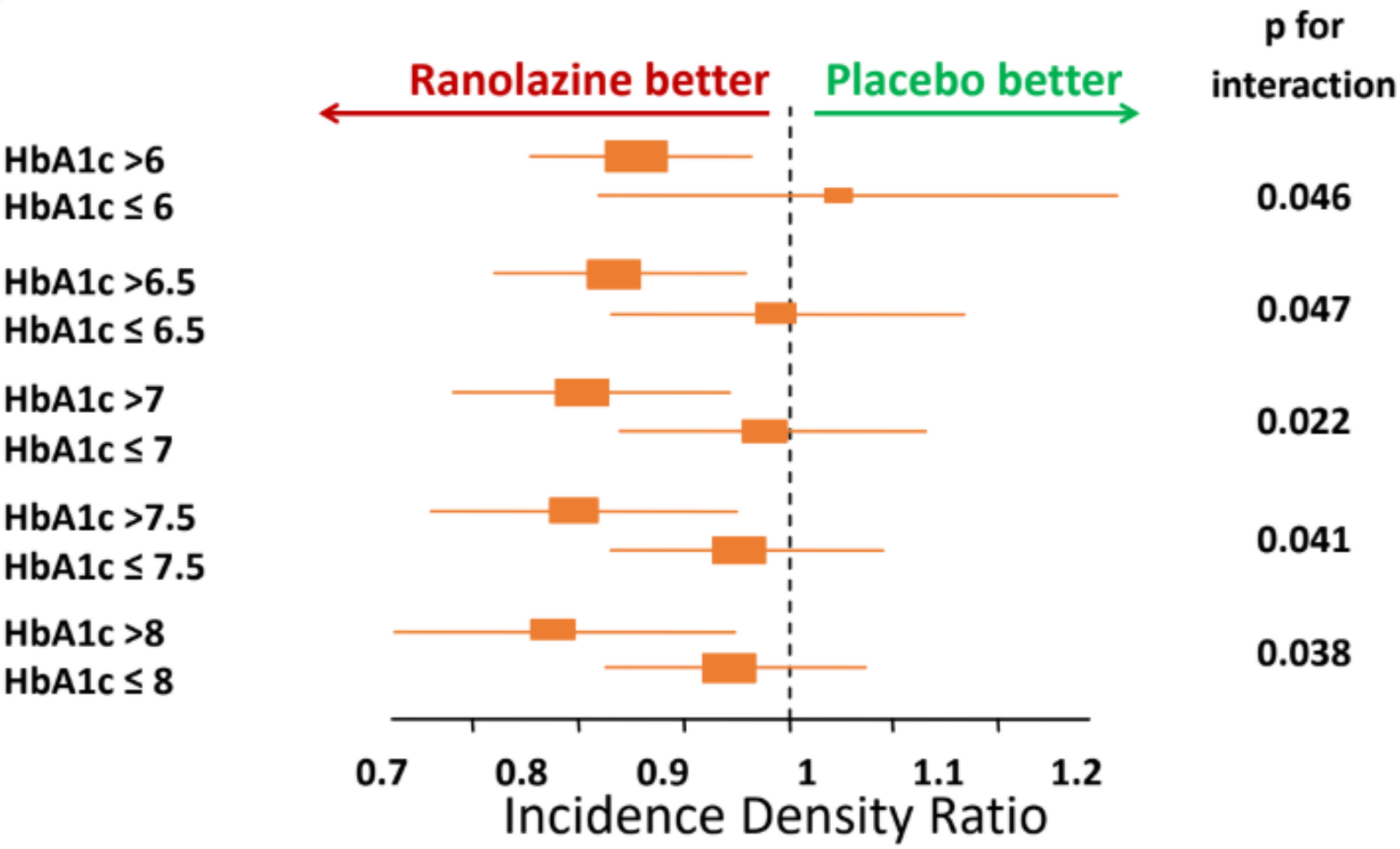
Secondary endpoint : Weekly Nitroglycerin Consumption



Randomised, double-blind, placebo-controlled study. Patients (n= 927) with type 2 diabetes, coronary artery disease, and chronic stable angina already on up to 2 antianginal agents were randomised to ranolazine 1,000 mg bid (n=462) or placebo (n=465) for 8 weeks

Kosiborod M, et al. J Am Coll Cardiol. 2013;61:2038-45.

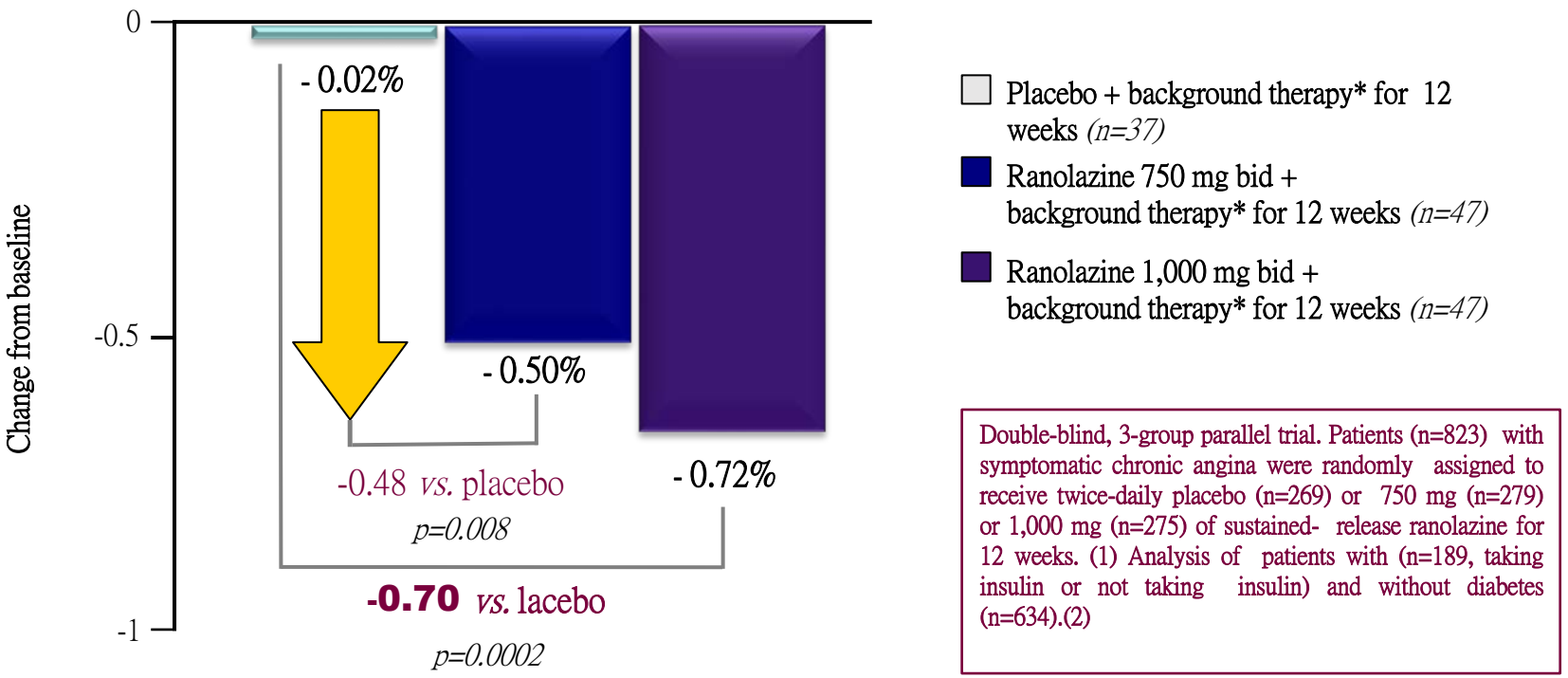
Exploratory Analysis – HbA1c



(Relative difference in the incidence rates of weekly angina frequency)

Kosiborod M, et al, J Am Coll Cardiol 2013;61(20):2038-45

Effect of Ranolazine on HbA1c in CSA patients with diabetes



Double-blind, 3-group parallel trial. Patients (n=823) with symptomatic chronic angina were randomly assigned to receive twice-daily placebo (n=269) or 750 mg (n=279) or 1,000 mg (n=275) of sustained- release ranolazine for 12 weeks. (1) Analysis of patients with (n=189, taking insulin or not taking insulin) and without diabetes (n=634).(2)

Background therapy: atenolol 50 mg od or amlodipine 5 mg od or diltiazem 180 mg od.
At baseline mean HbA1c in patients treated with placebo or ranolazine 750 mg bid or ranolazine 1,000 mg bid were 7.5%, 7.7% and 7.9%, respectively.

Chaitman BR, et al. JAMA 2004;291:309-16. 2. Data from Table II in Timmis AD, et al. Eur Heart J 2006;27:42-8.

Roles of Ranolazine

- As an add-on medication for sub-optimal angina control with traditional anti-angina drugs
  - Ranolazine provides effective angina relief when add-on with BBs/CCBs
- As add-on in bradycardia and/or hypotensive patients
  - No substantial effects on blood pressure and heart rate
- In CSA patients with diabetics
  - Ranolazine reduces the angina frequency and severity and may improve HbA1c in CSA patients with DM

Indications for revascularization in patients with stable angina or silent ischaemia

Extent of CAD (anatomical and/or functional)		Class[a]	Level[b]
For prognosis	Left main disease with stenosis >50%.[c] [68–71]	I	A
	Proximal LAD stenosis >50%.[c] [62,68,70,72]	I	A
	Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF ≤35%).[c] [61,62,68,70,73–83]	I	A
	Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR.[d] [24,59,84–90]	I	B
	Single remaining patent coronary artery with stenosis >50%.[c]	I	C
For symptoms	Haemodynamically significant coronary stenosis[c] in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy.[e] [24,63,91–97]	I	A

CAD = coronary artery disease; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LV = left ventricular; LVEF = left ventricular ejection fraction.

[a]Class of recommendation.

[b]Level of evidence.

[c]With documented ischaemia or a haemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89 (see section 3.2.1.1), or >90% stenosis in a major coronary vessel.

[d]Based on FFR <0.75 indicating a prognostically relevant lesion (see section 3.2.1.1).

[e]In consideration of patient compliance and wishes in relation to the intensity of anti-anginal therapy.

Recommendation for the type of revascularization in patients with stable CAD eligible for both PCI or CABG

Recommendations according to extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,101,139–144]	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.[68,70,73]	I	B	I	C
Left main CAD				
Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148]	I	A	I	A
Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148]	I	A	IIa	A
Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148]	I	A	III	B
Three-vessel CAD without diabetes mellitus				
Three-vessel disease with low SYNTAX score (0 - 22).[102,105,121,123,124,135,149]	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,149]	I	A	III	A
Three-vessel CAD with diabetes mellitus				
Three-vessel disease with low SYNTAX score 0–22.[102,105,121,123,124,135,150–157]	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,150–157]	I	A	III	A

Caveats : Choices of PCI Vs CABG

FAVOURS PCI
Clinical characteristics
Presence of severe co-morbidity (not adequately reflected by scores)
Advanced age/frailty/reduced life expectancy
Restricted mobility and conditions that affect the rehabilitation process
Anatomical and technical aspects
MVD with SYNTAX score 0–22
Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits
Severe chest deformation or scoliosis
Sequelae of chest radiation
Porcelain aorta[a]

FAVOURS CABG
Clinical characteristics
Diabetes
Reduced LV function (EF ≤35%)
Contraindication to DAPT
Recurrent diffuse in-stent restenosis
Anatomical and technical aspects
MVD with SYNTAX score ≥23
Anatomy likely resulting in incomplete revascularization with PCI
Severely calcified coronary artery lesions limiting lesion expansion
Need for concomitant interventions
Ascending aortic pathology with indication for surgery
Concomitant cardiac surgery

Conclusions

- Medical therapy is the foundation of treatment for SCAD/CCS
- First-line medications are less evidence-based than the new 2nd line drugs
- Current guidelines recommend single drug & combination therapy with consideration of comorbidities and haemodynamic status
- Newer 2nd line anti-anginal drugs improve symptoms but without negative haemodynamic impact
- The selection of revascularization therapy should consider patient's clinical characteristics, coronary anatomy and procedure risks

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