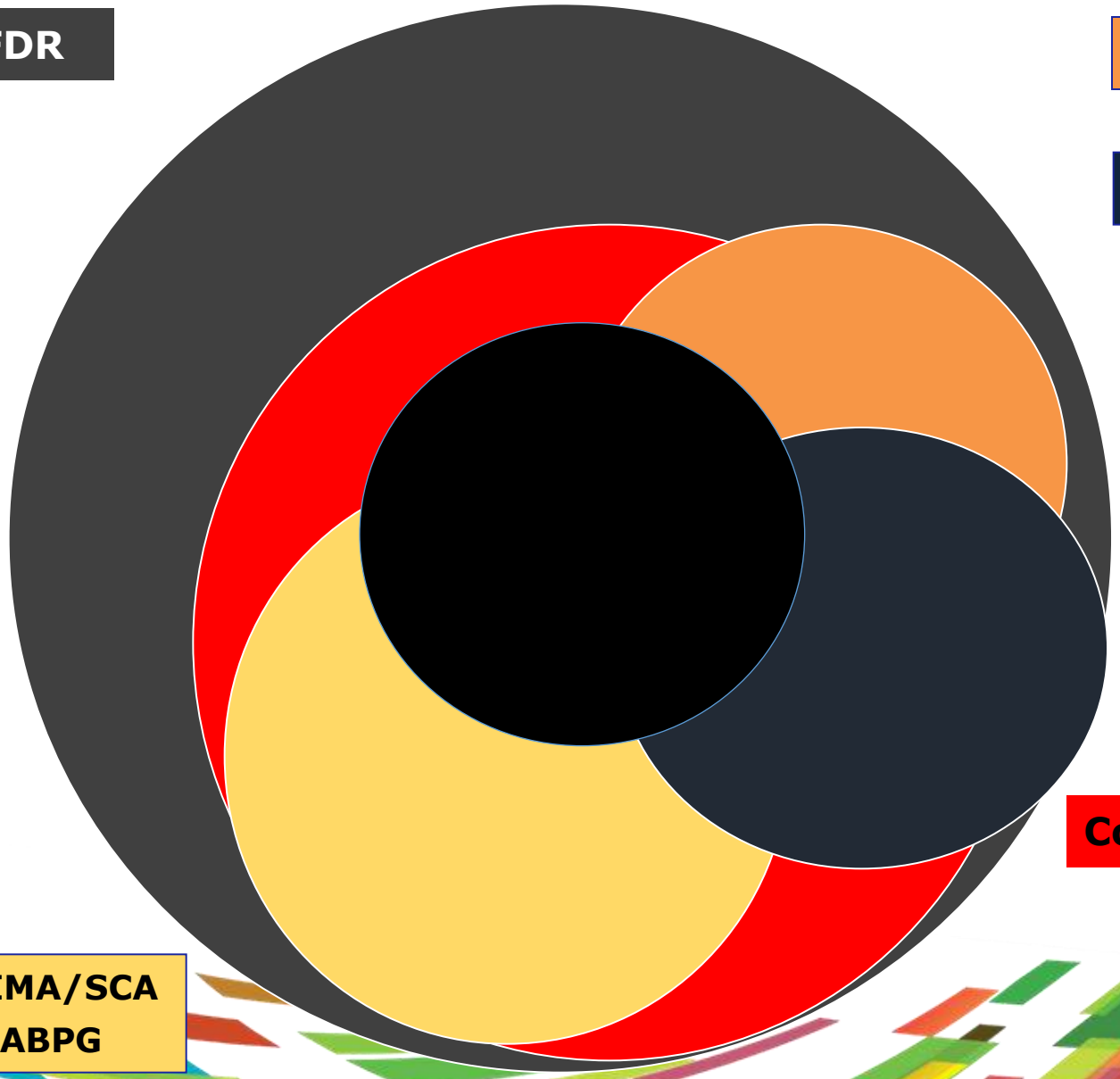
72° Congresso Nazionale
FIMG
Metis
Medicina di Famiglia: cambiare per mantenere i propri valori

Angina Stabile, come utilizzare i nuovi approcci terapeutici

Dott. Marco Marini
SOD Cardiologia-Emodinamica-UTIC
AOU Ospedali Riuniti di Ancona

3-8 ottobre 2016
Domus de Maria (CA)

Angina Stabile: come utilizzare i nuovi approcci terapeutici



Angina Stabile: come utilizzare i nuovi approcci terapeutici

Universo cardiopatia ischemica cronica

Angina Stabile: come utilizzare i nuovi approcci terapeutici

Comorbilità:
- BPCO
- CKD
- Anemia

Mortalità annua media tra 2% e 9%

Rivascolarizzazioni:
- PCI
- CABPG

Angina Stabile: come utilizzare i nuovi approcci terapeutici

EDITORIAL

The Challenges with Chronic Angina

E. Magnus Ohman, M.B., and Karen P. Alexander, M.D.

Should therapies to treat chronic stable angina reduce the risk of major cardiovascular events such as death and myocardial infarction? Although this may be a laudable target, the majority of treatments that are currently in use, such as nitrates, calcium-channel blockers, and beta-blockers, have not been proved to achieve this goal. Still, these agents have been recommended as first-line therapy for angina[1] because of their presumptive safety in this context and their ability to lower blood pressure, reduce symptoms, and improve quality of life.

Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study

What is already known on this topic

Contemporary data on
outside randomised co
recent clinical trials th
to 2.9%

Previous reports of the
stable coronary disease
populations and preda

What this study adds

In this contemporary evaluation of the prognosis associated with stable angina, the incidence of death and myocardial infarction was 2.3/100 patient years

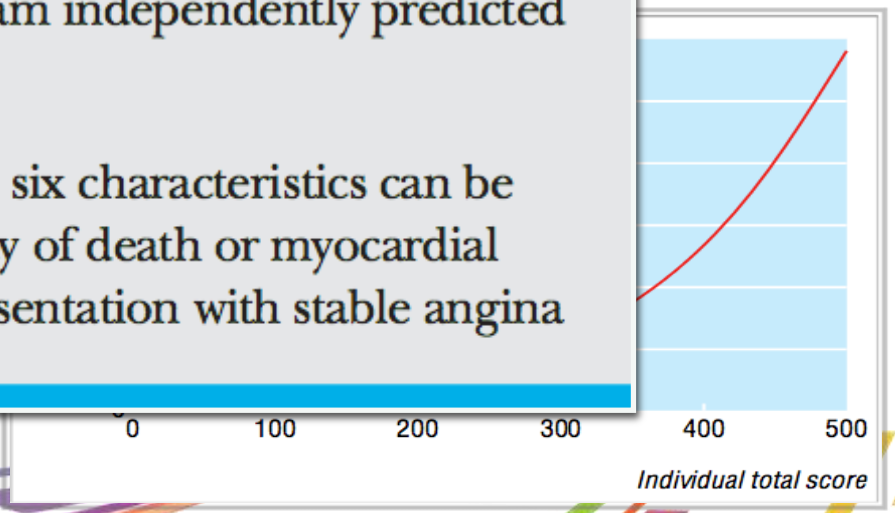
Comorbidity, diabetes, severity of angina, shorter duration of symptoms, left ventricular dysfunction, and ST changes on the resting electrocardiogram independently predicted outcome

A simple score involving these six characteristics can be used to estimate the probability of death or myocardial infarction in the year after presentation with stable angina

Table 6 Score sheet
stable angina

Risk factor		
Comorbidity*		
No		
Yes		
Diabetes		
No		
Yes		
Angina score		
Class I		
Class II		
Class III		
Duration of symptoms		
≥6months		
<6 months		
Abnormal ventricular fur		
No		
Yes		
ST depression or T wave		
No	0	
Yes	34	
		Total=

P value*
0.0008
0.007
0.002
0.05
0.05
<0.0001
0.004



BMJ 2006 Feb 4;332(7536):262-7.

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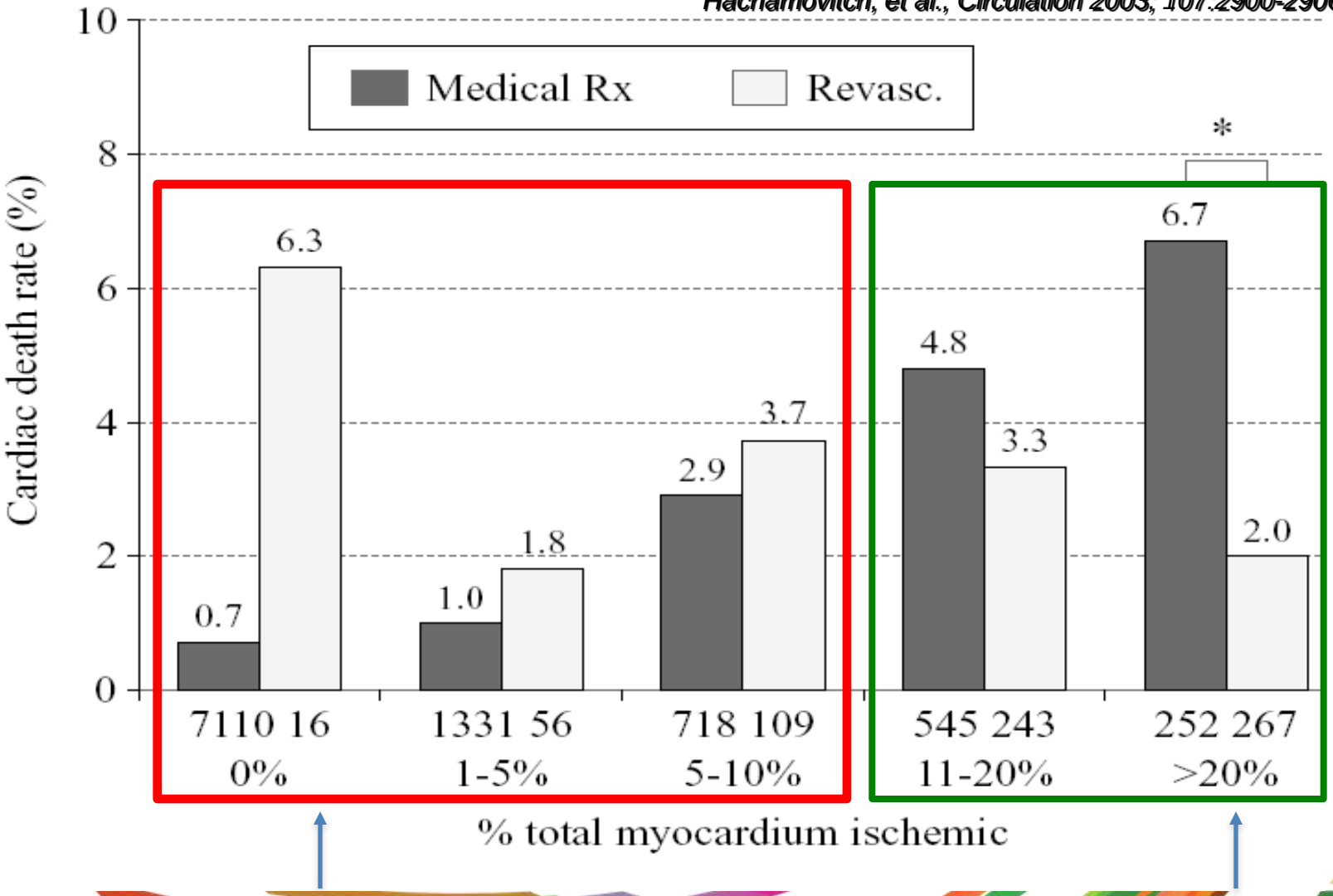
Hachamovitch, et al., Circulation 2003; 107:2900-2906



Treating CAD may be ineffective

Treating IHD improves prognosis

Angina Stabile: come utilizzare i nuovi approcci terapeutici

Valutazione prognostica e del rischio di eventi in paziente con SCAD/Angina

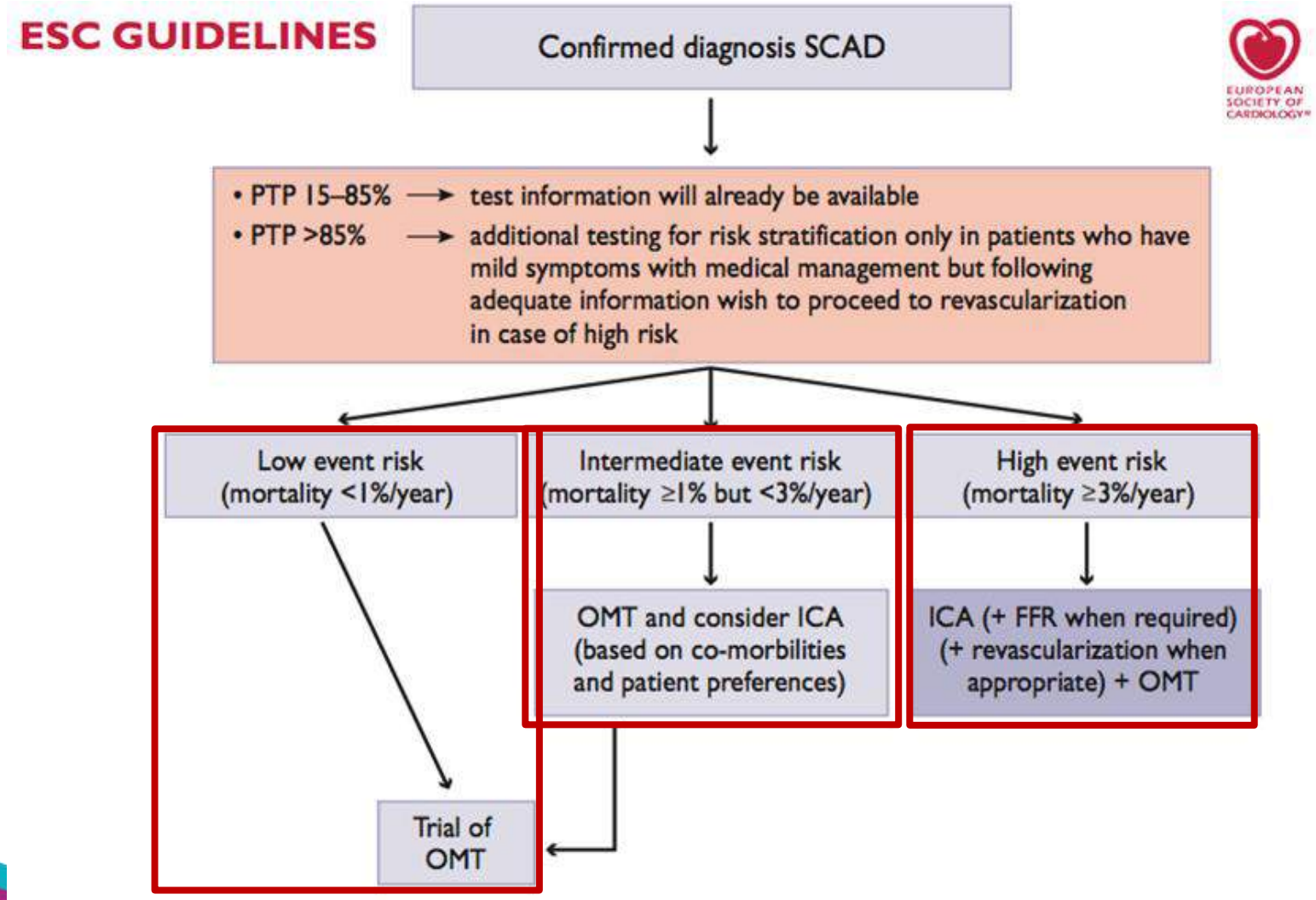
(1) Valutazione clinica

(2) Funzione ventricolare sn

(3) Esito degli stress test

(4) Anatomia coronarica

Angina Stabile: come utilizzare i nuovi approcci terapeutici



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Key points

NHS
National Institute for Health and Clinical Excellence

Issued: July 2011 last modified: December 2012

- ✓ **Lifestyle changes are vital in the management of stable angina, including smoking cessation, healthy diet, weight loss and control of lipid levels**
- ✓ Associated conditions, such as hypertension and diabetes, should be treated according to relevant guidance
- ✓ Revascularisation should be considered in selected patients
- ✓ Medical therapy → new ….and classic approach

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Antianginal Drugs

Drug class	O_2 Supply: Coronary blood flow	O_2 Demand: Heart rate	O_2 Demand: Arterial pressure	O_2 Demand: Venous return	O_2 Demand: Myocardial contractility
β-blockers	—	↓	↓	—	↓
DHP CCBs	↑	↑*	↓	—	↓
Non-DHP CCBs	↑	↓	↓	—	↓
Long-acting nitrates	↑	↑/—	↓	↓	—

CCB = calcium channel blocker, DHP = dihydropyridine *Except amlodipine

Boden WE et al. Clin Cardiol. 2001;24:73-9
Gibbons RJ et al. ACC/AHA 2002 Chronic Angina Guidelines
Kerins DM et al. The Pharmacological Basis of Therapeutics. 10th ed

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Limitations of Conventional Antianginal Therapies

Drug Class

Limitations	Beta Blockers	Nitrates	Calcium Antagonists
Comorbidity Challenges	• COPD • Bradycardia • A-V conduction problems • Peripheral Vascular Disease • Sick Sinus Syndrome	• Left ventricular outflow tract obstruction	• Bradycardia • Heart failure • Left ventricular dysfunction • Sick sinus syndrome • A-V conduction problems
Side Effects	• Sexual dysfunction • Fatigue • Depression • Hypotension • Syncope	• Headache • Syncope • Tolerance • Hypotension	• Flushing • Dizziness • Hypotension • Edema • Fatigue

Adapted from Gibbons et al. ACC/AHA 2002 Guideline Update for Chronic Stable Angina

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Combination with beta-blocker or calcium channel blocker vs monotherapy in stable angina: lack of benefits

Study	Combinations	Findings
TIBET - Fox KM *Eur Heart J* 1996;17:96-103	Atenolol Nifedipine SR Combination 608 patients	**No additive benefit of combined therapy**
IMAGE - Savonitto S *J Am Coll Cardiol* 1996;27:311-316	Metoprolol Nifedipine SR Combination 249 patients	**No additive benefit of combined therapy**
CESAR - Knight C and Fox KM *Am J Cardiol* 1998;81:133-136	Amlodipine + Atenolol vs Diltiazem + Atenolol	**No additive benefit of combined therapy**
Meta-analysis (22 studies) **Klein W, Jackson G, and Tavazzi L** *Coron Artery Dis* 2002; 13:427-436	β-Blocker Calcium antagonist Combination	**No additive benefit of combined therapy after 6 hours**

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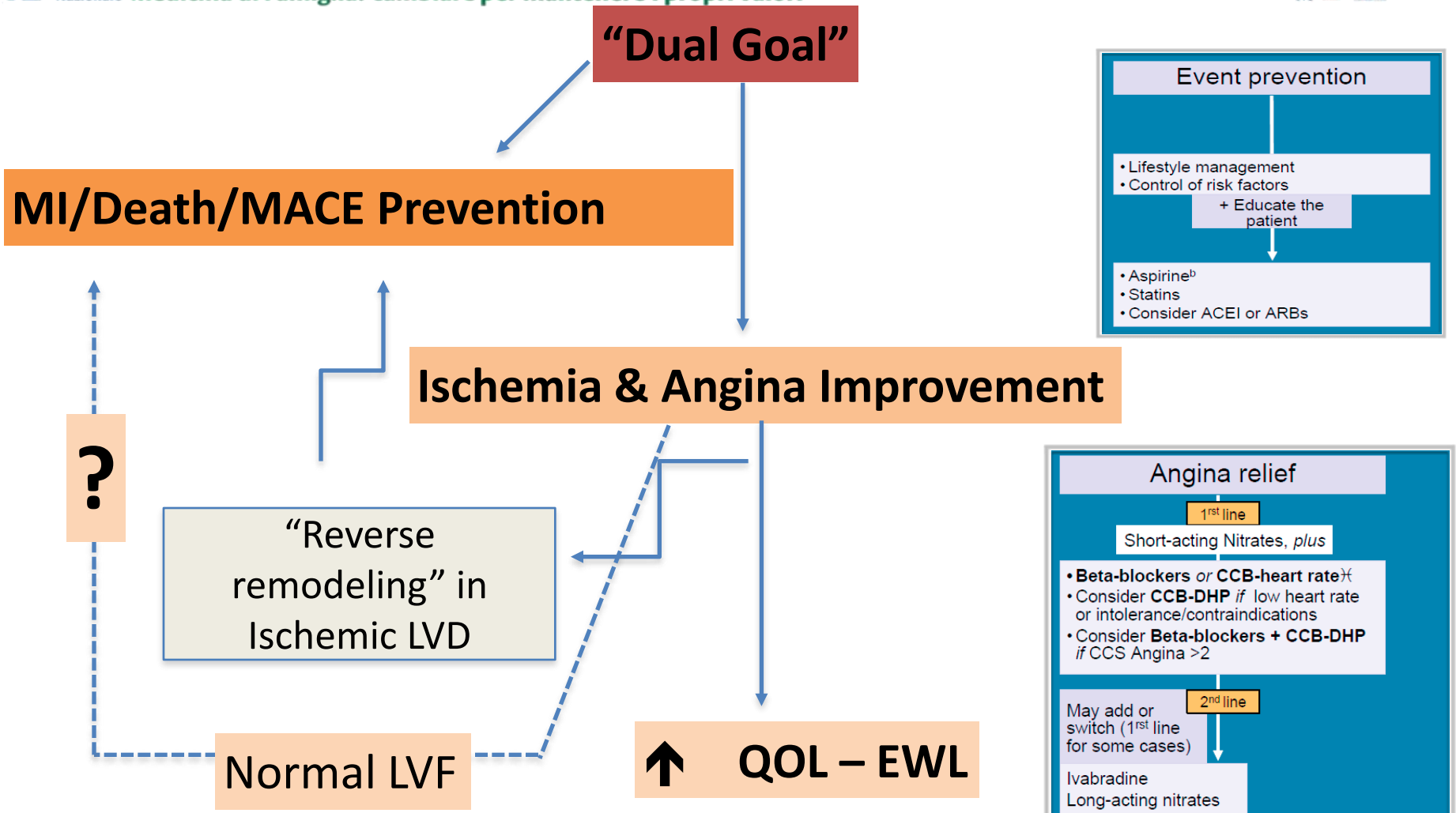
Nuovi Concetti

“Dual Goal”

MI/Death/MACE Prevention

- ASA/Clopidogrel/DAPT
- Statins
- ACE-I /ARB (**LVD/HBP**)

Optimal Medical Therapy in SCAD

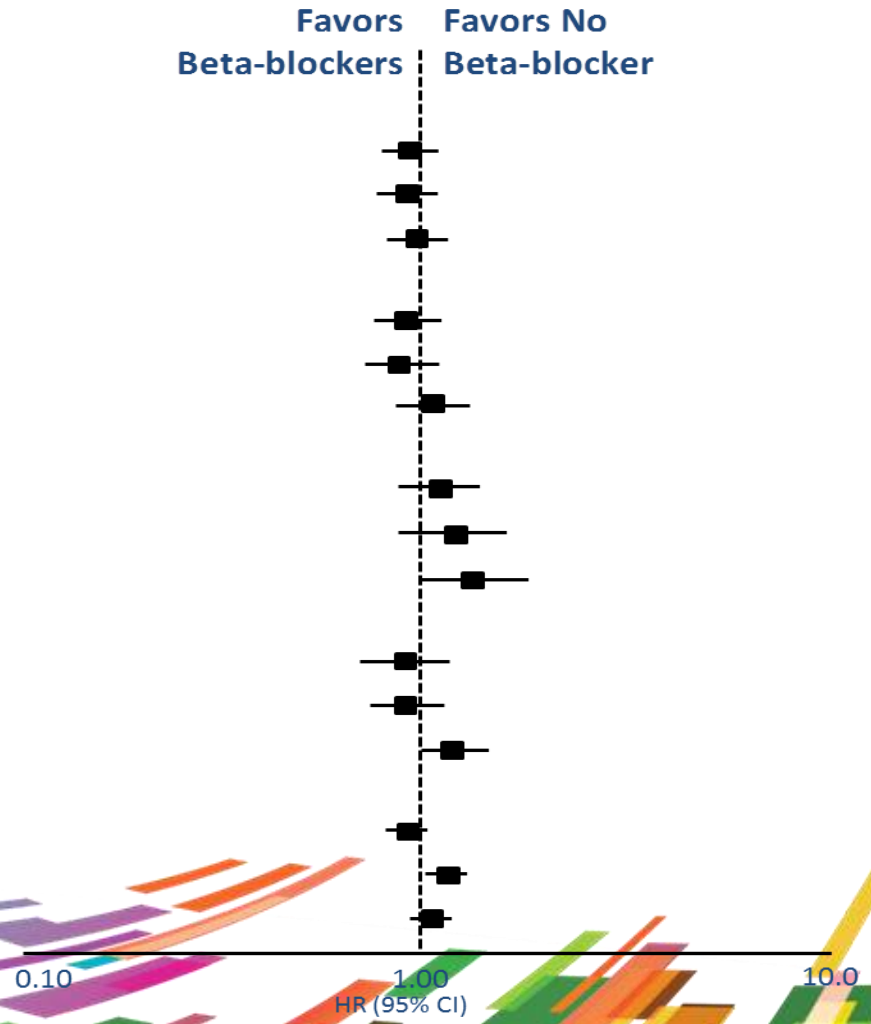


Optimal Medical Therapy in SCAD

No prognostic value of β-blockers in CAD patients (LVEF > 45%)

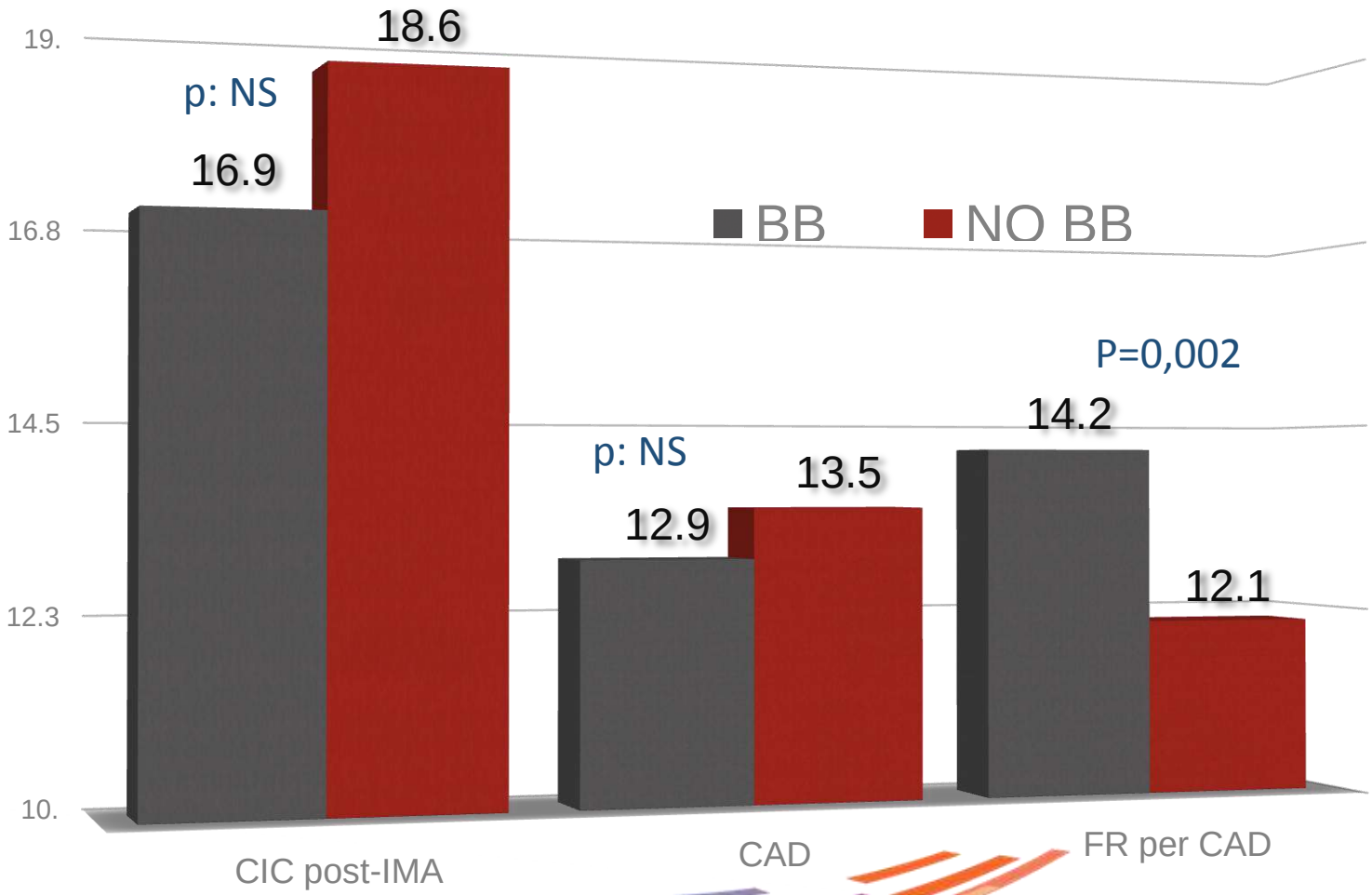
Bangalore S, et al. *JAMA*. 2012;308(13):1340-1349.

	HR (95% CI)	*P* Value
Death		
Prior MI	0.93 (0.80-1.08)	0.34
Known CAD without MI	0.91 (0.77-1.07)	0.25
Risk factor without MI	0.97 (0.82-1.14)	0.71
Cardiovascular death		
Prior MI	0.91 (0.76-1.09)	0.31
Known CAD without MI	0.90 (0.72-1.11)	0.32
Risk factor without MI	1.05 (0.85-1.30)	0.66
Nonfatal MI		
Prior MI	1.10 (0.87-1.41)	0.42
Known CAD without MI	1.24 (0.91-1.69)	0.16
Risk factor without MI	1.36 (0.97-1.90)	0.08
Nonfatal stroke		
Prior MI	0.87 (0.66-1.13)	0.28
Known CAD without MI	0.89 (0.69-1.16)	0.39
Risk factor without MI	1.22 (0.99-1.52)	0.06
Hospitalization		
Prior MI	0.94 (0.84-1.05)	0.30
Known CAD without MI	1.17 (1.04-1.30)	0.01
Risk factor without MI	1.07 (0.95-1.22)	0.26

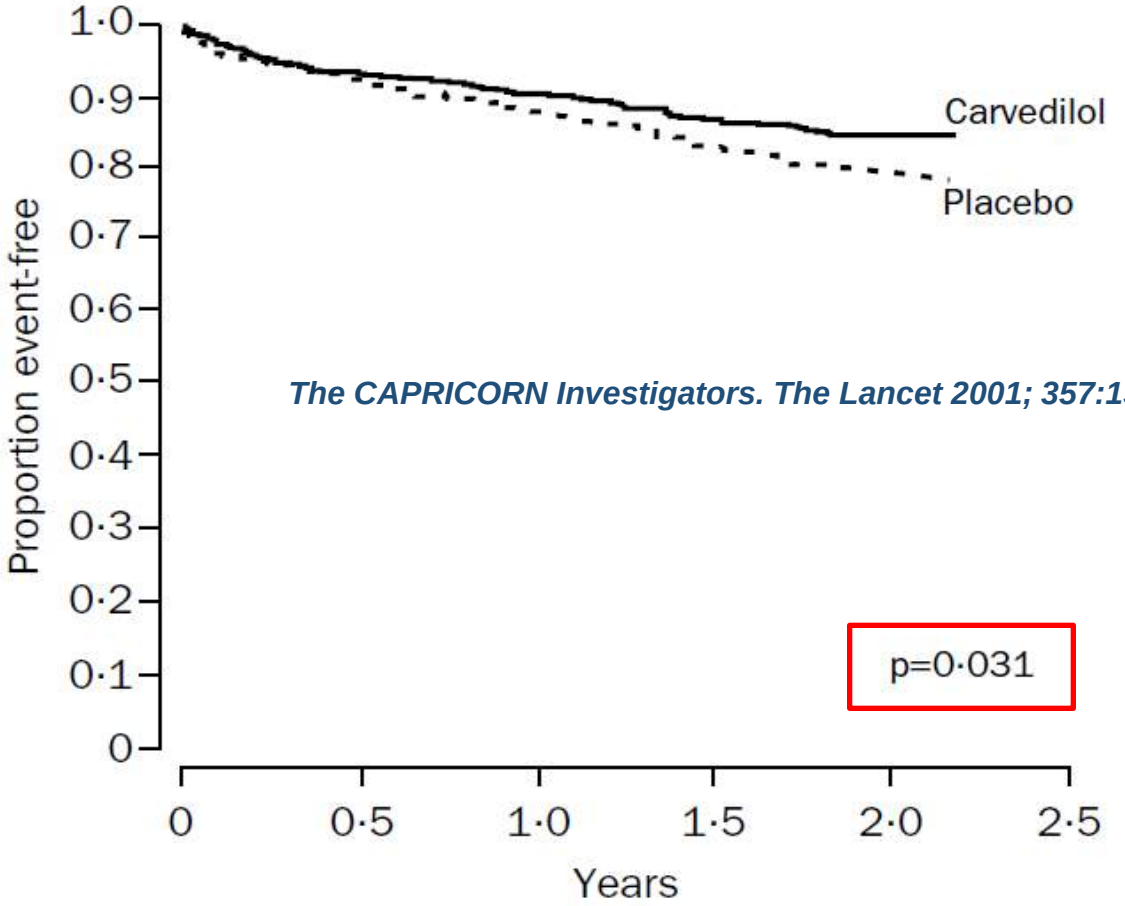


Registro REACH - Incidenza morte CV, IMA, Stroke

Bangalore S et al, JAMA 2012; 308:1340-9



CAPRICORN – All-Cause Mortality



The CAPRICORN Investigators. The Lancet 2001; 357:1385-90

Numbers at risk

Carvedilol	975	856	648	364	117	16
Placebo	984	861	638	358	123	8

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 43, No. 10, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.09.071

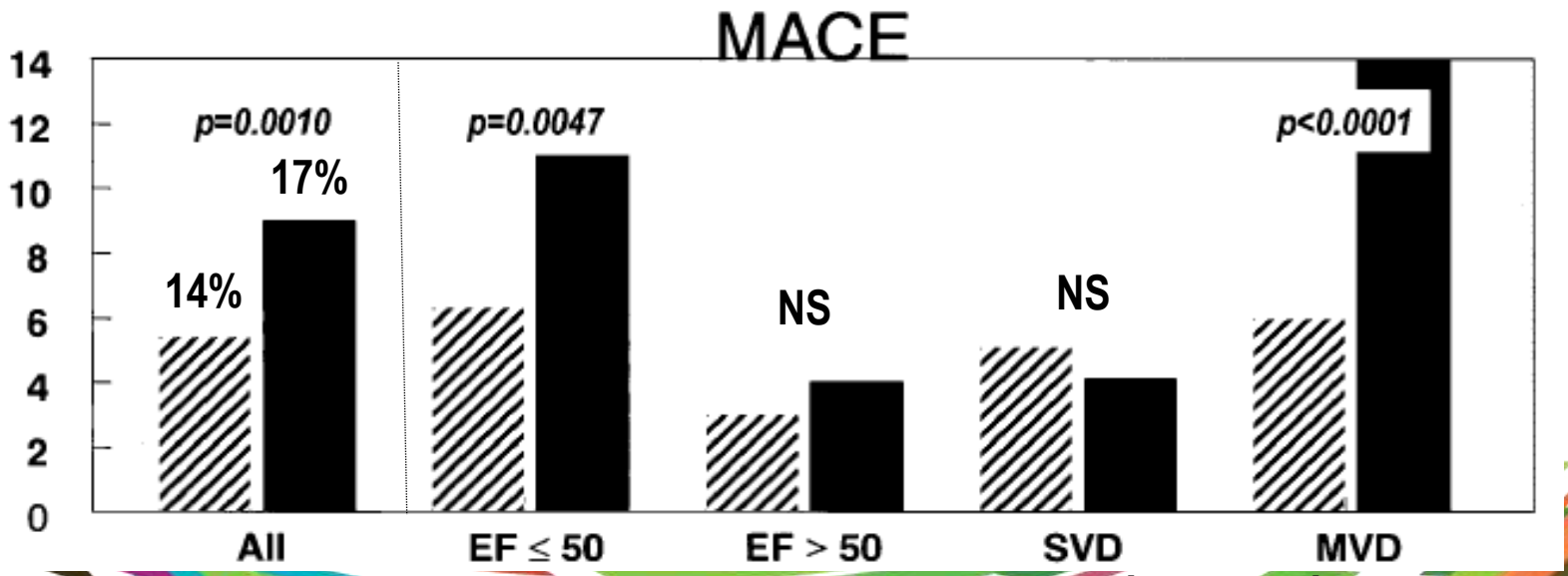
Does Beta-Blocker Therapy Improve Clinical Outcomes of Acute Myocardial Infarction After Successful Primary Angioplasty?

Steven J. Kernis, MD,* Kishore J. Harjai, MD, FACC,* Gregg W. Stone, MD, FACC,†
Lorelei L. Grines, PHD,* Judith A. Boura, MS,* William W. O'Neill, MD, FACC,*
Cindy L. Grines, MD, FACC*

Royal Oak, Michigan; and New York, New York

monovasale multivasale

PCI 1a
FU 6 mesi



Kernis SJ et al, JACC 2004; 43:1773-9

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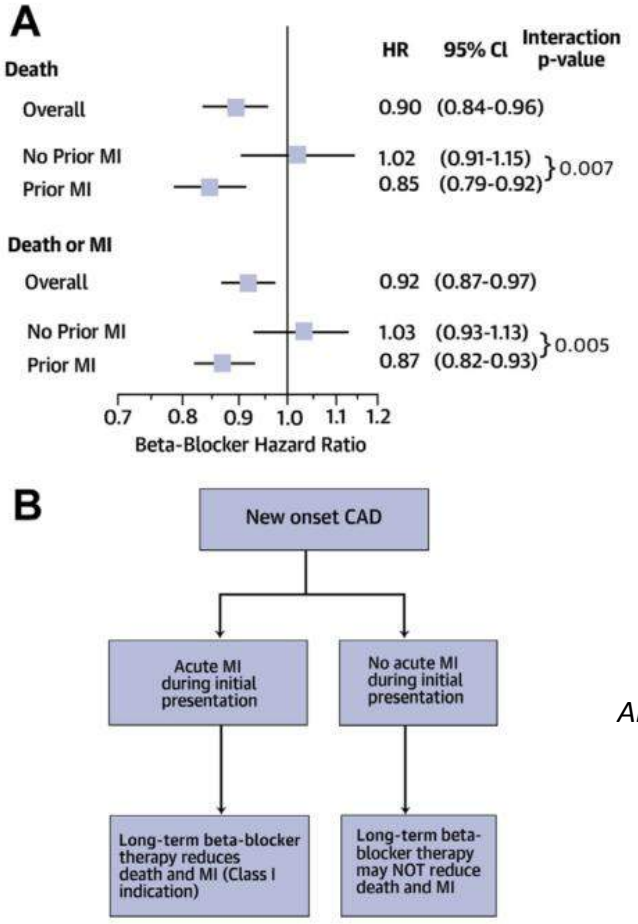
Beta-Blocker Therapy and Cardiac Events Among Patients With Newly Diagnosed Coronary Heart Disease



Andersson et al. JACC VO L. 64 , N O . 3, 20 1 4

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"Dual Goal"

MI/Death/MACE Prevention

Ischemia & Angina Improvement

- **Beta-blockers**
- **CCB-DHP**
- **CCB-HR lowering**
- **Ivabradine**
- **Nitrates**
- **Nicorandil**
- **Ranolazine**
- **Trimetazidine**

Optimal Medical Therapy in SCAD

Efficacia

- Riduzione dei sintomi → rivascolarizzazioni
- Miglioramento capacità di esercizio
- Riduzione della ischemia

Safety

- Side-effects (anche rari) → N° pts trattati > 40.000
- DDI

Meccanismo di azione

- Target congrui con l' effetto atteso
- Obiettivi di trattamento → guida al trattamento

Applicabilità al singolo paziente

- Fisiopatologia
- Parametri clinici
- Modelli clinici testati

Benefici Prognostici "Aggiuntivi" a AA/LLT/ACE-I

- FVS conservata
- DVS asintomatica
- DVS con HF

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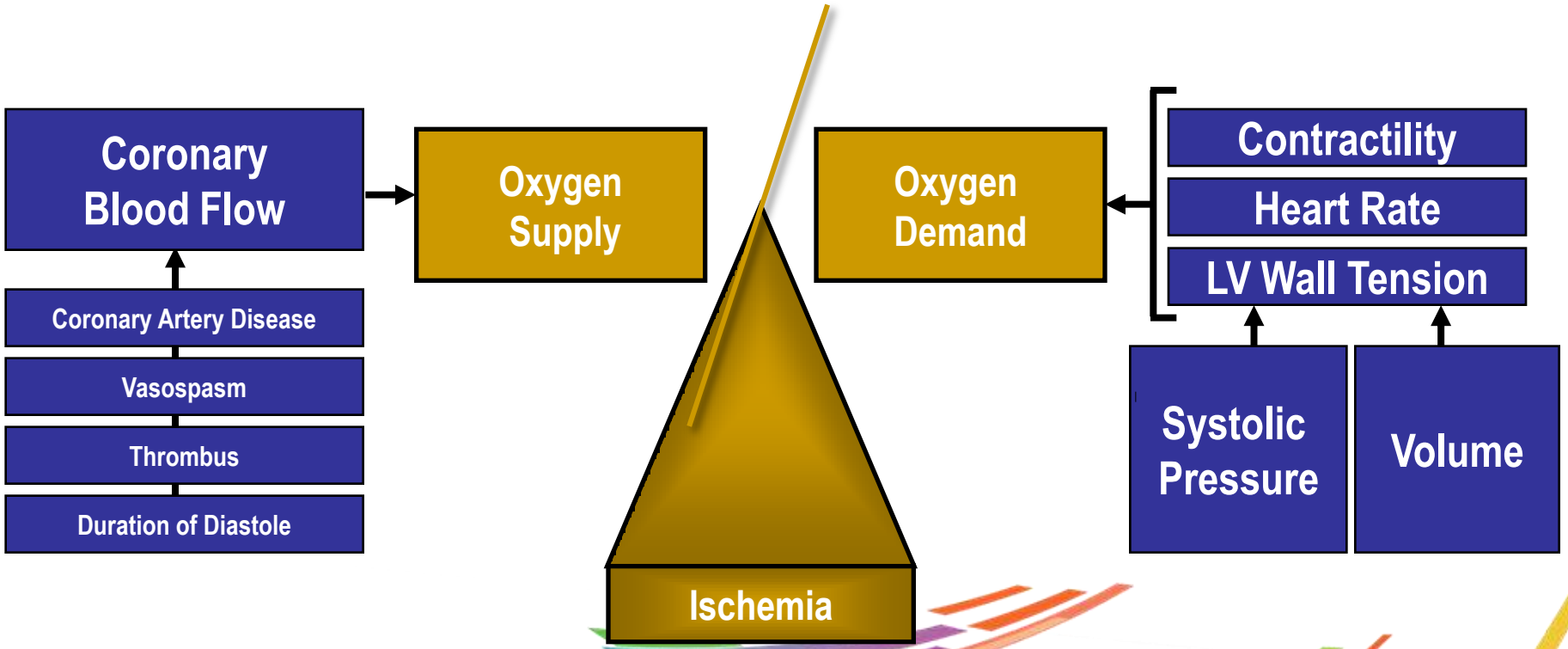
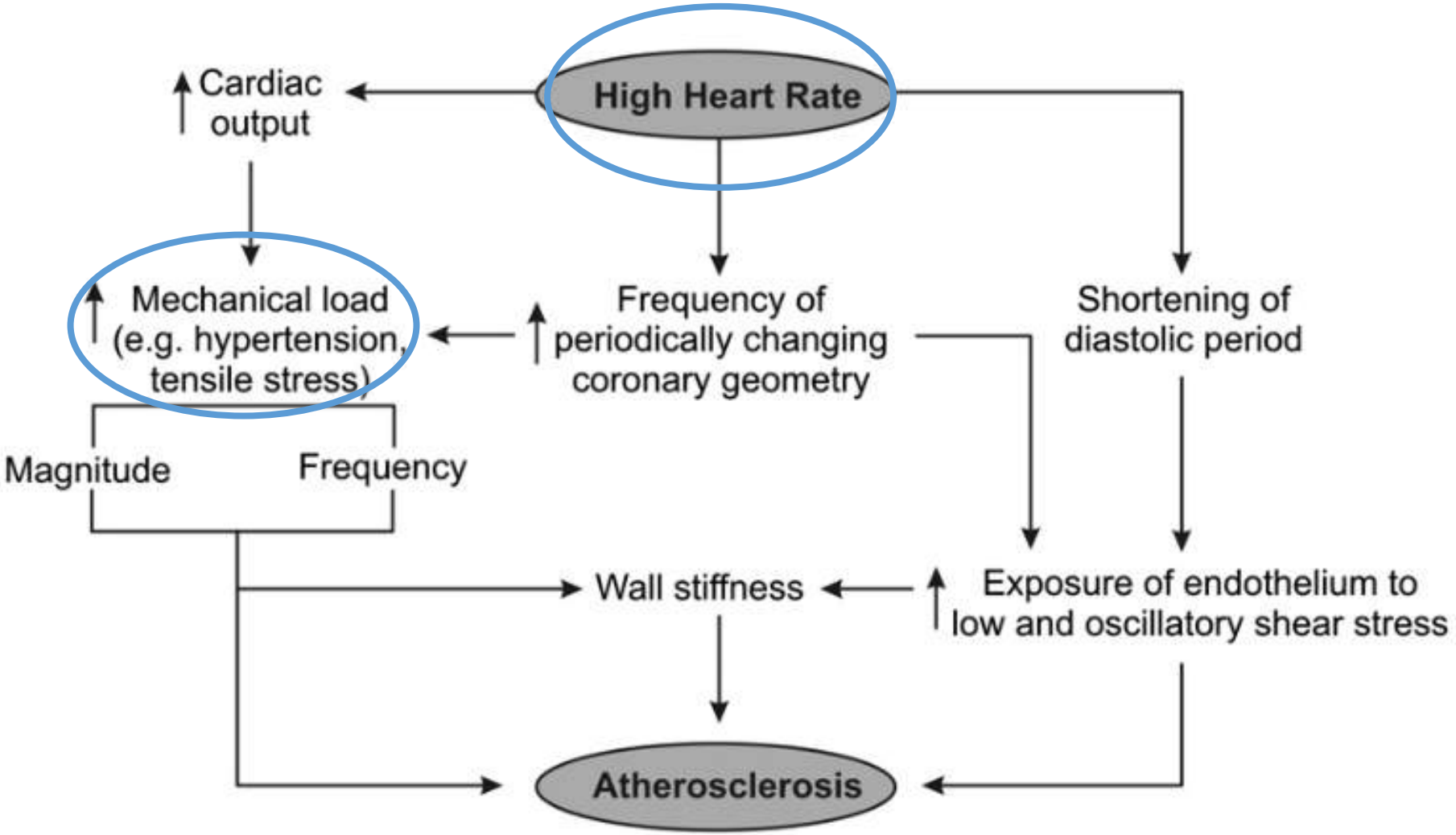
Myocardial Ischemia: Unbalanced Oxygen Supply and Demand



Adapted from Kern MJ. In: Braunwald's Heart Disease. 7th ed. 2005

The role of heart rate in cardiovascular disease



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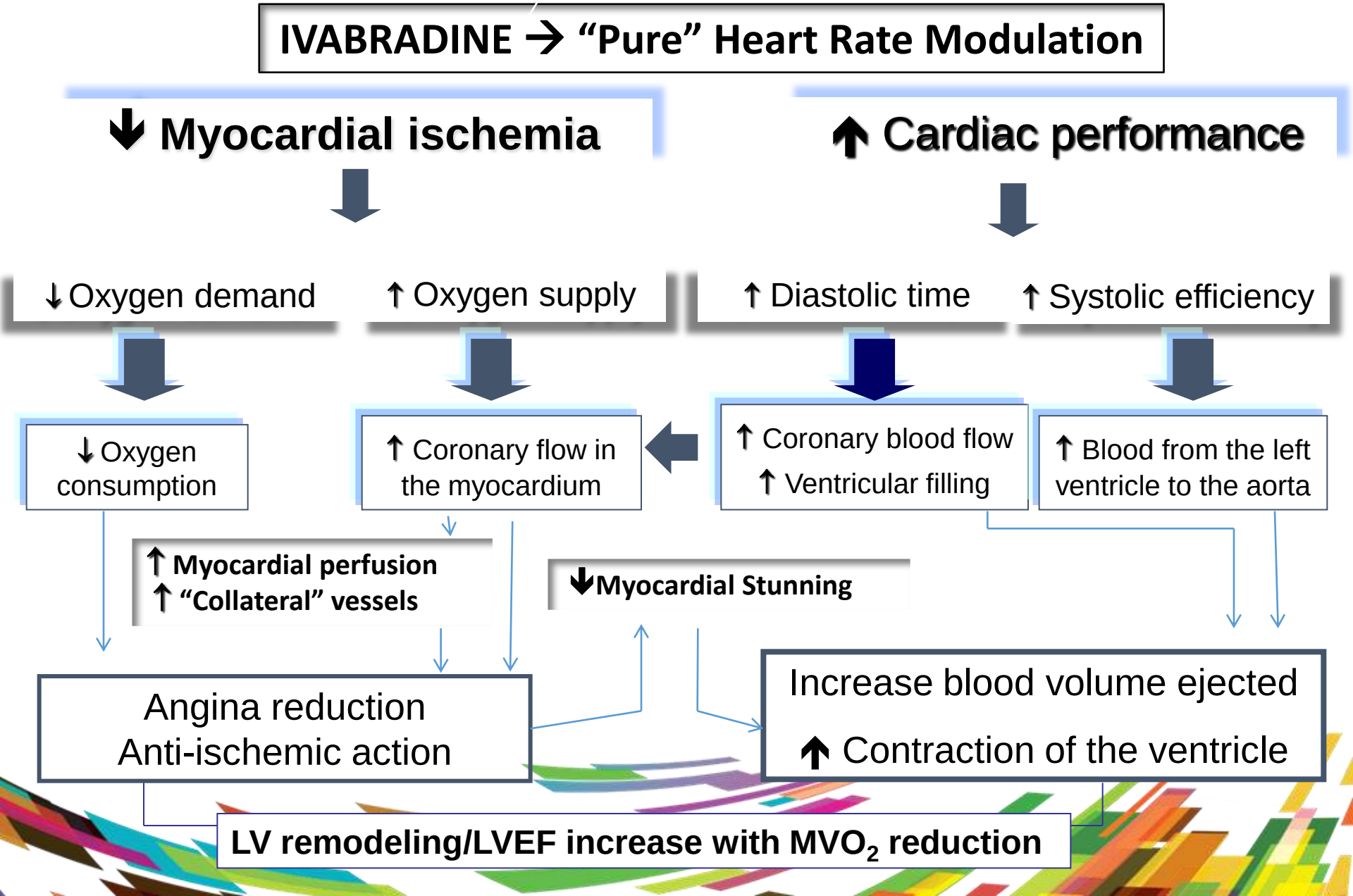
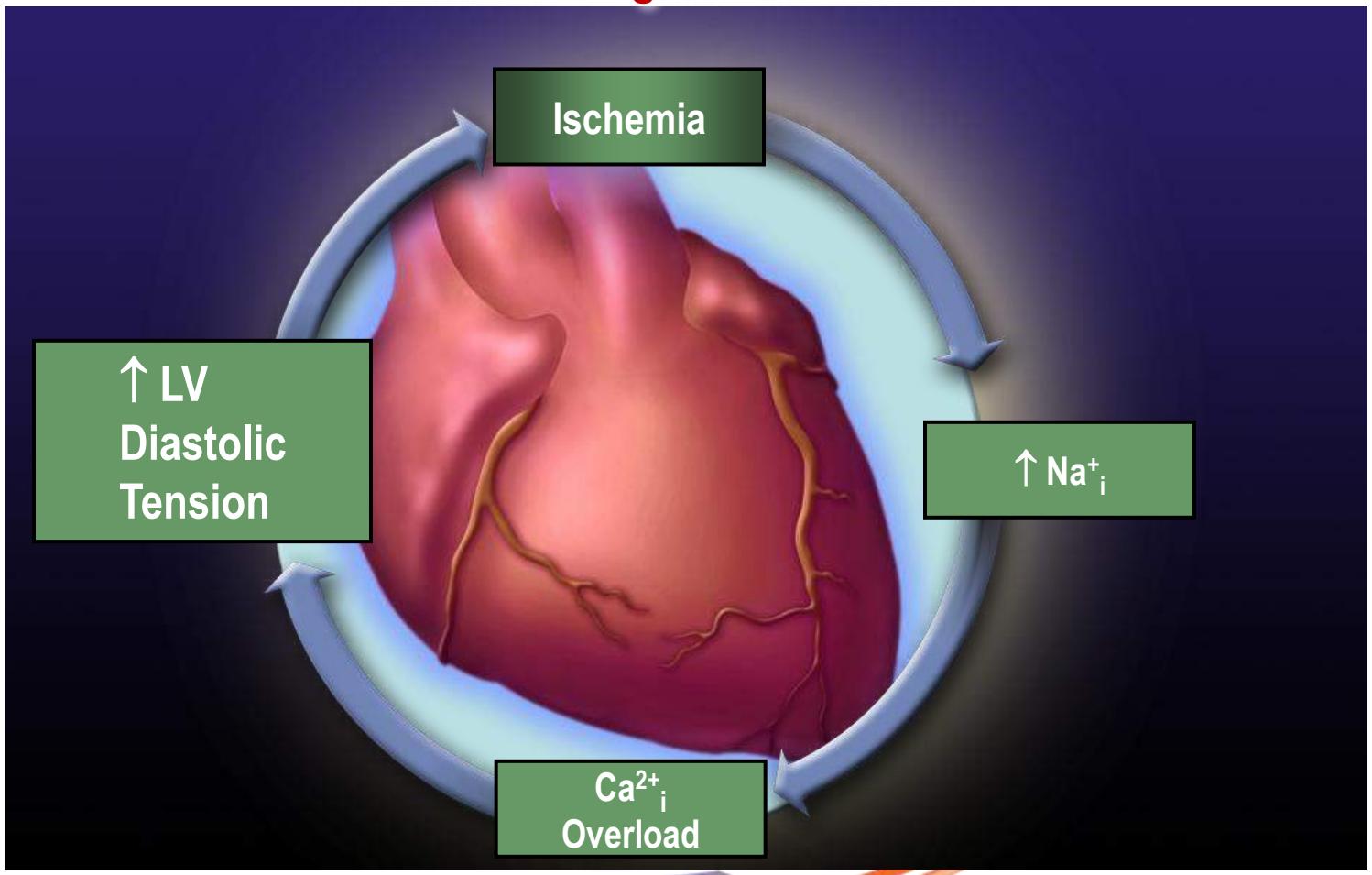


The Cycle of Ischemia

Ischaemia "begets" Ischaemia



Jansen MA et al. Circulation. 2004

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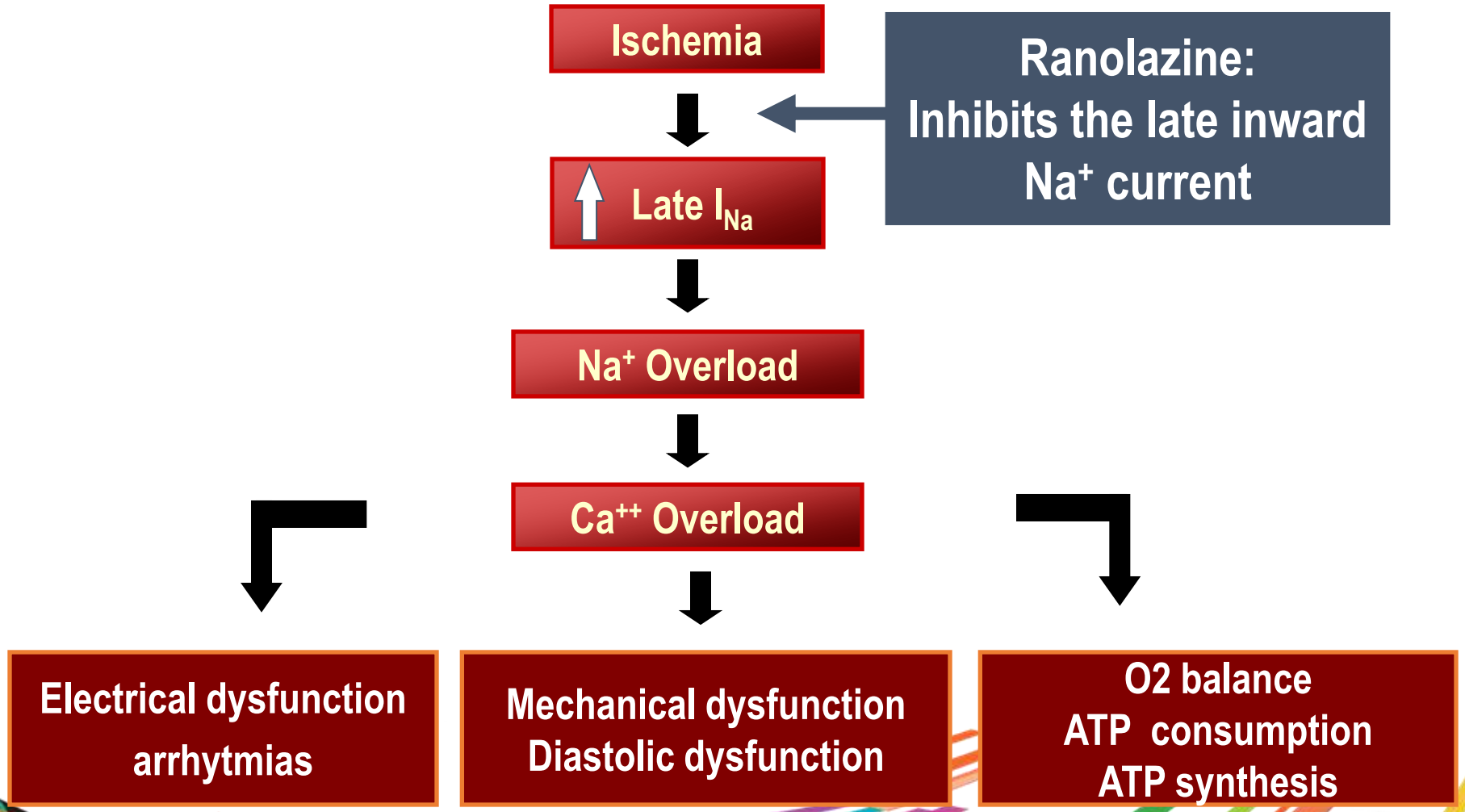

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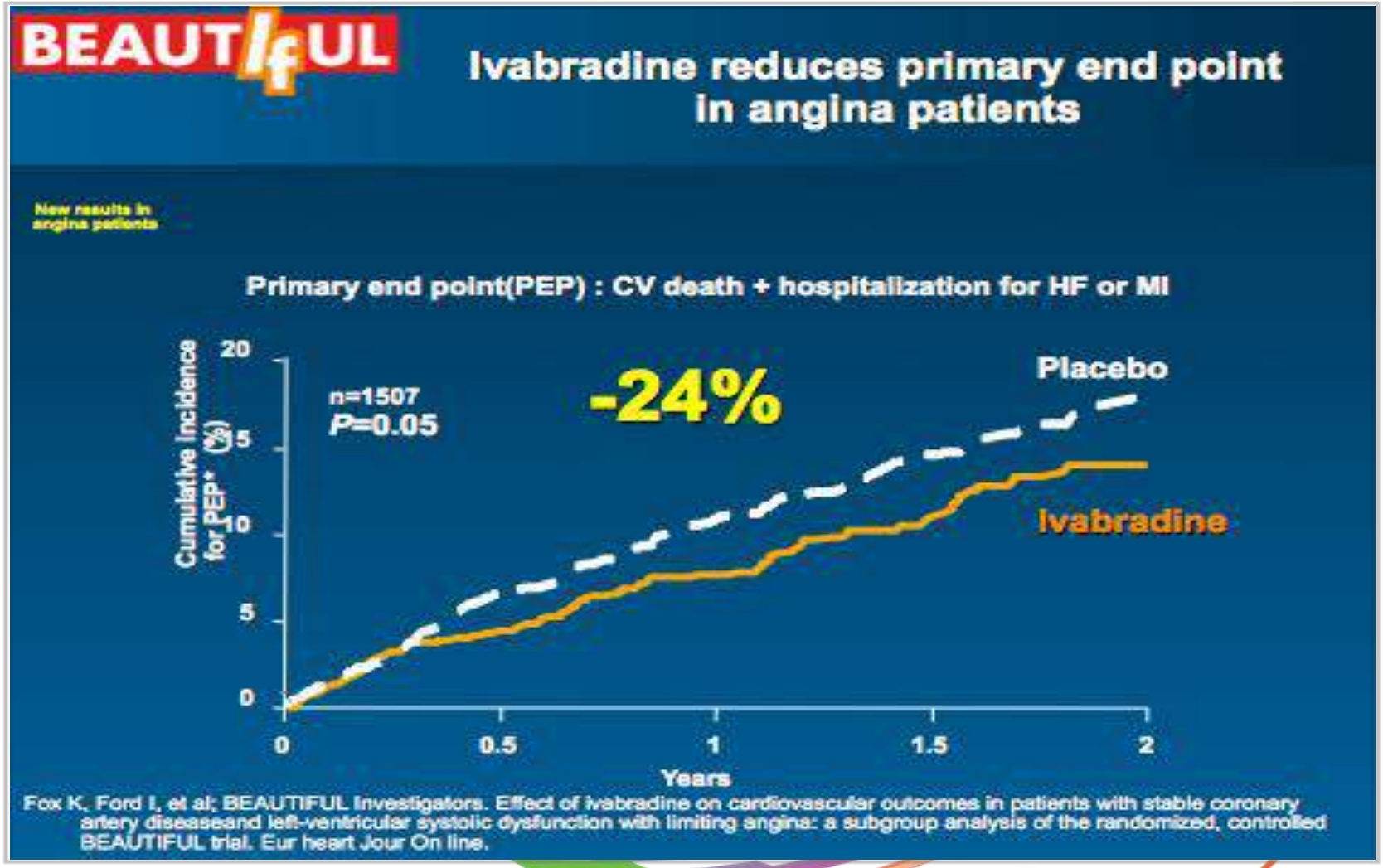
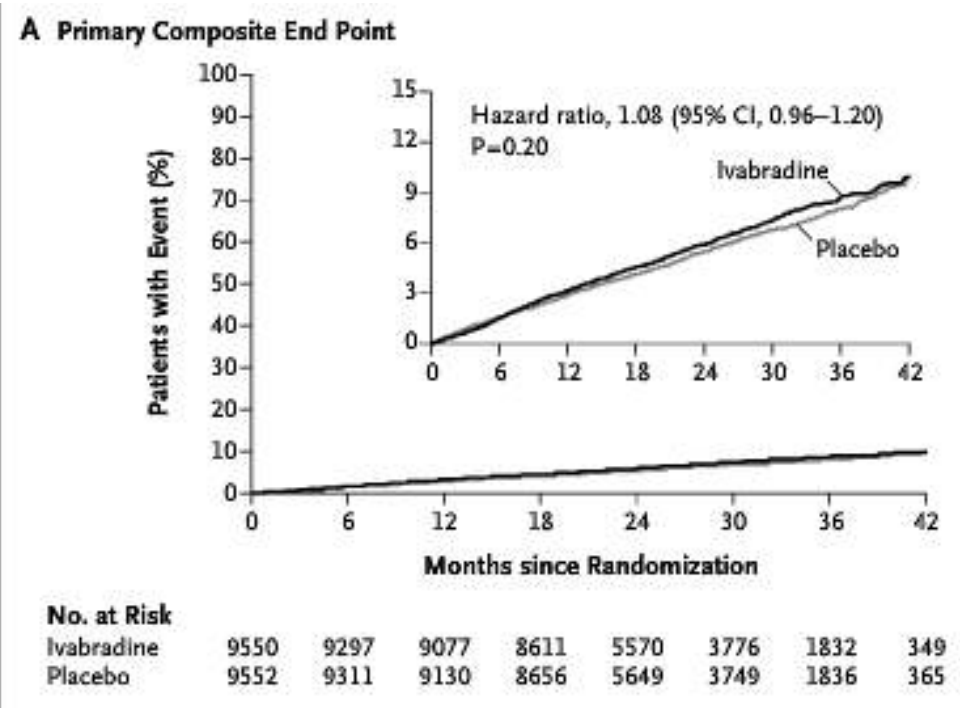
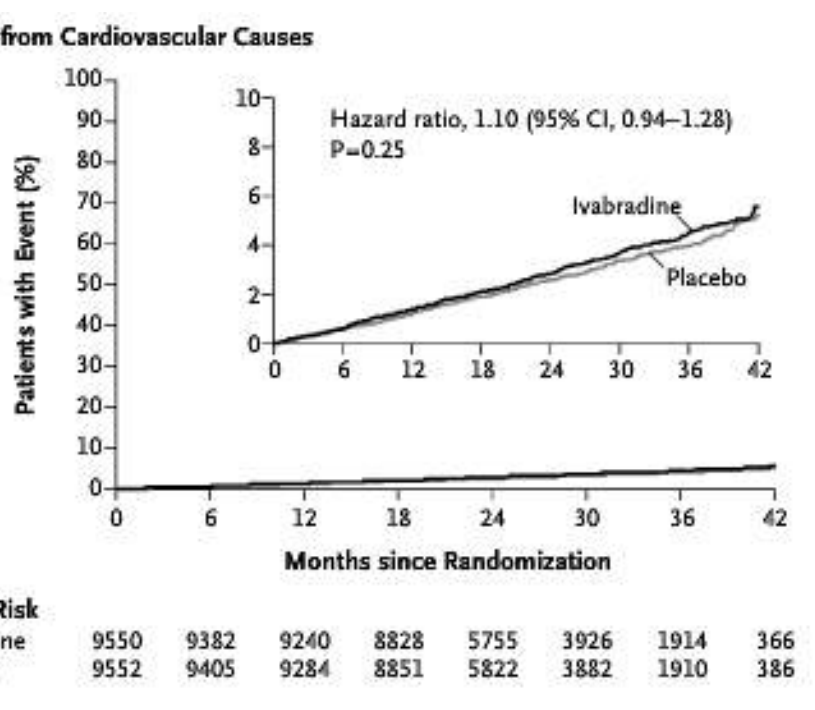
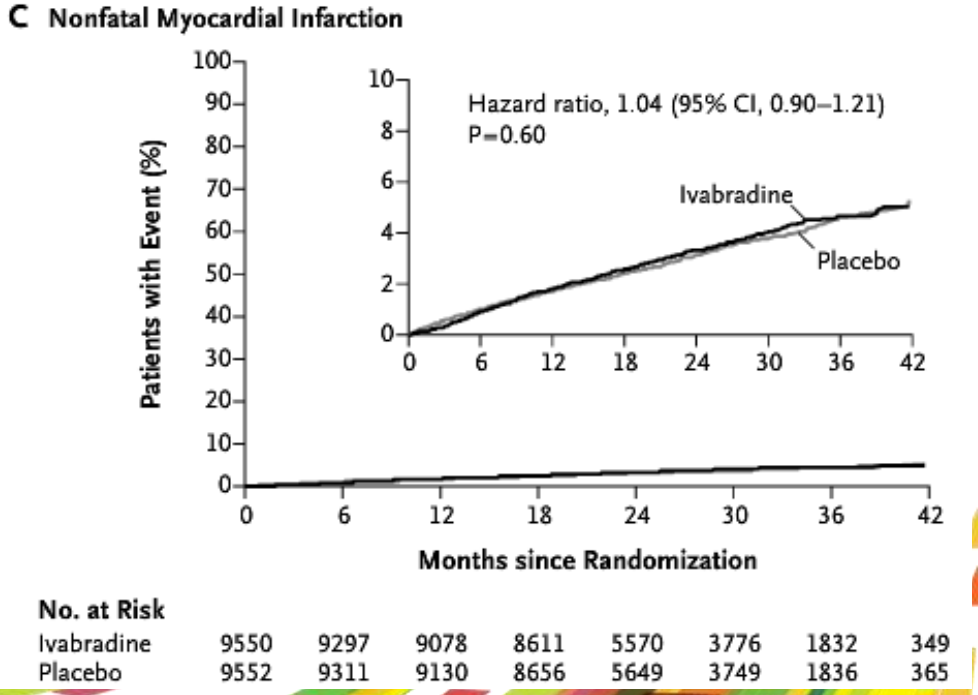




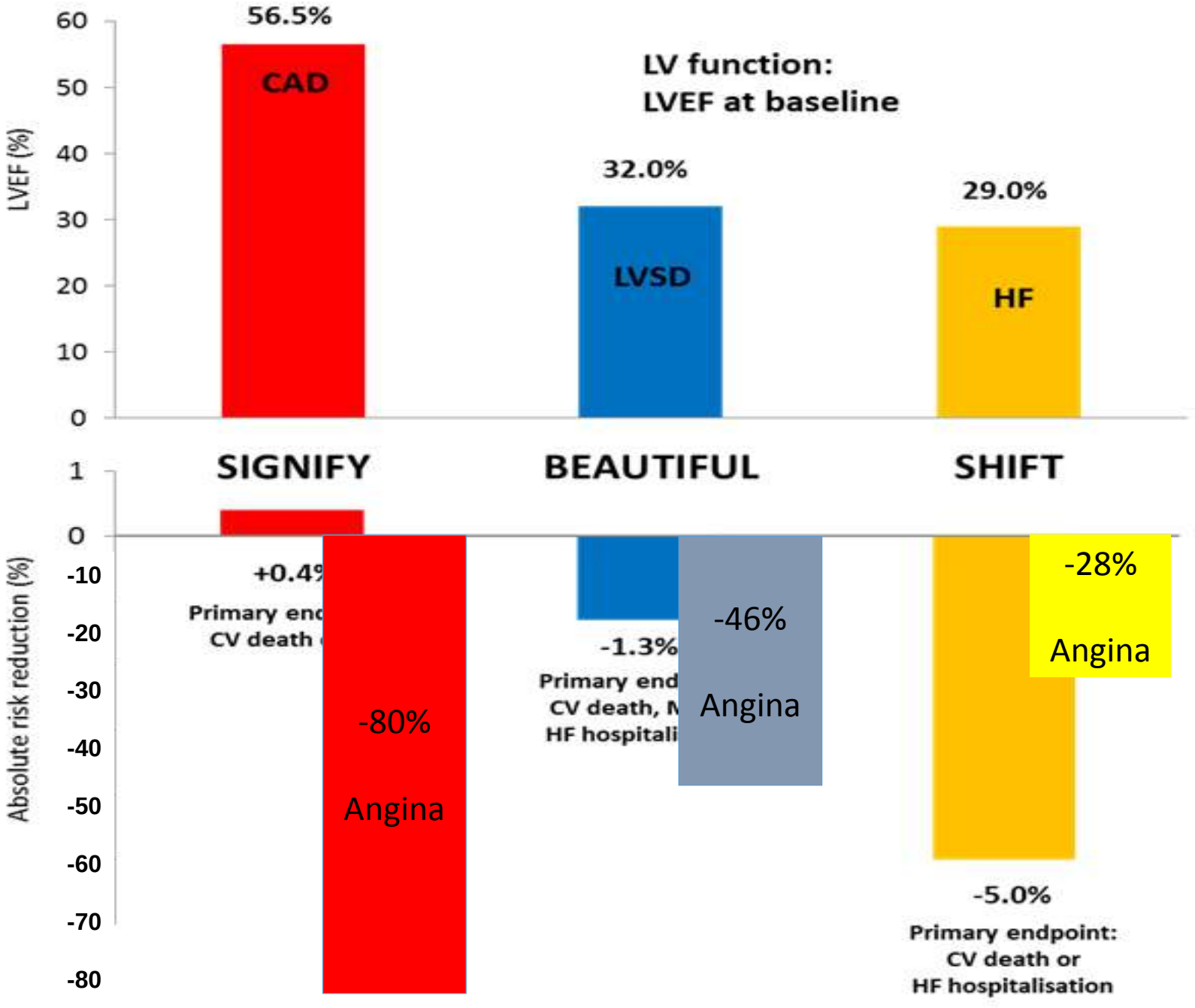


La fc è un marker di rischio ma non è un FDR nella SCAD con FVS > 45%

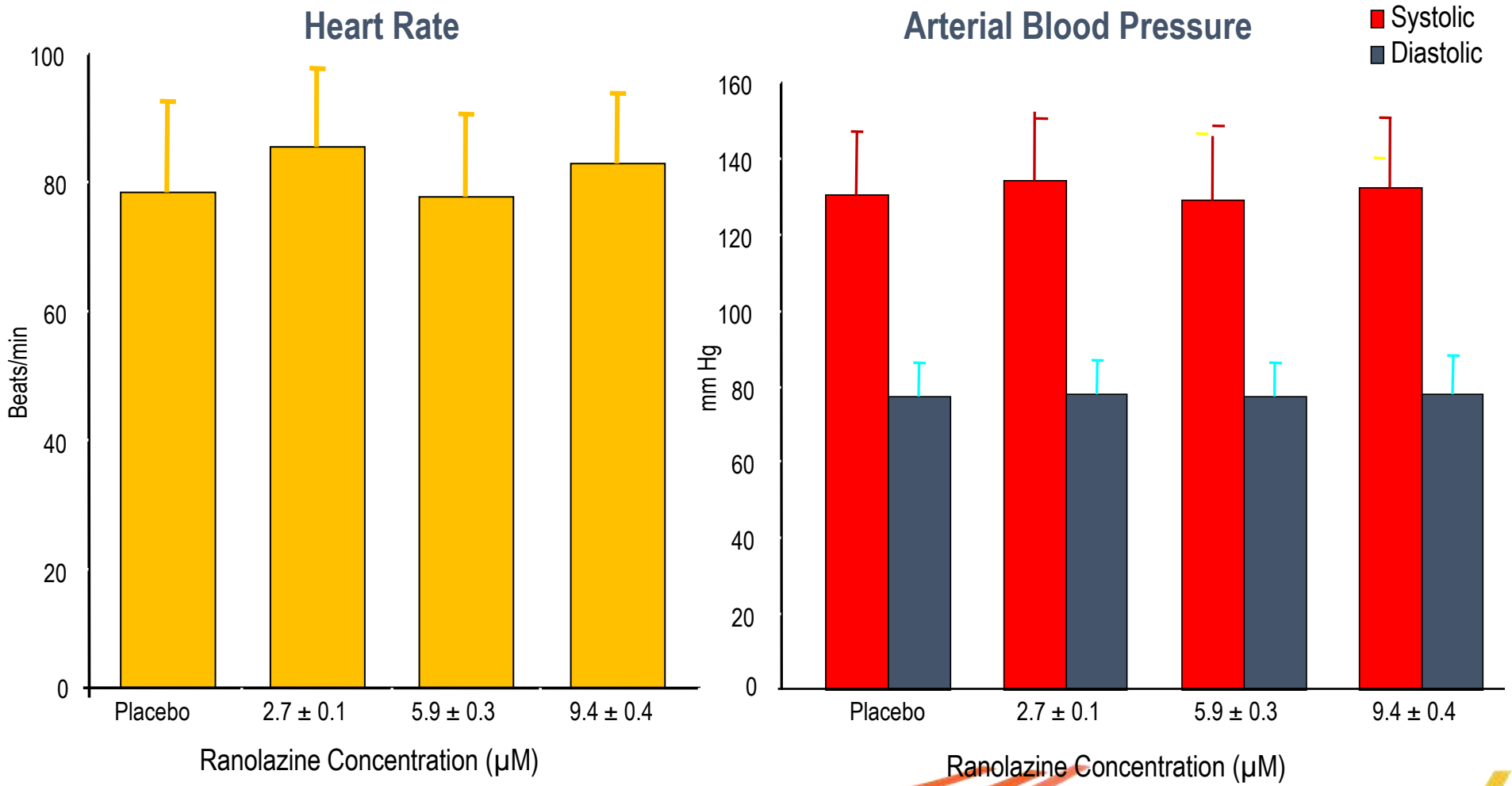


SIGNIfY

Study assessing the morbidity-mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease


LV function:
LVEF at baseline
LVEF (%)
60
50
40
30
20
10
0
56.5%
CAD
32.0%
LVSD
29.0%
HF
SIGNIFY
BEAUTIFUL
SHIFT
Absolute risk reduction (%)
1
0
-10
-20
-30
-40
-50
-60
-70
-80
+0.4%
Primary end
CV death
-80%
Angina
-1.3%
Primary end
CV death, M
HF hospitali
-46%
Angina
-28%
Angina
-5.0%
Primary endpoint:
CV death or
HF hospitalisation

Hemodinamic changes vs Ranolazine dose



MARISA - FDA Review Documents, NDA 21-256, December 9, 2003

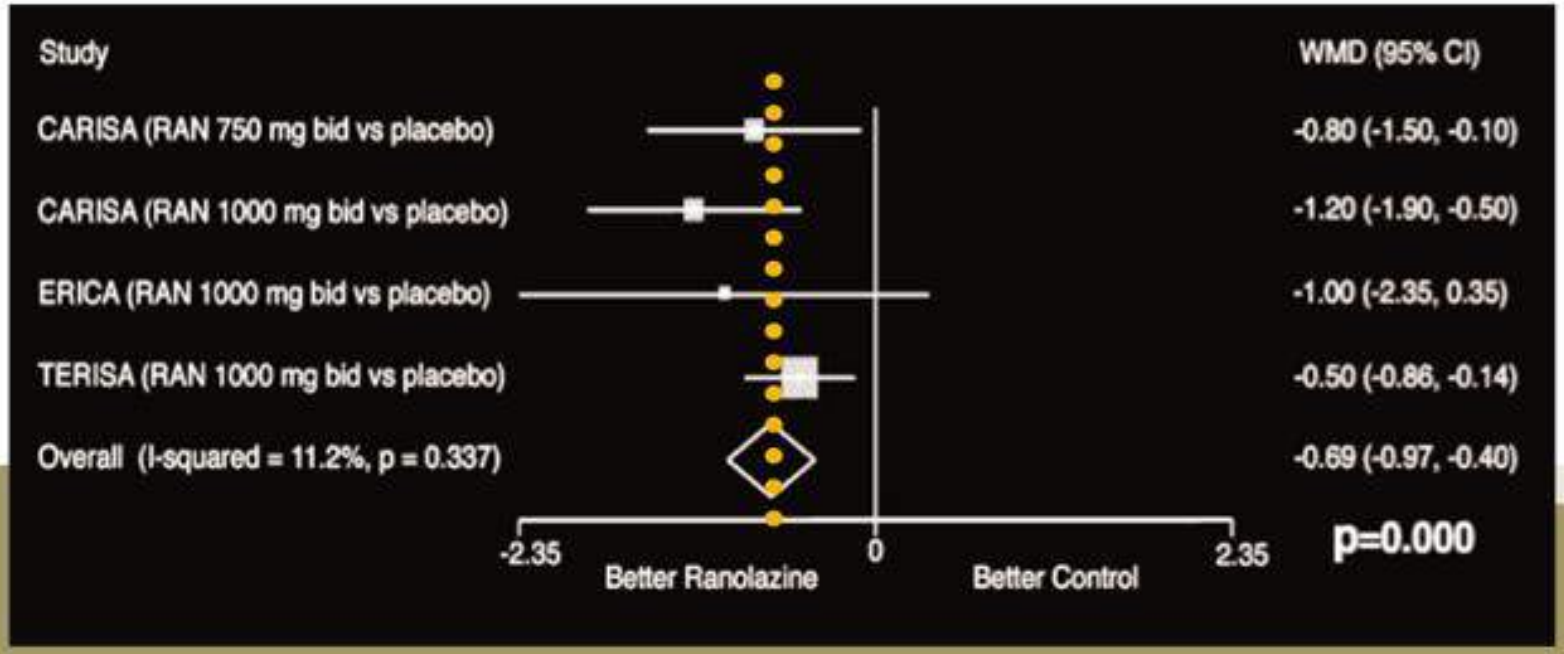
Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta analysis

Savarese, Int. J Cardiol 2013

Gianluigi Savarese[a], Giuseppe Rosano[b], Carmen D'Amore[a], Francesca Musella[a], Giuseppe Luca Della Ratta[a], Angela Maria Pellegrino[a], Tiziana Formisano[a], Alice Vitagliano[a], Annapaola Cirillo[a], Gennaro Cice[c], Luigi Fimiani[a], Luca del Guercio[d], Bruno Trimarco[a], Pasquale Perrone-Filardi[a,*]

[a] Department of Advanced Biomedical Science, Federico II University, Naples, Italy / [b] Clinical and Experimental Research Center, IRCCS San Raffaele, Rome, Italy
[c] Division of Cardiology , Second University of Naples, Naples, Italy / [d] Department of vascular and Endovascular Surgery, Federico II University, Naples, Italy

Mean difference estimate of weekly angina onset in Ranolazine versus control study groups



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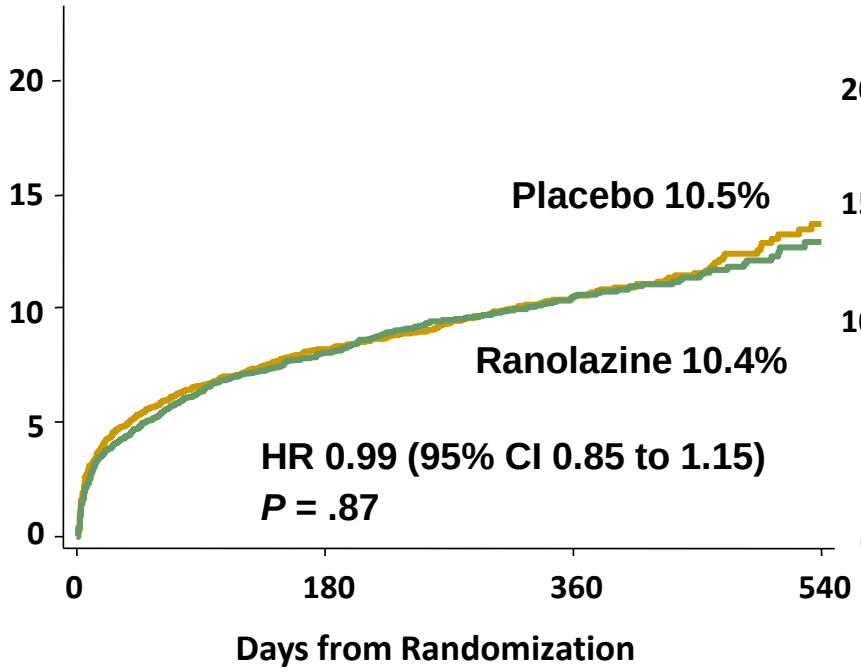
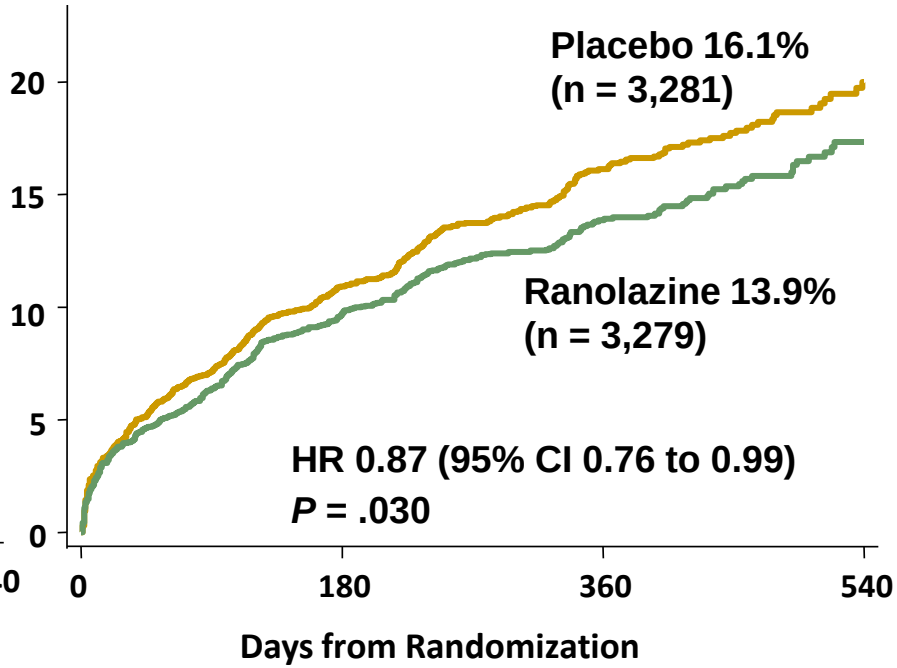
MERLIN

(6560 pts NSTEMI/UA; > 3000 SCAD)

CV Death or MI (%*)



Recurrent Ischemia (%*)



***KM Cumulative Incidence at 12 months**

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

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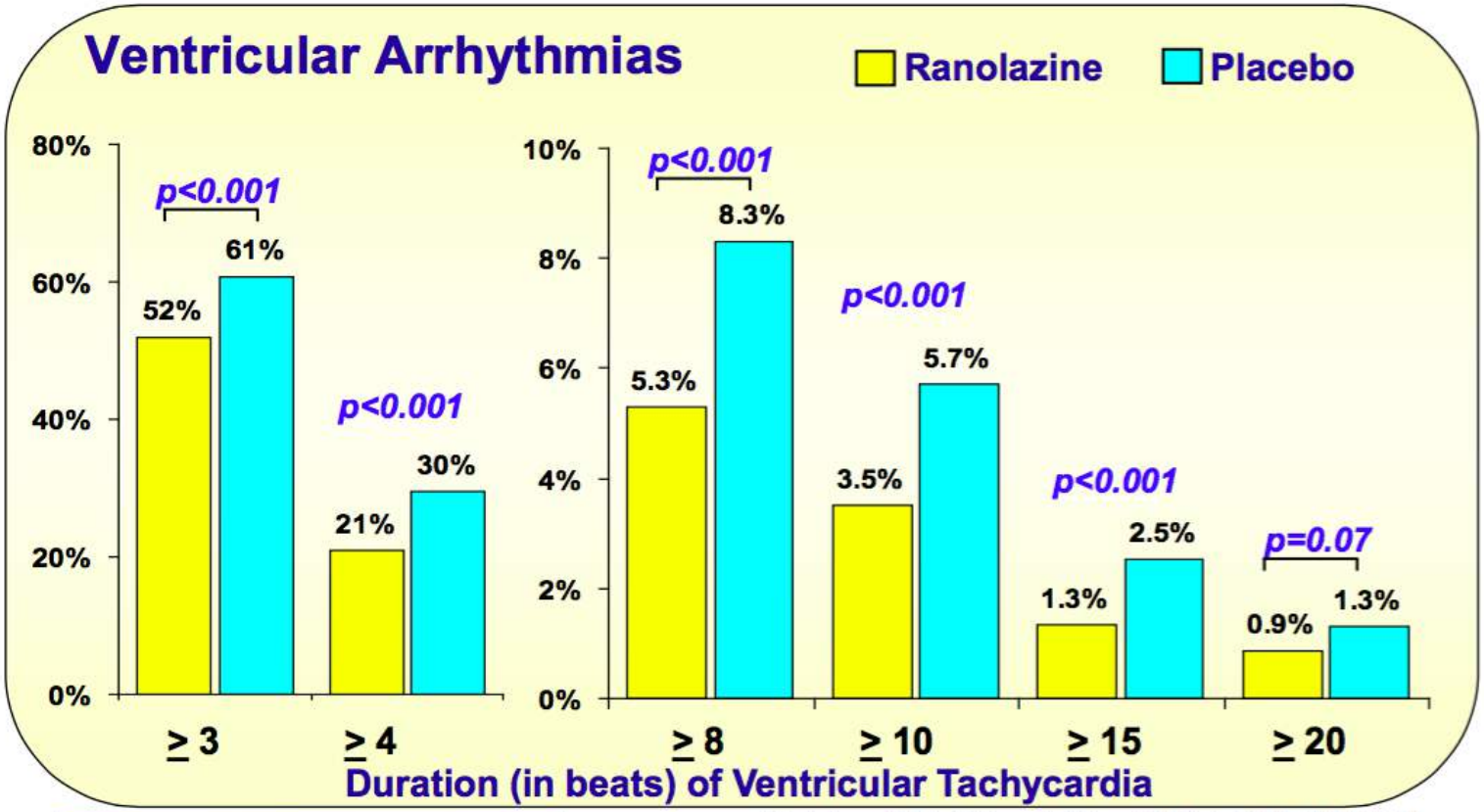
MERLIN – TIMI 36 *Results*



Scirica BM, Circulation 2007; 116:1647-52

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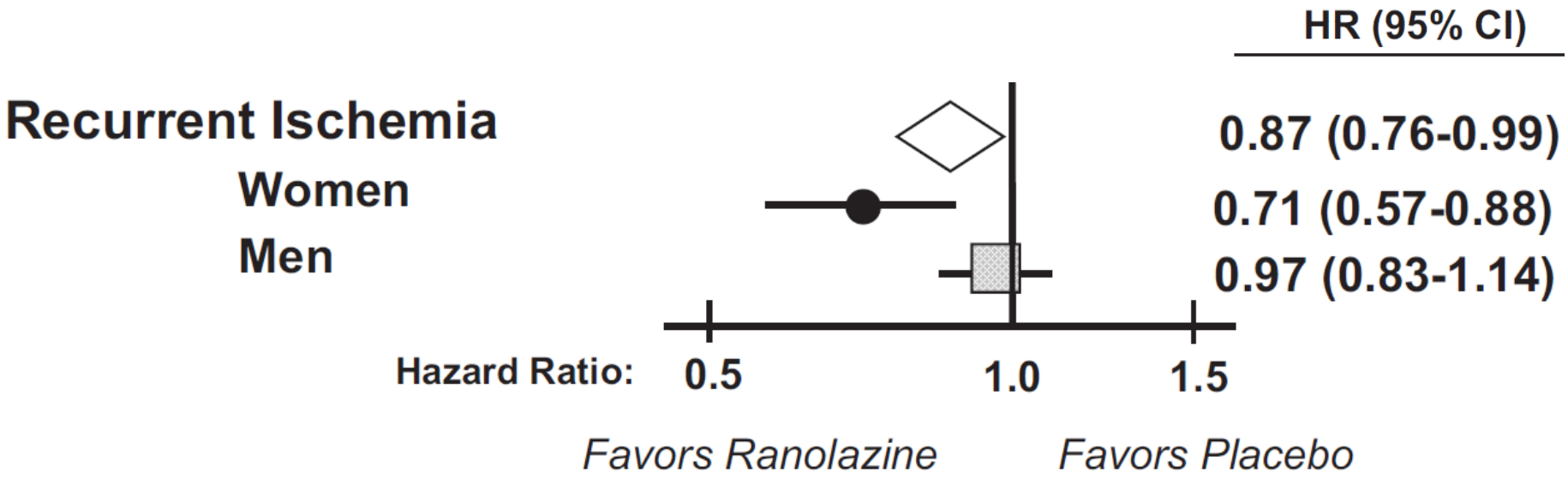
Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease

Observations From Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36)



Mega J, Circulation 2010

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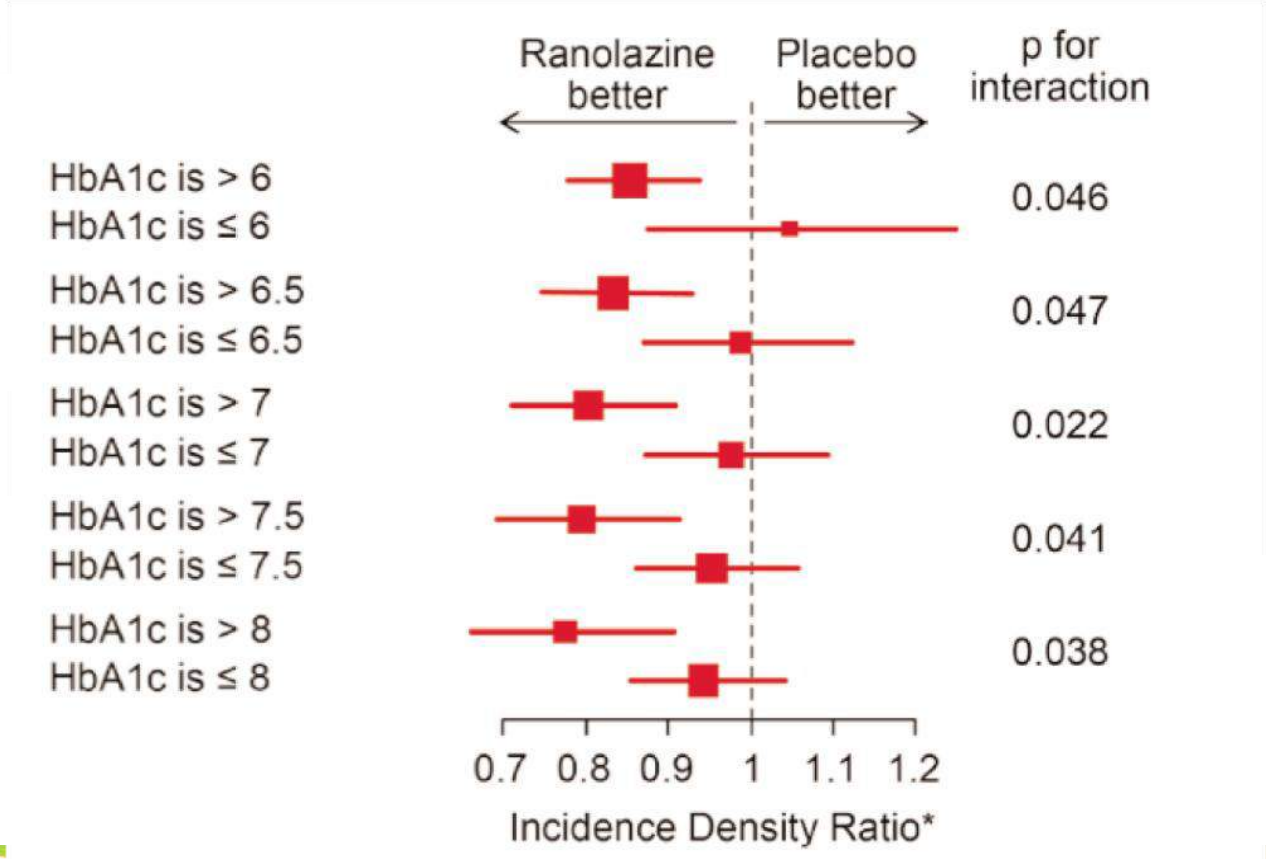
Evaluation of Ranolazine in Patients with Type 2 Diabetes Mellitus and Chronic Stable Angina. Results from the TERISA randomized clinical trial

Kosiborod MJ Am Coll Cardiol 2013



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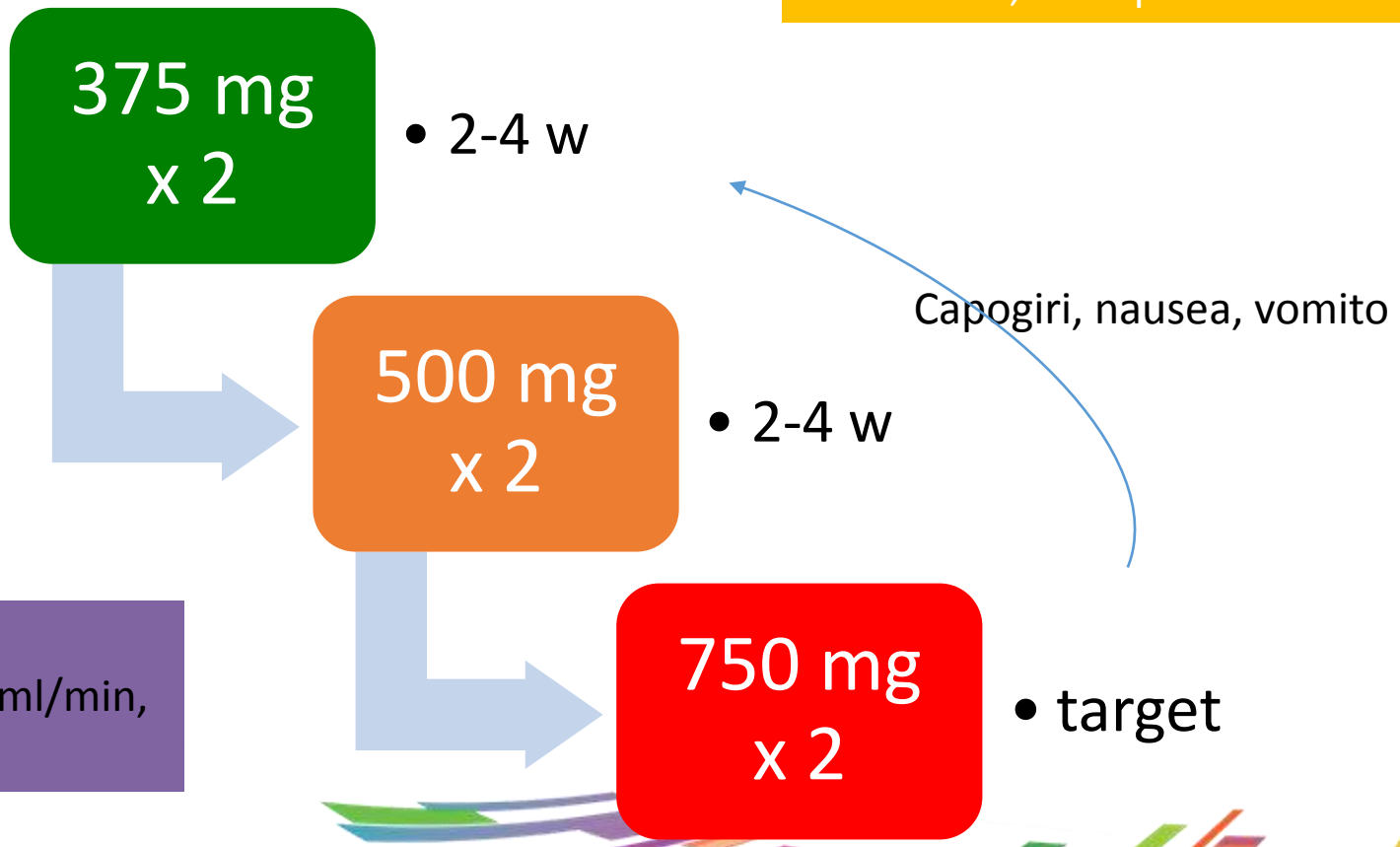
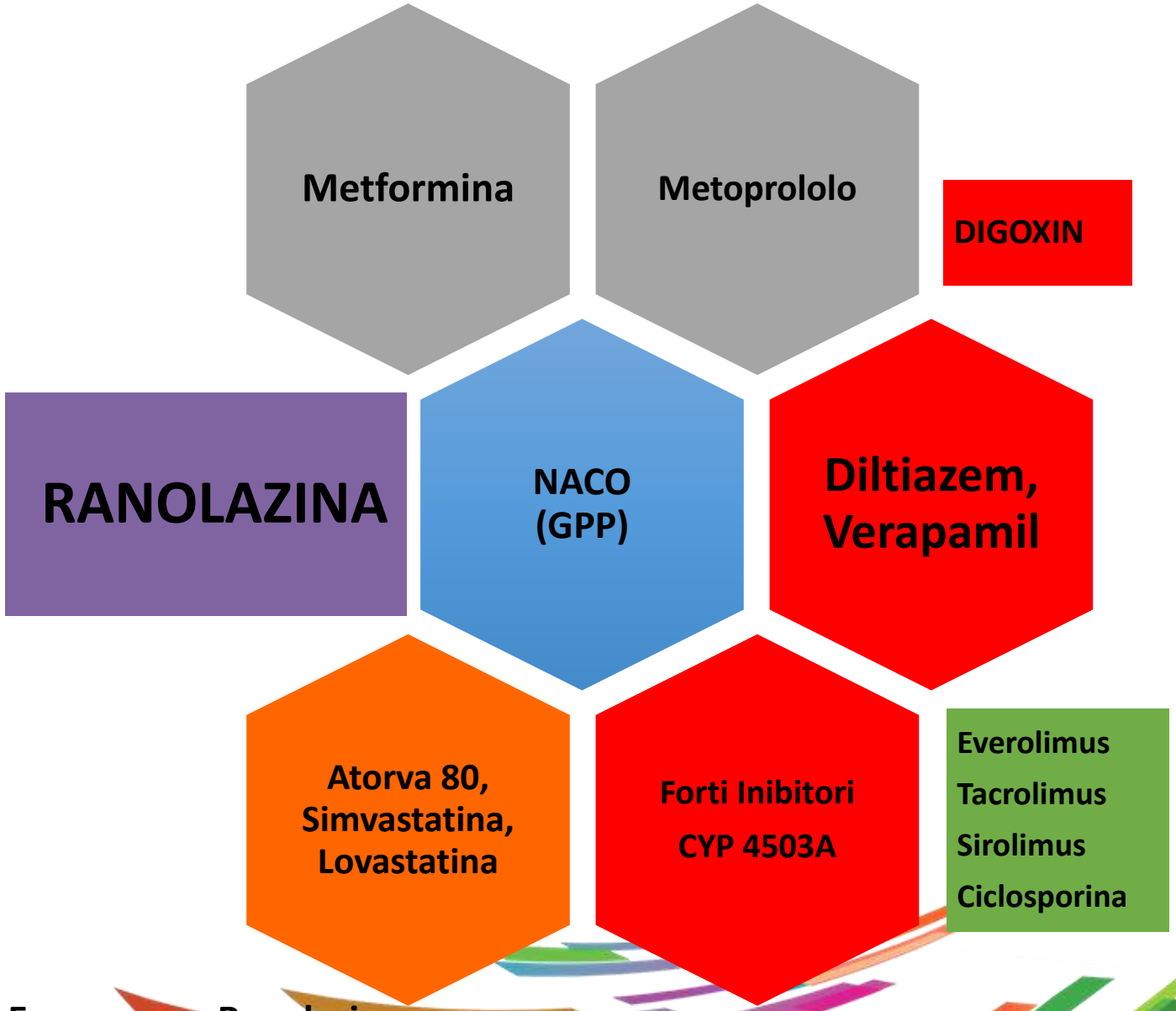
Ranolazina : schema posologico

Controindicazioni :
IRC severa , Ins. Epatica severa



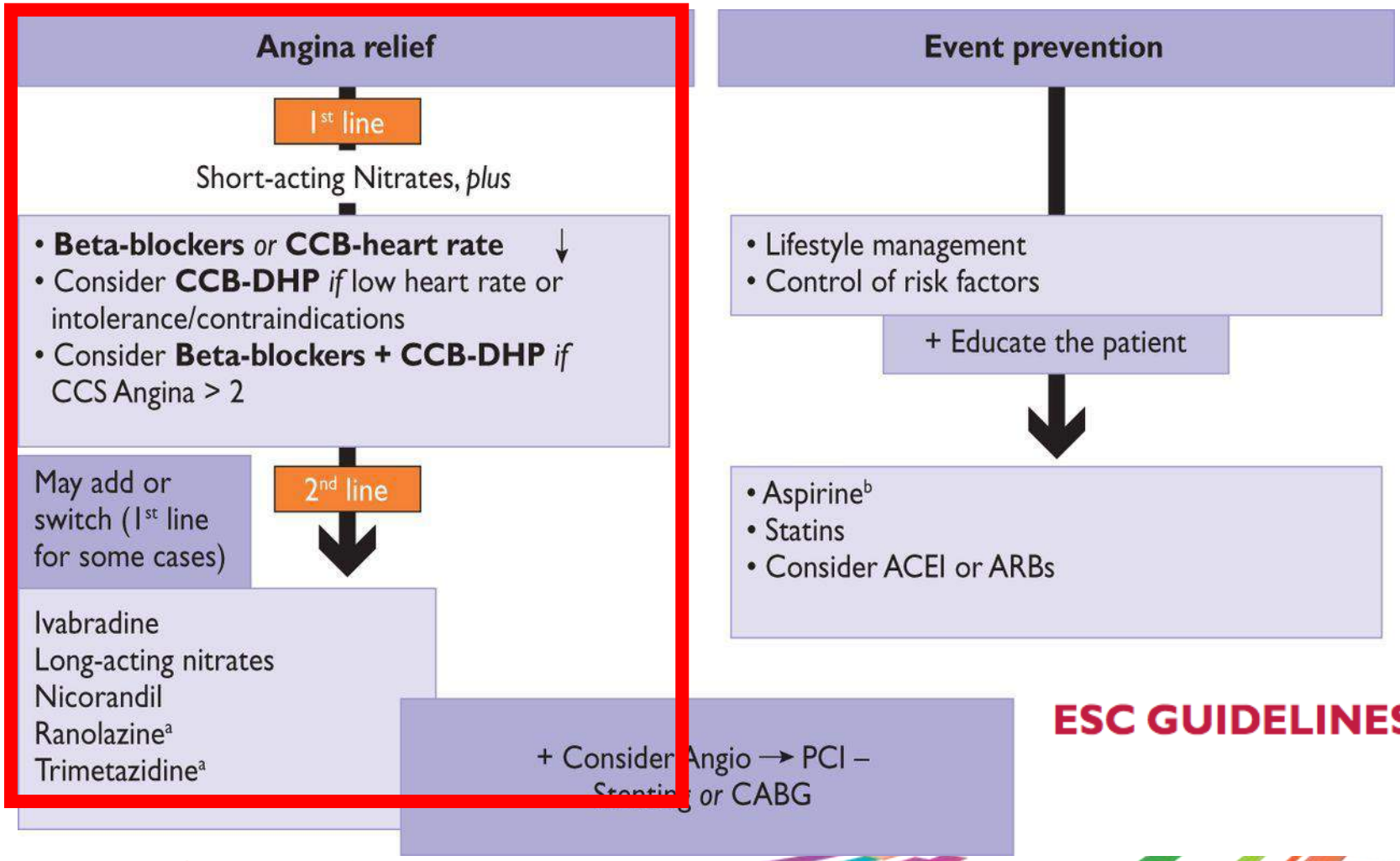
Cautela :
Anziani, GFR 30-60 ml/min,
Sottopeso, HF III-IV

EMA . Europa.eu : Ranolazina



EMA . Europa.eu : Ranolazina

Medical management of patients with stable CAD



ESC GUIDELINES

EUROPEAN SOCIETY OF CARDIOLOGY®

ESC Guidelines. Eur Heart J 2013; 34: 2949-3003

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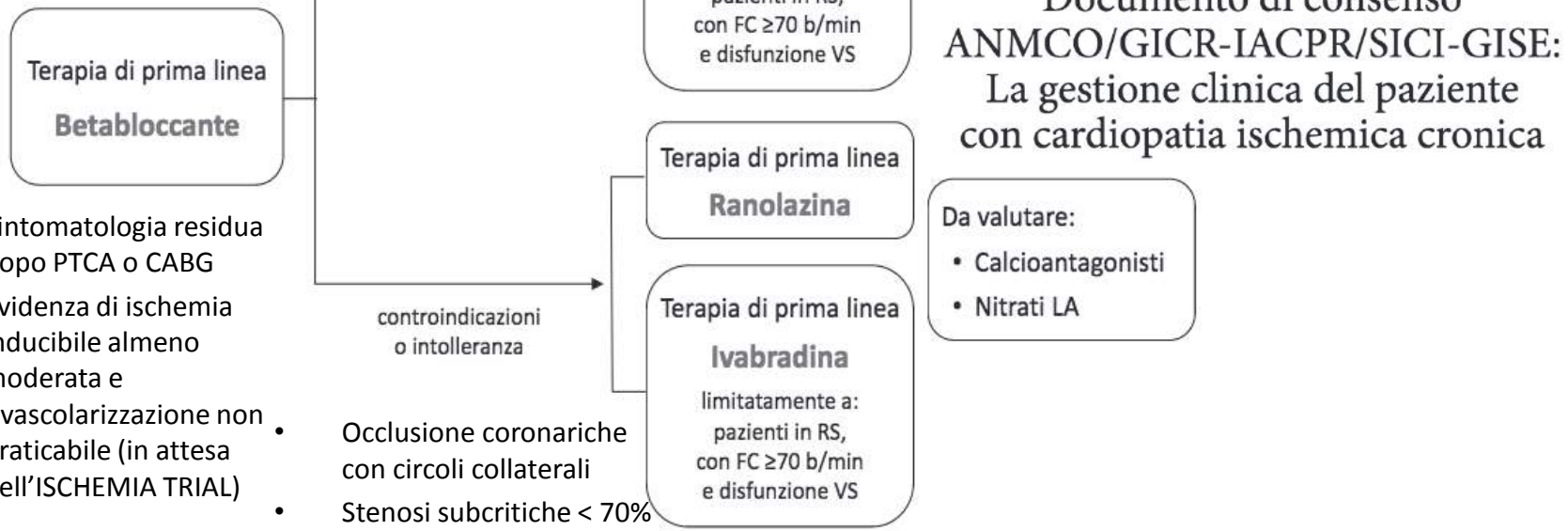
- Post IM sintomatico e/o con DVS
- SCAD e storia di aritmie

- Sintomatologia residua dopo PTCA o CABG
- Evidenza di ischemia inducibile almeno moderata e rivascolarizzazione non praticabile (in attesa dell'ISCHEMIA TRIAL)



- Persistenza di sintomi e/o scompenso e/o DVS
- Donne con angina
- Angina e DM

- Occlusione coronariche con circoli collaterali
- Stenosi subcritiche < 70%
- Rivascolarizzazione non praticabile

Documento di consenso ANMCO/GICR-IACPR/SICI-GISE: La gestione clinica del paziente con cardiopatia ischemica cronica

GRAZIE PER L'ATTENZIONE