



SABATO 2 MARZO

TERAPIA DELLA CARDIOPATIA ISCHEMICA STABILE. IL VECCHIO ED IL NUOVO

Claudio Cavallini

*Struttura Complessa di Cardiologia
Azienda Ospedaliera-Universitaria Ospedale S. Maria della
Misericordia, Perugia*

CONFLITTI DI INTERESSE

- Nessuno da dichiarare

Terapia della
cardiopatía
ischemica
stabile.
Il vecchio ed
il nuovo



Angina Stabile e prognosi

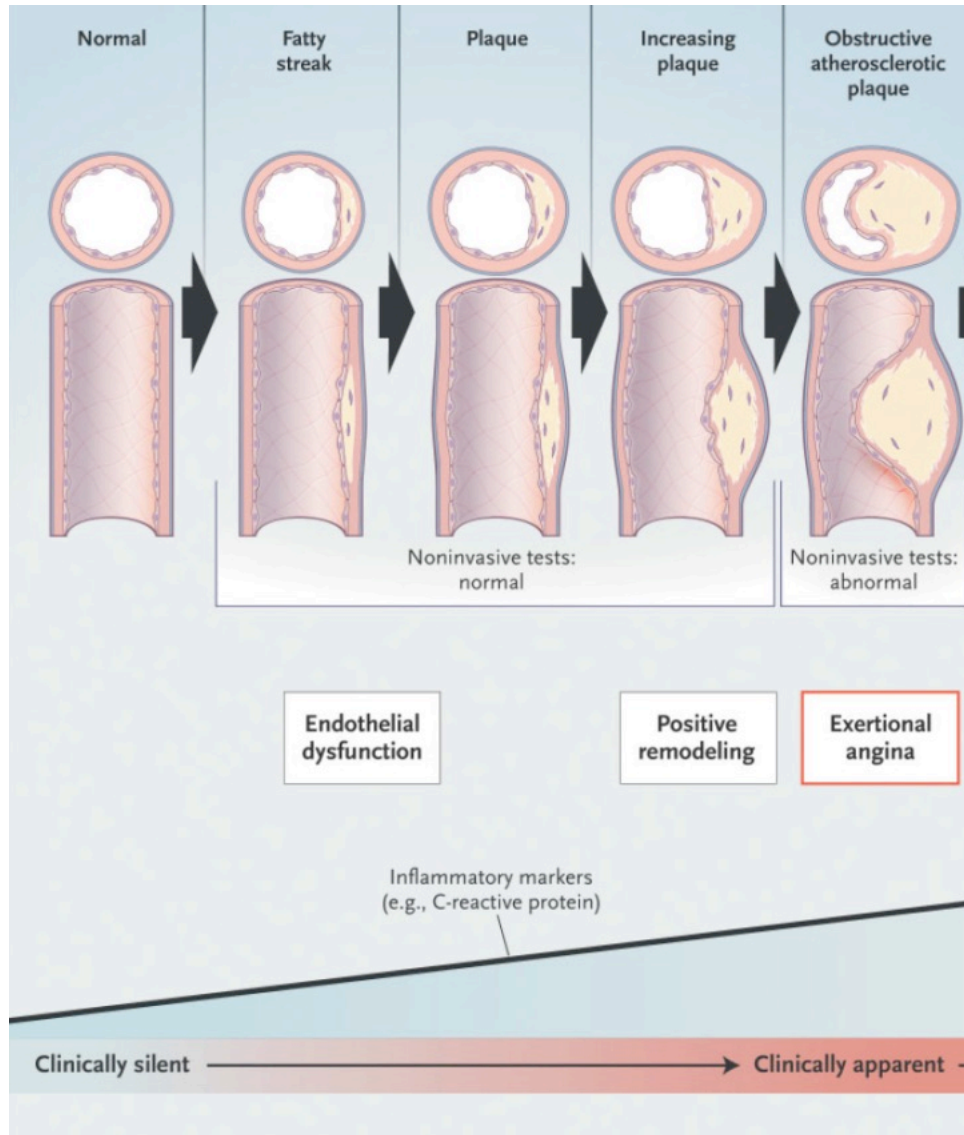


**Il Vecchio: Beta-Bloccanti e
Ca-Antagonisti**



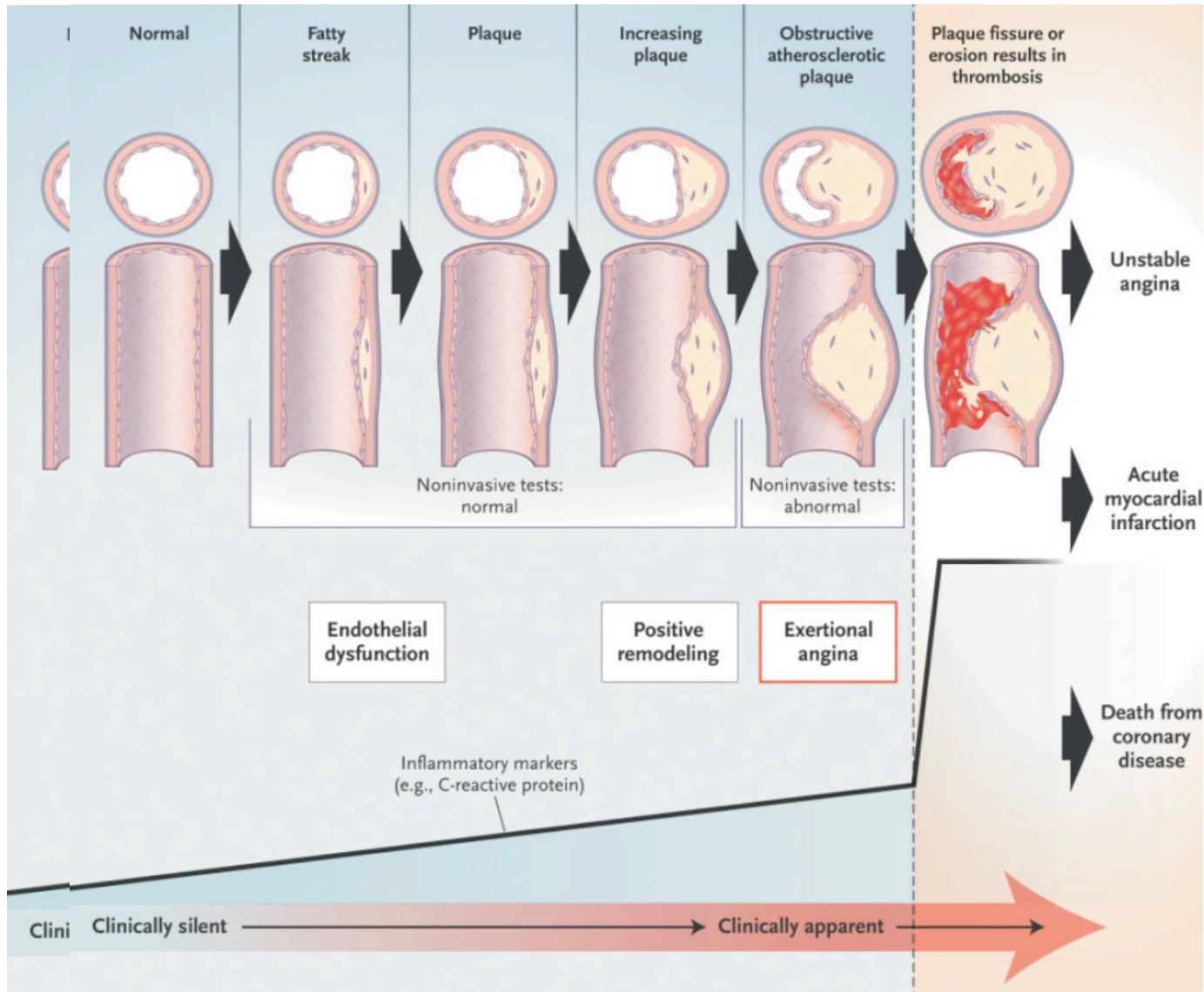
**Il Nuovo: Ivabradina e
Ranolazina**

SCAD: The Current Paradigm



N Engl J Med. 2005 Jun 16;352(24):2524-33.

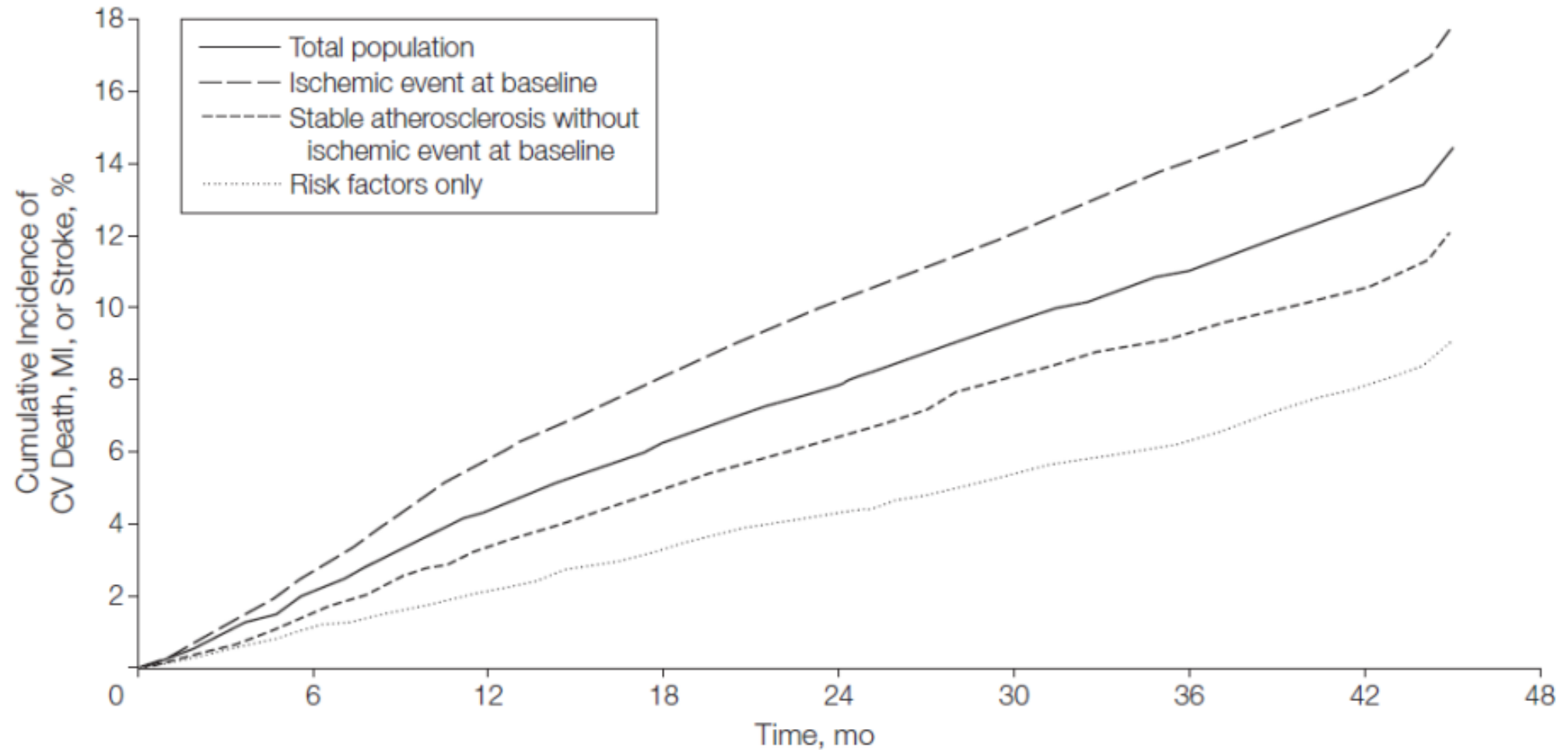
CAD: the current Paradigm



CARDIOPATIA ISCHEMICA STABILE

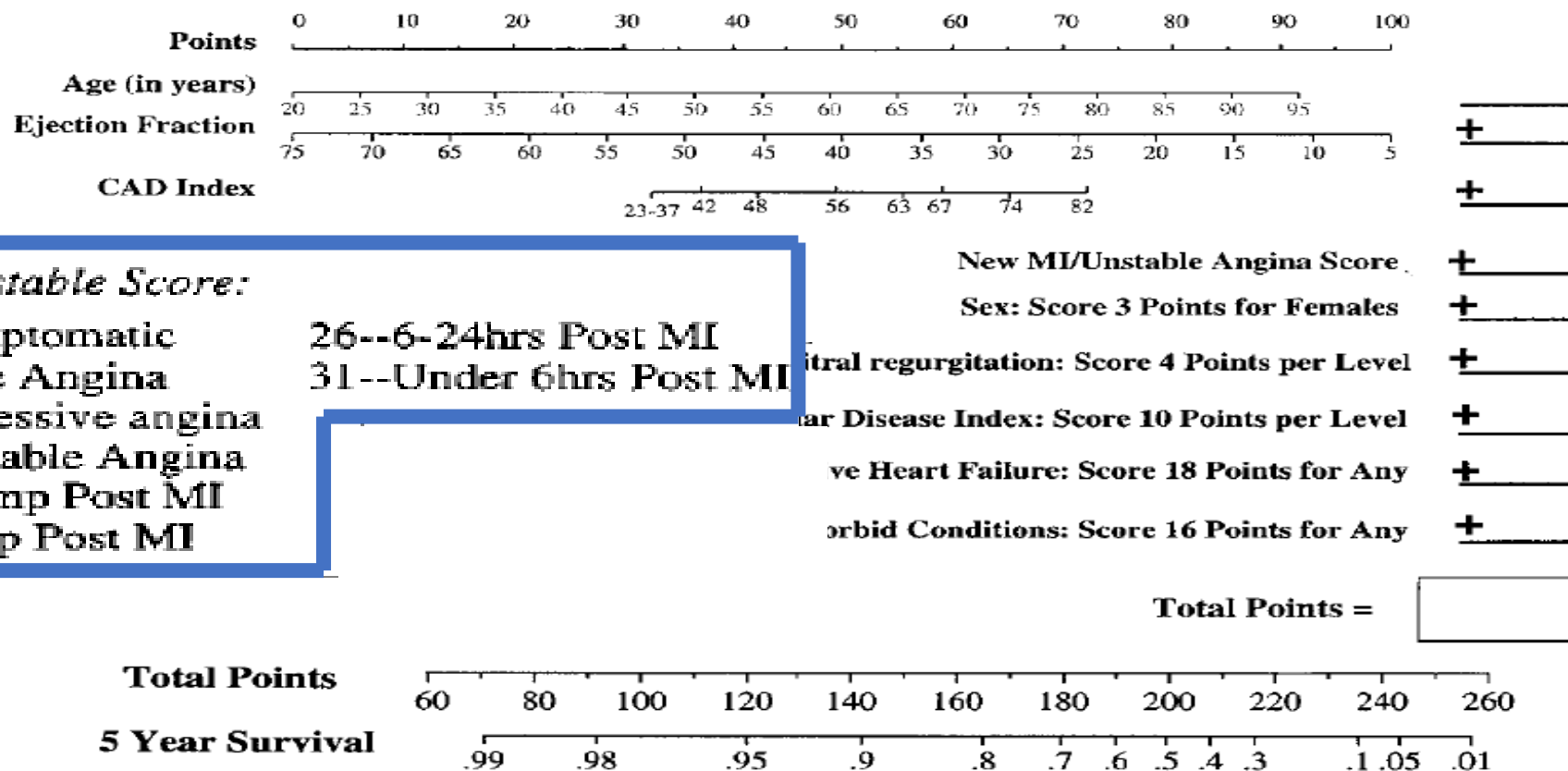
- Aterosclerosi coronarica non ostruttiva
- Coronaropatia ostruttiva senza ischemia
- Cardiopatia ischemica silente
- Angina stabile
- Post-infarto (>12 mesi)

Prognosi dei pazienti affetti da malattia CV



Task Force 5. Stratification of Patients Into High, Medium and Low Risk Subgroups for Purposes of Risk Factor Management

ROBERT M. CALIFF, MD, FACC, CHAIR, PAUL W. ARMSTRONG, MD, FACC,
 JOSEPH R. CARVER, MD, FACC, RALPH B. D'AGOSTINO, SR., PHD,
 WILLIAM E. STRAUSS, MD, FACC



Linee guida ESC - Algoritmo di trattamento farmacologico

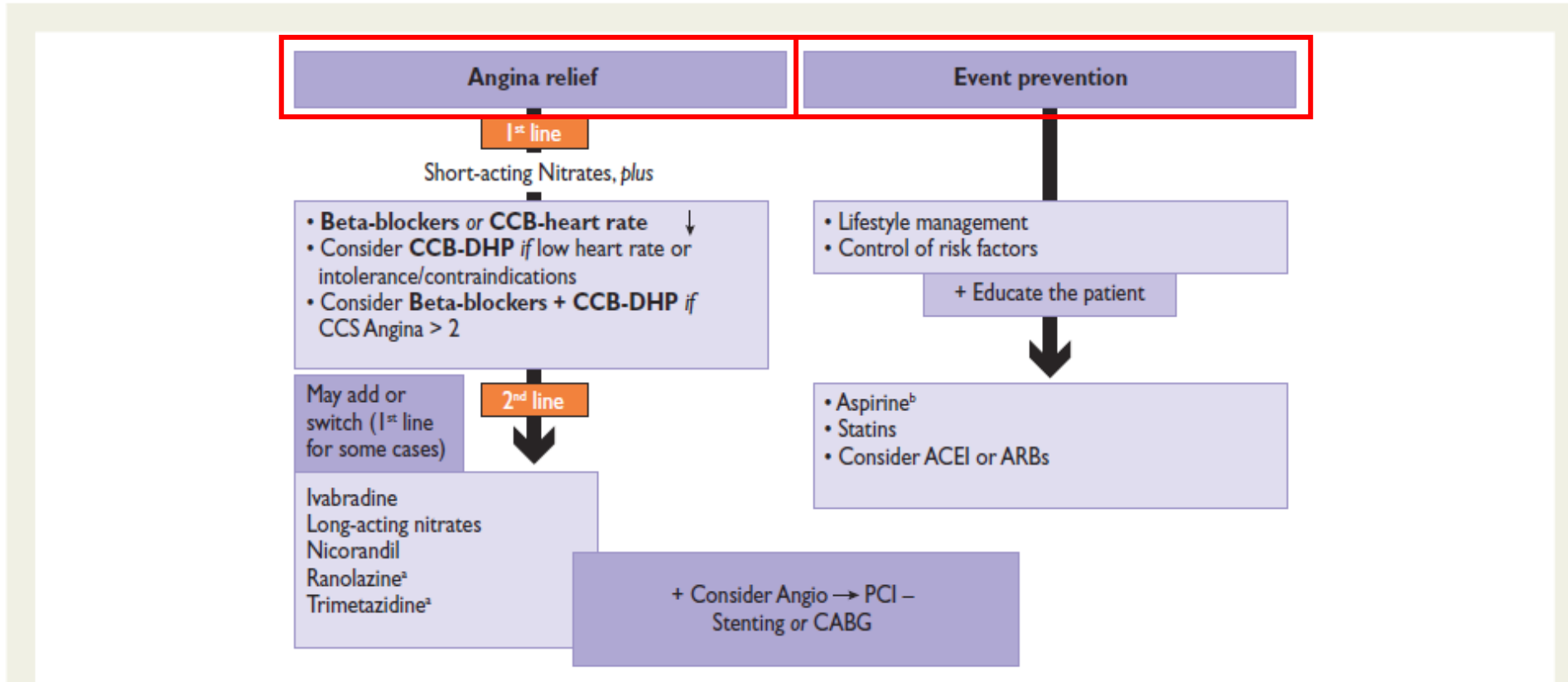
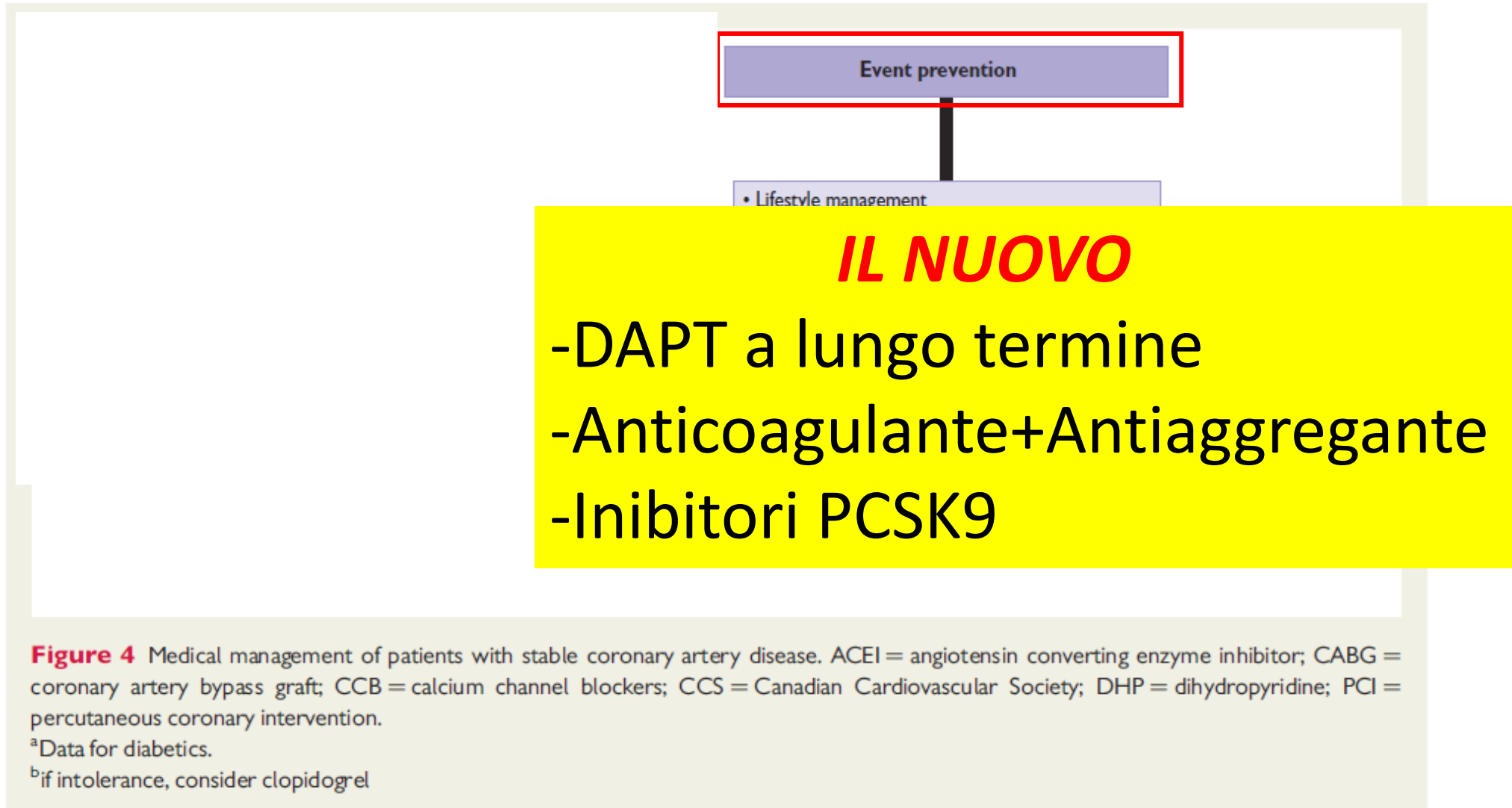


Figure 4 Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

^aData for diabetics.

^bif intolerance, consider clopidogrel

Linee guida ESC - Algoritmo di trattamento farmacologico



Linee guida ESC - Algoritmo di trattamento farmacologico

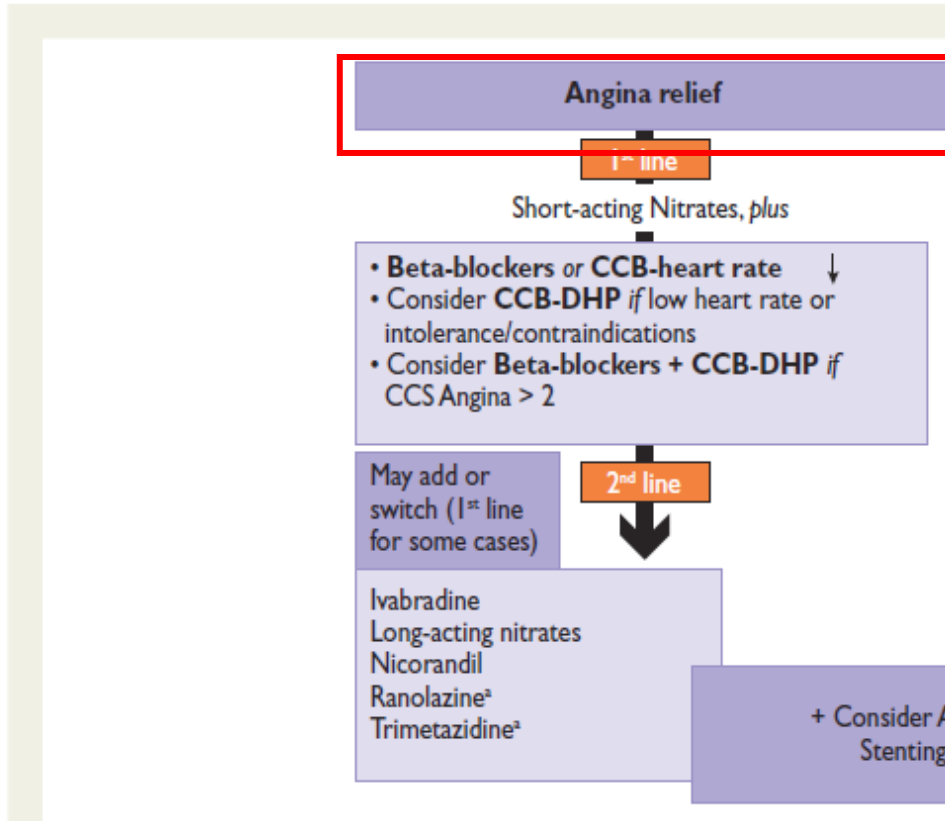


Figure 4 Medical management of patients with stable coronary artery disease or previous coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; PCI = percutaneous coronary intervention.

^aData for diabetics.

^bif intolerance, consider clopidogrel

Angina Pectoris

- 8.2 Mln di persone affette negli USA
- Una delle cause più frequenti di scadente qualità di vita
- Sottostimata e sotto-trattata nel 42% dei casi

TRIAL CLINICI RANDOMIZZATI CON CONFRONTO TRA FARMACI ANTIANGINOSI

Table 1 Trials directly comparing beta-blockers, calcium antagonists, long-acting nitrates, nicorandil, trimetazidine, and ivabradine for stable angina

Authors	Medication	N of patients per arm	Dosage	FU	At trough or peak activity Results for PEP
Beta-blockers vs. other					
van der Does et al. ¹³	BB vs. CCB	74 (CARV)/69 (NIF)	25 mg bid/20 mg od	4 weeks	At trough (12 h after last intake) TED at W4 (W × min): NS 350 ± 195 to 471 ± 226 (CARV) 387 ± 286 to 471 ± 261 (NIF)
Ardissino et al. ¹⁵	BB vs. CCB	138 (MET)/126 (NIF)	200 mg od/20 mg bid	6 weeks	At peak (1 h and 4 h after last intake) PEP: TST <1 mm at W6 S TST: 68 s (MET) vs. 42 s (NIF), P < 0.05 in favour of MET
Detry et al. ¹⁶	BB vs. Trimetazidine	71 (TMZ)/78 (Prop)	20 mg tid/40 mg tid	3 months	TED: 44 s (MET) vs. 33 s (NIF), NS At peak (3–4 h after last intake) PEP: number of AA, TED, TST >1 mm at D90: NS AA: -3.5 (TMZ) vs. -5.5 (Prop), P = 0.117 TED (s): 33 (TMZ) vs. 33 (Prop), P = 0.982 TST (s): 50 (TMZ) vs. 64 (Prop), P = 0.481
Fox et al. ¹⁷	BB vs. CCB	177 (ATEN)/175 (NIF)	50 mg bid/SR 20 mg bid	1 year	At peak (2–6 h after last intake) TED at W6: NS 91.4 (10) s (ATEN) vs. 90.5 (11.1) (NIF) (treadmill) 63.2 (11) (ATEN) vs. 63.6 (13.3) (NIF) (bicycle)
Hauf-Zachariou et al. ¹⁸	BB vs. Verapamil	126 (CARV)/122 (VER)	25 mg bid/120 mg tid	12 weeks	At trough (prior to the morning medication) PEP: TED at W12: NS 380 (9) to 436 (11) (Carved) vs. 386 (9) to 438 (11) (VER), P = 0.6841
Pehrsson et al. ²⁰	BB vs. CCB	116 (AML)/116 (ATEN)	10 mg od/100 mg	10 weeks	At peak (2–3 h after intake) PEP: TST >1 mm (NS) by Week 10: NS 1 min (AML) vs. 0.8 (ATEN)
Tardif et al. ²²	Ivabradine vs. BB	632 (IVA)/307 (ATEN)	7.5 or 10 mg bid/100 mg	4 months	At trough (12 h after last intake) PEP: TED at M4 (s): NS Change: +86.8 ± 129.0 (IVA) vs. +78.8 ± 133.4 s (ATEN), P < 0.001 for non-inferiority
Li et al. ²⁵	Ivabradine vs. BB	166 (IVA)/166 (ATEN)	5 or 7.5 mg bid/12.5 or 25 mg bid	12 weeks	At trough (before morning intake) PEP: TED at W12: NS Change: +84.1 ± 130.5 s (IVA) vs. 77.8 ± 126.6 s (ATEN), P = 0.0011 for non-inferiority
Calcium antagonist vs. other					
Guermonprez et al. ¹⁴	Nicorandil vs. Diltiazem	50 (NIC)/56 (DILT)	20 mg bid/60 mg tid	90 days	At peak (nicorandil was given at 8 h and 20 h, TET was done at 10 h) Work to peak exercise by D90: NS 42.3 ± 19 to 49.2 ± 24.4 kJ (NIC) From 37.3 ± 18.6 to 46.8 ± 20.6 kJ (DILT), P = 0.44
Chatterjee ¹⁹	CCB vs. Nicorandil	57 (NIC)/64 (AML)	20 mg bid/10 mg od	8 weeks	At trough (12–24 h after last intake) TED, W8 (min): NS 6.7 ± 0.3 to 7.2 ± 0.3 (NIC) 7.3 ± 0.4 to 7.9 ± 0.4 (AML)
Koylan et al. ²¹	Trimetazidine vs. Diltiazem	58 (TMZ)/58 (DILT)	20 mg tid/60 mg tid	28 days	No information if it was at peak or at trough PEP: TED at D28 (NS) 443.8 ± 117.1 to 477.5 ± 196.7 s (TMZ) 476.1 ± 187.5 to 493.5 ± 189.3 s (DILT)

Table 1 Continued

Authors	Medication	N of patients per arm	Dosage	FU	At trough or peak activity Results for PEP
Ruzyllo et al. ²³	Ivabradine vs. CCB	791 (IVA)/404 (AML)	7.5 or 10 mg bid/10 mg od	3 months	At trough (12 h after last intake) PEP: TED at M3 (NS) Change: 27.6 ± 91.7 (IVA) vs. 31.2 ± 92.0 s (AML), P-value for non-inferiority <0.001
Long acting nitrates vs. other					
Zhu et al. ²⁴	LAN vs. Nicorandil	115 (NIC)/117 (ISMN)	5 mg tid/20 mg bid	2 weeks	At peak (30 min and 2 h after intake) PEP: TST <1 mm by W2: NS Change: 59.7 ± 128.6 (NIC) vs 67.7 ± 119.1, P = 0.623

AML, amlodipine; ATEN, atenolol; BB, beta blocker; CCB, dihydropyridine calcium channel blockers; CARV, carvedilol; DILT, diltiazem; ISMN, isosorbide mononitrate; IVA, ivabradine; LAN, long acting nitrates; MET, metabolic equivalent; MET, metoprolol; NIC, nicorandil; NIF, nifedipine; NS, not specified; PEP, primary endpoint; Prop, propranolol; TED, total exercise duration; TMZ, trimetazidine; VER, verapamil; W, week. Studies shaded had more than 300 patients.

Terapia della
cardiopatía
ischemica
stabile.
Il vecchio ed
il nuovo



Angina Stabile e prognosi



**Il Vecchio: Beta-Bloccanti e
Ca-Antagonisti**

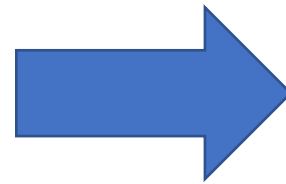


Il Nuovo: Ivabradina e
Ranolazina

Beta bloccanti

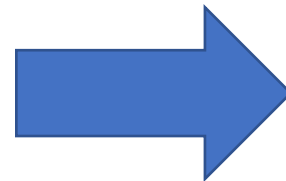
Farmaci di prima linea (in particolare nei pazienti infartuali)

- ↓ Frequenza cardiaca
 - ↓ Postcarico
 - ↓ Doppio prodotto
 - ↓ Contrattilità
-



↓ consumo O₂

- ↑ Tempo di diastole
- ↑ Perfusionione coronarica



↑ perfusione coronarica

Meta-analisi in pazienti con angina

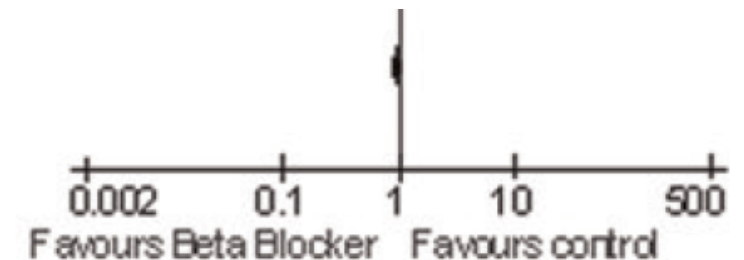
The impact of beta-blockers on mortality in stable angina: a meta-analysis

H L Huang* and K A A Fox†

*University of Edinburgh, Edinburgh, Scotland, UK; †President of British Cardiovascular Society, Professor of Cardiology, Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, Scotland, UK
E-mail: k.a.a.fox@ed.ac.uk

Total (95% CI)	9536	9823	100.0%	0.98 [0.86, 1.11]
Total events	552	583		

Heterogeneity: $\chi^2 = 17.13$, $df = 15$ ($P = 0.31$) $I^2 = 12\%$
Test for overall effect: $Z = 0.35$ ($P = 0.73$)



REACH registry: beta bloccanti ed eventi CV

44 708 patients

Known prior MI matched cohort

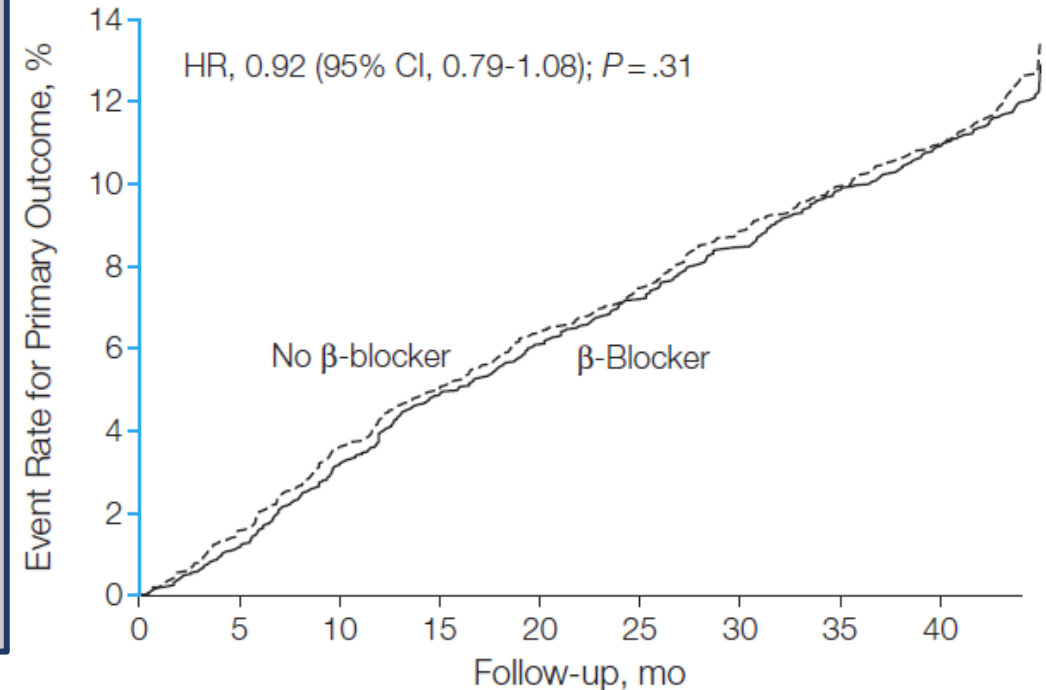
Perchè?:

- Trattamento più aggressivo della SCA
- Migliori strategie di riperfusione
- Migliore prevenzione secondaria (statine, ACE-i,...)
- Beneficio del farmaco solo in fase precoce?

Follow-up, mo

No. at risk					
No β -blocker	3379	3165	2850	2357	2029
β -Blocker	3379	3178	2899	2424	2061

Known CAD without MI matched cohort



No. at risk					
No β -blocker	3599	3420	3105	2615	2270
β -Blocker	3599	3447	3148	2634	2251

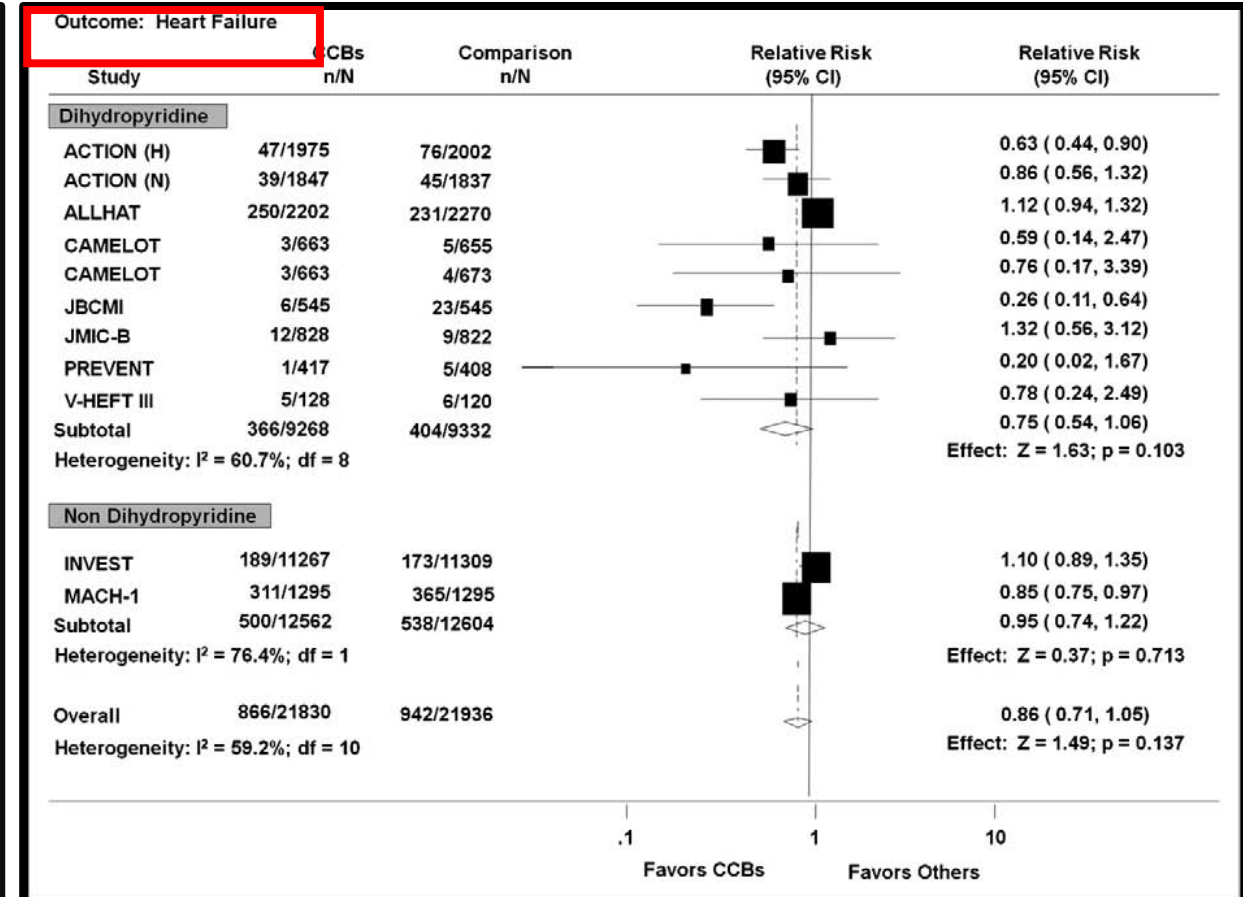
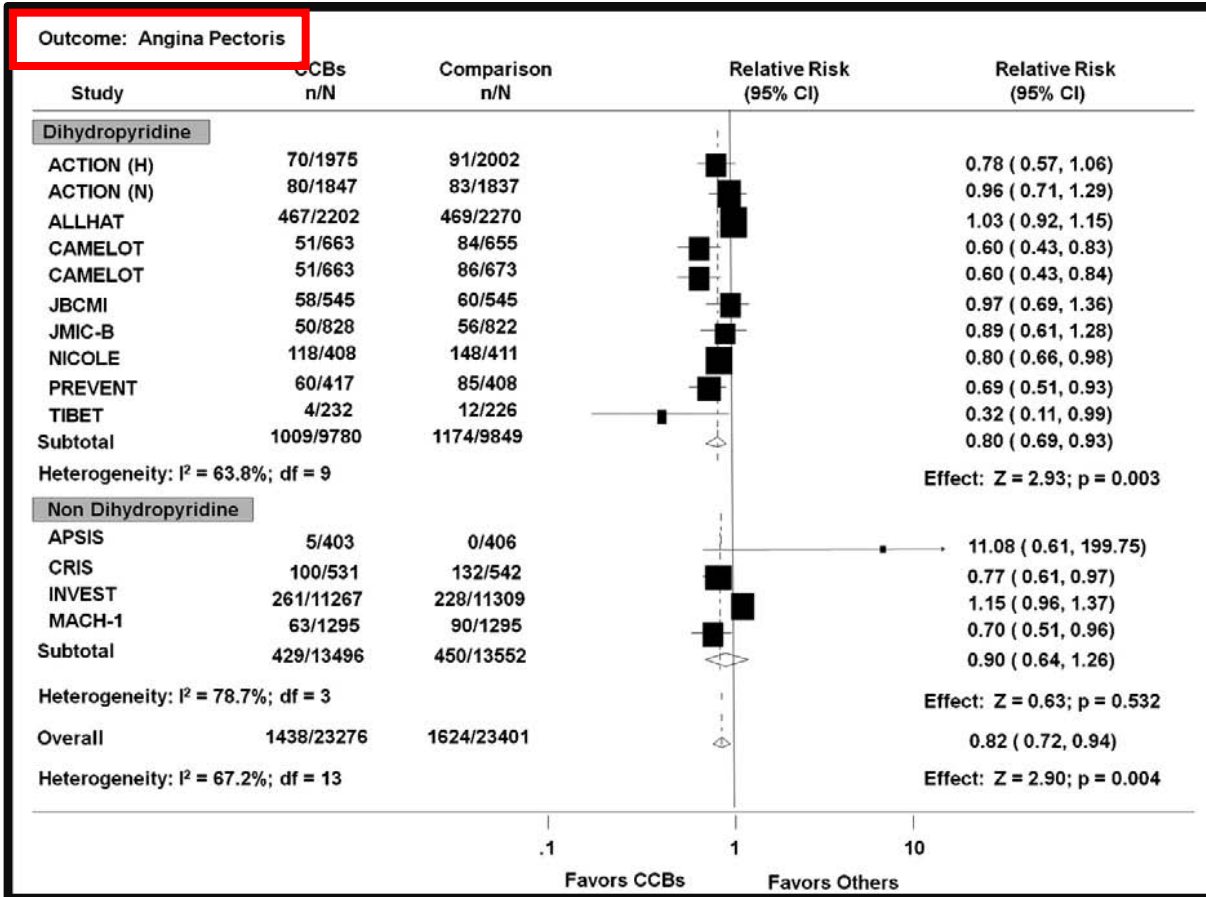
Beta Bloccanti e cardiopatia ischemica stabile

Farmaci di 1° scelta in

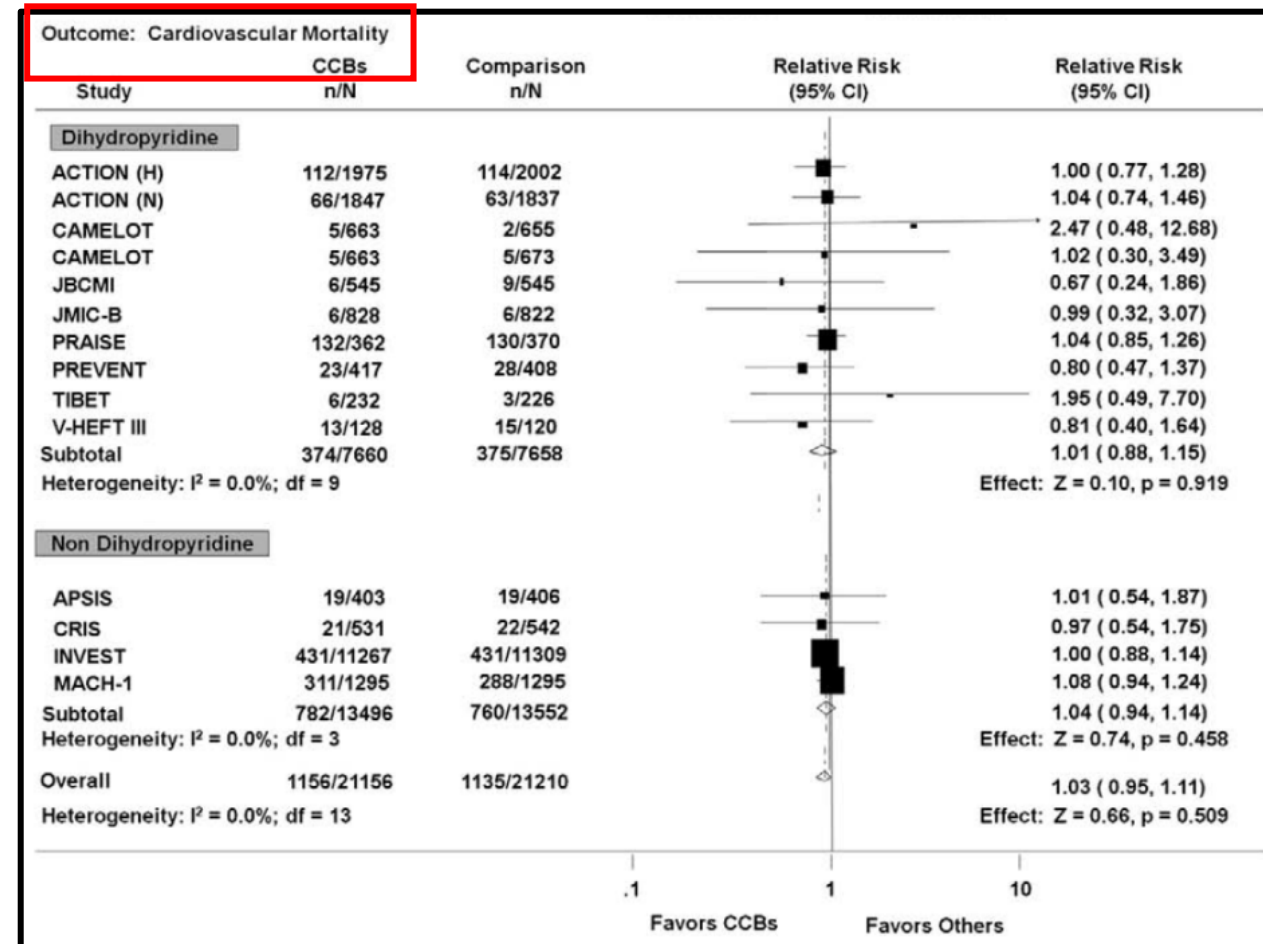
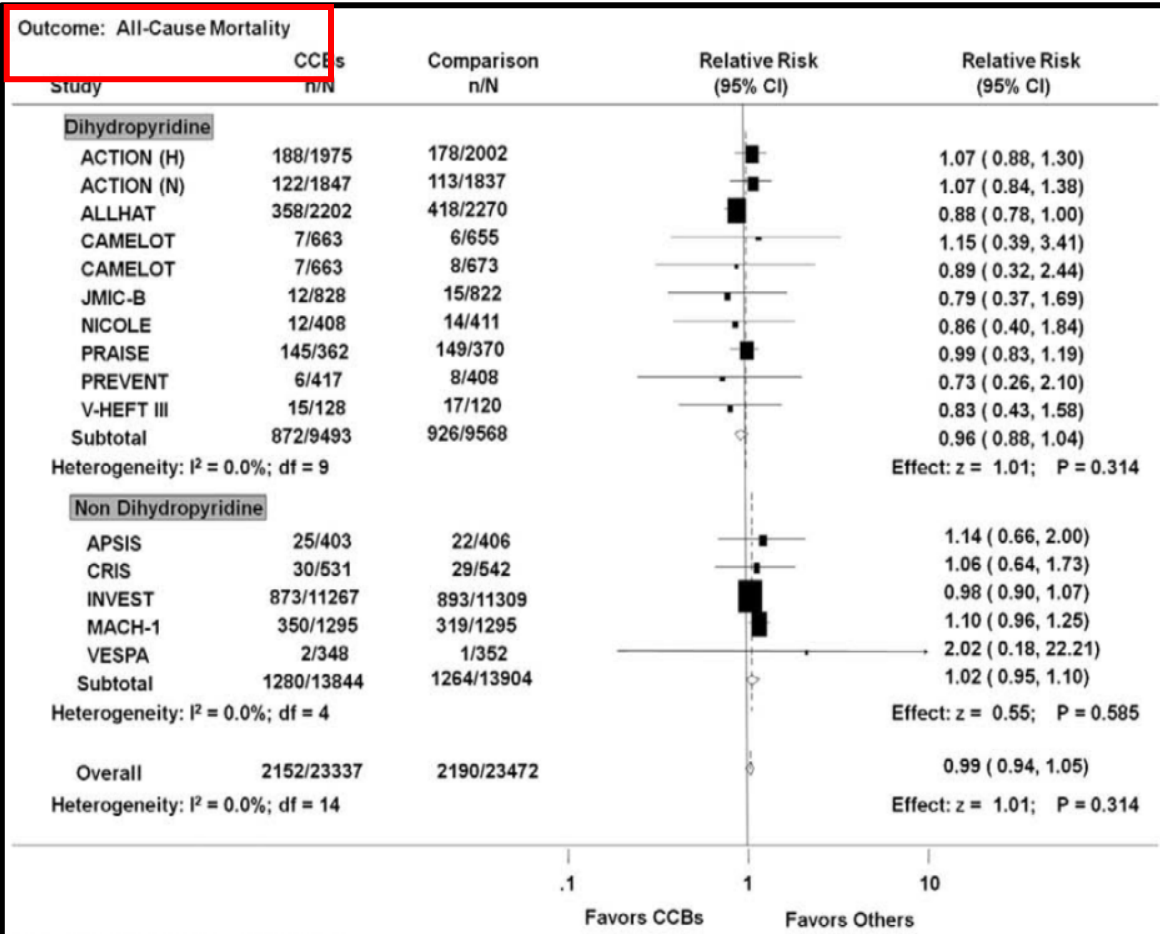
- Pazienti sintomatici
- Pazienti con disfunzione ventricolare sinistra
- Pazienti post-infarto? (<3 aa)



Ca-Antagonisti



Calcio antagonisti



Ca-Antagonisti

- Non influenzano la prognosi
- I Non-Diidropyridinici sono una alternativa ai B-Bloccanti
- I Diidropyridinici:
 - in monoterapia in pazienti bradicardici
 - associati ai B-Bloccanti in caso di angina persistente
- Entrambi: Farmaci di scelta nell' angina vasospastica



Terapia della
cardiopatía
ischemica
stabile.
Il vecchio ed
il nuovo



Angina Stabile e prognosi

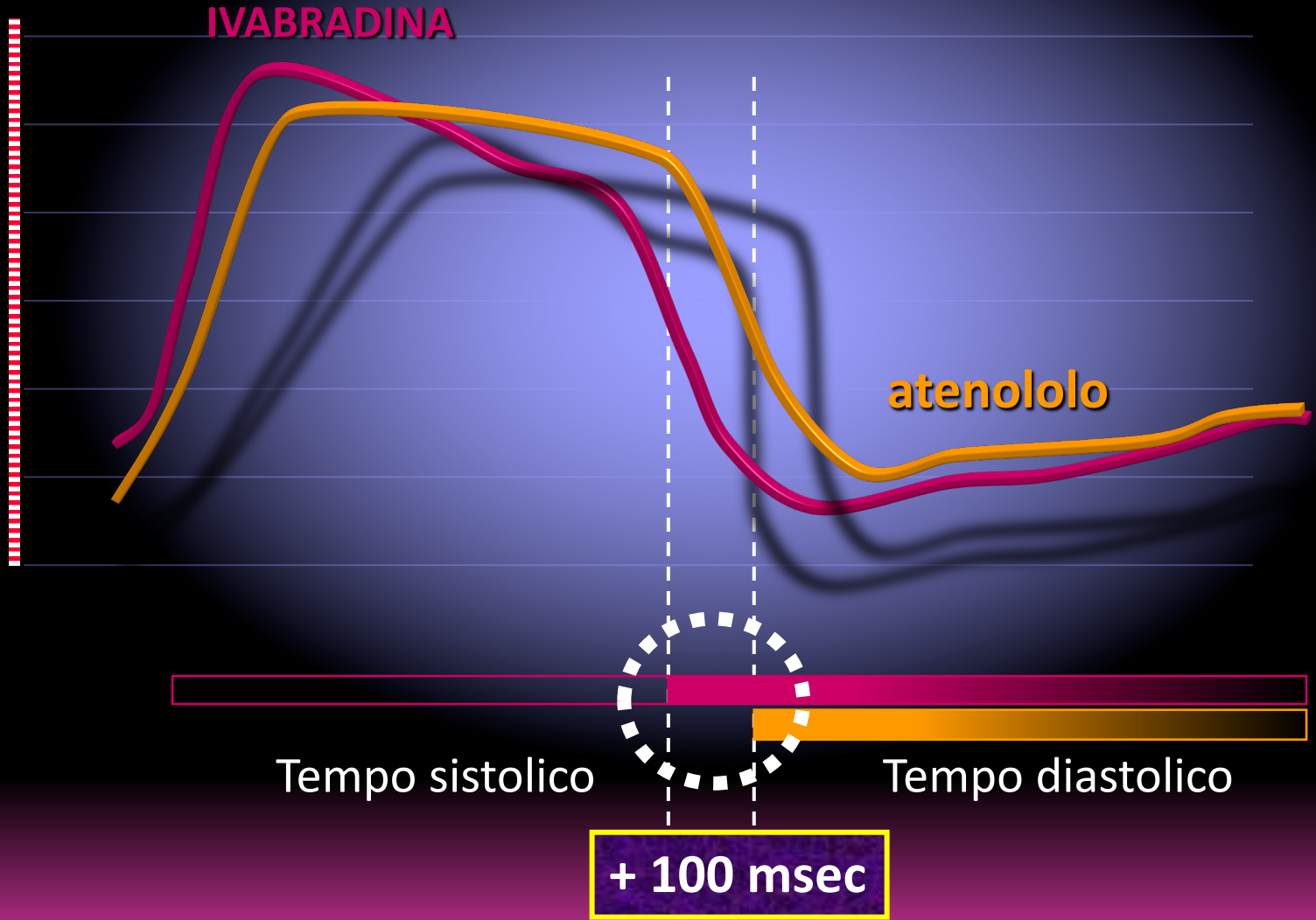


Il vecchio: Beta-Bloccanti e
Ca-Antagonisti



**Il Nuovo: Ivabradina e
Ranolazina**

Ivabradina aumenta il tempo di riempimento diastolico (Colin, Am J Physiol Heart Circ Physiol 2003)



Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina

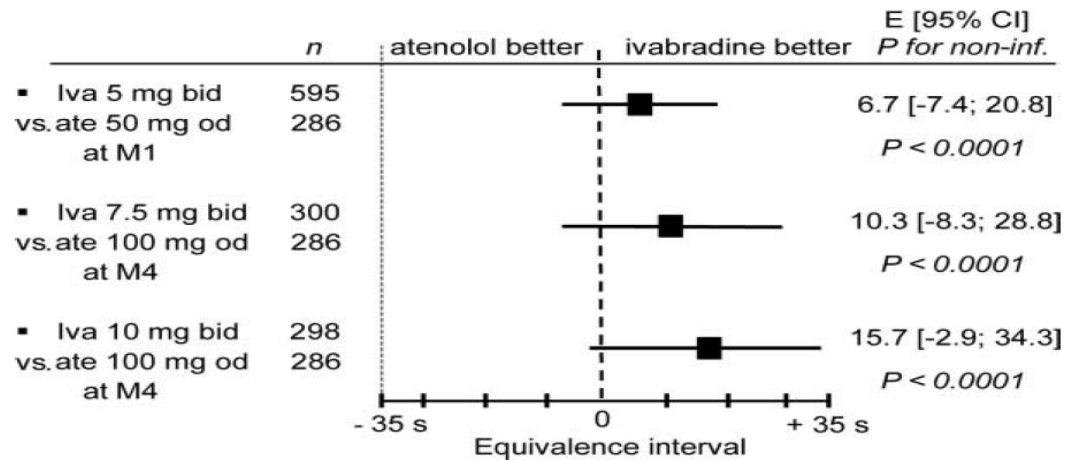


Figure 3 Effects on total exercise duration at trough of drug activity.

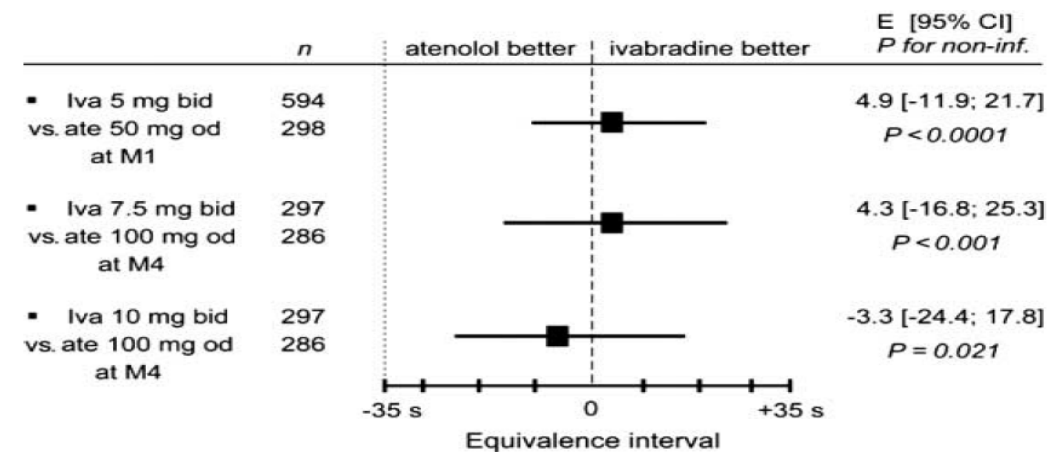


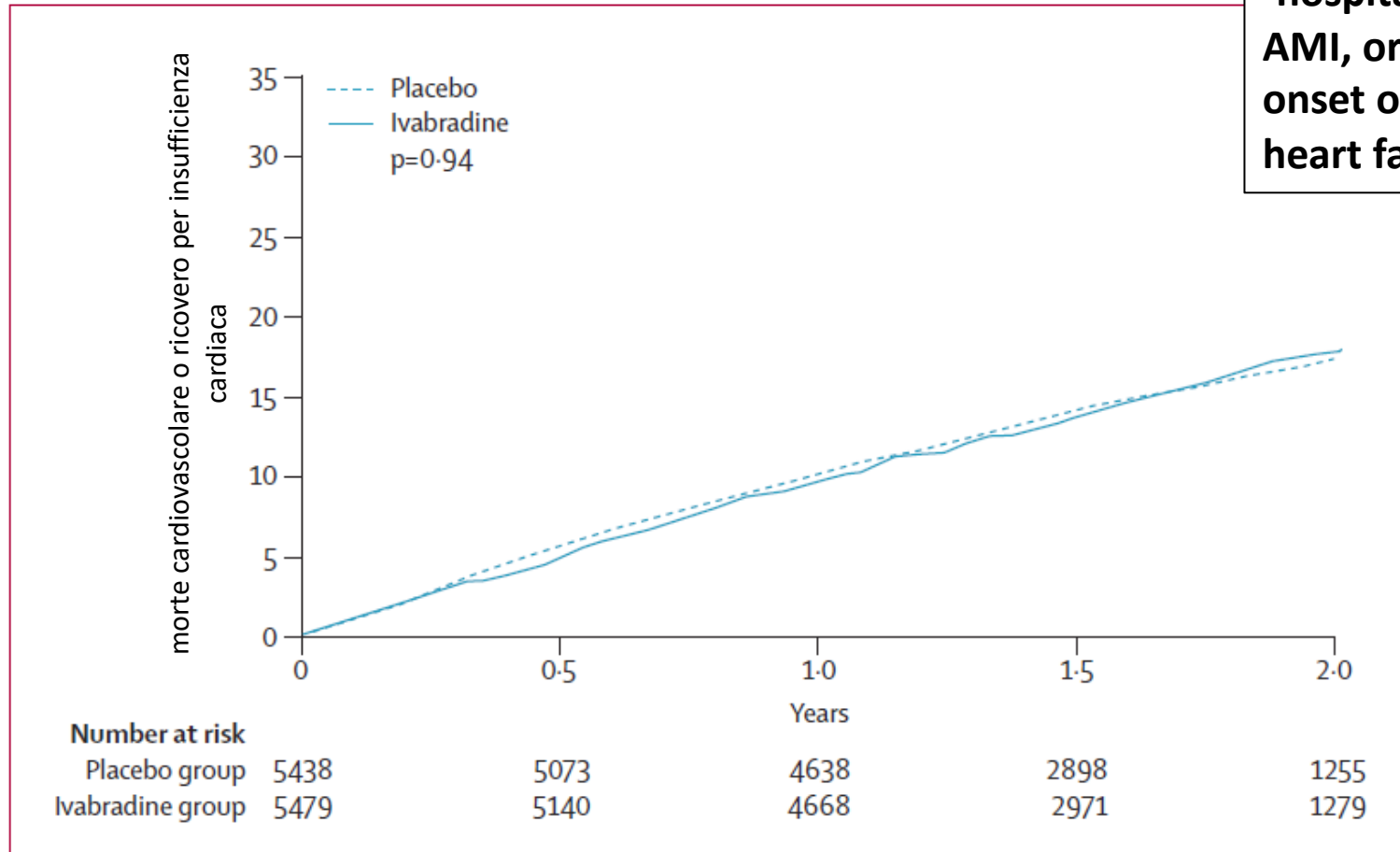
Figure 4 Effects on time to 1 mm ST segment depression (TST) at trough of drug activity.

BEAUTIFUL trial

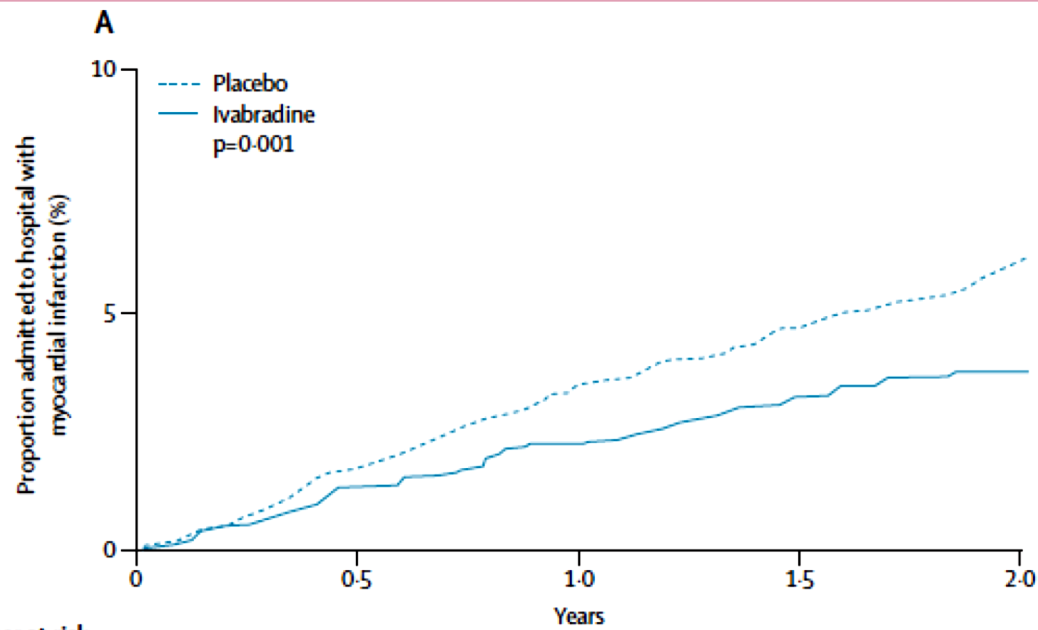
10.917 pazienti CAD ed FE <40%

Primary end-point

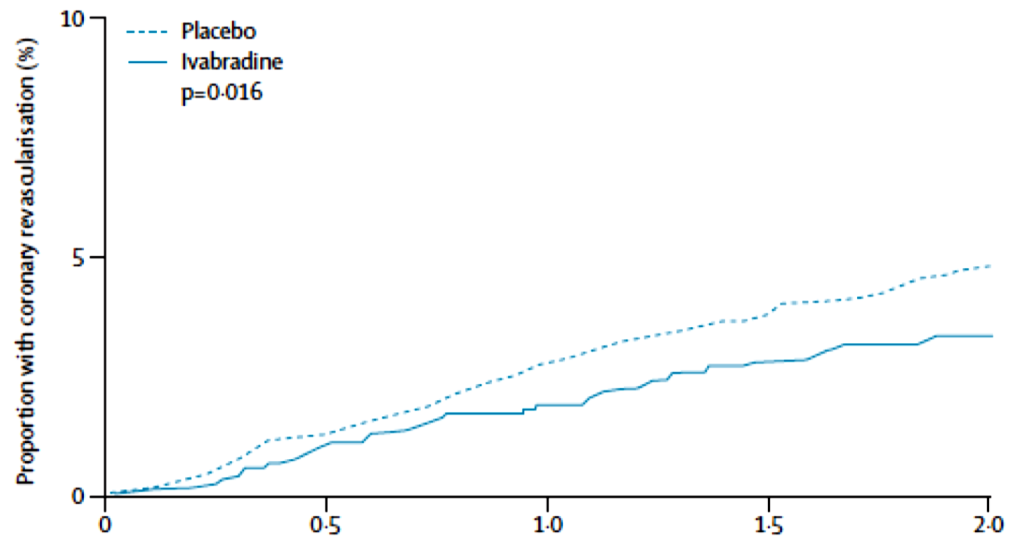
composite of:
-cv death,
-hospitalization for
AMI, or for for new
onset or worsening
heart failure



Sottogruppo di pazienti con frequenza cardiaca a riposo >70 bpm

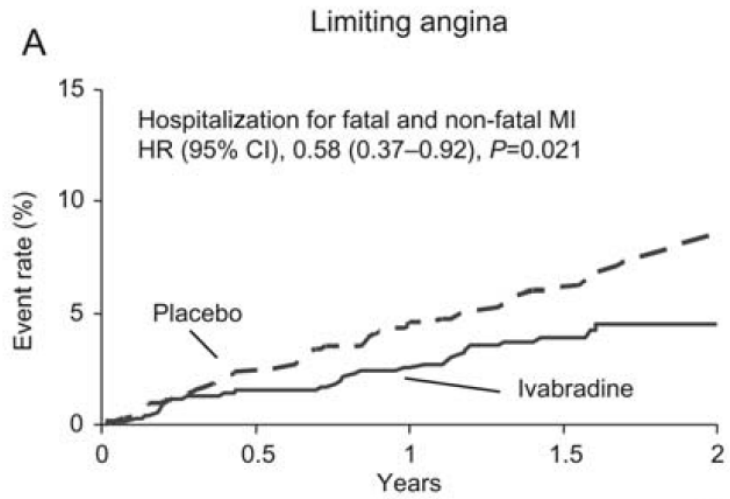


Number at risk					
Placebo group	2693	2548	2347	1493	617
Ivabradine group	2699	2573	2364	1503	632

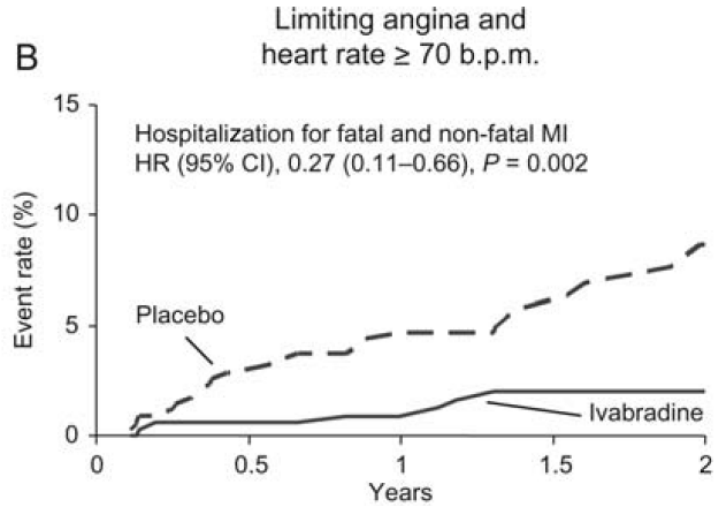


Number at risk					
Placebo group	2693	2552	2347	1483	624
Ivabradine group	2699	2571	2356	1495	629

Sottogruppo di pazienti con angina limitante (CCS 2-3)



Placebo:	773	723	660	398	182
Ivabradine:	734	692	644	406	181



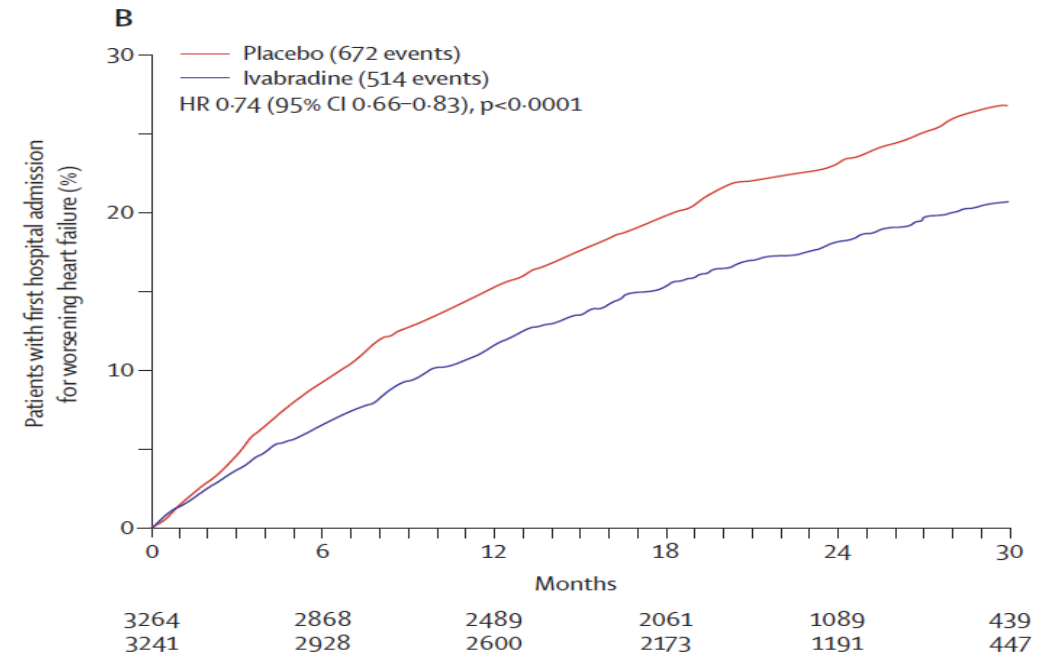
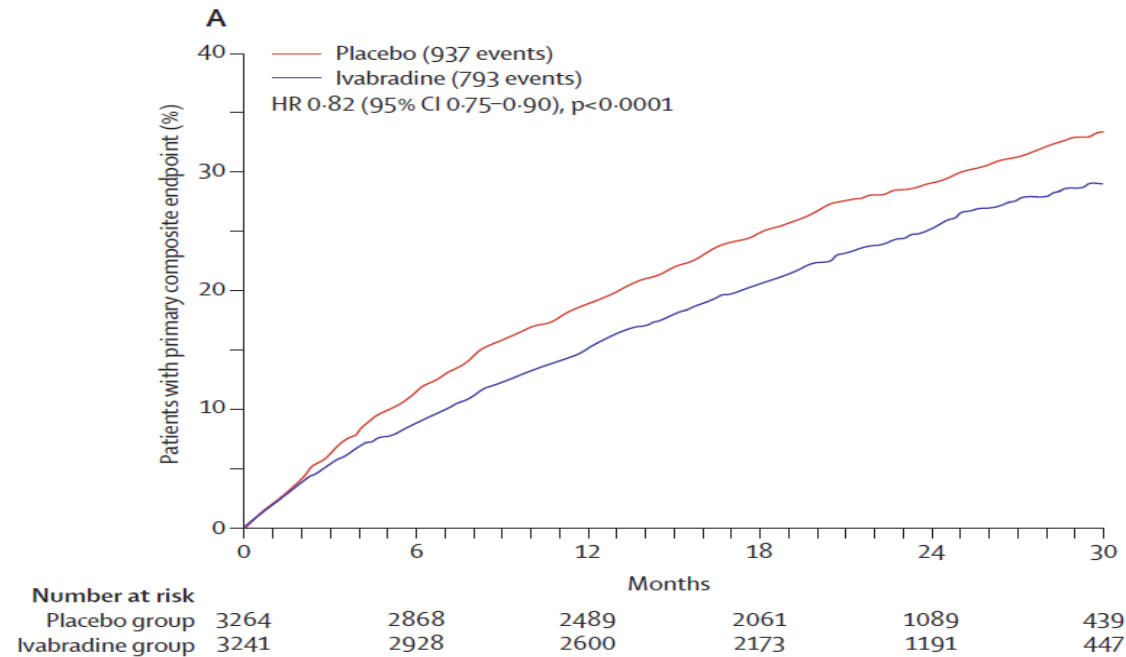
Placebo:	363	336	310	199	75
Ivabradine:	349	328	305	194	85

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study



Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

6558 pts HF + EF \leq 35% F.C. > 70 on top of Beta-Blockers



SIGNIFY

- 19.100 pazienti SCAD
- FC a riposo >70 bpm
- Non storia di scompenso cardiaco
- (FE media 56%)

The NEW ENGLAND JOURNAL of MEDICINE

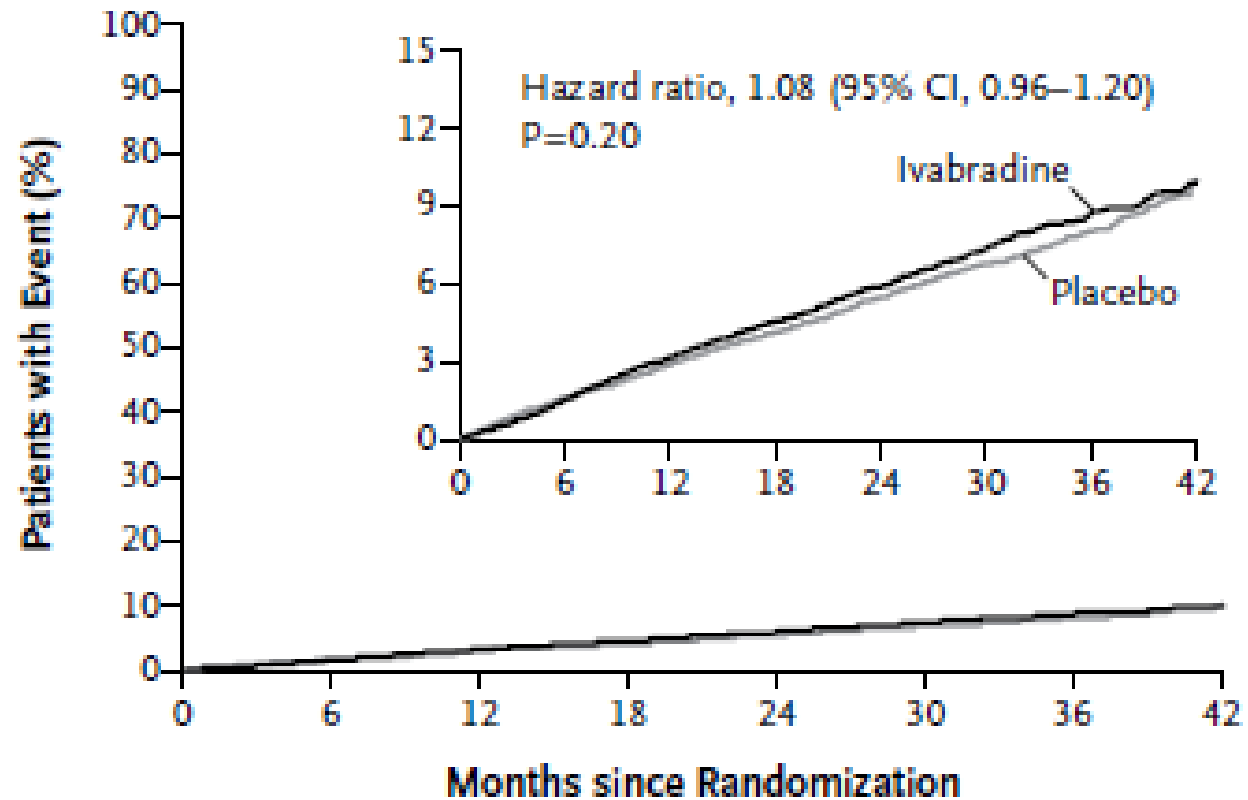
ESTABLISHED IN 1812

SEPTEMBER 18, 2014

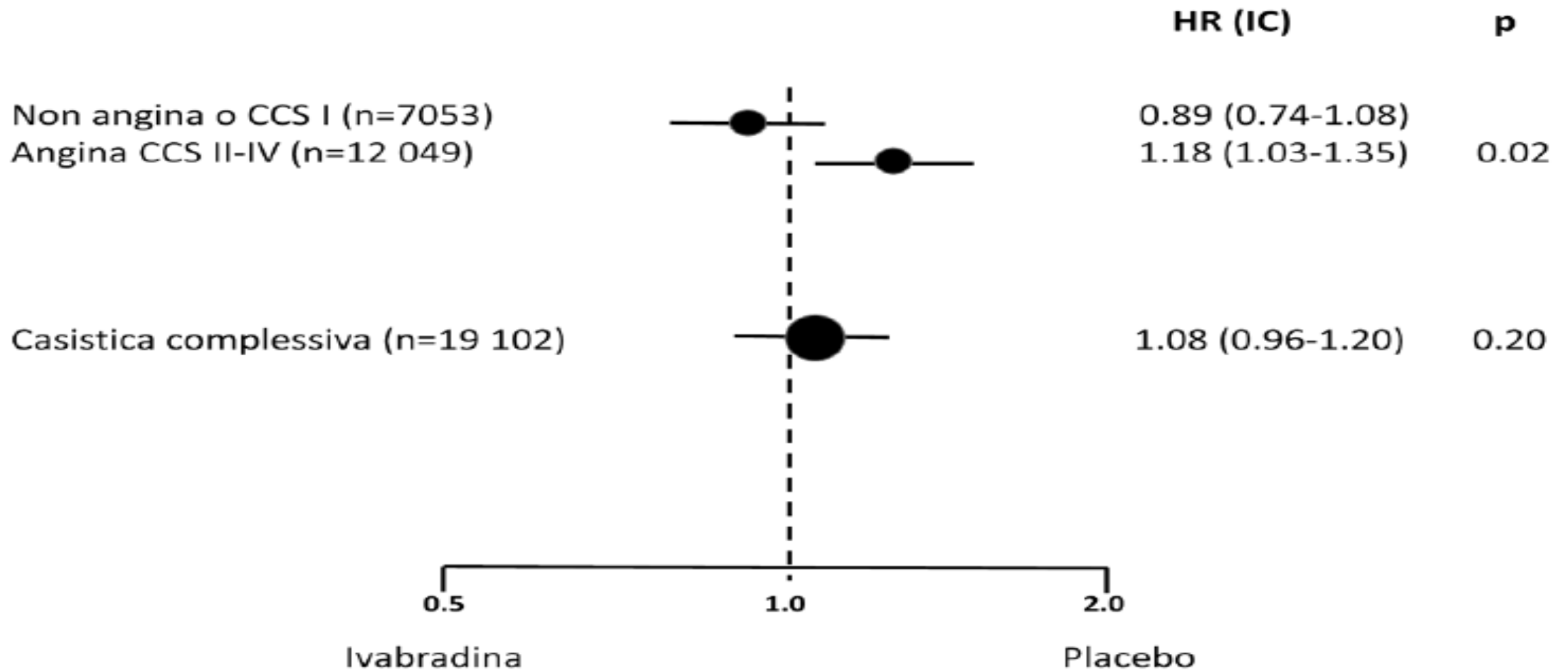
VOL. 371 NO. 12

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

A Primary Composite End Point (CV Mortality/MI)



SIGNIFY trial: Analisi per sottogruppi



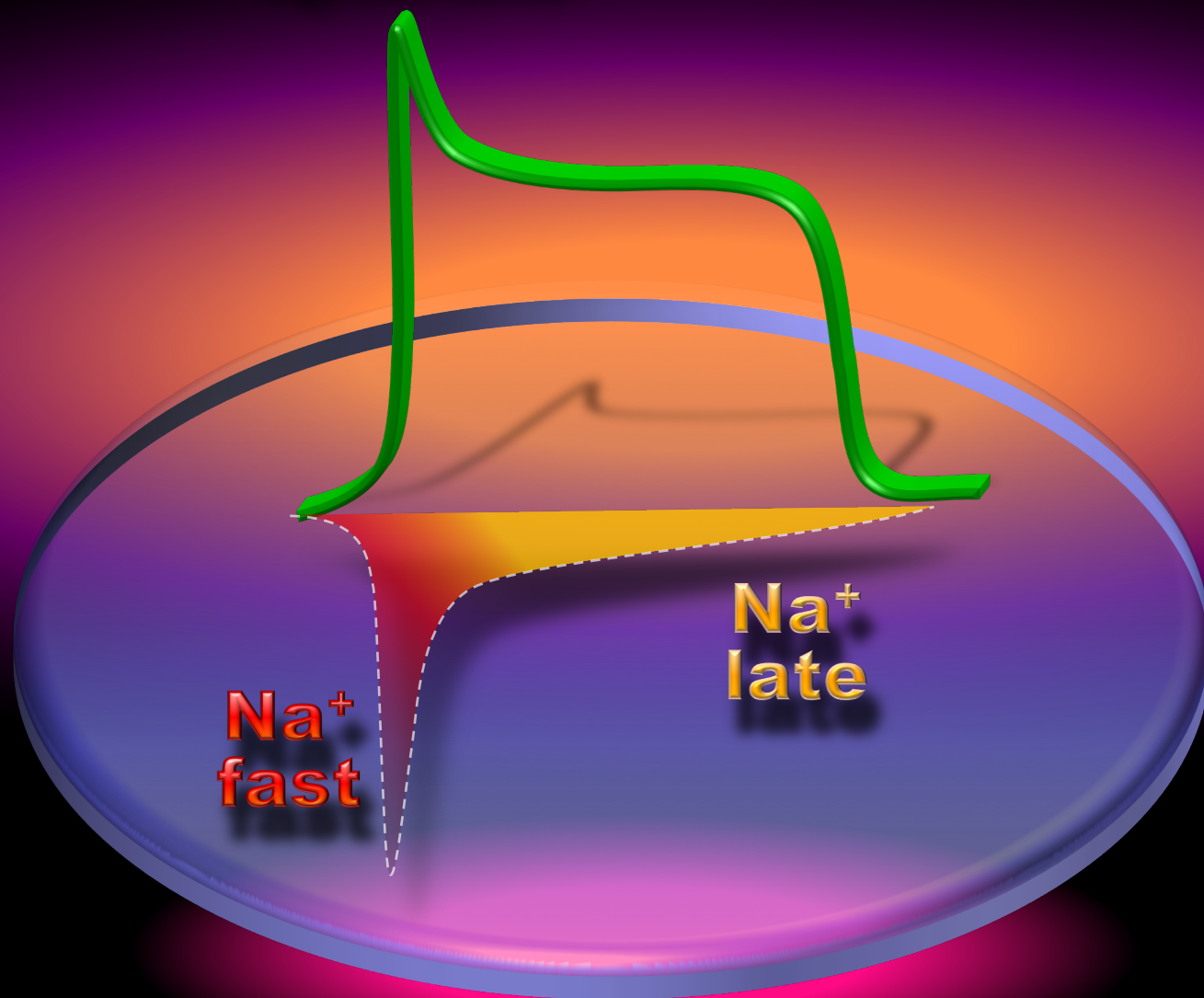
IVABRADINA

- E' in grado di migliorare l'angina
- Il possibile impatto sfavorevole su morte cv e infarto ne sconsigliano l'utilizzo nei pazienti senza scompenso cardiaco o disfunzione ventricolare sinistra



RANOLAZINA

upstroke



Ranolazina

Inibisce la corrente tardiva del sodio (*late INa*) durante la ripolarizzazione



↓ concentrazione del Na intracellulare



↓ concentrazione del Ca intracellulare



↓ tensione di parete



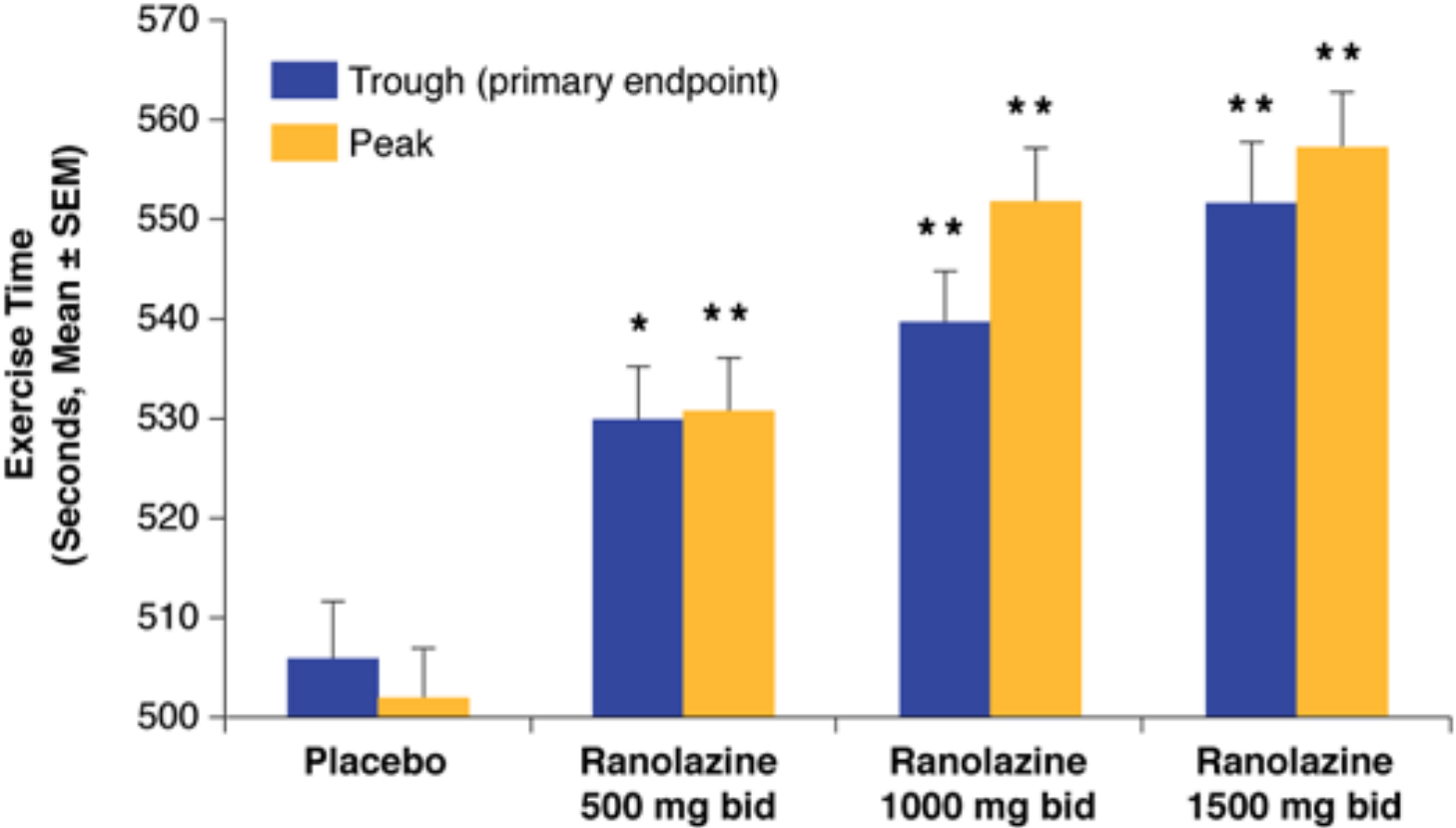
↓ consumo di ossigeno



↓ angina

Inoltre possibile riduzione della
ossidazione degli acidi grassi

MARISA trial



N = 191

Angina cronica sintomatica

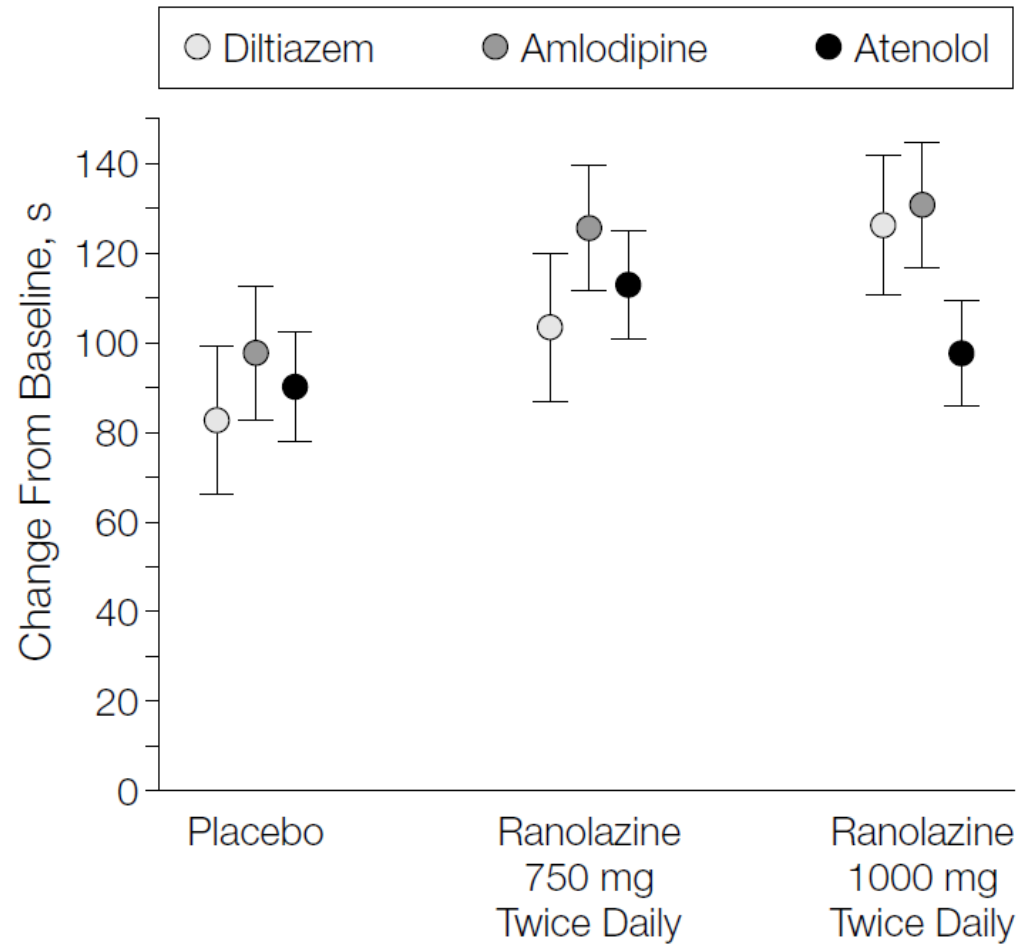
Wash-out da antianginosi

Randomizzazione crossover a ranolazina 500, 1000, 1500 mg bid vs placebo

Peak: ca. 4 ore dalla dose

Trough: ca. 12 ore dalla dose

CARISA trial

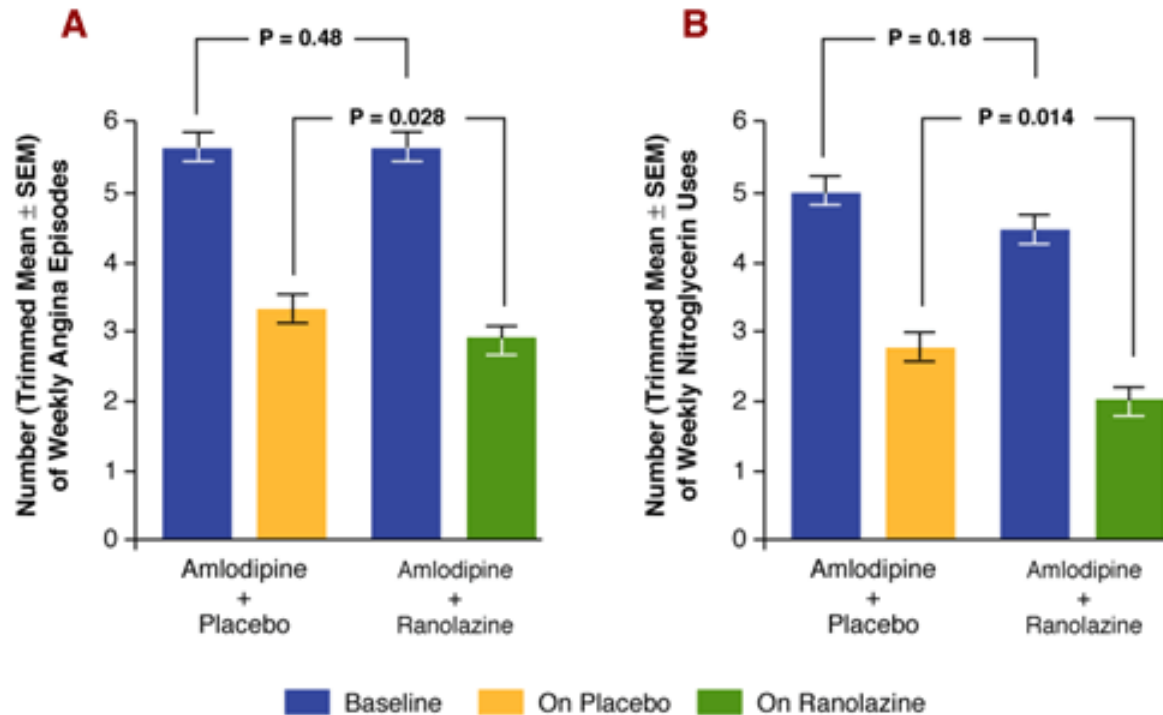


N = 823

Angina cronica sintomatica

Randomizzazione a placebo vs. due diversi dosaggi di ranolazina (750 mg oppure 1000 mg x 2/die) in associazione a dosaggi standard di atenololo (50 mg), amlodipina (5 mg) o diltiazem (180 mg).

ERICA trial



N= 565

Angina con almeno 3 episodi settimanali e in terapia con amlodipina 10 mg.

Randomizzati a ranolazina 1000 mg bid vs. placebo

Follow-up di 6 settimane

Ranolazina nella sindrome coronarica acuta



MERLIN – TIMI 36

Primary Results

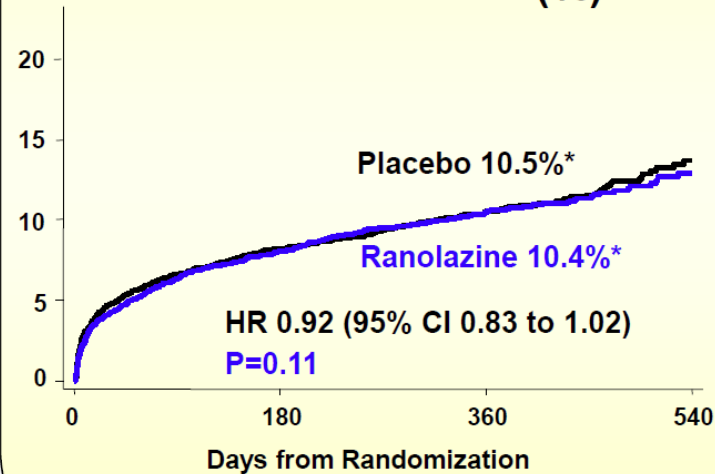


Primary Endpoint - CV Death, MI, or Recurrent Ischemia

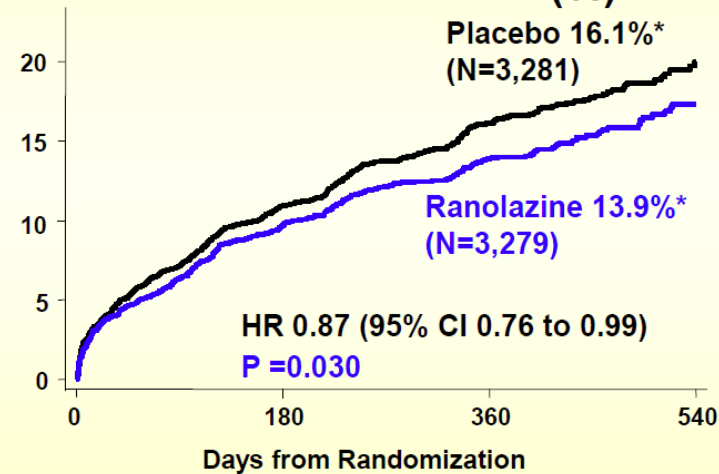
21.8% for Ranolazine vs. 23.5% for Placebo

HR 0.92 (95% CI 0.83 to 1.02), P = 0.11

CV Death or MI (%)



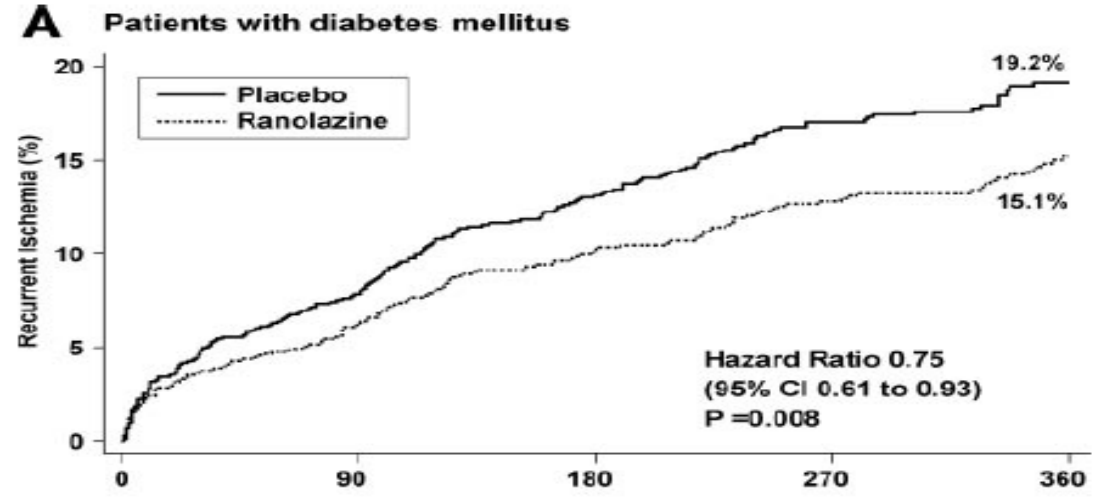
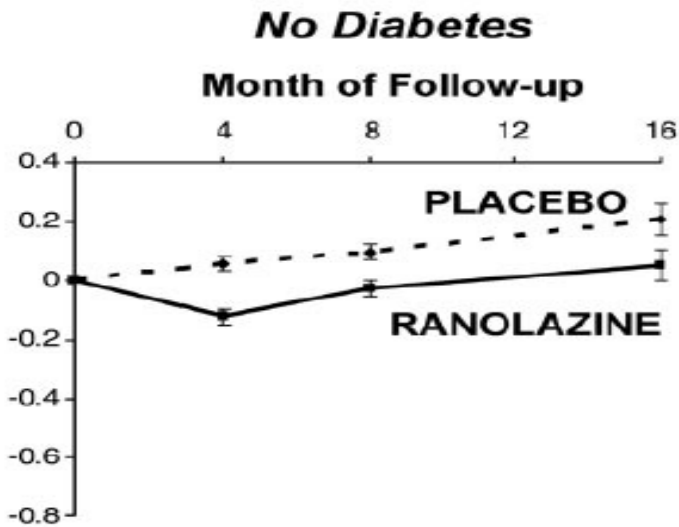
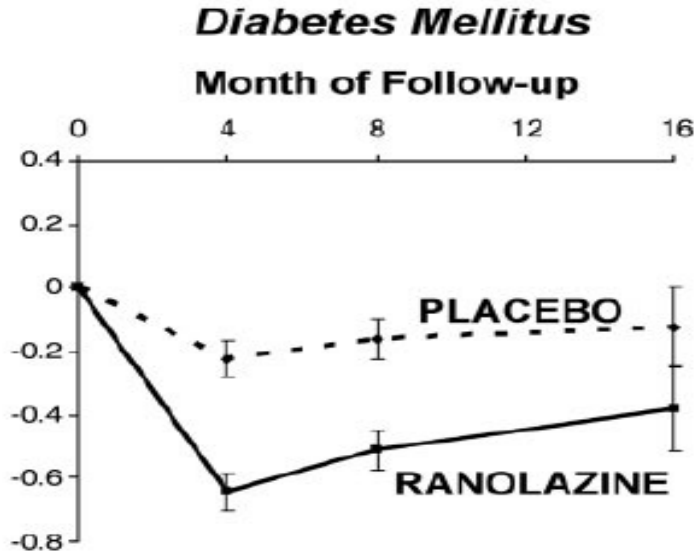
Recurrent Ischemia (%)



*KM Cumulative Incidence (%) at 12 months

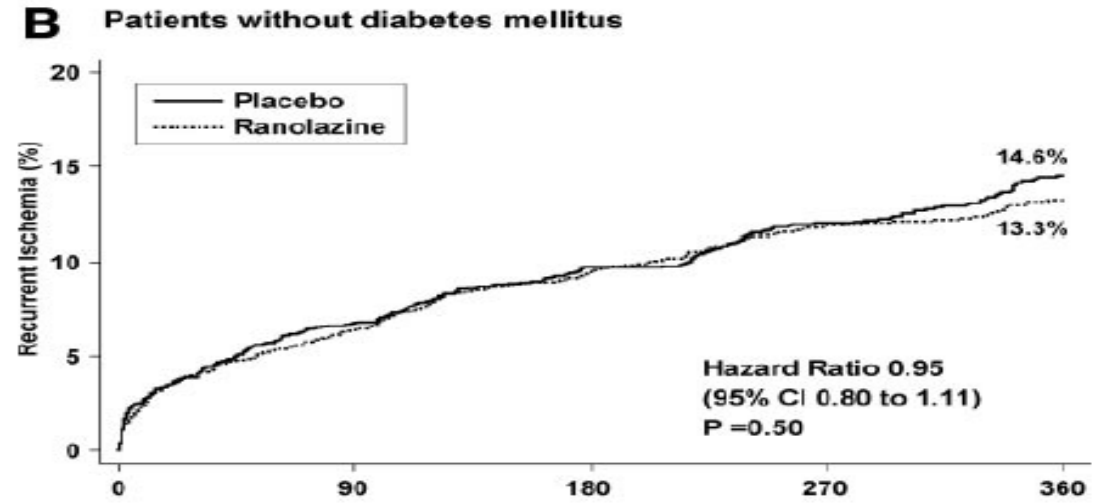
Morrow DA et al, JAMA 2007;297(16):1775-83

Change in HbA1C



No. at risk

Ranolazine	1104	976	847	636
Placebo	1116	985	853	616



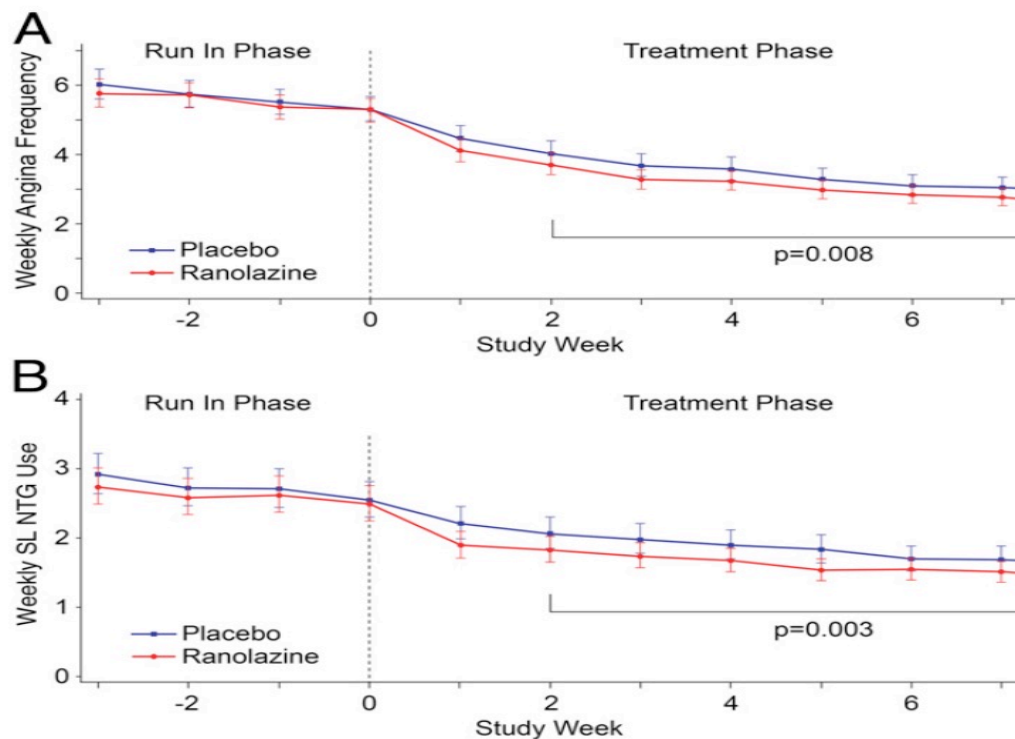
No. at risk

CLINICAL RESEARCH

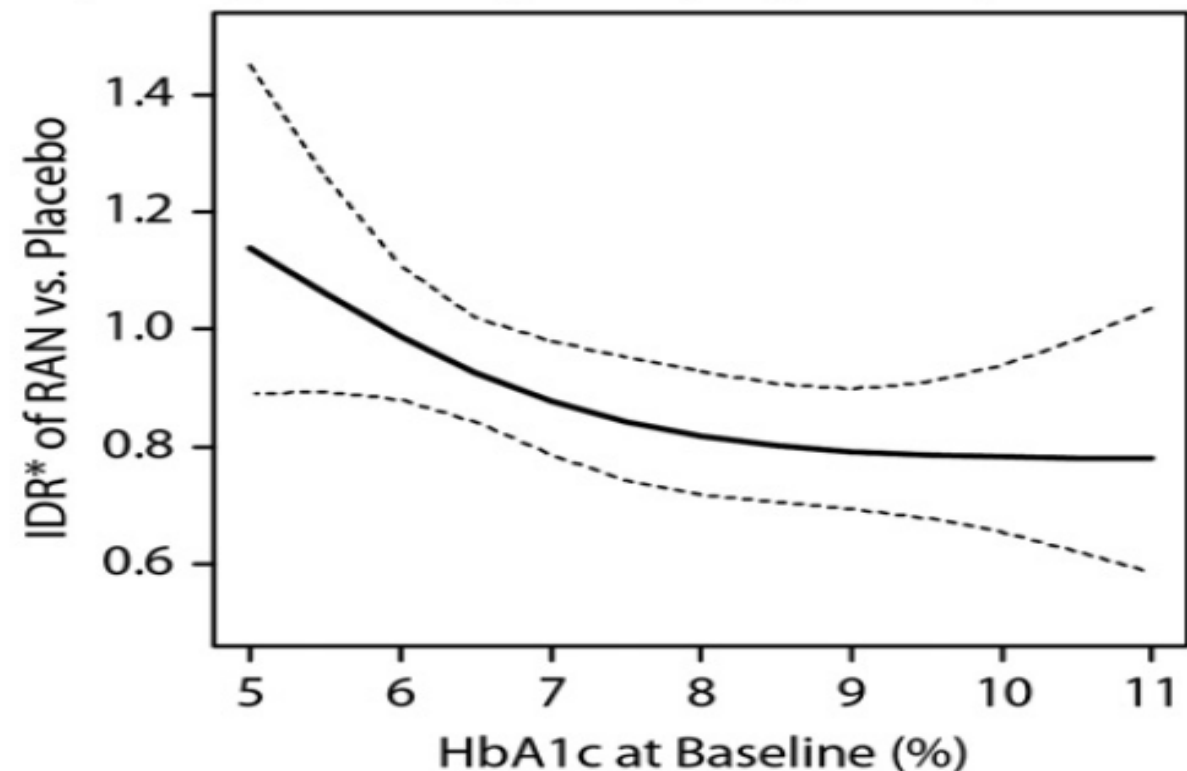
Late-Breaking Clinical Trials

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina

Results From the TERISA Randomized Clinical Trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina)



A) Angina Frequency by Diary



RANOLAZINA

- Nessun impatto sulla prognosi
- Trattamento di scelta per pazienti ipotensi e bradicardici
- Beneficio maggiore nei pazienti con diabete mal controllato

- Costo di circa 1000 euro/anno a paziente
(principale ostacolo alla sua diffusione)



Take Home Messages

La terapia della CAD stabile: il vecchio e il nuovo

- Trattamento dell'angina e miglioramento della prognosi rappresentano obiettivi strategici differenti
- Il miglioramento della prognosi solo con interventi di prevenzione secondaria
- L'importanza del trattamento dell'angina troppo spesso sottovalutato
- Non c'è evidenza di superiorità dei nuovi rispetto ai vecchi e viceversa
- L'ivabradina migliora l'angina, ma con possibile impatto prognostico sfavorevole su pazienti con funzione v.sn. conservata
- La ranolazina in monoterapia è da preferire nei casi con bradicardia e ipotensione

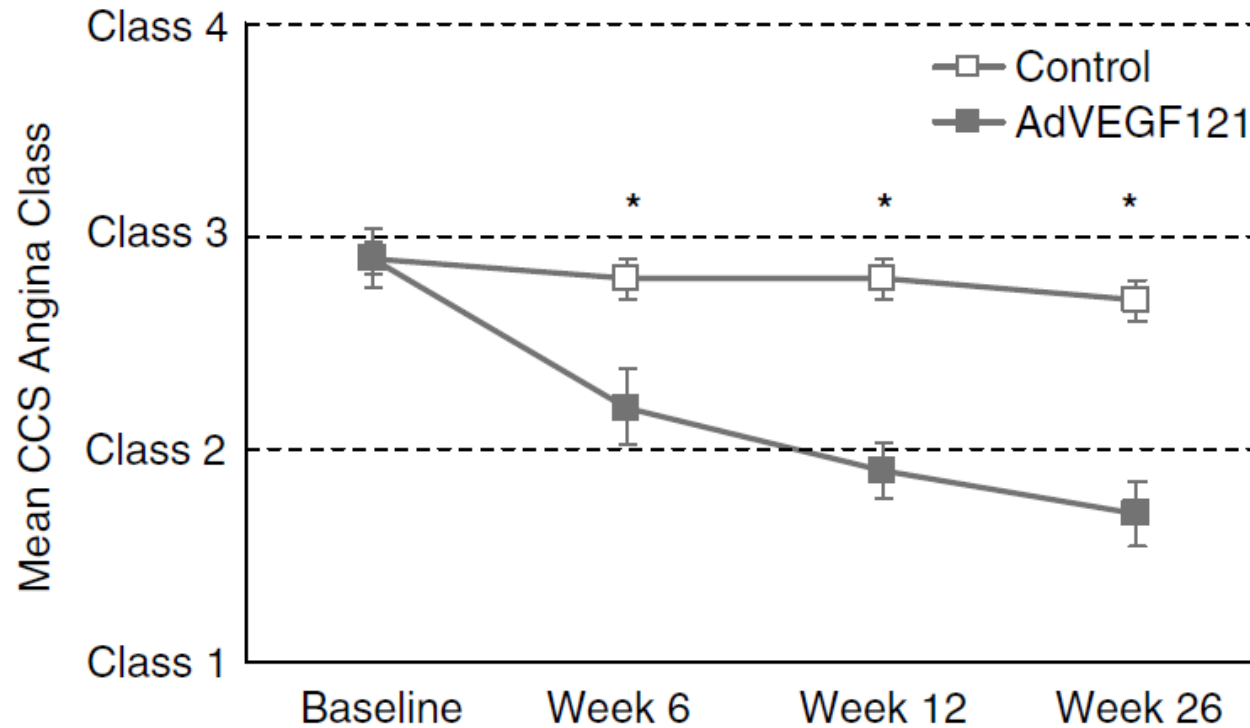
*Crisi è quel momento in cui il
vecchio muore
ed il nuovo stenta a nascere*

Antonio Gramsci 1891-1937

Il futuro...

Terapia genica: REVASC trial

Phase 2 randomized, controlled trial of AdVEGF₁₂₁
DJ Stewart *et al*



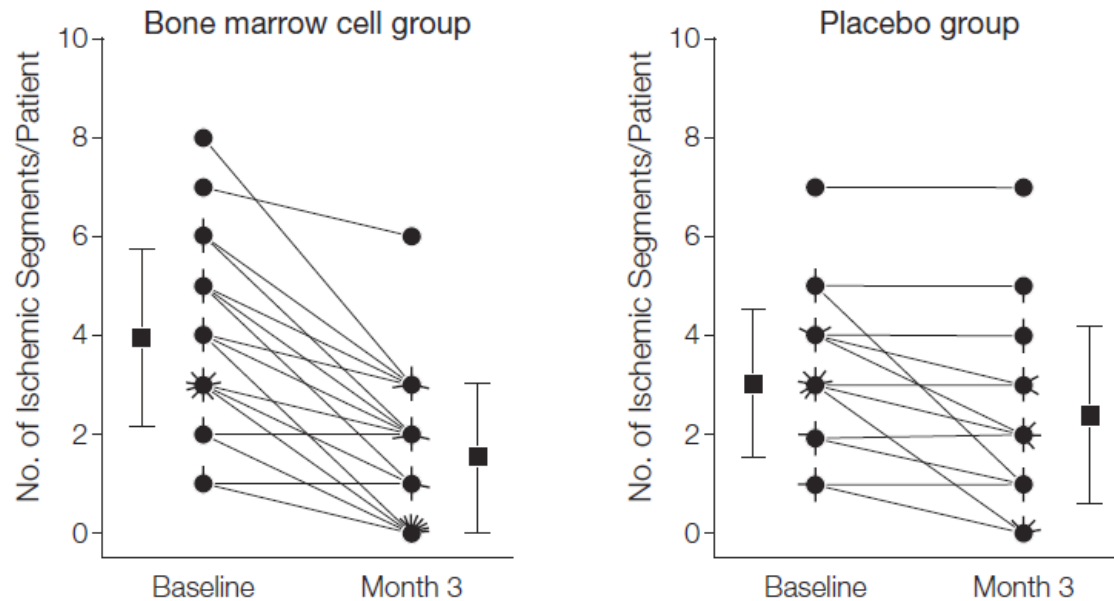
Iniezione intramiocardica di AdVEGF121
in pazienti affetti da angina cronica

VEGF121: a replication-deficient
adenoviral vector carrying the transgene
encoding for VEGF121

Parameter	AdVEGF121 (n = 32)	Control (n = 35)	P-value
Sex (male)	84%	94%	NS
Mean age (years)	61	60	NS
Resting left ventricular ejection fraction (s.d.)	53% (12)	52% (11)	NS
Previous myocardial infarction	69%	60%	NS
History of hypertension	75%	71%	NS
Dyslipidemia	41%	46%	NS
Current smoking	3%	0%	NS
Diabetes (type 1 or 2)	47%	23%	<0.05
CCS angina class III-IV	78%	80%	NS
Previous CABG (>2 previous CABG)	75% (21%)	77% (19%)	NS
Previous PCI (>2 previous PCI)	66% (48%)	26% (33%)	<0.05

Terapia cellulare e angina

Figure 2. Improvements in Segments With Inducible Myocardial Ischemia as Assessed by SPECT



N = 50 pazienti
randomizzati a terapia
cellulare vs. placebo

Iniezione intramiocardica
di **cellule CD34+** da
midollo osseo in pazienti
affetti da angina
refrattaria a terapia
medica e non
rivascolarizzabili

Prognosi dei pazienti affetti da CAD ostruttiva

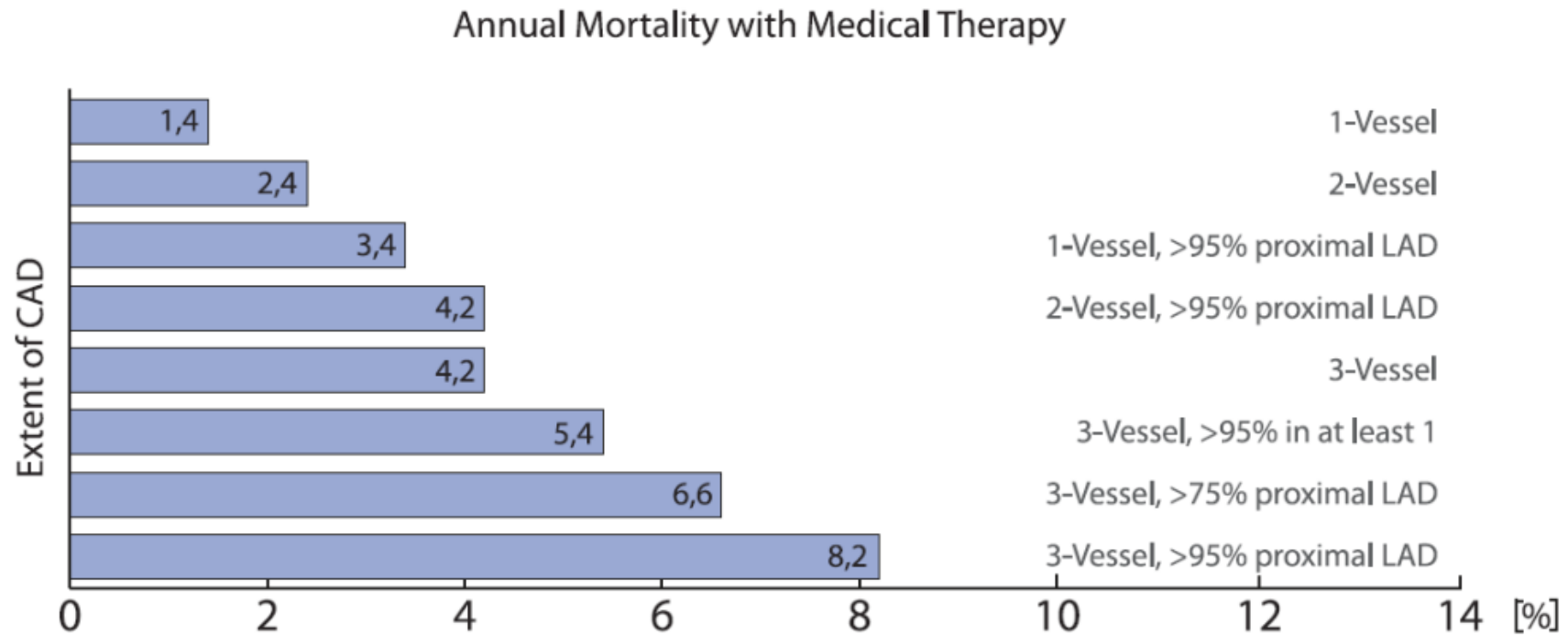
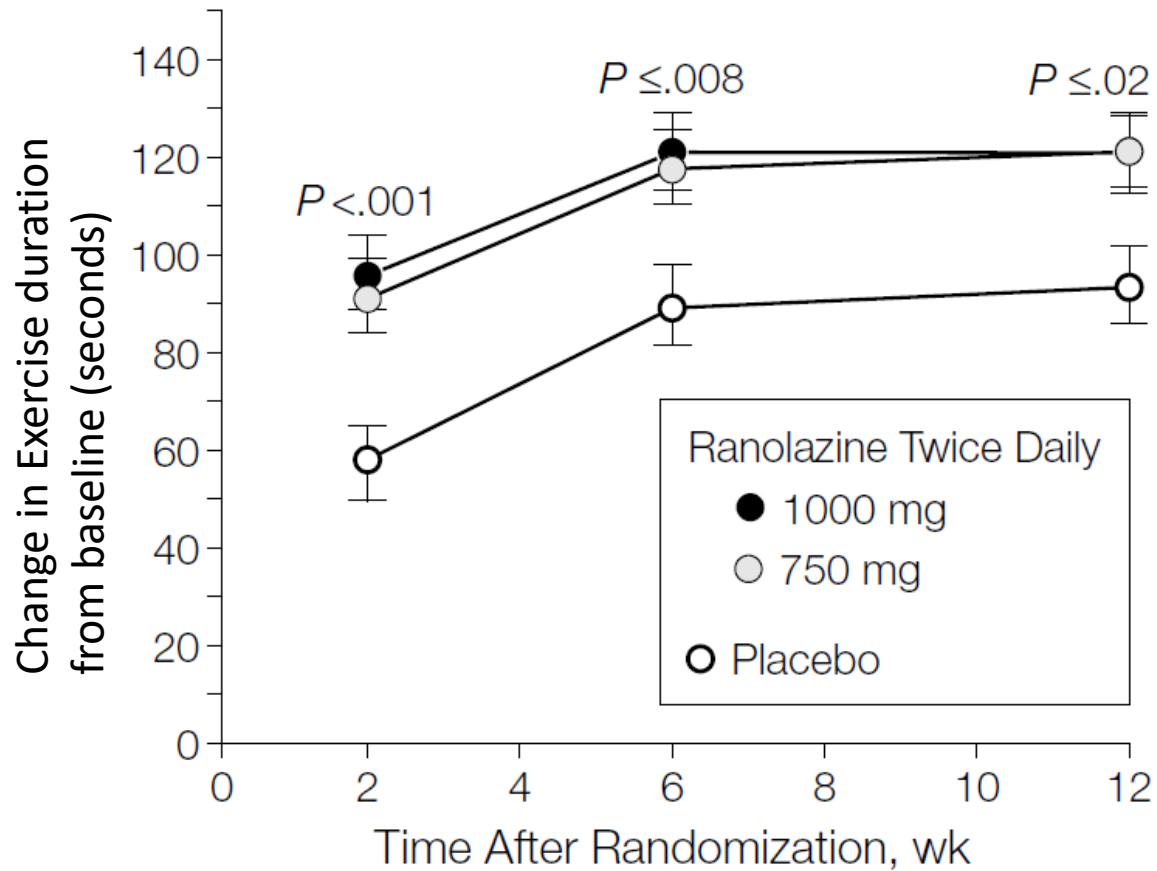


Figure W3 Cardiac death rates in patients on medical therapy with different extents of angiographically defined coronary artery disease. LAD = left anterior descending.⁴⁶

“ L’innovazione consiste nel fare le cose vecchie in modo nuovo ”

Joseph Alois Schumpeter 1883-1950

CARISA trial



N = 823

Angina cronica sintomatica

Randomizzazione a placebo vs. due diversi dosaggi di ranolazina (750 mg oppure 1000 mg x 2/die) in associazione a dosaggi standard di atenololo (50 mg), amlodipina (5 mg) o diltiazem (180 mg).