
# Trattamento della malattia coronarica stabile

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European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

ESC GUIDELINES

# 2013 ESC guidelines on the management of stable coronary artery disease

**The Task Force on the management of stable coronary artery disease of the Europ**

## 2. Introduction

Pazienti con angina stabile o sintomi correlati a coronaropatia

Pazienti con coronaropatia nota divenuti asintomatici con la terapia e che necessitano di regolare follow up

Pazienti che presentano sintomi per la prima volta ma considerati già in fase cronica stabile

history-taking reveals that similar symptoms were already present for several months). Hence, SCAD defines the different evolutionary phases of CAD, excluding the situations in, which coronary artery thrombosis dominates clinical presentation (acute coronary syndromes).

# Angina stabile

European Heart Journal
doi:10.1093/eurheartj/ehl002

ESC Guidelines

Guidelines c ble
angina pect
The Task Forc Angina Pectoris of
the European

## Definition and pathophysiology

Stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Less typically, discomfort may occur in the epigastric area. William Heberden first introduced the term 'angina pectoris' in 1772[2] to characterize a syndrome in which there was 'a sense of strangling and anxiety' in the chest, especially associated with exercise, although its pathological aetiology was not recognized until some years later.[3] It is now usual to confine the term to cases in which the syndrome can be attributed to myocardial ischaemia, although essentially similar symptoms can be caused by disorders of the oesophagus, lungs, or chest wall. Although the most common cause of myocardial ischaemia is atherosclerotic CAD, demonstrable myocardial ischaemia may be induced in the abscence by hypertrophic or dilated cardiomyopathy, aortic stenosis, or other rare cardiac conditions in the absence of obstructive atheromatous coronary disease, which are not considered in this document.

L’angina stabile è la manifestazione clinica più frequente di malattia coronarica

Interessa più del 5 % della popolazione al di sopra dei 40

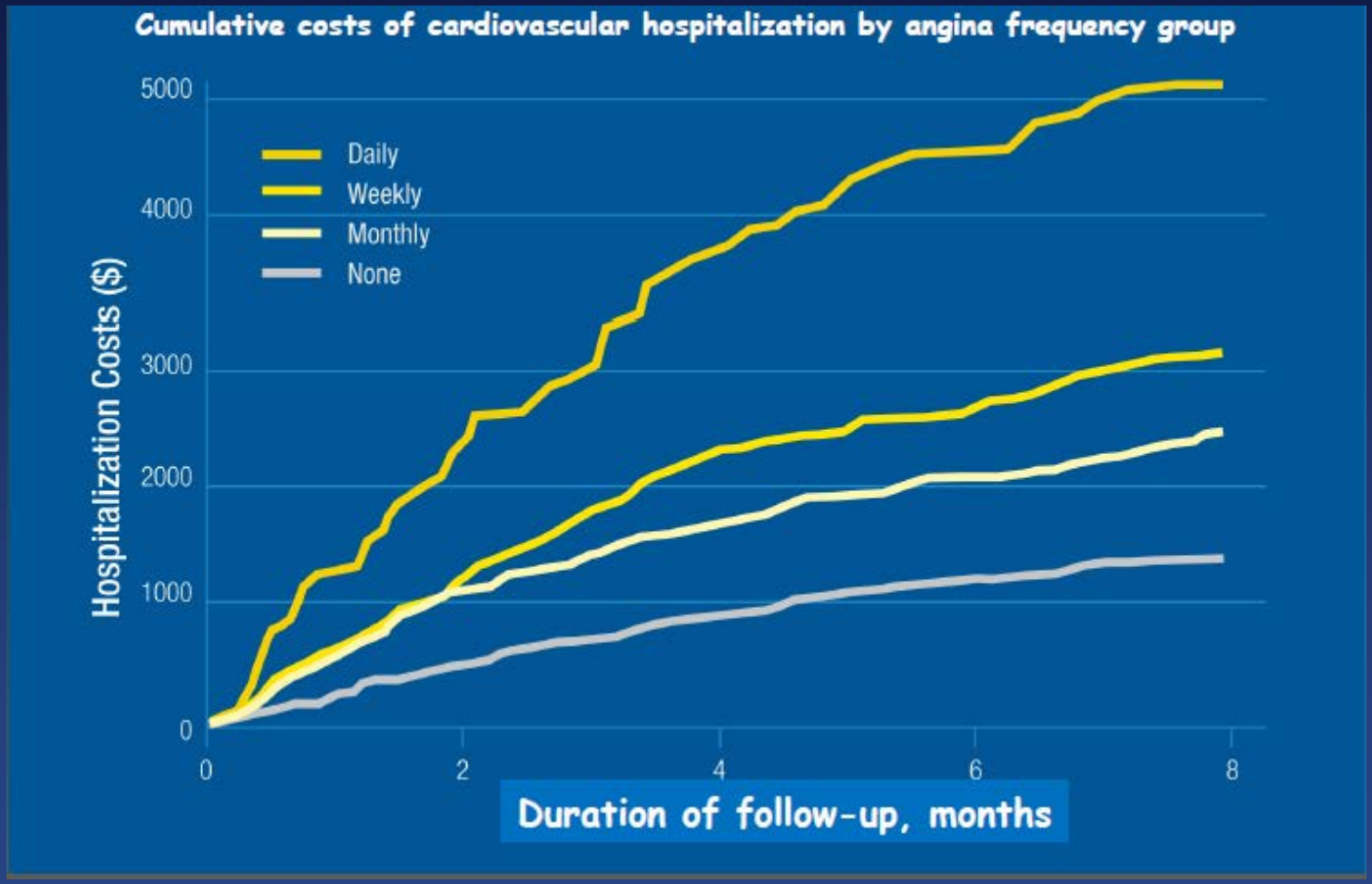
The prevalence of angina in population-based studies increases with age in both sexes, from 5–7% in women aged 45–64 years to 10–12% in women aged 65–84 and from 4–7% in men aged 45–64 years

Problematica rilevante dal punto di vista medico ed economico

is more prev
due to the hi
vascular angina—in women,[14,15] whereas the opposite is true in the elderly.

Available data suggest an annual incidence of uncomplicated angina pectoris of 1.0% in male western populations aged 45–65 years, with a slightly higher incidence in women under the age of 65.[13,16] There is a steep increase with age and the incidence in men and women 75–84 years of age reaches almost 4%.[16] The incidence of angina varies in parallel with observed international differences in CAD mortality.[16,17]

# Il costo dell'angina pectoris stabile è proporzionale alla frequenza degli attacchi




Analysis from MERLIN-TIMI 36; 5460 stable outpatients after ACS; median follow up: 12 months

*Arnold SV, et al. Circ Cardiovasc Qual Outcomes. 2009;2:344-353.*

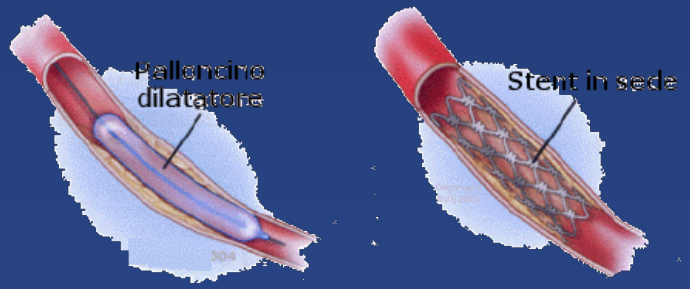
# Il trattamento della CAD stabile ha due obiettivi:

1) Miglioramento della qualità di vita del paziente tramite il controllo dei sintomi

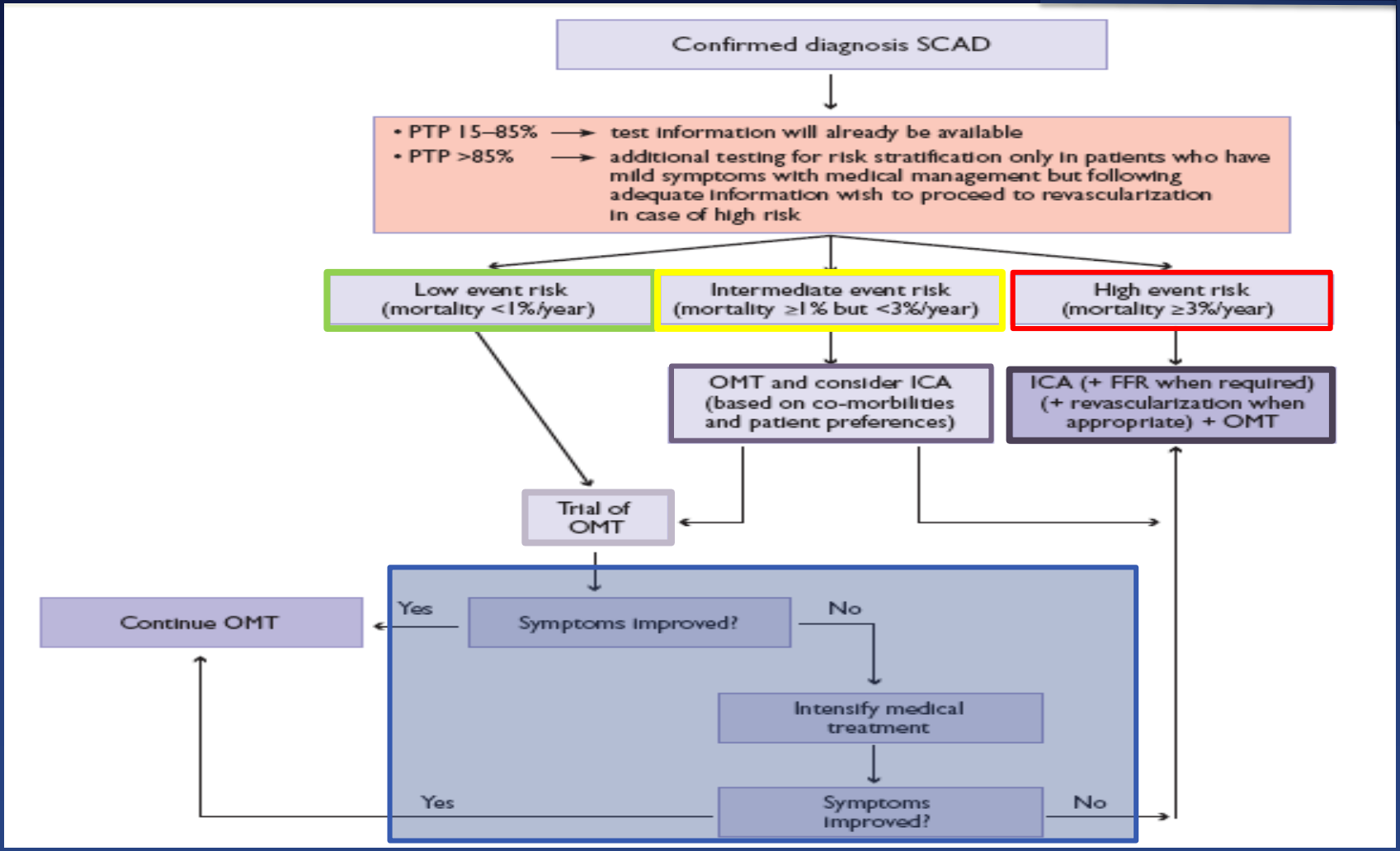
2) Miglioramento della prognosi

Per ottenere questi risultati 2 strategie :

TERAPIA MEDICA o RIVASCOLARIZZAZIONE (percutanea o chirurgica)




# Management del paziente con angina stabile




*ESC Guidelines on the management of stable angina pectoris, 2013*

**Nitrati (1880)**

Sir Thomas Lauder Brunton (1844 – 1916) fu il primo a utilizzare i nitrati nel trattamento del dolore anginoso (1874)

**Beta bloccanti (1965)**

Sir James W. Black sviluppò con successo il Propranololo alla fine degli anni ‘50

**ACE inibitori (1974)**

Nel 1956 Leonard Skegg studia l’enzima convertitore dell’angiotensina e il farmacologo Sergio Ferreira scoprì che il veleno del serpente *Bothrox jararaca* ne provocava l’inibizione in vitro

**Calcio Antagonisti (1975)**

Tra la metà degli anni 60’ e la metà degli anni ‘70 Fleckenstein studia i Bloccanti dei canali del Calcio

**Statine (1976)**

Nella seconda metà degli anni 70’ Akira Endo scopre la capacità di alcuni funghi di inibire la HMG CoA reduttasi: la Mevastatina è la prima statina. Nel 1978 la sperimentazione passa dall’animale all’uomo e nel 1987 la FDA approva l’uso clinico delle statine

# Fisiopatologia dell'ischemia miocardica

## 3. Definitions and pathophysiology (see web addenda)

Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia, which are usually inducible by exercise, emotion or other stress and reproducible—but, which may also be occurring spontaneously. Such episodes of ischaemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris). SCAD also includes the stabilized, often asymptomatic, phases that follow an ACS.

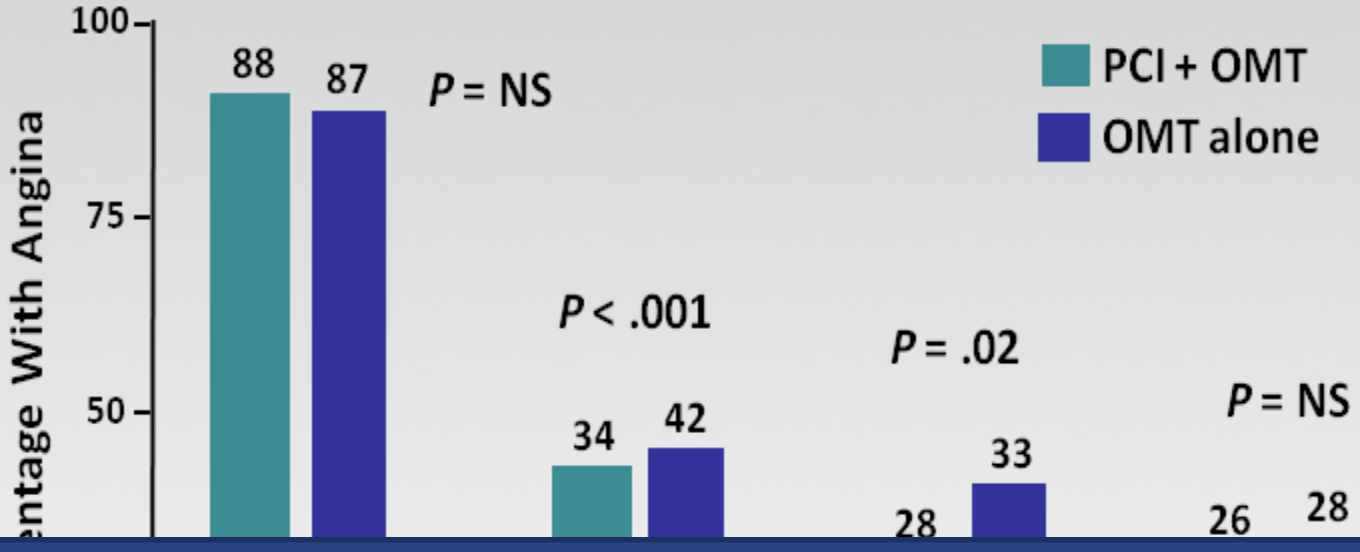
(NTG

Post-carico
alcioantagonisti
C
etabloccanti
ontrattilità
etabloccanti
carico vascolare
NTG

↓ Flusso Coronarico diastolico

↑ LVEDP

LV ipertrofia
LV Precarico

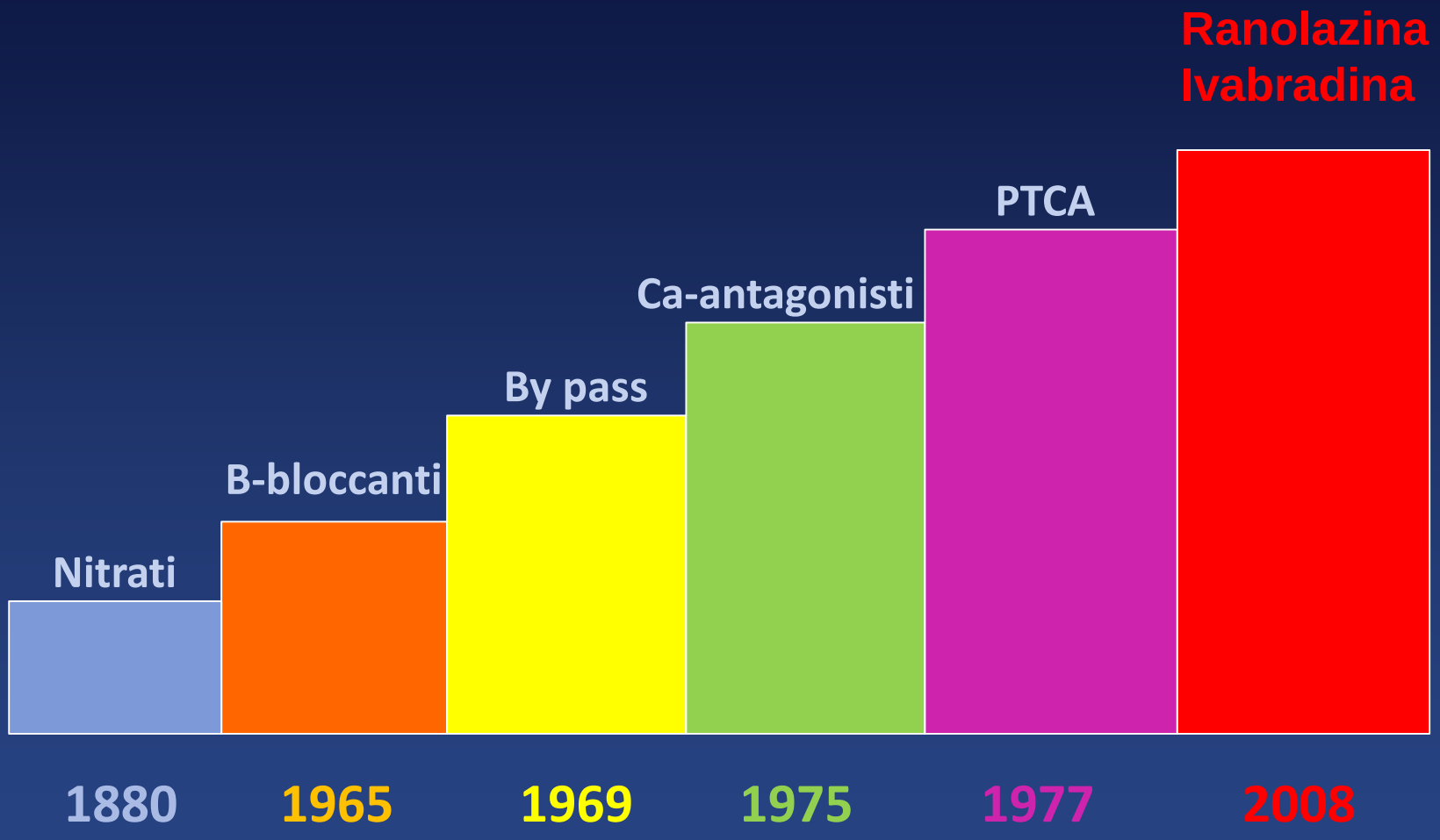



**Rivascolarizzazione incompleta**
**Restenosi intrastent/occlusione BPAC**
**Malattia microvascolare**
**Progressione della malattia aterosclerotica**
**Terapia inadeguata o impossibilità a titolare i farmaci tradizionali per effetti collaterali**



Boden WE, et al. *N Engl J Med.* 2007;356:1503-1516.

# Evoluzione della terapia antianginosa



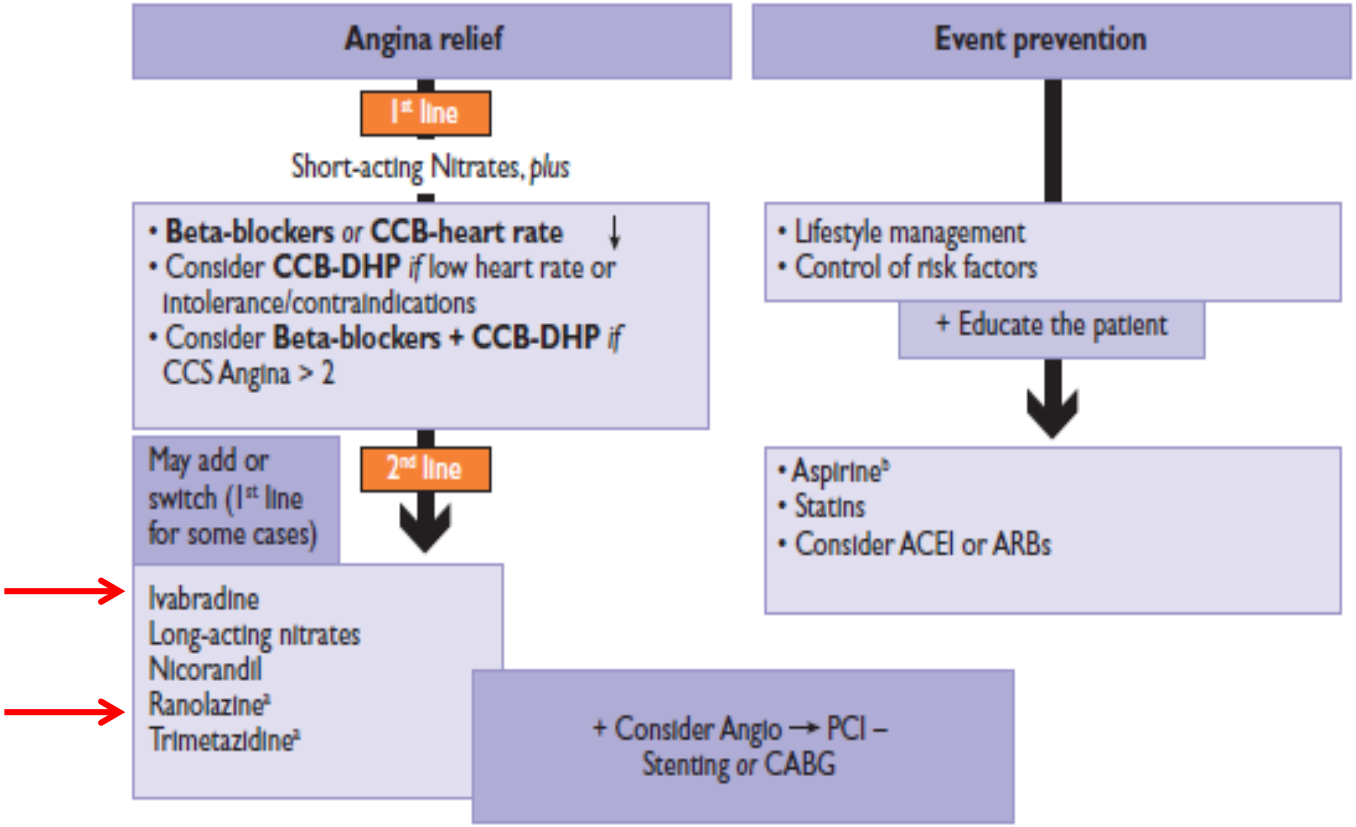



**Figure 4** Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

[a]Data for diabetics.

[b]if intolerance, consider clopidogrel

**Table 28** **Pharmacological treatments in stable coronary artery disease patients**

| Indication | Class [a] | Level [b] | Ref. [c] |
|---|---|---|---|
| **General considerations** | | | |
| Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention. | I | C | - |
| It is recommended to educate patients about the disease, risk factors and treatment strategy. | I | C | - |
| It is indicated to review the patient's response soon after starting therapy. | I | C | - |
| **Angina/ischaemia[d] relief** | | | |
| Short-acting nitrates are recommended. | I | B | 3, 329 |
| First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. | I | A | 3, 331 |
| For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance. | IIa | B | 177, 307, 3, 199, 284, 286, 308, 319-321, 328 |
| For second-line treatment, trimetazidine may be considered. | IIb | B | 313, 315 |
| According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients. | I | C | - |
| In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered. | IIa | C | - |
| In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. | IIa | B | 3, 365 |
| **Event prevention** | | | |
| Low-dose aspirin daily is recommended in all SCAD patients. | I | A | 333, 334, 366 |
| Clopidogrel is indicated as an alternative in case of aspirin intolerance. | I | B | 335 |
| Statins are recommended in all SCAD patients. | I | A | 62 |
| It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). | I | A | 348, 349, 351, 352 |

ACE = angiotensin converting enzyme; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.
[d] No demonstration of benefit on prognosis

*2013 ESC Guidelines on the management of stable CAD*

# Ivabradina

**Modulazione del canale If → rallentamento del flusso ionico in entrata e prolungamento del tempo di risalita del potenziale d'azione con una conseguente riduzione della frequenza cardiaca**

**Il blocco dei canali If da parte dell'ivabradina è funzione del loro grado di apertura. Tanto maggiore è l'apertura dei canali If tanto maggiore risulta la frequenza cardiaca e tanto maggiore il grado di blocco del canale da parte del farmaco**

**Depolarizzazione diastolica**

# IVABRADINA: profilo di tollerabilità

| | β-bloccanti | Verapamil Diltiazem | Ivabradina® |
|---|---|---|---|
| Frequenza cardiaca | ↓↓ | ↓ | ↓↓ |
| Contrattilità cardiaca | ↓ | ↓ | Ø |
| Conduzione cardiaca | ↓ | ↓ | Ø |
| Eccitabilità cardiaca | ↓ | Ø | Ø |
| Pressione arteriosa | ↓ | ↓ | Ø |

# Efficacia anti-ischemica di Ivabradina associata a betabloccante

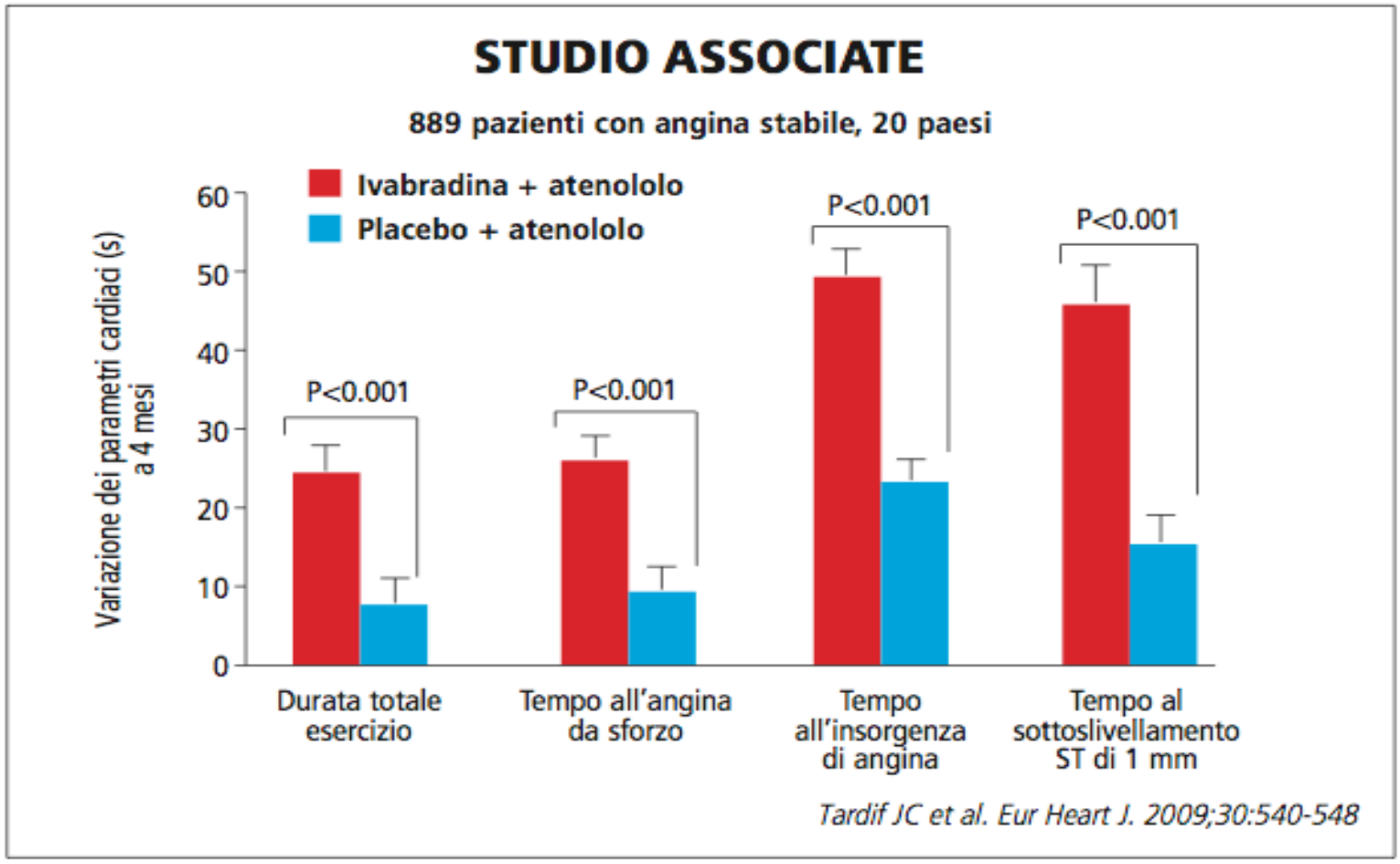



*Figura 2. Effetto di ivabradina sui parametri cardiaci nello studio ASSOCIATE.*

# Studio

**BEAUTIFUL**

MorBidity-mortality EvAlUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction

***Popolazione:***

CAD e LVD

≥ 55 anni o diabetici > 18 anni

CAD documentata

razione d'eiezione < 40%

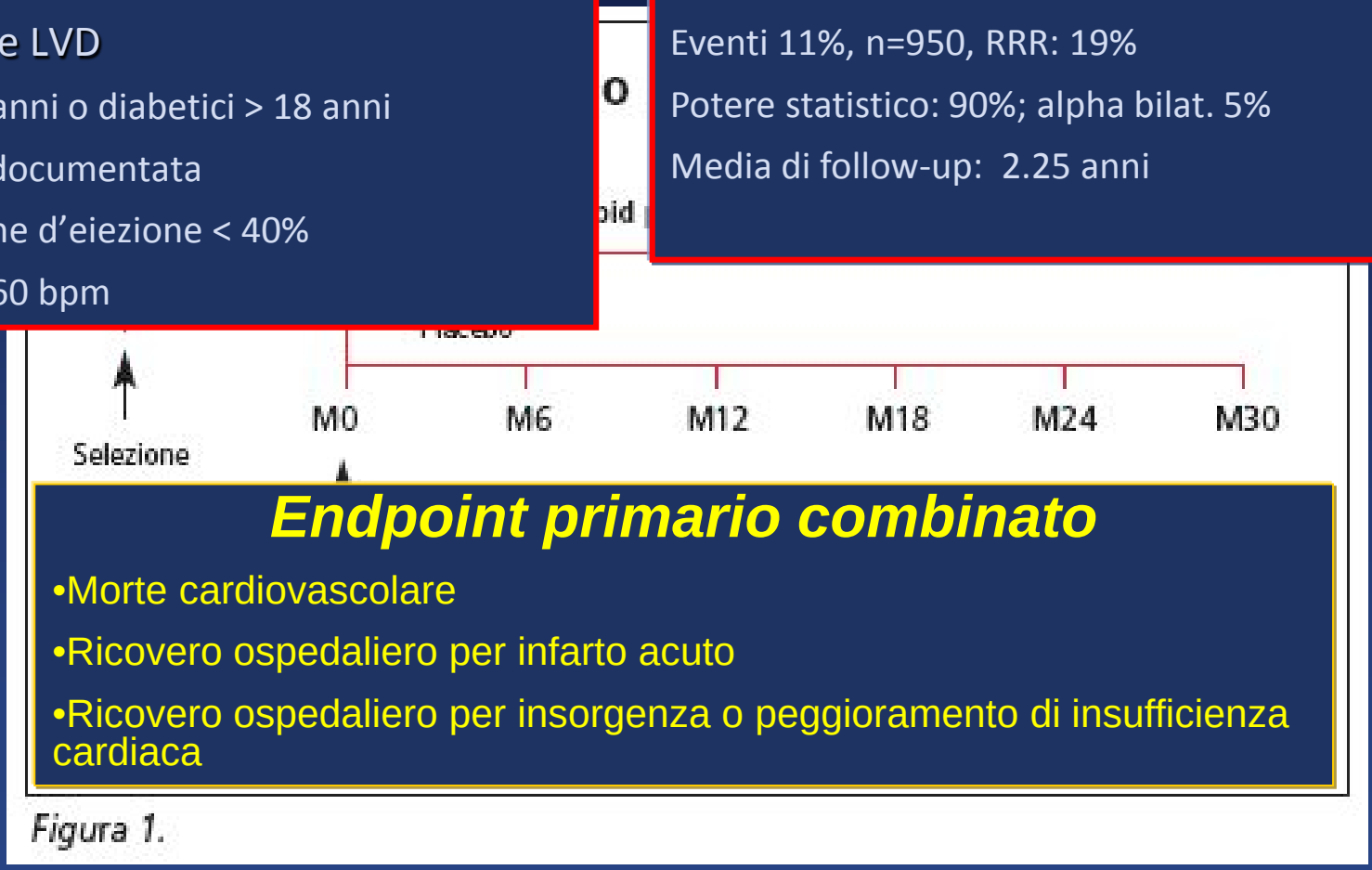
FC ≥ 60 bpm

***Metodi:***

Eventi 11%, n=950, RRR: 19%

Potere statistico: 90%; alpha bilat. 5%

Media di follow-up: 2.25 anni




***Endpoint primario combinato***

- Morte cardiovascolare
- Ricovero ospedaliero per infarto acuto
- Ricovero ospedaliero per insorgenza o peggioramento di insufficienza cardiaca

*Figura 1.*

# Risultati

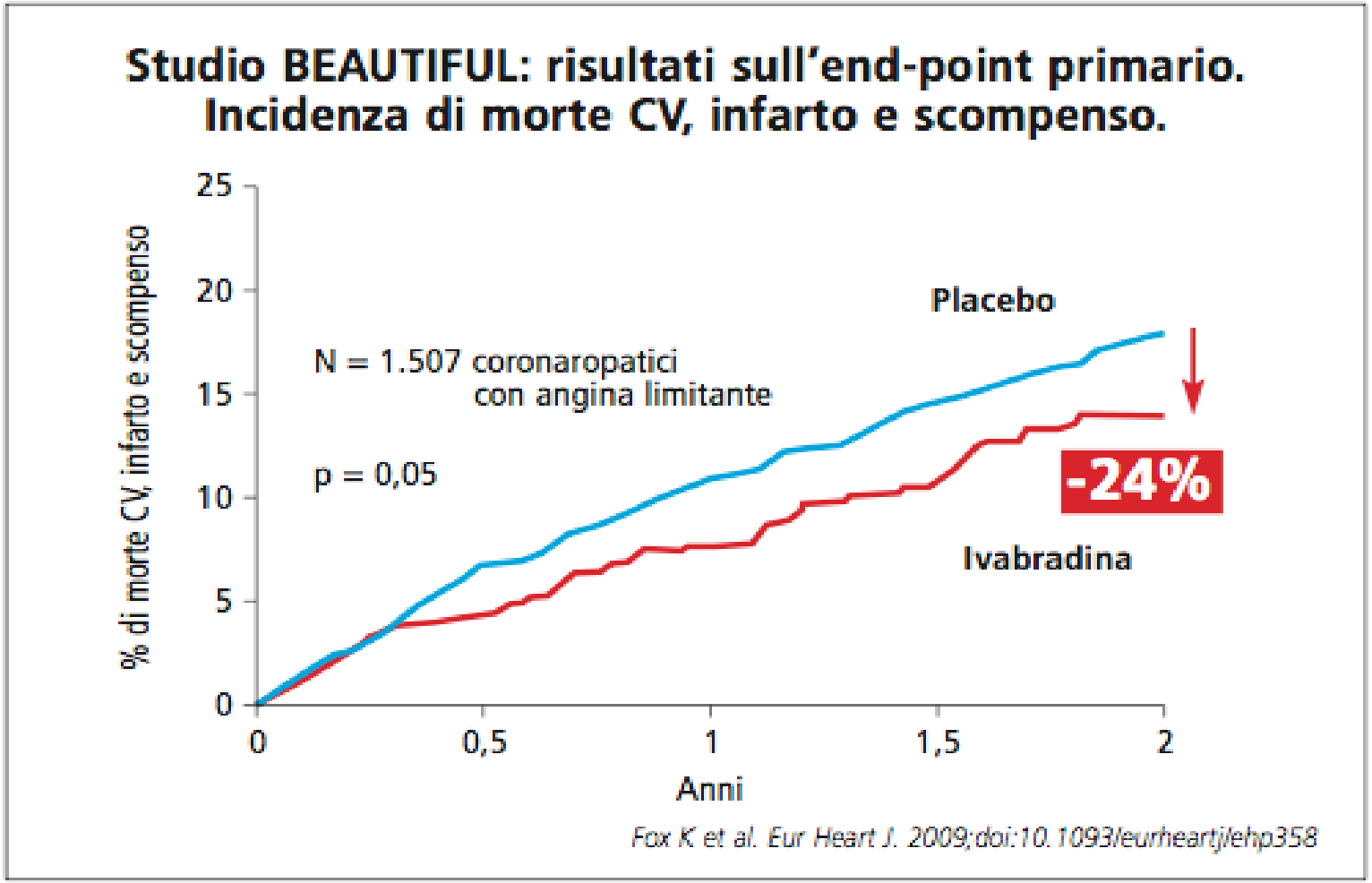
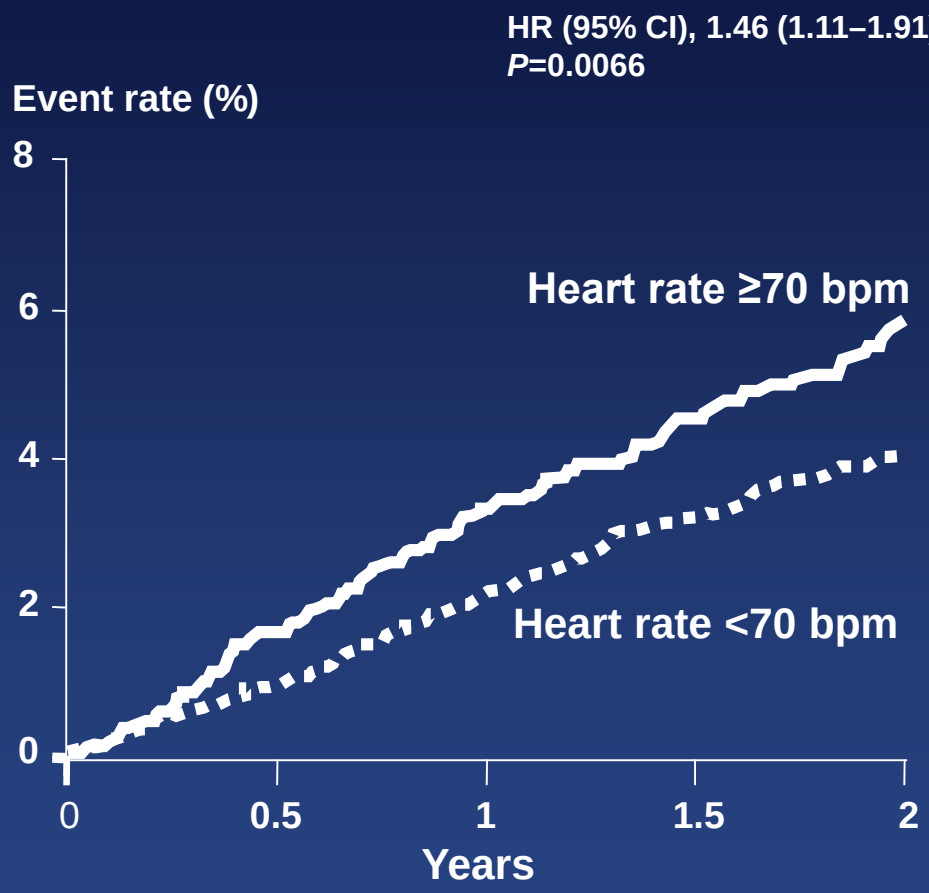
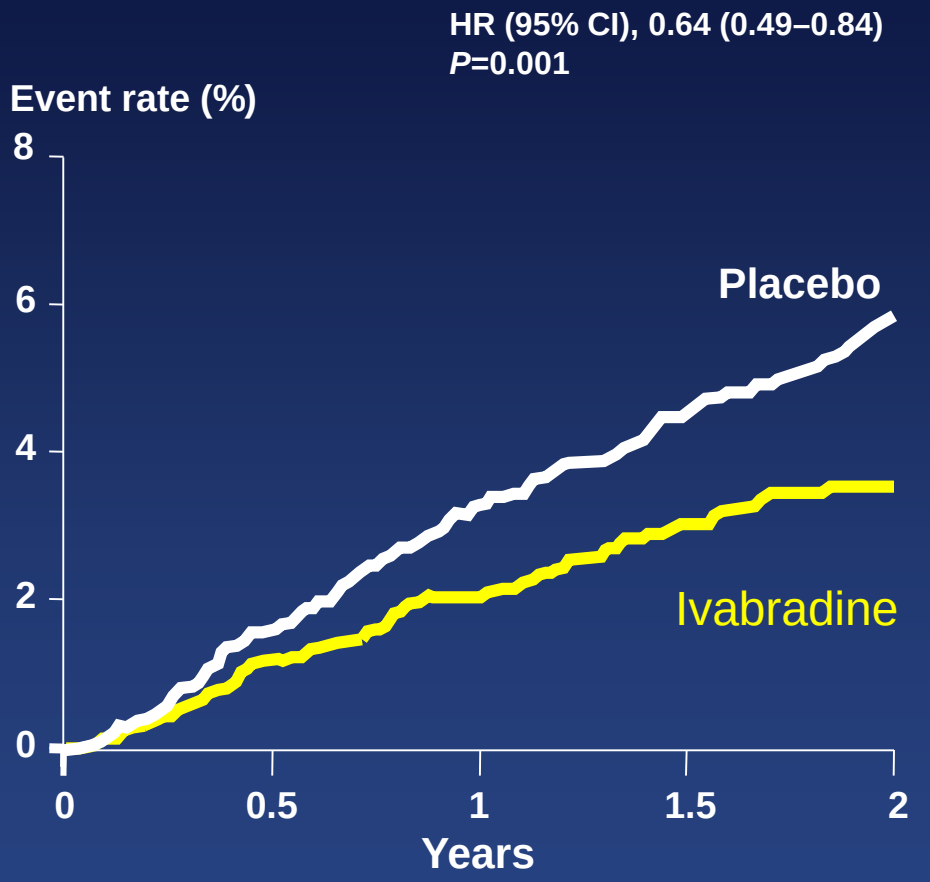



*Figura 1.*

# Effect of ivabradine on hospitalization for fatal/nonfatal MI in patients with stable CAD and LVSD




Overall placebo population (n=5438)




Patients with heart rate ≥70 bpm (n= 5392)

Fox K et al. *Lancet.* 2008;372:817-821.

Fox K et al. *Lancet.* 2008;372:807-816.

SIGNIfY

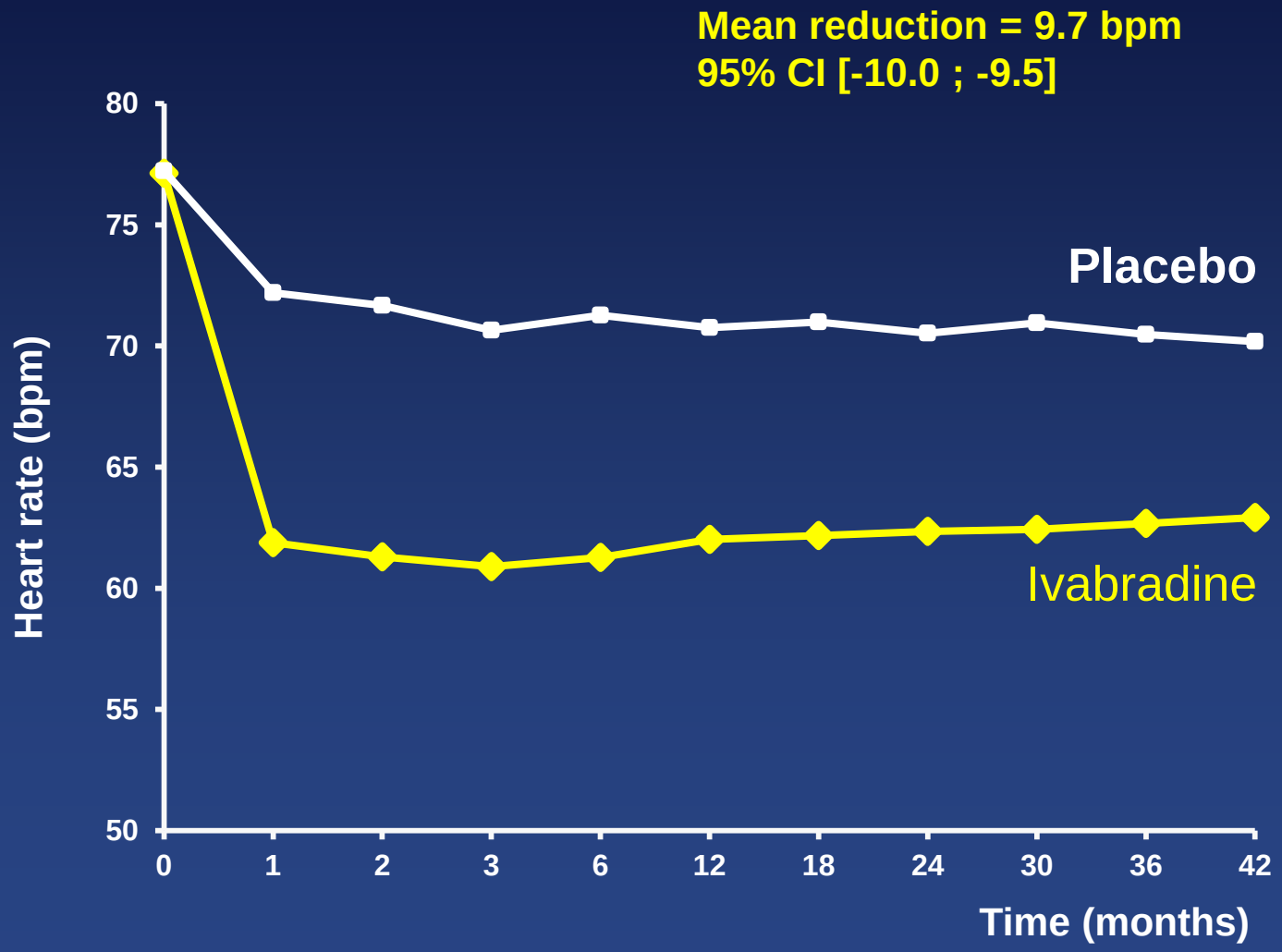
## *Population*

- ≥55 years, stable CAD
- With at least one other CV risk factor (including angina CCS class ≥II)
- Without clinical heart failure (LVEF >40%)
- HR ≥70 bpm

**19 102 patients randomized**

| Ivabradine (n=9550) | Placebo (n=9552) |
|---|---|
| 235 had incomplete follow-up<br>✓231 withdrew consent<br>✓3 lost to follow-up<br>✓1 medical reason | 200 had incomplete follow-up<br>✓199 withdrew consent<br>✓1 lost to follow-up |
| **9550 analyzed** | **9552 analyzed** |
| ✓ 6037 with angina<br>✓ 3513 with no angina | ✓ 6012 with angina<br>✓ 3540 with no angina |

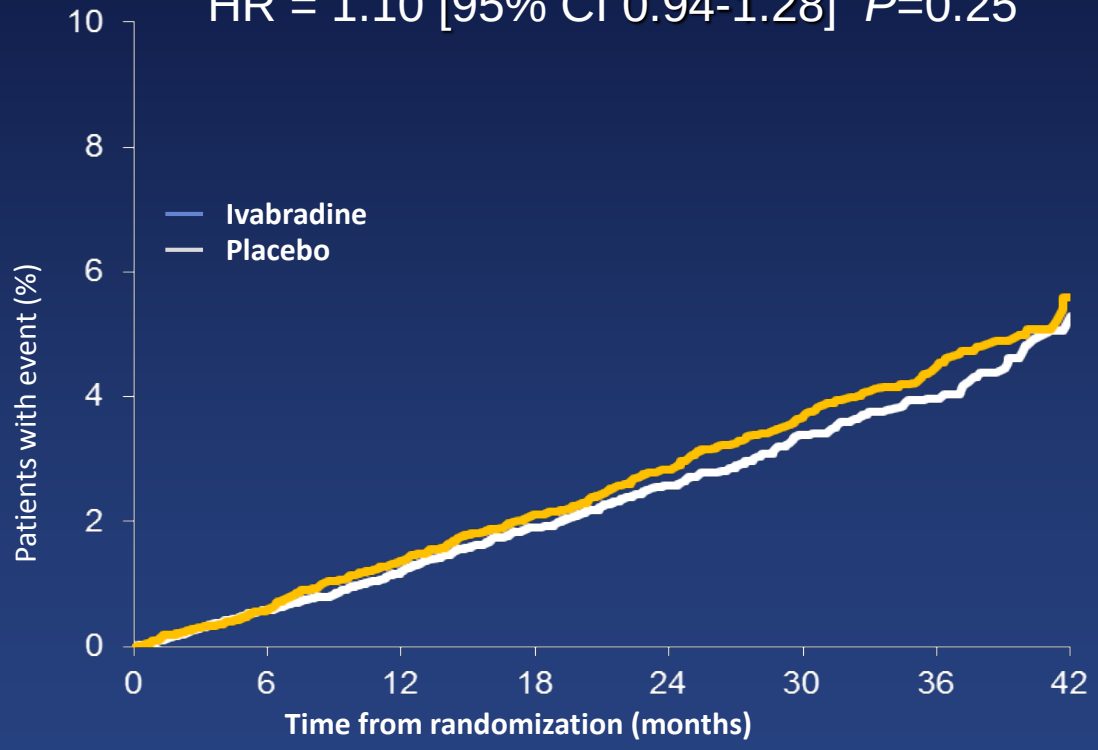
# Mean heart rate reduction



# Cardiovascular death

Ivabradine n=329 (1.49% PY)  Placebo n=301 (1.36% PY)

HR = 1.10 [95% CI 0.94-1.28]  *P*=0.25



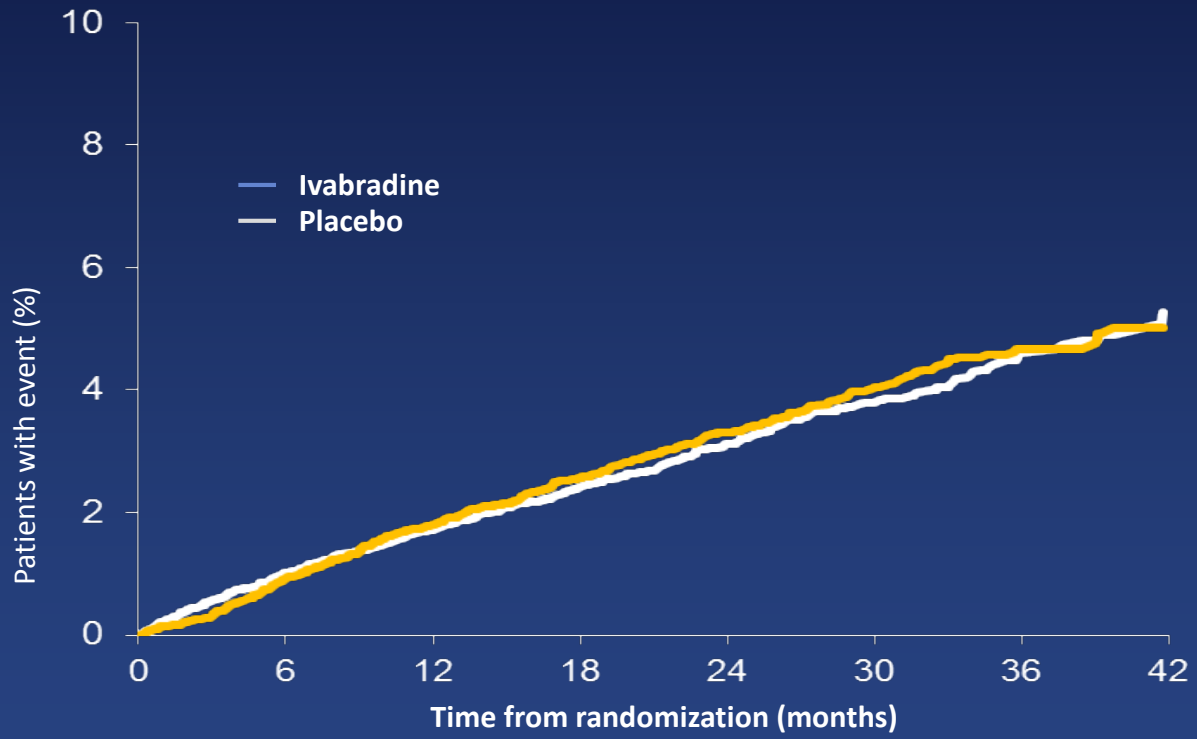

**Numbers at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ivabradine | 9550 | 9382 | 9240 | 8828 | 5755 | 3926 | 1914 | 366 |
| Placebo | 9552 | 9405 | 9284 | 8851 | 5822 | 3882 | 1910 | 386 |

# Nonfatal myocardial infarction

Ivabradine n=351 (1.63% PY) Placebo n=339 (1.56% PY)

HR = 1.04 [95% CI 0.90-1.21] *P*=0.60




| Numbers at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ivabradine | 9550 | 9297 | 9078 | 8611 | 5570 | 3776 | 1832 | 349 |
| Placebo | 9552 | 9311 | 9130 | 8656 | 5649 | 3749 | 1836 | 365 |

# Incidence of selected adverse events (n=19 083)

| | Ivabradine (n=9539) % (n) | Placebo (n=9544) % (n) |
|---|---|---|
| Symptomatic bradycardia | 7.9 (757) | 1.2 (110) |
| Asymptomatic bradycardia | 11.0 (1047) | 1.3 (126) |
| Atrial fibrillation | 5.3 (508) | 3.8 (362) |
| Phosphenes | 5.4 (512) | 0.5 (52) |

# Incidence of selected adverse events (n=19 083)

| | Ivabradine (n=9539) % (n) | Placebo (n=9544) % (n) |
|---|---|---|
| Ventricular tachycardia | 0.6 (54) | 0.4 (41) |
| Ventricular fibrillation | 0.3 (27) | 0.3 (26) |
| Torsades de pointes | 0 (1) | 0 (3) |

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*

**Fox K et al. *N Engl J Med.* Published online 31 August 2014.**

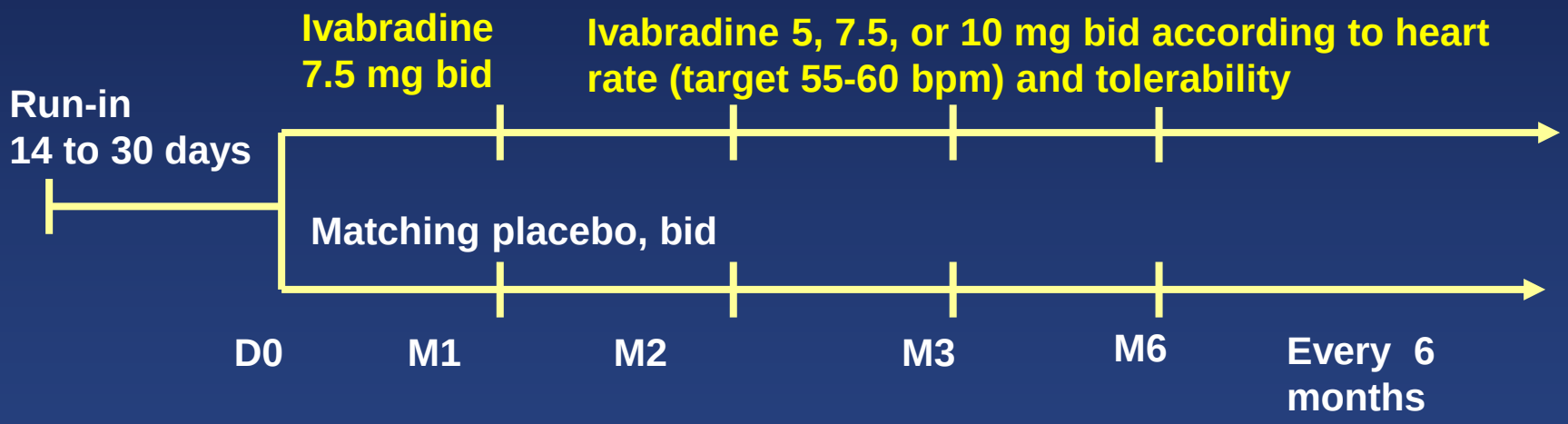
# Study design

## *Study outcomes*

- **Events: 2.8% PY placebo, N=19 102**
- **Median follow-up: 27.8 months**
- **51 countries - 1139 centres**

## *Population*

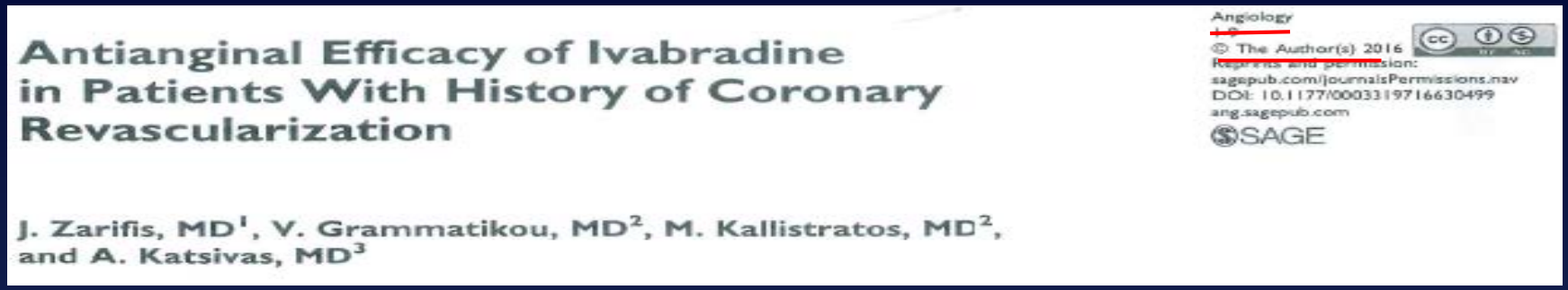
- ≥55 years, stable CAD
- With at least one other CV risk factor (including angina CCS class ≥II)
- Without clinical heart failure (LVEF >40%)
- HR ≥70 bpm




*Primary composite end point: cardiovascular death or nonfatal myocardial infarction*

- *Primary analysis: ivabradine versus placebo on primary end point*
- *Prespecified analysis: in patients with angina CCS class ≥II on primary end point*

Fox K et al. *Am Heart J.* 2013;166:654-661.



Antianginal Efficacy of Ivabradine in Patients With History of Coronary Revascularization

J. Zarifis, MD[1], V. Grammatikou, MD[2], M. Kallistratos, MD[2], and A. Katsivas, MD[3]

Angiology
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DOI: 10.1177/0003319716630499
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SAGE

Ivabradina aggiunta on top alla terapia betablocccante ottimizzata individualmente è associata in una analisi post hoc su 926 pazienti a riduzione degli eventi anginosi e a significativo miglioramento della qualità della vita in pazienti con malattia coronarica stabile e pregressa rivascolarizzazione coronarica.

The Role of Ivabradine in Cardiac Rehabilitation in Patients With Recent Coronary Artery Bypass Graft

Stefania Marazia, MD[1], Lucia Urso, MD[2], Marco Contini, MD[3], Marco Pano, MD[4], Salvatore Zaccaria, MD[4], Vincenzo Lenti, MD[1], Filippo M. Sarullo, MD[5], and Michele Di Mauro, MD[6]

Journal of Cardiovascular Pharmacology and Therapeutics
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DOI: 10.1177/1074248415575963
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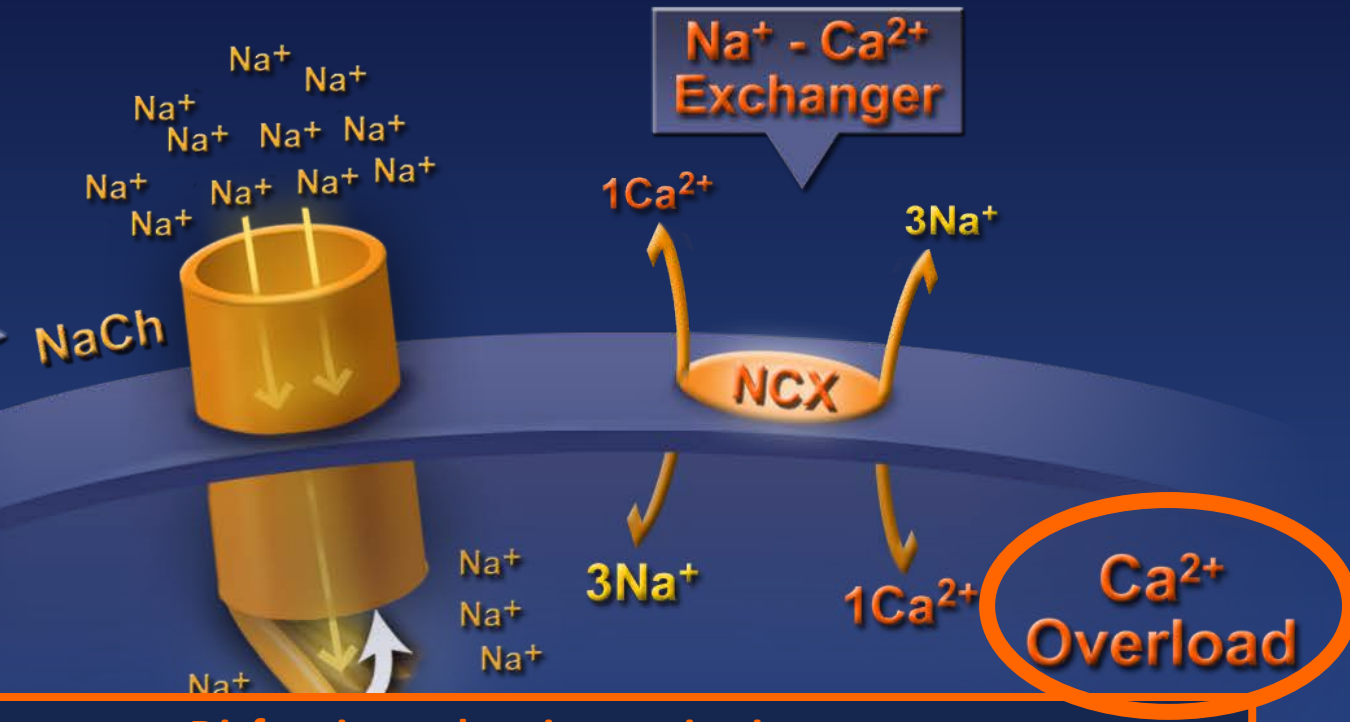
Durante riabilitazione cardiolgica i paziente post CABG l'aggiunta di ivabradina a basse dosi di bisoprololo migliora la capacità funzionale, incrementa il recupero della funzione sistolica e riduce la disfunzione diastolica

# Ranolazina: meccanismo d'azione

Nell'ISCHEMIA MIOCARDICA si verifica un'attivazione prolungata della corrente tardiva del sodio




**Disfunzione elettrica e aritmie**

**Disfunzione meccanica**

**Disfunzione metabolica**

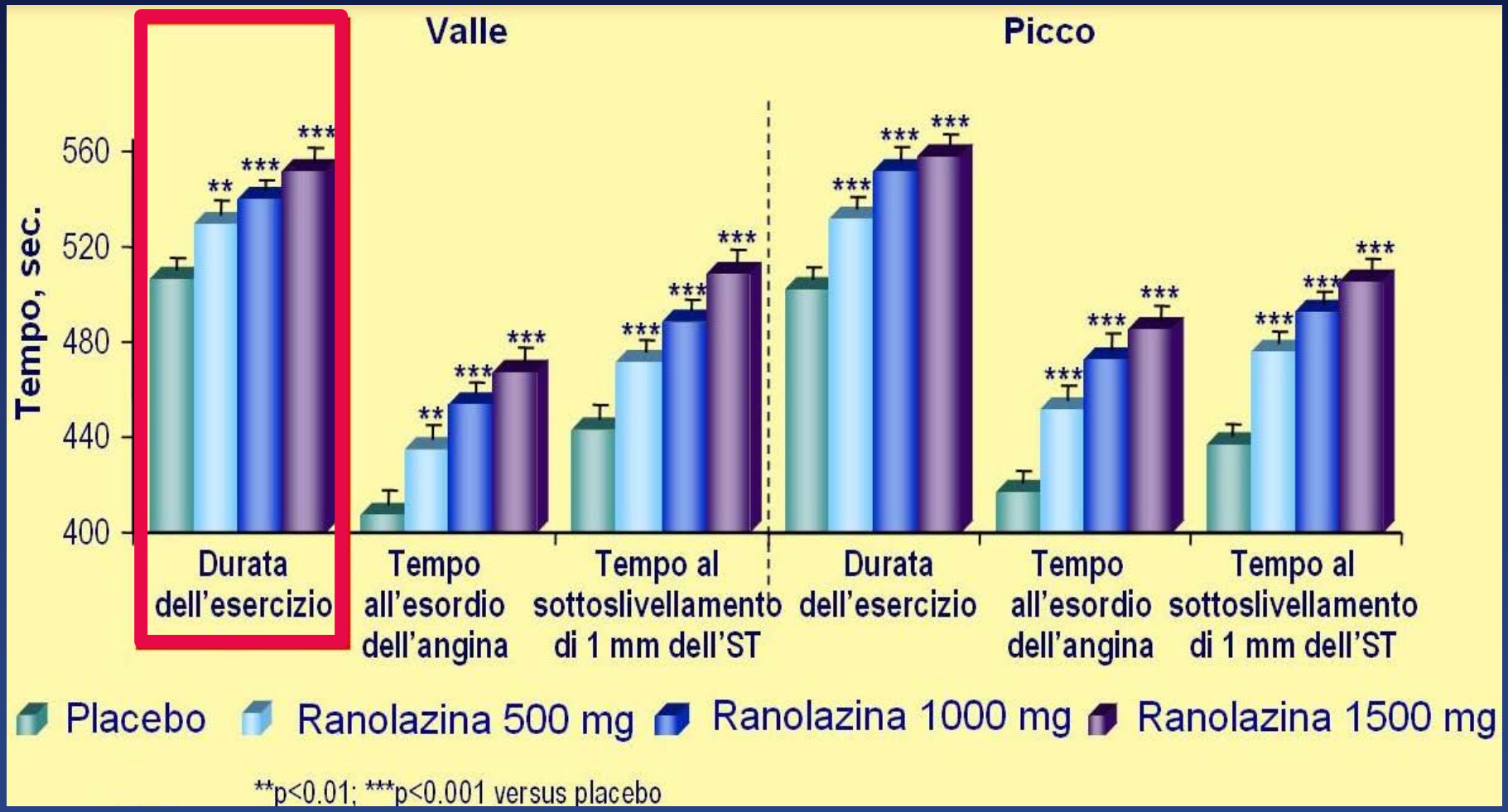

**La Ranolazina inibisce l'ingresso tardivo di $Na^+$ nel miocardiocita in modo frequenza, voltaggio e concentrazione-dipendente**

*Stone PH. Cardiology Clinics. 26, 4: 603-614 (2008)*

# RANOLAZINA e cardiopatia ischemica

Studio MARISA
Studio CARISA
Studio ERICA
Studio Merlin – TIMI 36
Studio MERLIN
Studio ROLE

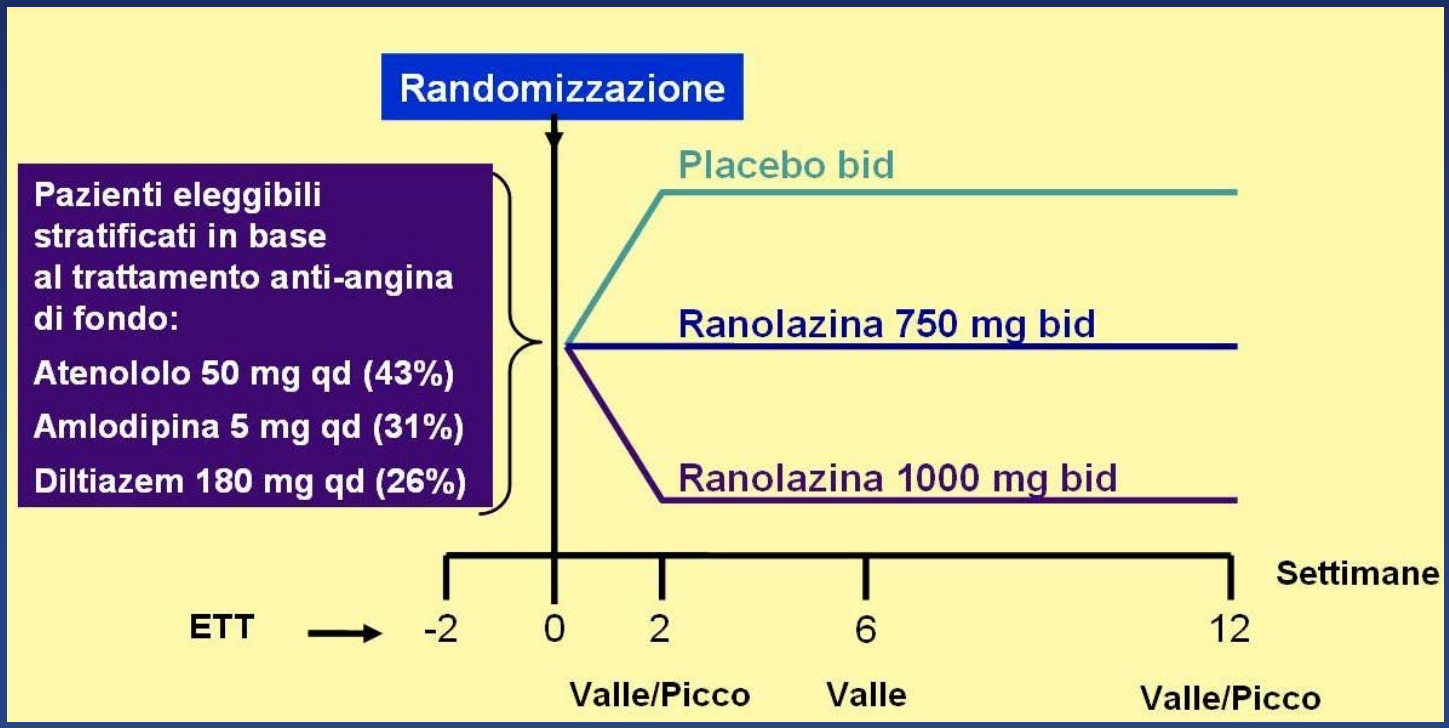
# MARISA: Monotherapy Assessment of Ranolazine In Stable Angina




*Chaitman, JACC 2004; 43: 1375 – 82*

# CARISA: Combination Assessment of Ranolazine In Stable Angina

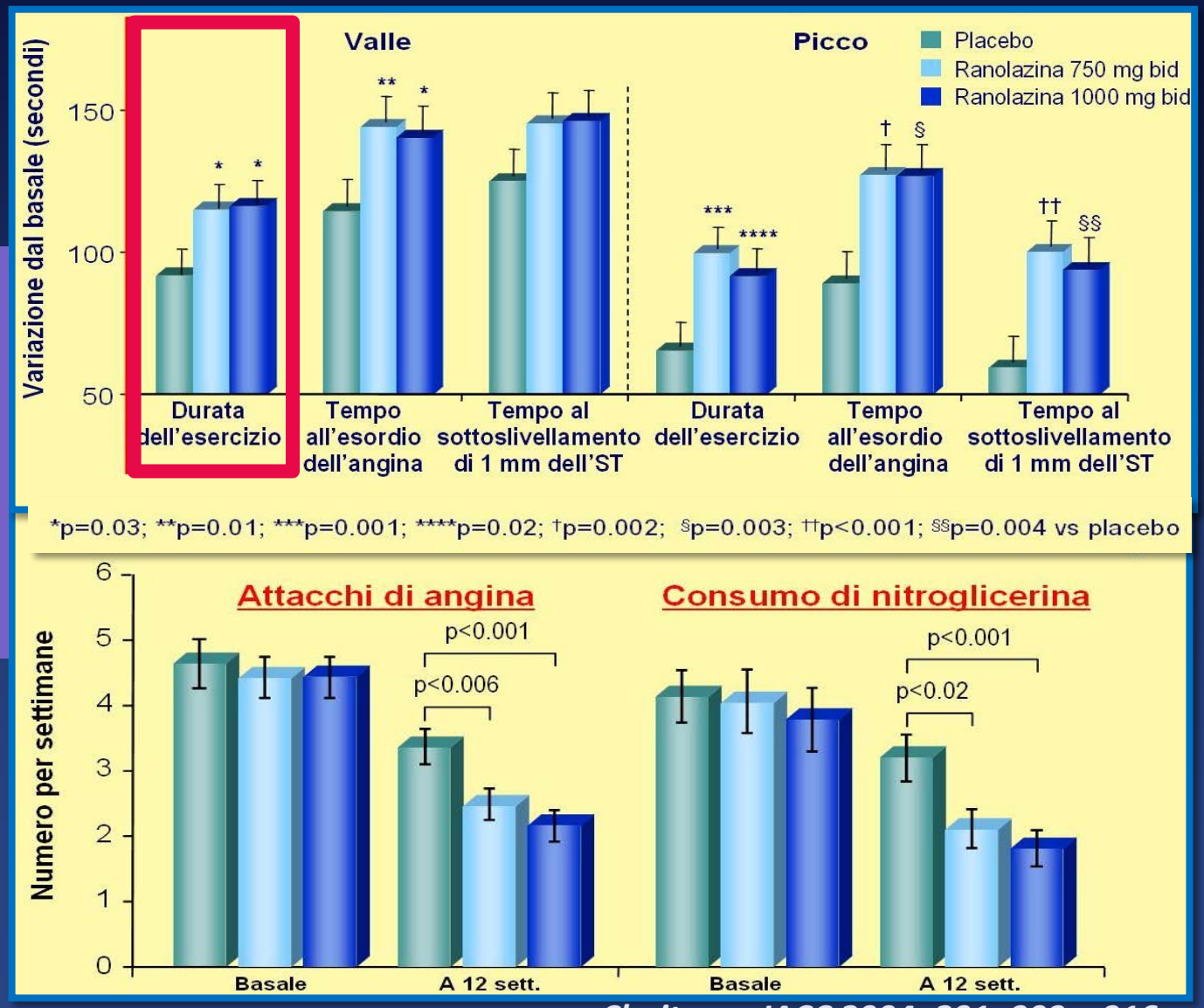
- Disegno: randomizzato, doppio cieco, placebo-controllato, per gruppi paralleli
- Popolazione: 823 pazienti con angina da sforzo da almeno 3 mesi già in trattamento con atenololo, diltiazem o amlodipina
- Obiettivo: efficacia di Ranolazina in presenza di terapia antischemica ottimizzata
- End point primario: durata dell'esercizio alla concentrazione a valle di Ranolazina




*Chaitman JACC 2004; 291: 303 – 316*

# CARISA: Combination Assessment of Ranolazine In Stable Angina

Ranolazina ha ampliato la soglia anginosa in pazienti già trattati con dosi ottimizzate di beta bloccante e Ca antagonista

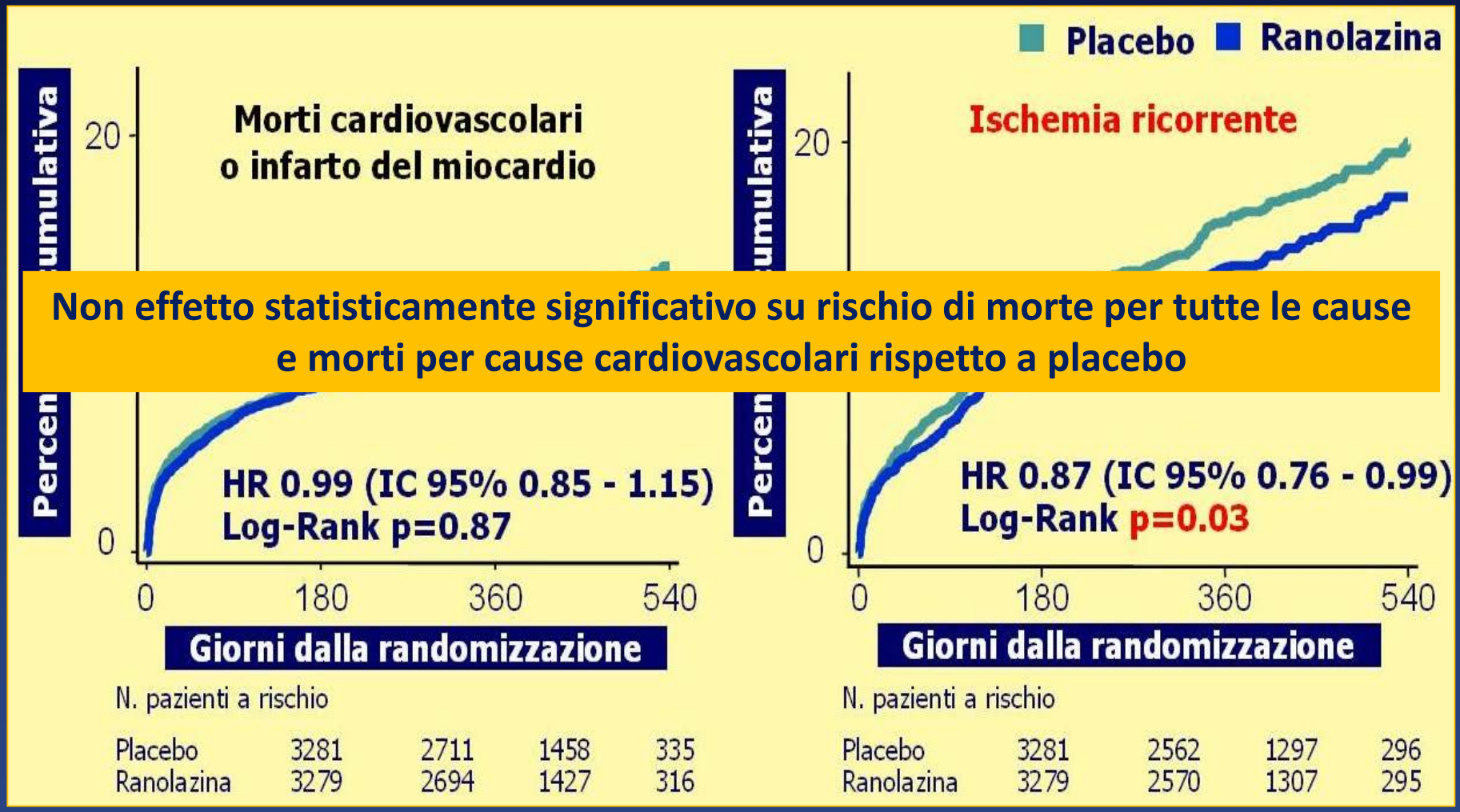



*Chaitman JACC 2004; 291: 303 – 316*

# **MERLIN TIMI 36:** Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes

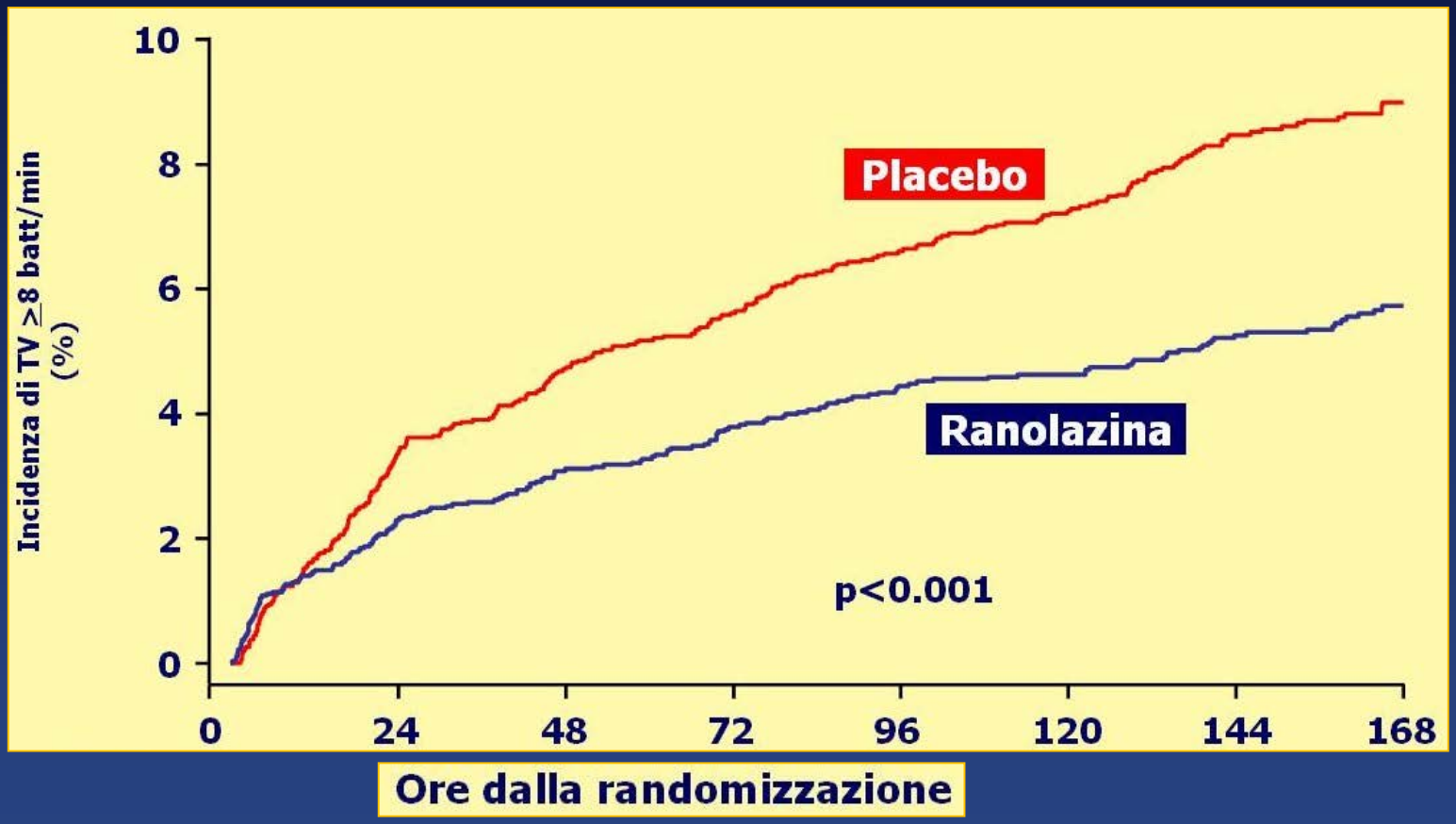

**Lo studio MERLIN TIMI 36 ha valutato per la prima volta l'efficacia e la sicurezza del trattamento con Ranolazina in pazienti affetti da sindrome coronarica acuta senza sopraslivellamento del tratto ST (UA/NSTEMI)**

# **MERLIN TIMI 36:** Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes




*Morrow JAMA 2007; 297: 1775 – 1783*

# **MERLIN TIMI 36:** Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes




**La terapia con Ranolazina ha significativamente ridotto gli episodi di tachicardia ventricolare all'Holter ECG**

# **MERLIN TIMI 36:** Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes

| | Anamnesi positiva per precedente angina | | Anamnesi negativa per precedente angina | | |
|---|---|---|---|---|---|
| Parametro di Outcome | Effetto medio del trattamento (IC 95%) | P | Effetto medio del trattamento (IC 95%) | P | P per l'interazione |
| Frequenza dell'angina (Quest. SAQ) | 3.43 (1.81, 5.05) | <0.001 | 0.33 (-1.50, 2.16) | 0.724 | 0.003 |
| Limitazioni fisiche (SAQ) | 1.79 (-0.07, 3.64) | 0.059 | -1.15 (-3.21, 0.91) | 0.274 | 0.191 |
| Qualità della vita (SAQ) | 2.66 (1.19, 4.13) | <0.001 | 0.72 (-0.85, 2.29) | 0.369 | 0.022 |
| Soddisfazione per la terapia (SAQ) | 1.46 (0.46, 2.46) | 0.004 | -0.01 (-1.09, 1.07) | 0.990 | 0.022 |
| Componente fisica del SF-12 | 0.80 (0.04, 1.57) | 0.040 | 0.35 (-0.45, 1.16) | 0.387 | 0.326 |
| Componente mentale del SF.-12 | 0.91 (0.17, 1.64) | 0.016 | -0.24 (-1.02, 0.54) | 0.551 | 0.012 |
| Score Dispnea | -0.12 (-0.22, -0.03) | 0.013 | 0.03 (-0.08, 0.14) | 0.612 | 0.171 |
| EuroQol-5D | 0.015 (0.003, 0.026) | 0.011 | 0.004 (-0.008, 0.017) | 0.497 | 0.144 |

**Effetti del trattamento con Ranolazina vs placebo dopo 12 mesi di terapia sulla qualità di vita (MERLIN TIMI 36 QOL )**

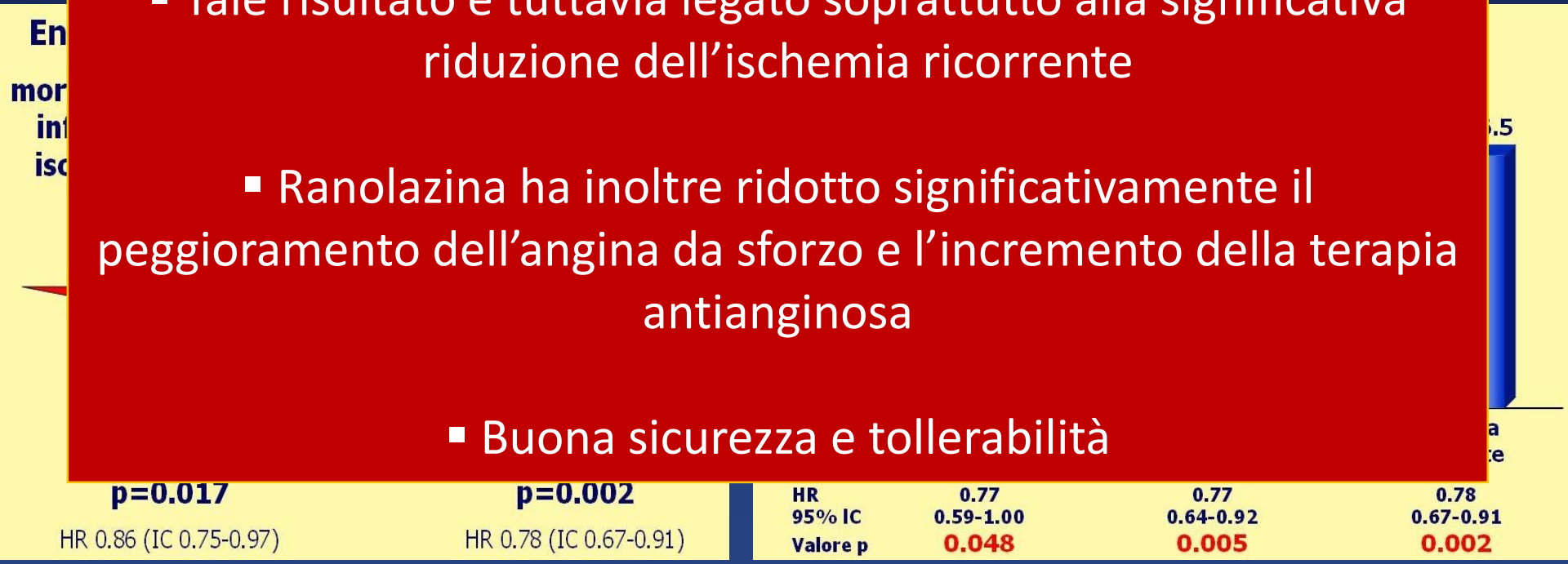
# **MERLIN TIMI 36:** Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST elevation acute coronary syndromes

- Ranolazina ha mancato l'End Point primario di riduzione degli eventi CV maggiori
- Ranolazina ha significativamente ridotto gli episodi di ischemia ricorrente e le tachiaritmie post infartuali
- Buon profilo di sicurezza e tollerabilità

*Successivamente una sottopopolazione di questo studio è stata randomizzata e trattata nello studio MERLIN*

# Studio MERLIN:

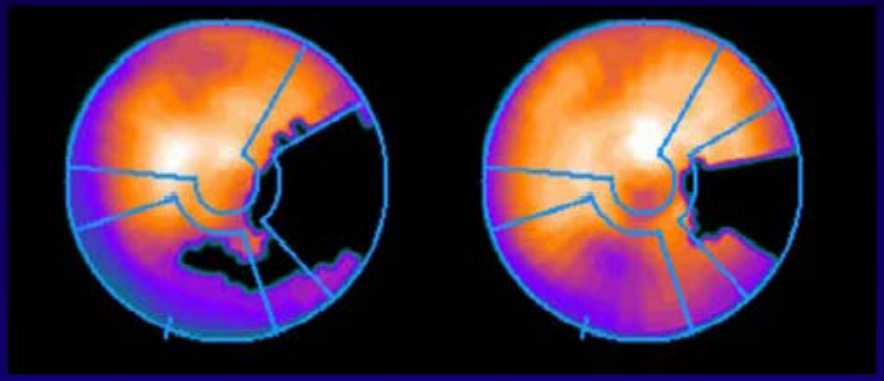
- **Disegno**: randomizzato, doppio cieco, placebo controllato, gruppi paralleli
- Ranolazina ha significativamente ridotto l'end point primario composito (morte CV, IMA, ischemia ricorrente)
- Tale risultato è tuttavia legato soprattutto alla significativa riduzione dell'ischemia ricorrente
- Ranolazina ha inoltre ridotto significativamente il peggioramento dell'angina da sforzo e l'incremento della terapia antianginosa
- Buona sicurezza e tollerabilità



# Efficacia di Ranolazina nel migliorare la perfusione miocardica

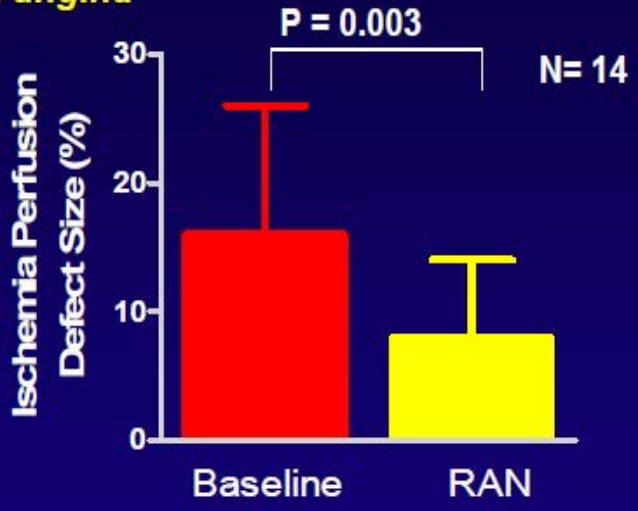
## Myocardial Perfusion Imaging in Patients with Coronary Artery Disease Treated with Ranolazine

***Exploratory study in 20 patients with CAD and angina***



**Before Ranolazine**
**PDS* = 25% of LV**
**Peak HR = 142 bpm**

**After Ranolazine**
**PDS* = 11% of LV**
**Peak HR = 142 bpm**



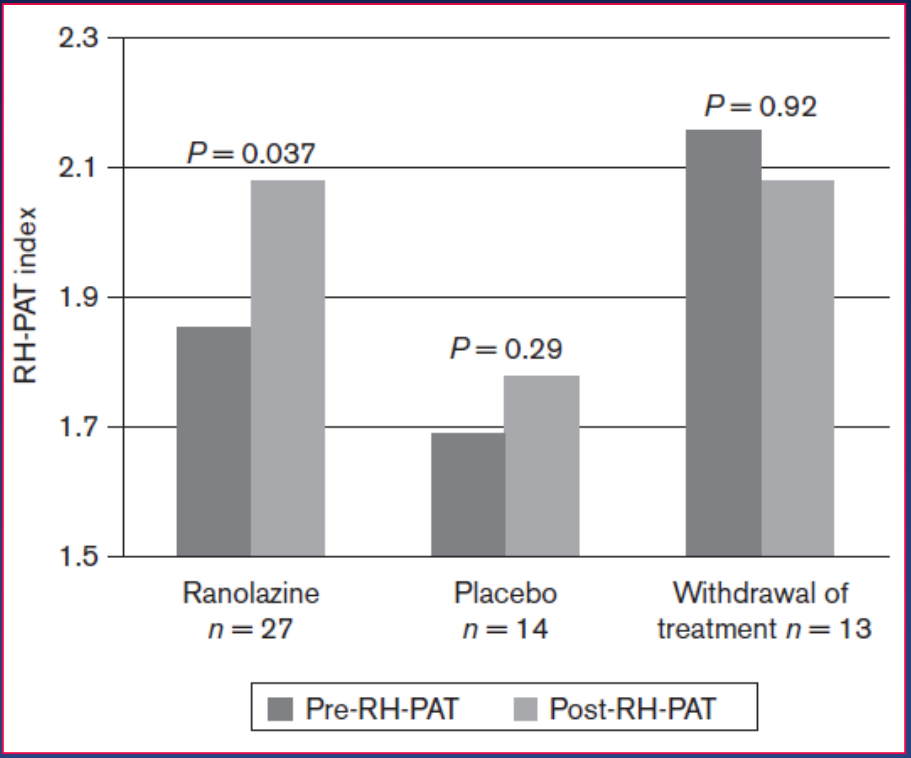

- Treadmill exercise time increased by 32 seconds (p=0.017, n=20)
- Angina reduced in 15 patients (75%) after ranolazine treatment.
- Improvement in the extent and severity of ischemia was noted in 14 patients (70%). Among these patients, ischemia PDS (% LV) decreased from 16 ± 10 to 8 ± 6 (p=0.003, n=14)
- Among the 15 patients with reduced angina, 11 (73%) had an improvement in perfusion.

Venkataraman R, et al. *JACC Imaging* 2009 (in press); Courtesy of Ami Iskandrian, MD

***PDS: perfusion defect size**

# RANOLAZINA e funzione endoteliale?

## Ranolazine improves endothelial function in patients with stable coronary artery disease




| Variable | Pretreatment | Posttreatment | *P* value |
|---|---|---|---|
| EDV RH-PAT index | 1.85 ± 0.42 | 2.08 ± 0.57 | 0.037 |
| EIV RH-PAT index | 1.46 ± 0.5 | 1.45 ± 0.50 | 0.86 |
| ESR (mm/h) | 26 ± 32 | 30 ± 74 | 0.72 |
| Fibrinogen (mg/dl) | 328 ± 99 | 323 ± 108 | 0.50 |
| Nitric oxide (μmol/l) | 22 ± 7 | 25 ± 9 | 0.15 |
| ADMA (μmol/l) | 0.66 ± 0.12 | 0.60 ± 0.11 | 0.02 |
| Hs-CRP (mg/dl) | 0.4 ± 0.8 | 0.3 ± 0.61 | 0.05 |
| HgbA1c (%) | 8.37 ± 2.5 | 7.86 ± 1.7 | 0.13 |
| LDL (mg/dl) | 74 ± 21 | 77 ± 23 | 0.42 |
| HDL (mg/dl) | 48 ± 12 | 49 ± 13 | 0.47 |

*N* = 27. Values represented as mean ± SD.
ADMA, asymmetric dimethylarginine; EDV, endothelium-dependent vasodilatation (flow-mediated); EIV, endothelium-independent vasodilatation (nitroglycerin-mediated); ESR, erythrocyte sedimentation rate; HgbA1C, hemoglobin A1C; Hs-CRP, high-sensitivity C-reactive protein; RH-PAT, reactive hyperemia peripheral arterial tonometry.
*P* values are calculated by Wilcoxon's signed rank test.

**Deshmukh SH et al, Coronary Artery Disease 2009**

# Revisione delle evidenze sull'utilizzo di Ranolazina nei setting clinici

| Disease State | Studies Supporting Benefit (First Author and Reference No.) | Studies Not Supporting Benefit (First Author and Reference No.) | Guideline Recommendation |
|---|---|---|---|
| Chronic stable angina | Pepine[23]<br>Chaitman[24]<br>Chaitman[25]<br>Stone[26]<br>Rousseau[27]<br>Kosiborod[28] | Thadani[22] | CCS 2009: weak recommendation based on moderate-quality evidence<br>ACCF/AHA 2012: class of recommendation IIa, level of evidence B<br>ESC 2013: class of recommendation IIa, level of evidence B |
| Incomplete revascularization after PCI | | Weisz[31] | Insufficient evidence to support regular use |
| Acute coronary syndrome | | Morrow[32] | Insufficient evidence to support regular use |
| Microvascular coronary dysfunction | Mehta[39]<br>Villano[40]<br>Tagliamonte[41] | Bairey Merz[11] | Conflicting evidence; could consider use in refractory cases |
| New-onset and paroxysmal AF | Koskinas[43]<br>Reiffel[44] | Scirica[5] | Insufficient evidence to support regular use |
| Chronic AF | | De Ferrari[47] | Insufficient evidence to support regular use |
| Postoperative cardiac surgery AF | Tagarakis[51] | Bekeith[53] | Insufficient evidence to support regular use |
| Glycometabolic effect | Chaitman[25]<br>Morrow[32]<br>Eckel[56] | | Insufficient evidence to support regular use |

ACCF indicates American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention.

J Am Heart Assoc. 2016;5:e003196 doi: 10.1161/JAHA.116.003196.

# Angina a coronarie indenni

**Angina vasospastica** → spasmo focale delle arterie coronariche epicardiche prevalentemente nel loro tratto distale per iperreattività delle cellule muscolari lisce della parete vascolare a fattori ad azione vasocostrittrice

**Angina microvascolare** → diversi meccanismi; ipotizzate anomalie funzionali del microcircolo in condizioni di stress per presenza di disfunzione endoteliale che determina un'incrementata risposta a vasocostrittori e ridotta risposta a vasodilatatori

**Table 29** Treatment in patients with microvascular angina

| Recommendations | Class [a] | Level [b] | Ref. [c] |
|---|---|---|---|
| It is recommended that all patients receive secondary prevention medications including aspirin and statins. | I | B | 371 |
| ß-blockers are recommended as a first line treatment. | I | B | 372 |
| Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated. | I | B | 367 |
| ACE inhibitors or nicorandil may be considered in patients with refractory symptoms. | IIb | B | 368 |
| Xanthine derivatives or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs. | IIb | B | 373–375 |

# Angina vasospastica

Chronic preventive treatment of vasospastic angina is mainly based on the use of CCBs.[376] Average doses of these drugs (240–360 mg/day of verapamil or diltiazem, 40–60 mg/day of nifedipine) usually prevent spasm in about 90% of patients. Long-acting nitrates can be added in some patients to improve the efficacy of treatment and should be scheduled to cover the period of the day in which ischaemic episodes most frequently occur, in order to prevent nitrate tolerance. β-Blockers should be avoided, as they might favour spasm by leaving α-mediated vasoconstriction unopposed by β-mediated vasodilation.

# Conclusioni

**La sintomatologia anginosa resta una condizione estremamente frequente nonostante l'ottimizzazione delle tecniche di rivascolarizzazione miocardica**

**I dati in letteratura confermano l'efficacia anti-ischemica ed anti-anginosa dei nuovi farmaci, in particolare di Ranolazina ed Ivabradina in aggiunta o in sostituzione alla terapia antianginosa classica**

**Non effetti emodinamici su pressione e frequenza cardiaca.**

**Buona sicurezza e tollerabilità.**