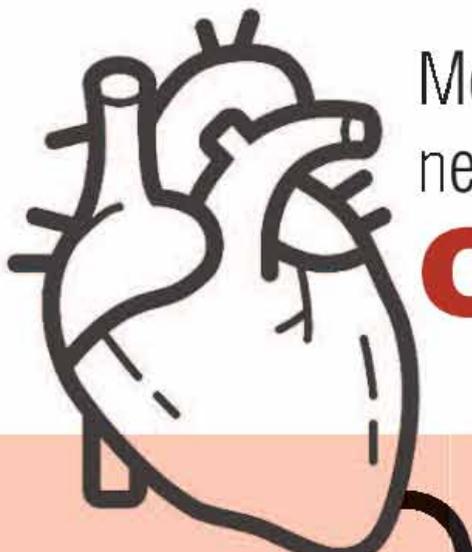


SULLE SPONDE DEL TICINO
SULLE SPONDE DEL TICINO
SULLE SPONDE DEL TICINO



Modelli organizzativi
nella Sanità di oggi

CARDIO Focus



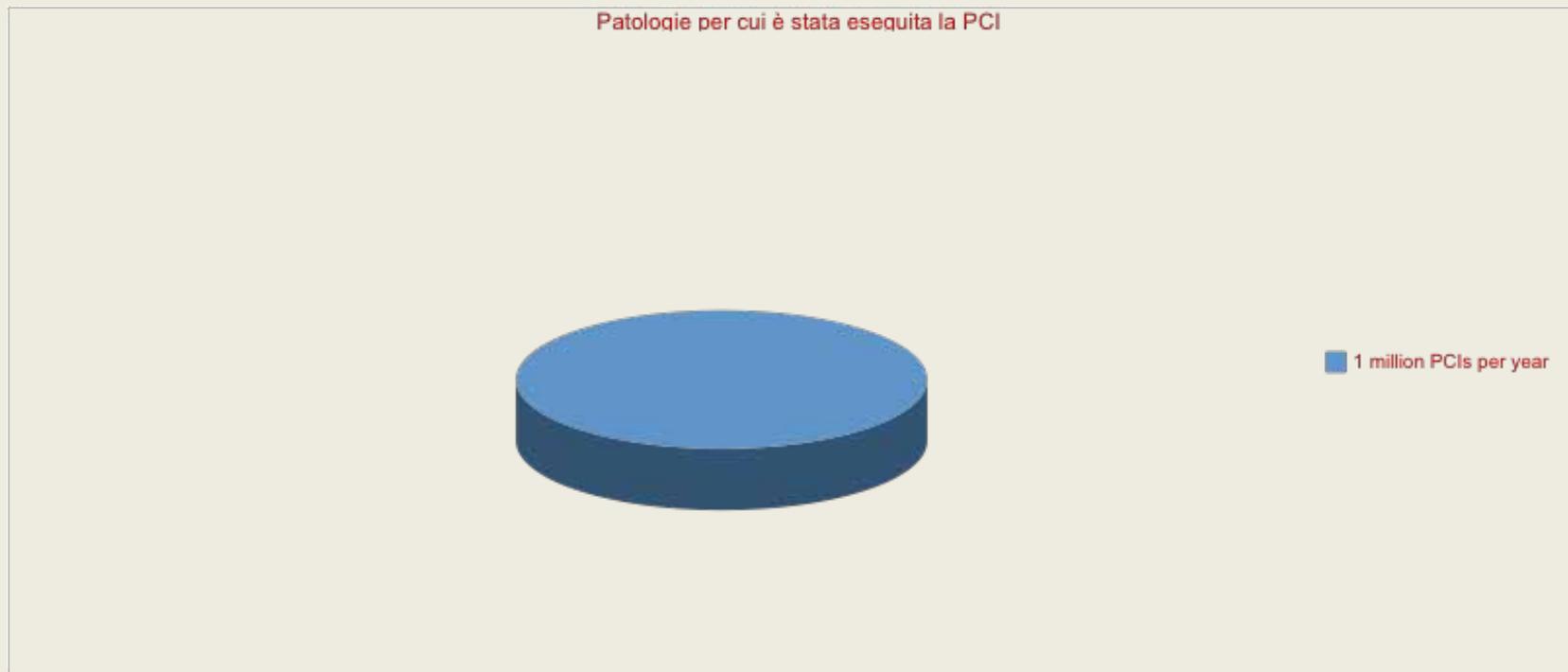
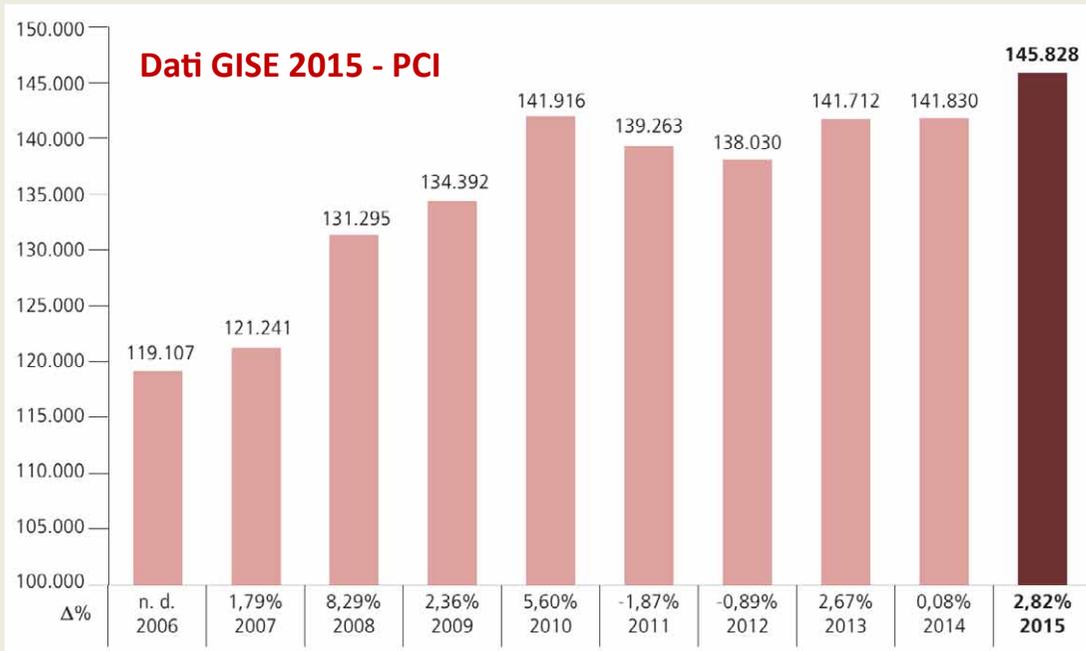
**Terapia della cardiopatia ischemica dopo
rivascolarizzazione incompleta o in pazienti
non rivascolarizzabili**

Alessandro Lupi

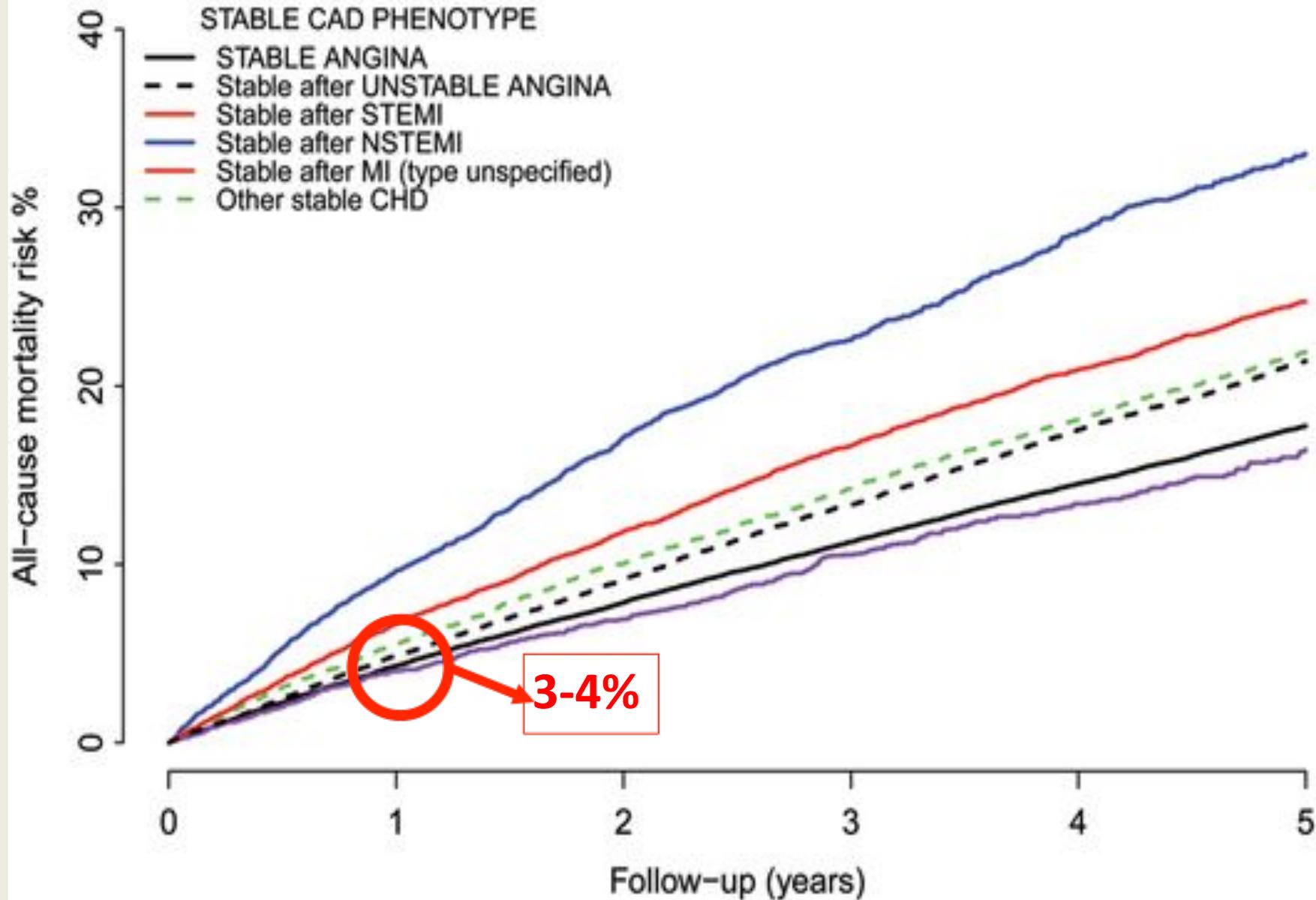
Ospedali riuniti di Domodossola & Verbania



Il peso crescente della PCI nella gestione della CAD stabile: dati GISE 2015

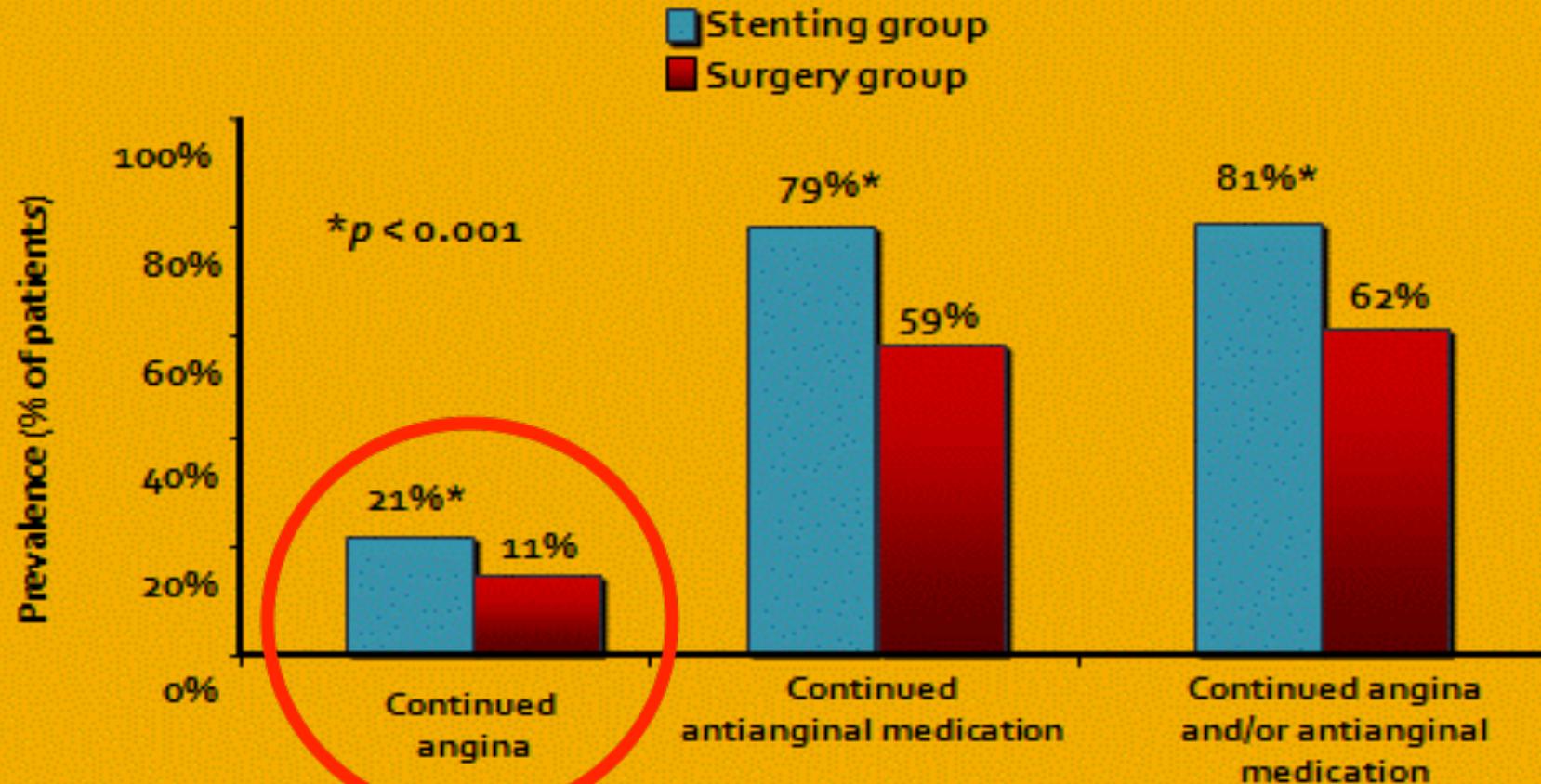


All-cause mortality



Il problema del RISCHIO DELLA PCI: il rischio se la PCI è complessa non è negligibile e non è molto più basso della chirurgia, a fronte di un rischio di mortalità non altissimo del pz con CAD stabile

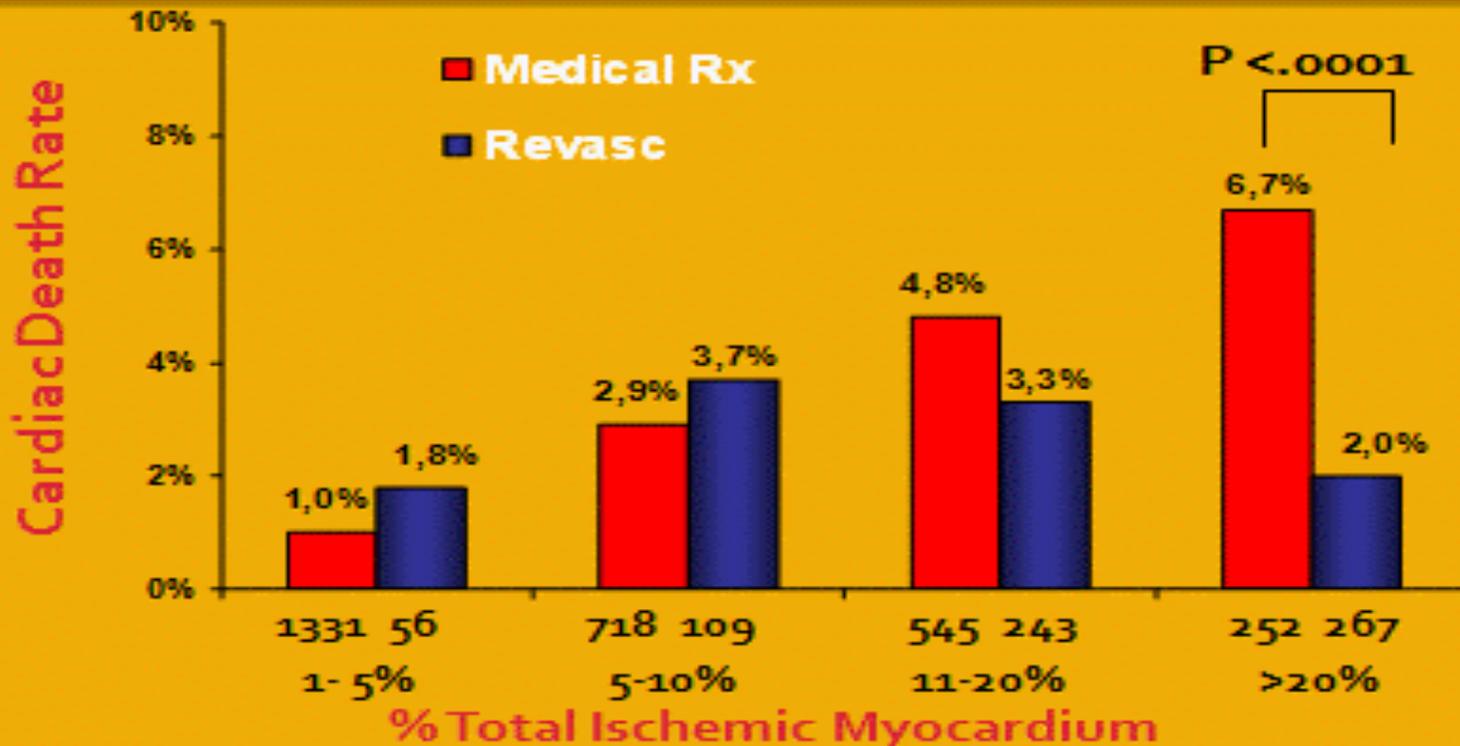
Continued angina and antianginal medication use 12 months after revascularization for angina (n=1205)



Serruys PW, et al. *N Engl J Med.* 2001;344:1117-1124

Il problema dell'ANGINA RESIDUA: la PCI, come anche la chirurgia, non sempre riesce ad affrancare il paziente con CAD dalla terapia medica.

PCI e % miocardio ischemico



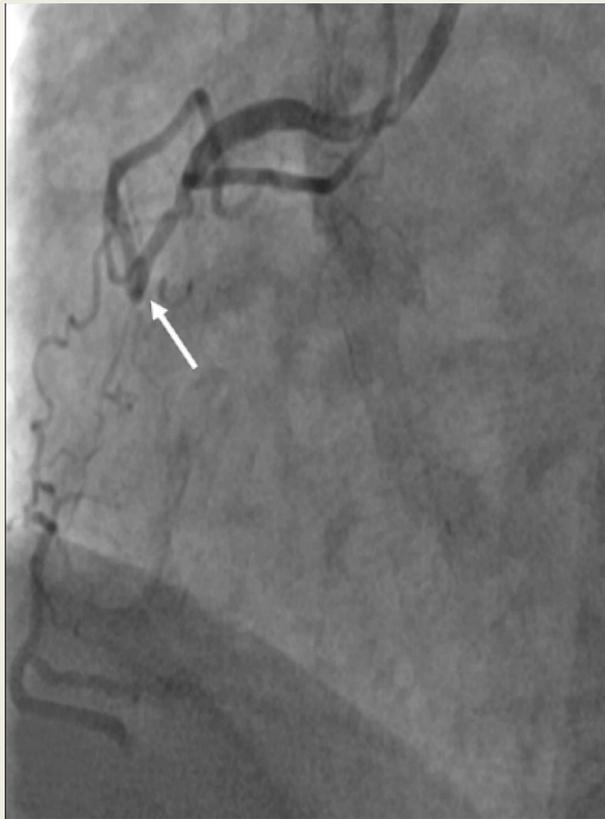
Hachamovitch et al Circulation. 2003; 107:2900-2907.

Lo studio COURAGE

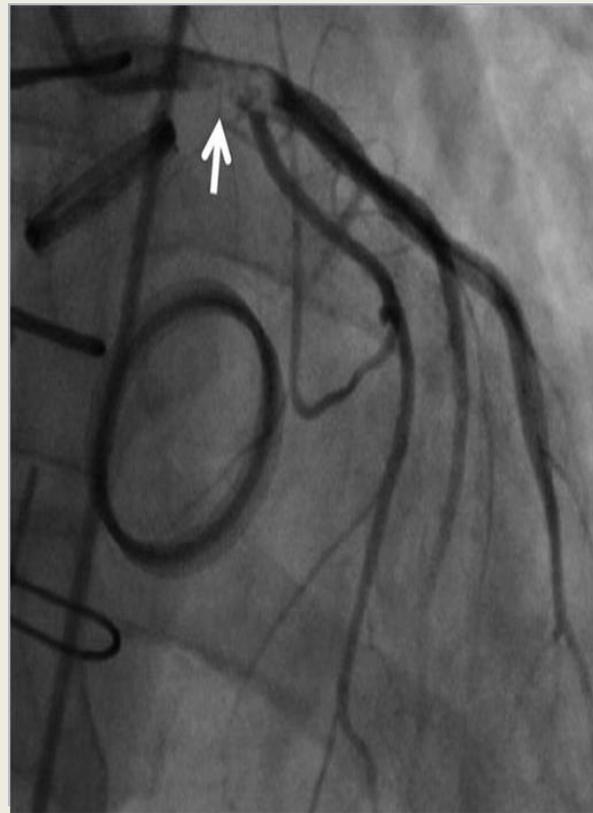


Boden WE et al. *N Engl J Med*. 2007;356:1503-16.

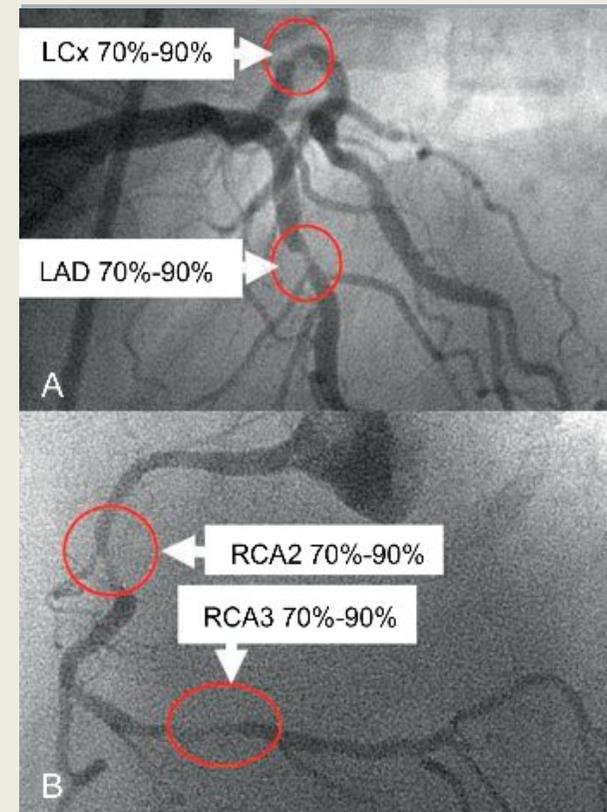
CAD stabile con rivascularizzazione incompleta



**CTO non
disostruibile ma
non candidabile a
BPAC**

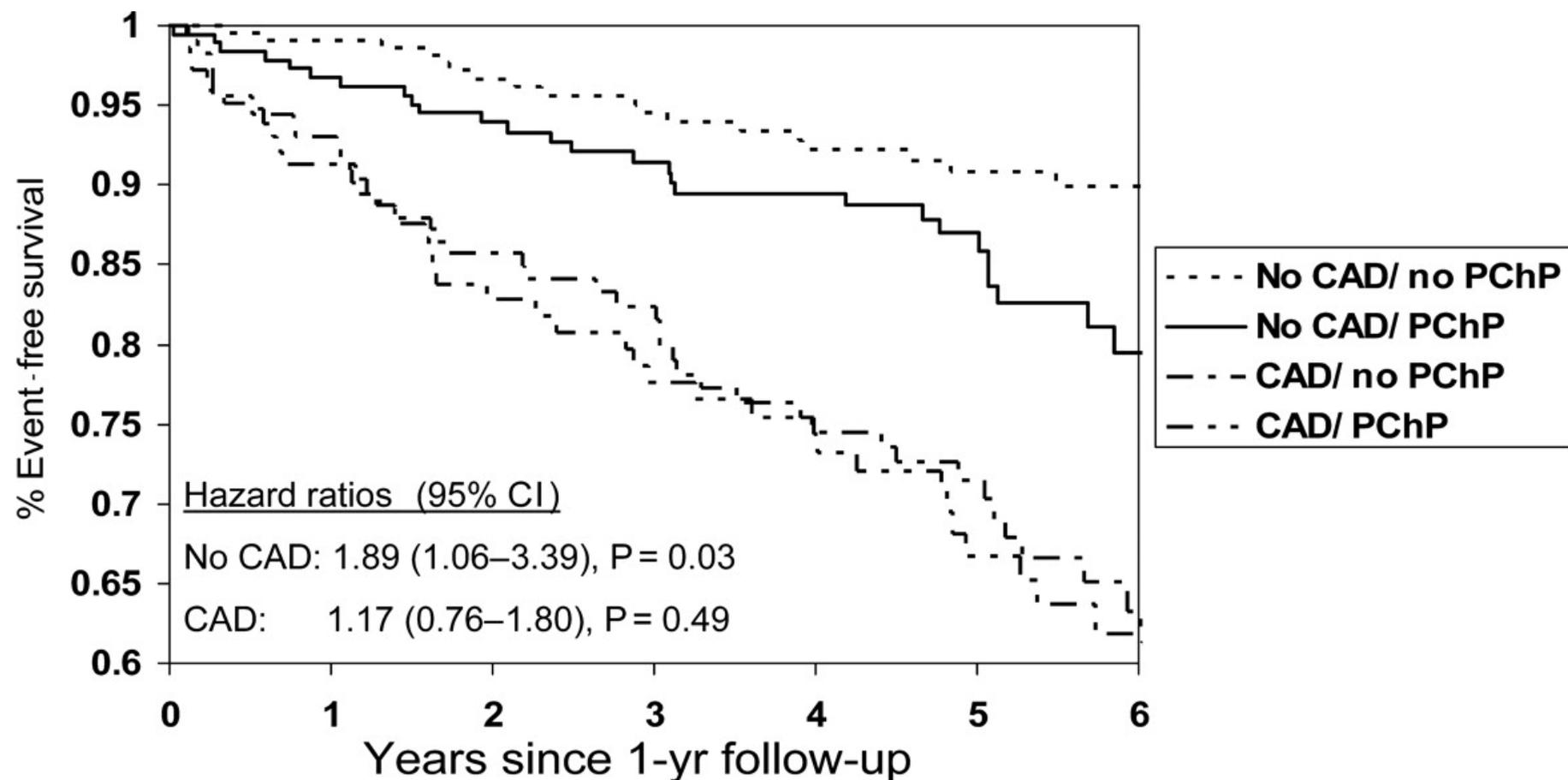


**PCI ad altissimo
rischio o non
possibile, grande
anziano**



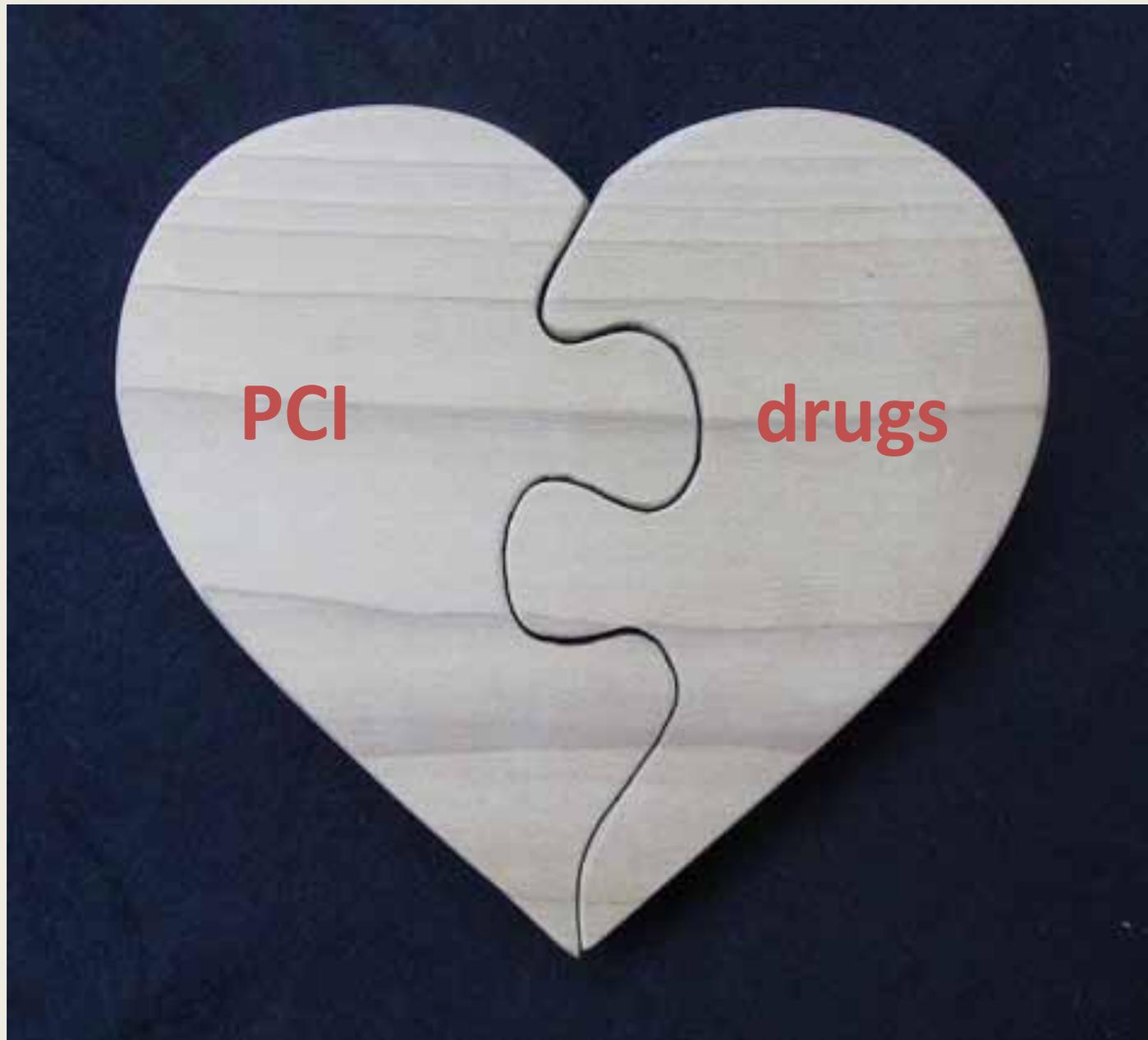
**STEMI, procedure
stadiate**

Event-free survival from CV events by CAD and Persistent Chest Pain.

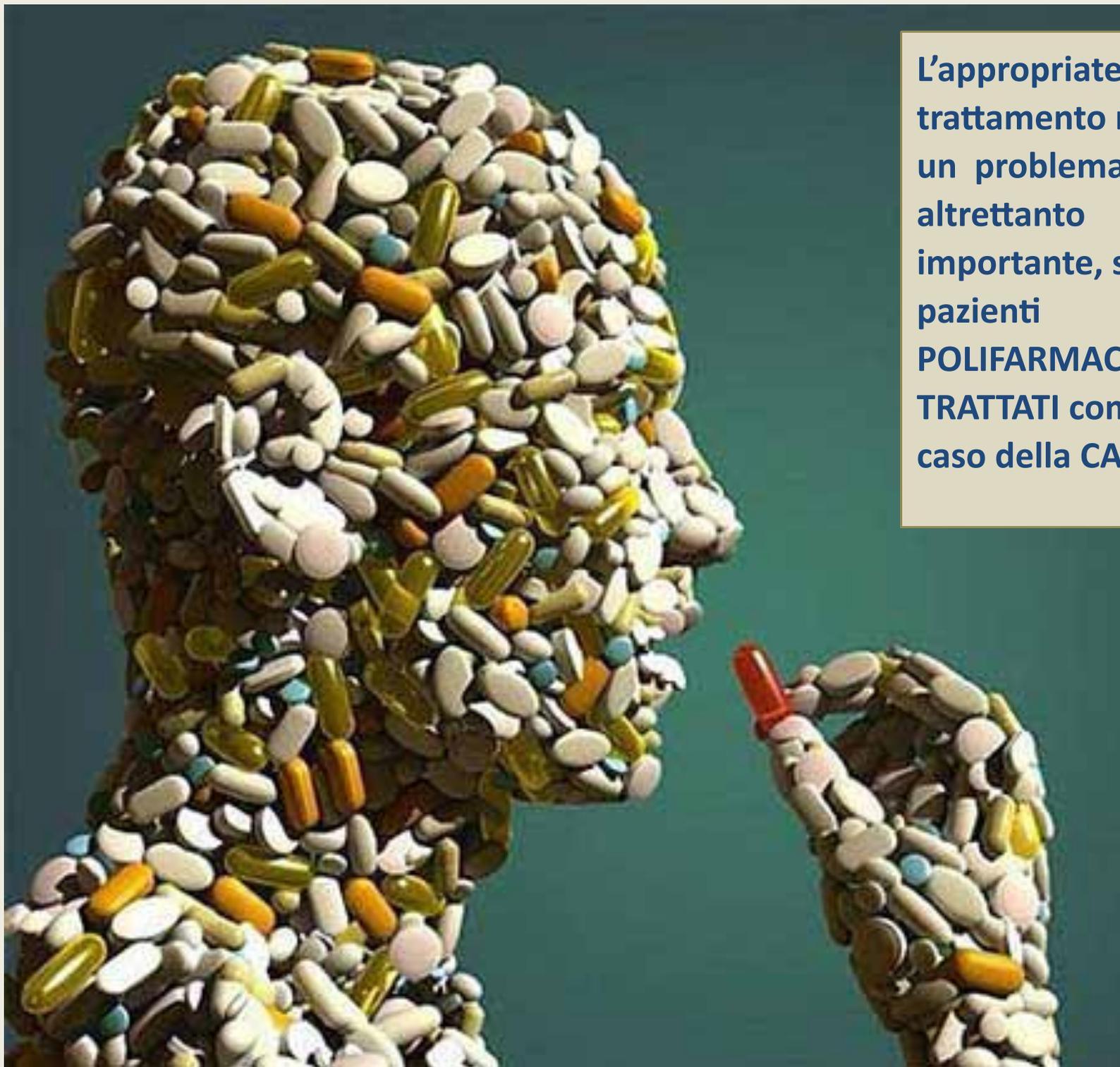


B. Delia Johnson et al. Eur Heart J 2006;27:1408-1415

Il problema della CAD residua emodinamicamente non rilevante ma correlata ad ischemia inducibile & eventi

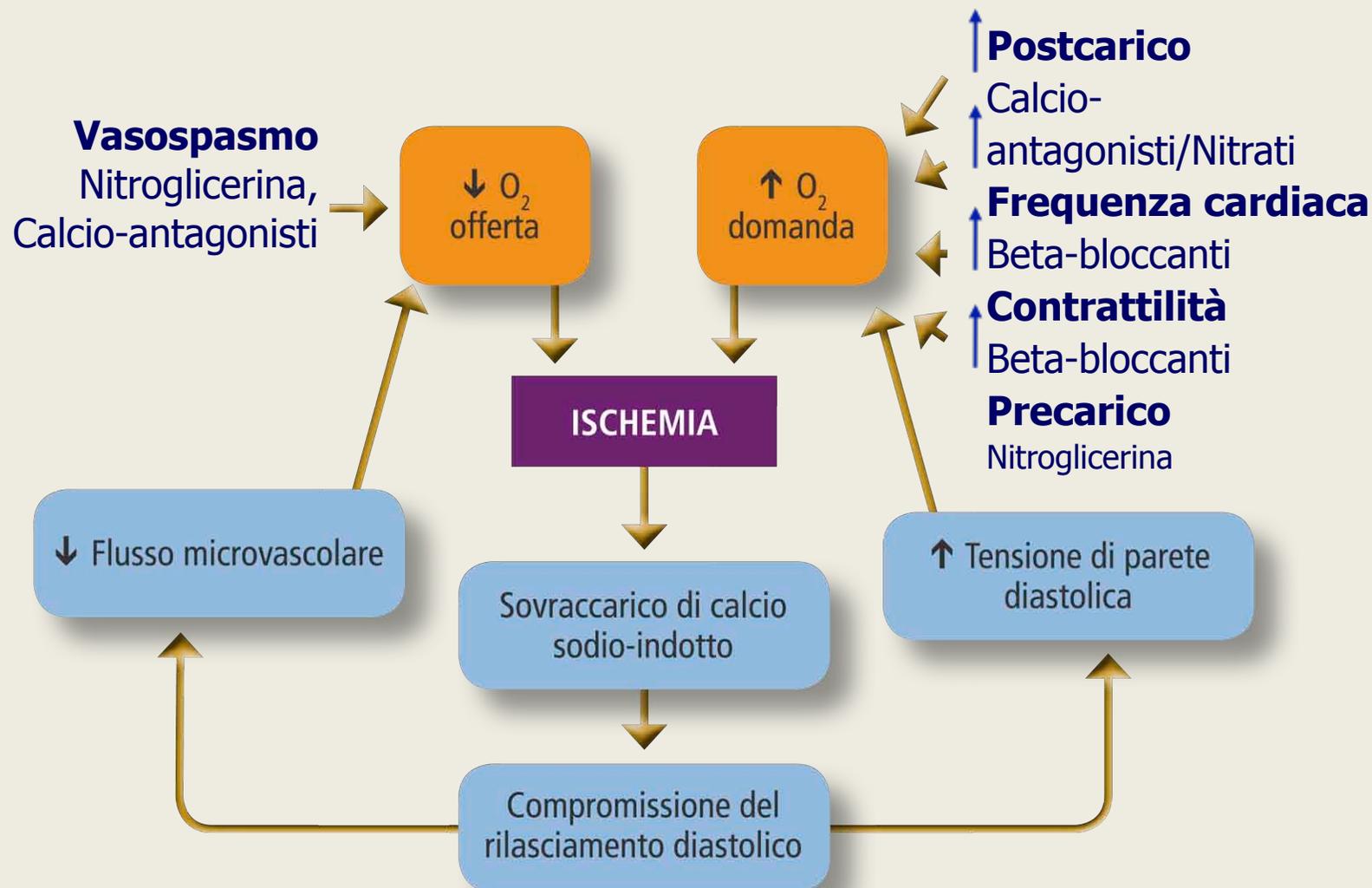


**QUINDI UNA TERAPIA MEDICA RISULTA SPESSO NECESSARIA
ANCHE DOPO PCI DI SUCCESSO**

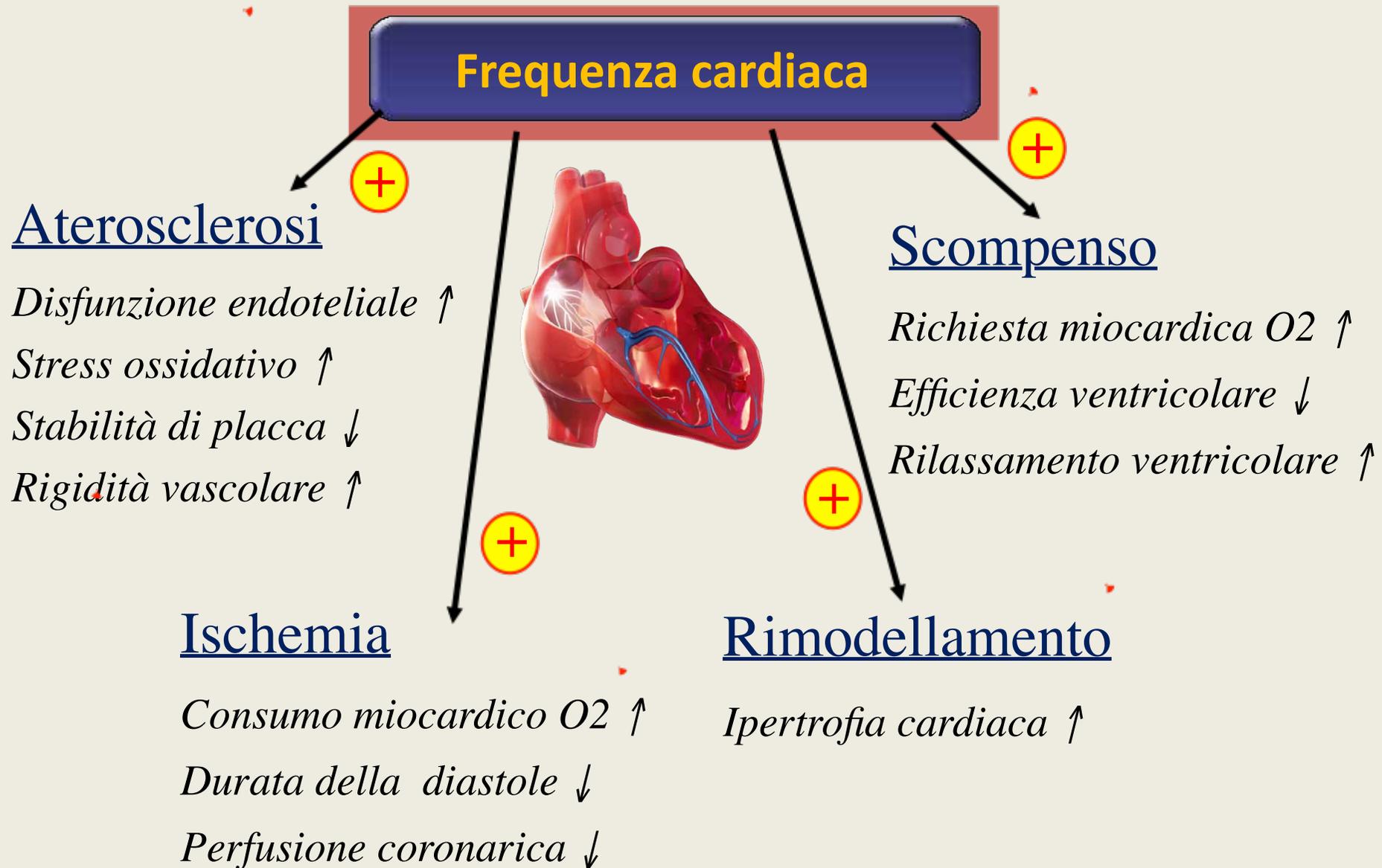


L'appropriatezza del
trattamento medico è
un problema
altrettanto
importante, specie in
pazienti
**POLIFARMACO -
TRATTATI** come nel
caso della CAD

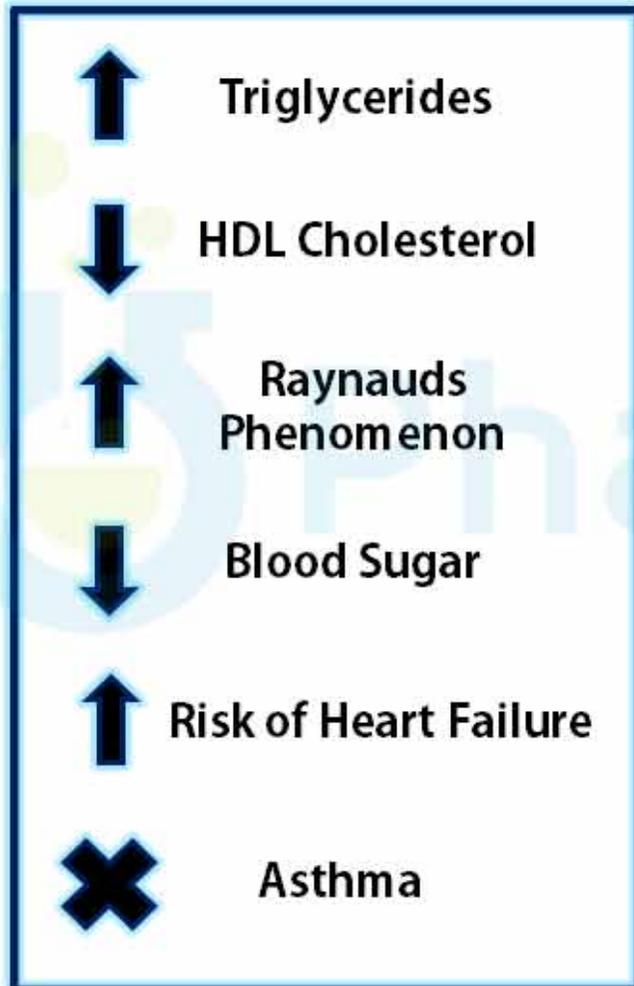
PRINCIPALI DETERMINANTI DEL CONSUMO O₂ MIOCARDICO



EFFETTI FISIOPATOLOGICI SFAVOREVOLI SUL CUORE E SUI VASI DELLA FC ELEVATA



Adverse Effects of Beta Blockers



Precipitate acute heart failure in patients with pre-existing poor left ventricular function.

Sleep disturbances, vivid dreams, and nightmares - particularly with lipophilic beta blockers (propranolol, metoprolol).

Glucagon is used in the treatment of beta blocker overdose, as it increases cardiac contractions and decreases renal vascular resistance.

Nonselective beta blockers may cause bronchospasm, which may be reversed using an anticholinergic - such as tiotropium.

Other adverse effects include fatigue, dizziness, nausea, diarrhoea, cold extremities, and bradycardia.

 @PharmaFactz

APPROCCIO FARMACOLOGICO ALLA FC: i beta-bloccanti

Inibitore ad alta affinità e specificità per il funny channel

- Riduce la pendenza della depolarizzazione diastolica spontanea del NSA

- Prolunga la durata della diastole = diminuisce la Fc

Non influisce su ...

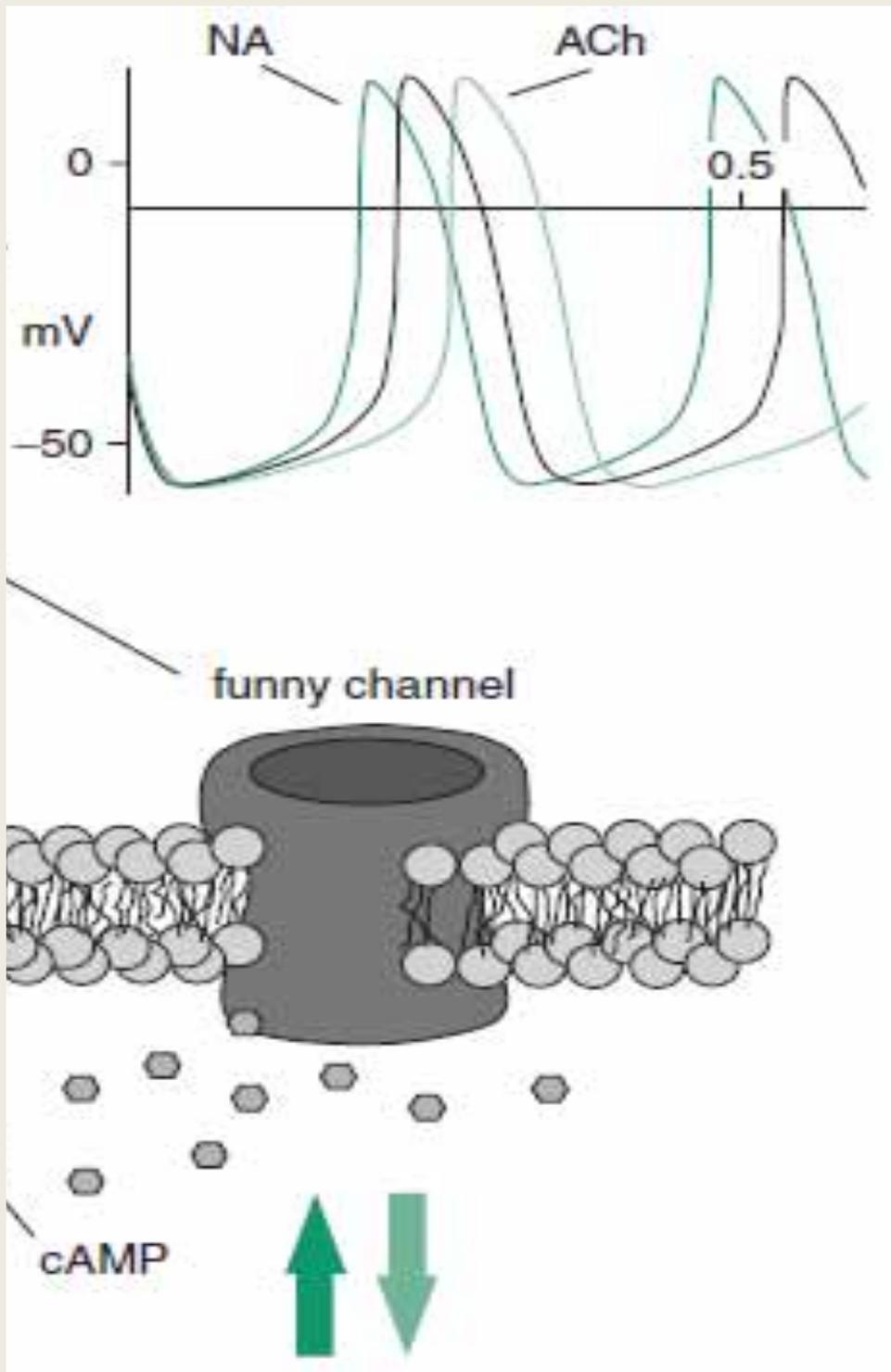
- Ripolarizzazione

- Pressione sanguigna

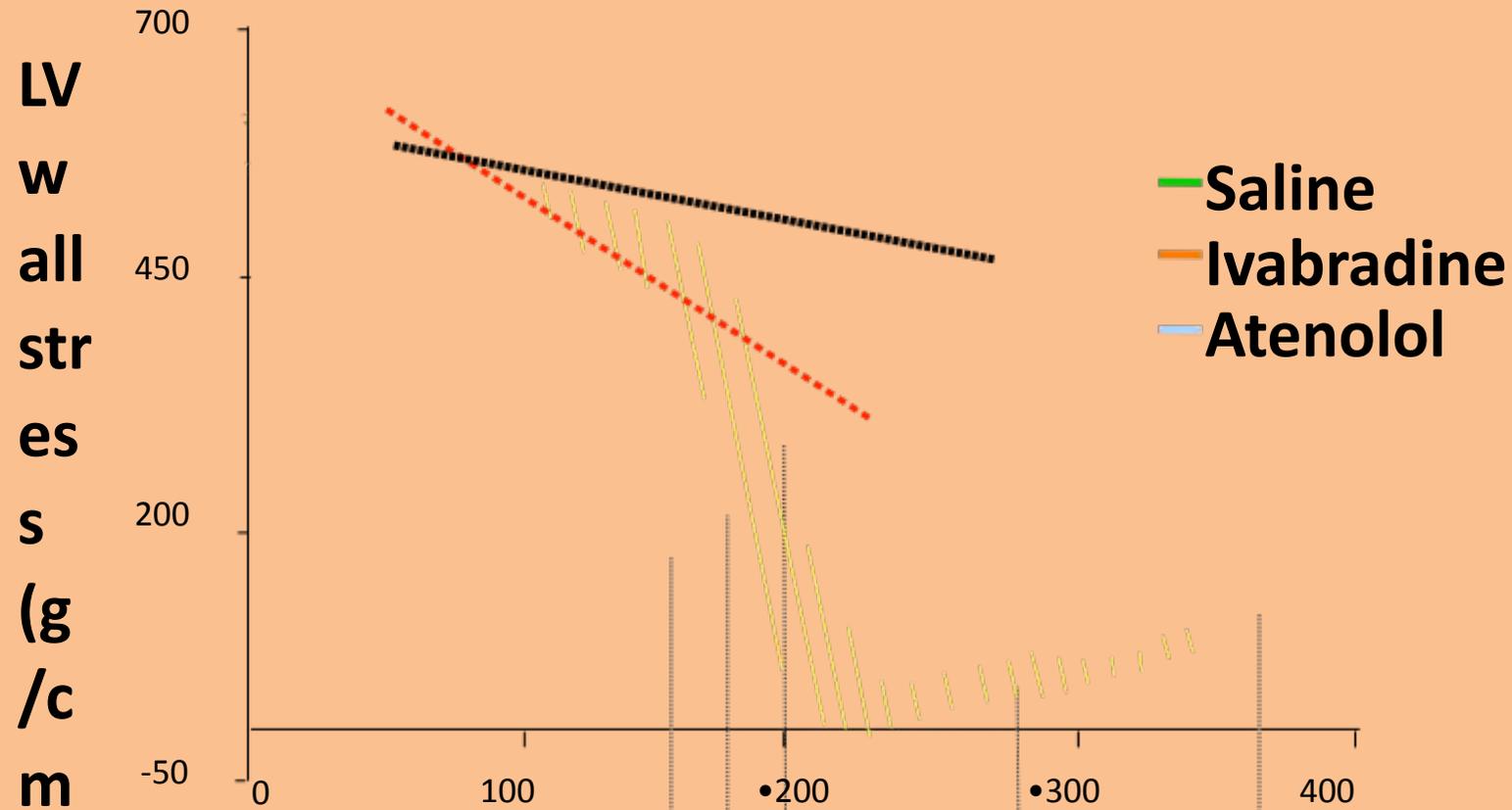
- Contrattilità miocardica

=

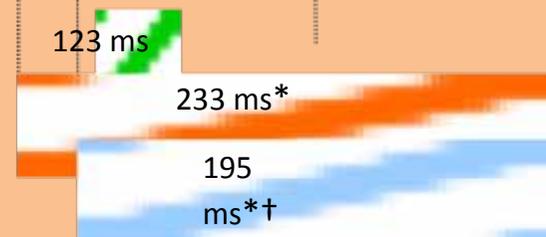
**RIDOTTI EFFETTI
COLLATERALI**



EFFETTI SULLA DIASTOLE DI IVABRADINA E BETA-BLOCCO A CONFRONTO



Il vantaggio di IVR rispetto ai BB non è tanto nell'intervallo R-R, quanto nel rilasciamento diastolico più rapido di circa 40 msec



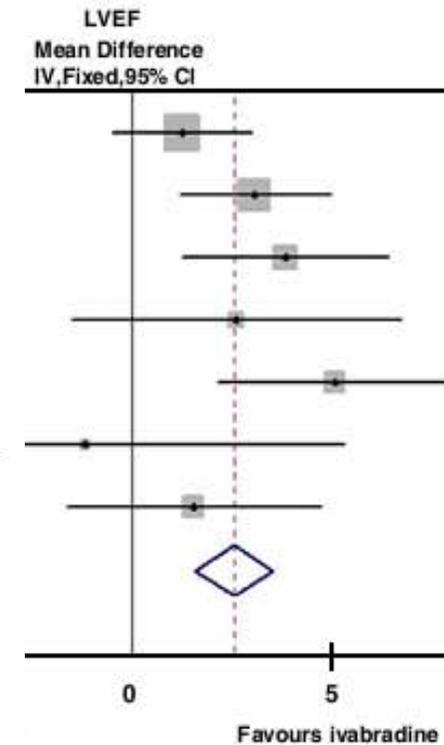
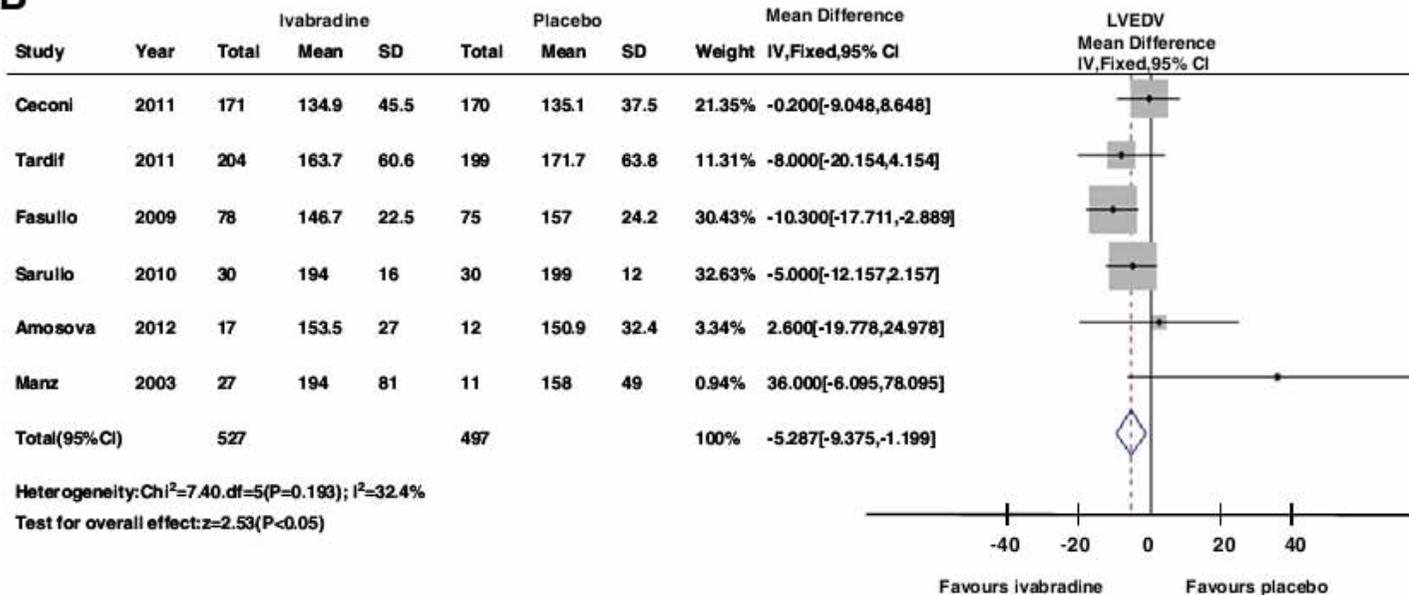
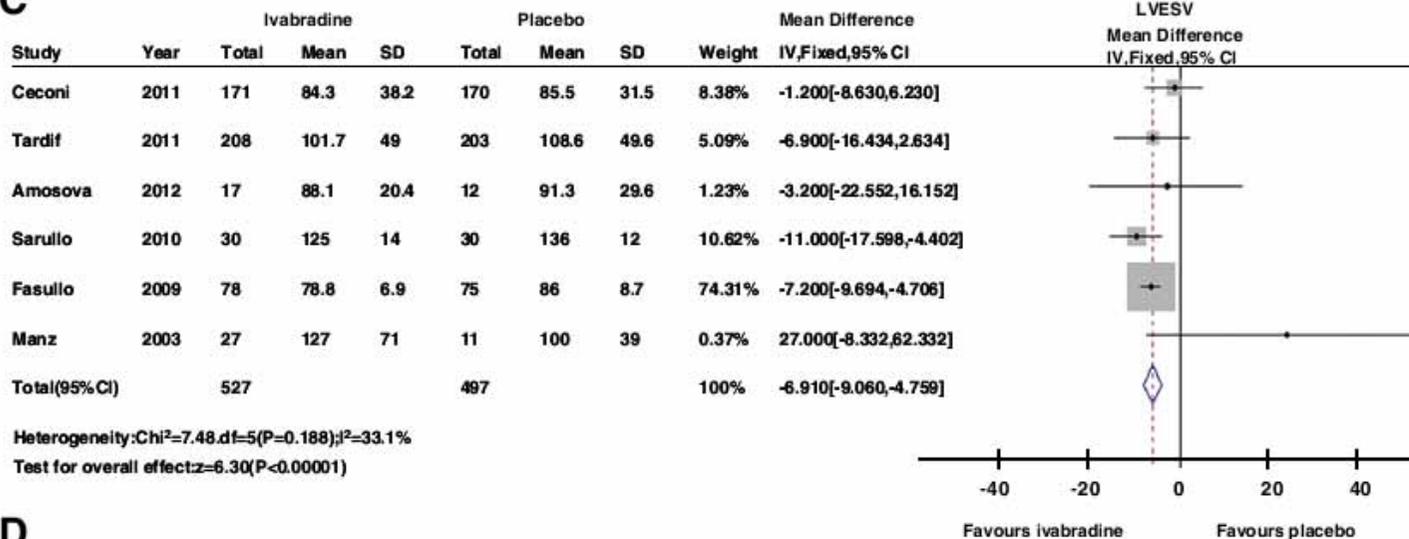
* $P < 0.05$ vs saline
 † $P < 0.05$ vs ivabradine



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

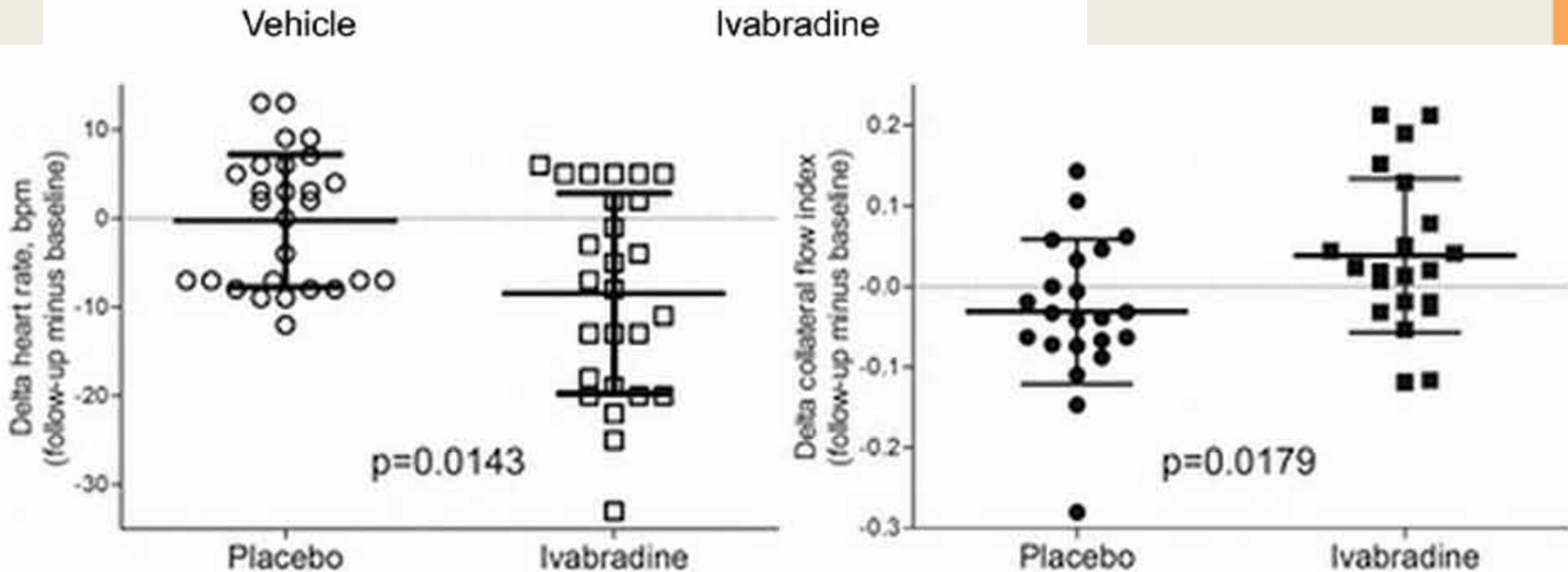
RRR: relative risk reduction

STUDIO BEAUTIFUL: RIDUZIONE DELL'END POINT COMPOSITO NEI PAZIENTI CON FC > 70 BPM

B**C****D**

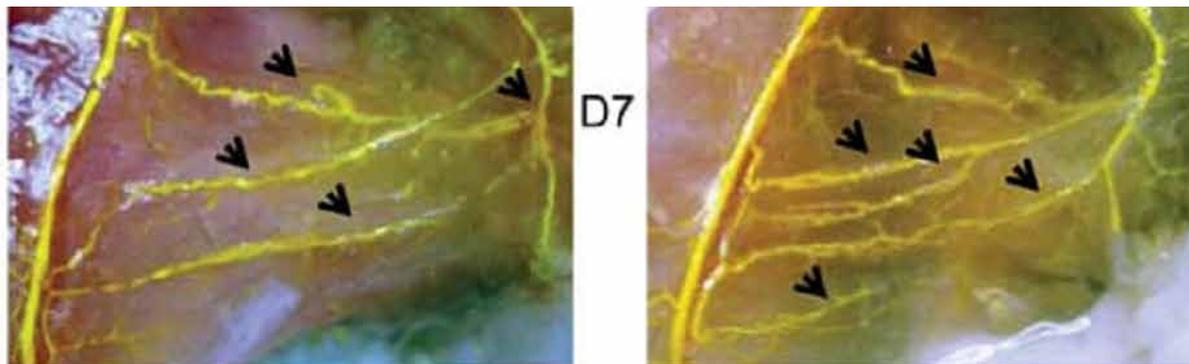
Peng Int J Cardiol 2013

EFFETTI DELL'IVABRADINA SULLA FUNZIONE SISTOLICA VENTRICOLARE SIN



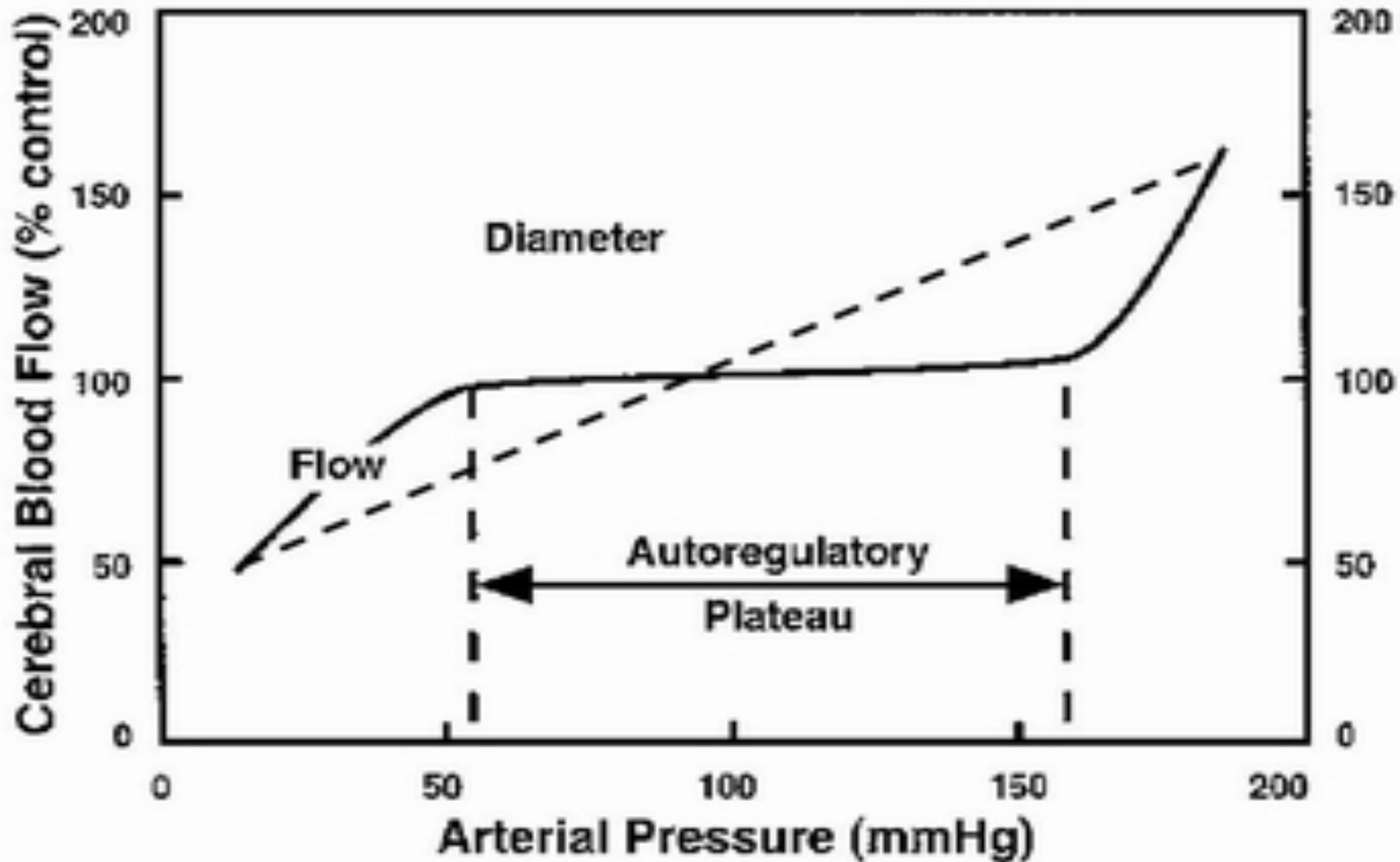
Delta heart rate and delta CFI

Gloekler et al, Heart 2014



Schirmer et al, EHJ 2012

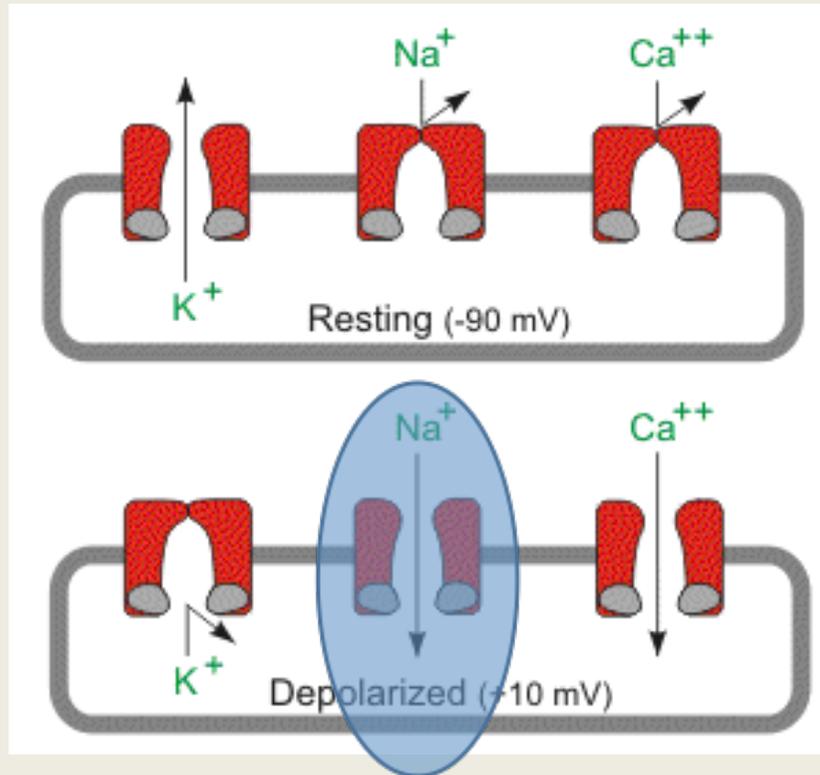
EFFETTO DELL'IVABRADINA SUI COLLATERALI CORONARICI



National Stroke Research Institute

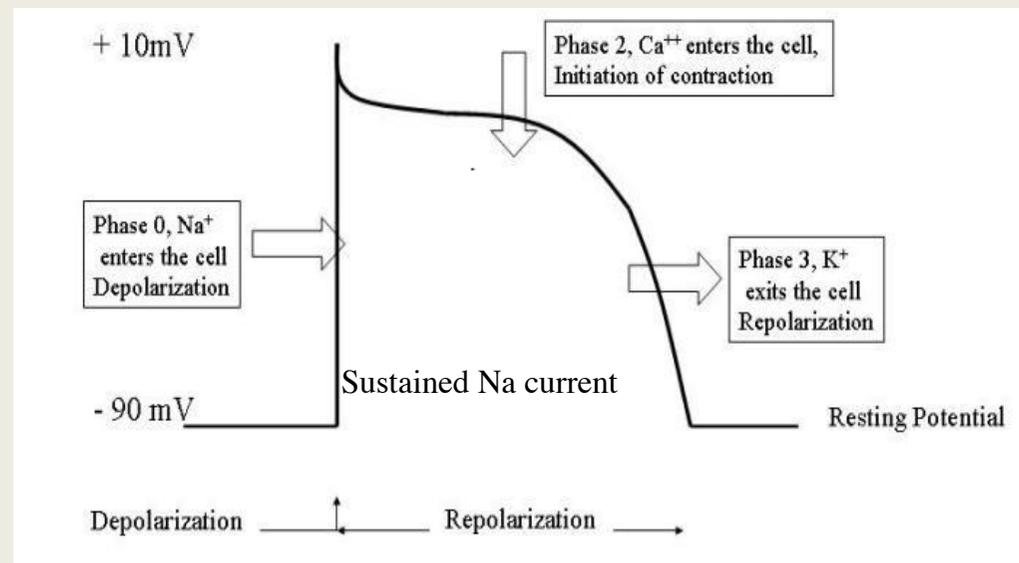
IOTESI: IVABRADINA IN PREVENZIONE PRIMARIA

Ranolazina: allunga late INa



L'ischemia riduce la disattivazione
del canale del Na⁺ in fase 2

Pertanto la corrente del Na⁺ si prolunga nella sua componente tardiva (late INa).



Ranolazina: effetto anti-ischemico

Development of Ischemia

- ↑ O₂ Demand
- Heart rate
 - Blood pressure
 - Preload
 - Contractility

↓ O₂ Supply

Conventional
anti-ischemic
medications

- ✓ β blockers
- ✓ Nitrates
- ✓ Ca⁺⁺ blockers

Ischemia
(Ca⁺⁺ overload)

Ranolazine

Consequences of Ischemia

- Electrical instability
- Myocardial dysfunction
(↓ systolic function/
↑ diastolic stiffness)

Compression
of nutritive
blood vessels

Ranolazina: ritmo & diastole

‡ 35

RANOLAZINE

Decreases Late Sodium Current (I_{Na})

Decreases Calcium Overload*

Improves Relaxation
(Positive Lusitropy)

- ↓ Ca_i^{2+} transient duration
- ↓ Relaxation Time
- ↑ Rate of relax. (↑ LV-dP/dt)
- ↓ LV IVRT

1. Anti-Ischemic
(antianginal, ↑ LV function)

Improves Electrical Stability

- ↓ Prolong APD
- ↓ Afterpotentials (EADs, DADs)
- ↓ Abnormal Automaticity (↓ DD)
- ↓ Disp. of Repolarization (↓ Reentry)

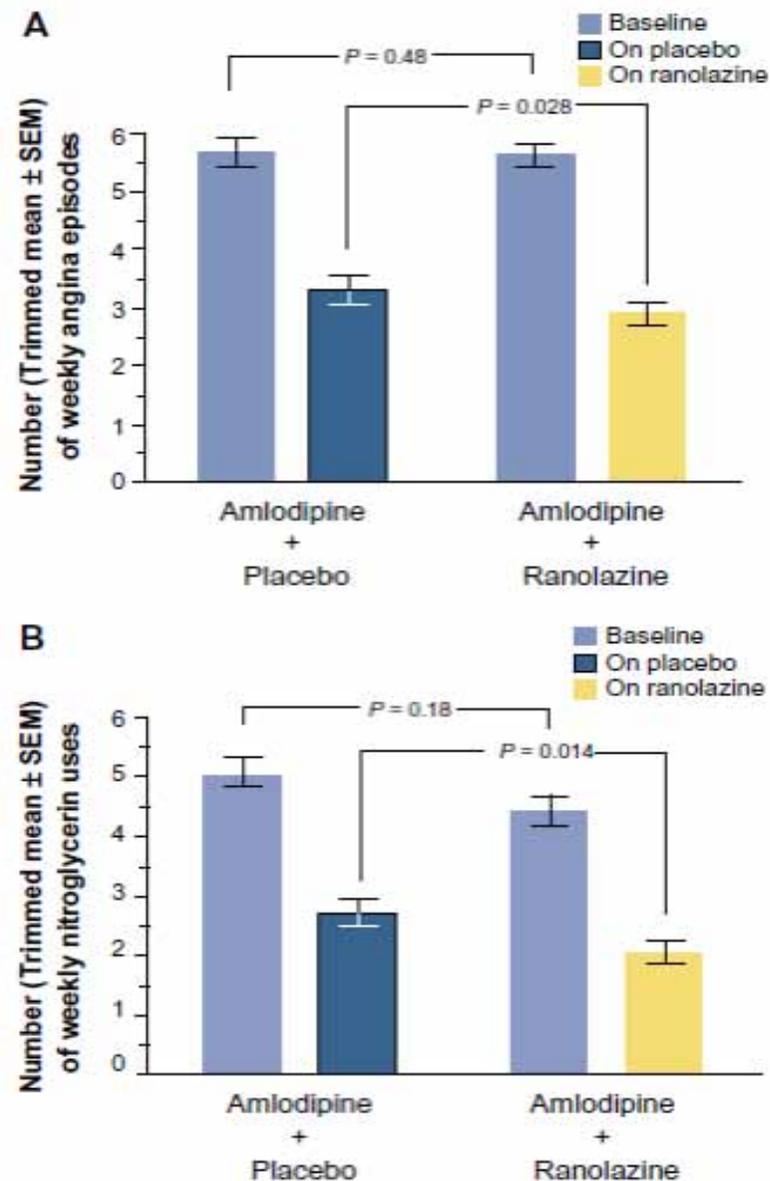
2. Anti-Arrhythmic

Effetto antianginoso: studio ERICA

- 565 patients with symptomatic (>3 angina attacks/week) chronic angina assuming amlodipine 10 mg daily were randomized to placebo or ranolazine 1000 mg bid for 6 weeks

- The primary endpoint was the frequency of anginal episodes per week.

The benefit was evident across all subgroups. Patients with >4-5 anginal episodes/week derived a greater treatment effect



Change for nitrates to treat ED

Switching from Nitrate Therapy to Ranolazine in Patients with Coronary Artery Disease Receiving Phosphodiesterase Type-5 Inhibitors for Erectile Dysfunction

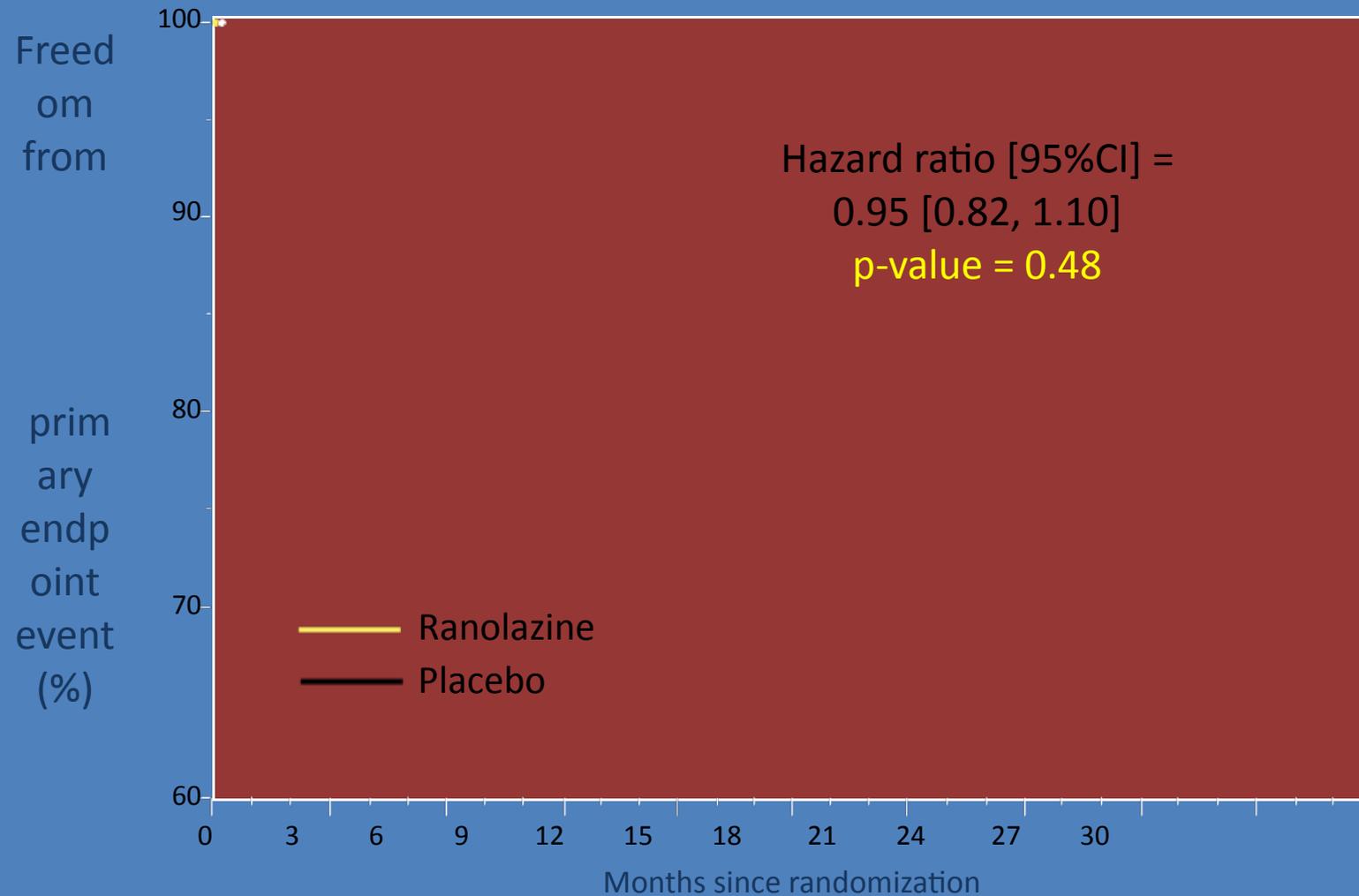
Dioma U. Udeoji and Ernst R. Schwarz

Department of Cardiology, Pacific Heart, Los Angeles, CA, USA and Cedars-Sinai Medical Center, Los Angeles, CA, USA.

ABSTRACT: Coronary artery disease (CAD) and erectile dysfunction (ED) frequently coexist. The introduction of phosphodiesterase type-5 (PDE-5) inhibitors has revolutionized medical management of organic ED; however, in patients with angina pectoris, a common symptom of CAD, coadministration of PDE-5 inhibitors and nitrates has been implicated in CAD-related deaths following sexual activity. The mechanism of action of PDE-5 inhibitors results in a potential cumulative drop in blood pressure (BP); thus, these agents are contraindicated in patients receiving nitrates. Beta-blockers and calcium channel antagonists are considered the mainstays of antianginal therapy, but may not be tolerated by all patients. Ranolazine is an antianginal agent that produces minimal reductions in heart rate and BP. Here we report three cases of men with CAD, chronic angina, and concomitant ED. We describe our treatment approach in these patients, using ranolazine as a potential substitute to nitrate therapy.

KEYWORDS: myocardial ischemia, arteriosclerosis, erectile dysfunction, phosphodiesterase type-5 inhibitors

RIVER-PCI: PRIMARY COMPOSITE ENDPOINT



No. at risk

Ranolazine	1317	1164	1101	1018	945	891	813	500	266	134	30
Placebo	1287	1165	1098	1028	960	879	788	461	271	128	45

RIVER-PCI: Compliance

	Ranolazine (n=1322)	Placebo (n=1297)	<i>P</i> Value
Follow-up duration, median (IQR)	644 (575-757)	642 (575-761)	0.49
On study-drug duration, median (IQR)	579 (229-674)	586 (361-688)	0.004
Drug discontinuation	529 (40.0%)	463 (35.7%)	0.006
- Due to an adverse event	189 (14.3%)	137 (10.6%)	0.004
Drug discontinuation ≤12 months	373 (28.2%)	295 (22.7%)	0.01

ESC GUIDELINES 2013

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 β -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%) β -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

Pazienti con CAD:

- Rivascolarizzazione incompleta
- NSTEMI / STEMI
- Ischemia residua e/o sintomi residui
- Angina cronica stabile

Va si inadatti a
PCI
Malattia diffusa dei
piccoli vasi

CT
O
Lesioni 50% -
70%

DIMISSIONE

RS
Fc basale > 60 bpm

**B-bloccante bassa dose + Ivabradina 5 mg x
2**
in aggiunta a terapia convenzionale

Visita controllo 1-3 mesi

**Titolazione B-Bloccante e Ivabradina
e verifica obiettivi terapeutici**

Visite controllo successive

Persistenza sintomi

**Valutare associazione con Ranolazina /
Trimetazidina**

Considerare inizio terapia
con
Ivabradina 2,5 mg x 2 in
donne a
basso peso o Fc < 70

Considerare **Ranolazina**
in FA o BAV o in
presenza di aritmie
ventricolari

Paziente dopo PCI

Vasi inadatti a PCI
Malattia diffusa dei piccoli vasi

Lesioni 50% - 70% FFR
Paziente (aged, fragile, comorb)

Rivascolarizzazione completa:

(prevenzione secondaria)

ASA
P2Y12 inhibitors
Statine
Beta-blocco (?) – ACE-inibitore

Rivascolarizzazione incompleta:

(prevenzione secondaria)

ASA
P2Y12 inhibitors
Statine

Staged:

Beta-blocco mid dose
+
a) Ivabradina 5mg x 2 se:
Fc>60/min
controindicazioni a BB
effetti collaterali da BB
b) Ranolazina 500mg x 2 se:
FA, BAV, aritmie ventricolari
c) Nitrati o Ca++ se:-
eGFR<30ml/min

Rivalutazione a 1-3 mesi
Titolazione Ivabradina
Aggiungere Ranolazina
Aggiungere Nitrati /Ca++/TMZ

nrv Stenosis:

Beta-blocco mid dose
+
a) Ivabradina 5mg x 2 se:
Fc>60/min
controindicazioni a BB
effetti collaterali da BB
b) Ranolazina 500mg x 2 se:
FA, BAV, aritmie ventricolari
c) Nitrati o Ca++ se:-
eGFR<30ml/min

Rivalutazione a 1-3 mesi

nrv CTO:

Beta-blocco a bassa dose
+
a) Ivabradina 5mg x 2 se:
Fc>60/min
controindicazioni a BB
effetti collaterali da BB
b) Ivabradina 7,5mg x 2 se:
Fx>70/min
c) Ranolazina 750mg x 2 se:
FA, BAV, aritmie ventricolari
d) Nitrati o Ca++ se:
eGFR<30ml/min

Small vessel / diffuse non-critical CAD / Syndrome X:

Beta-blocco mid dose
+
a) Ivabradina 5mg x 2 se:
Fc>60/min
controindicazioni a BB
effetti collaterali da BB
b) Ranolazina 500mg x 2 se:
FA, BAV, aritmie ventricolari
c) Nitrati o Ca++ se:-
eGFR<30ml/min

Rivalutazione a 1-3 mesi
Titolazione Ivabradina
Aggiungere Ranolazina
Aggiungere Nitrati /Ca++/TMZ
Teofillinici

Grazie per l'attenzione!