

CONGRESSO REGIONALE CFC LOMBARDIA

LA TERAPIA DELLA CARDIOPATIA ISCHEMICA NELL'ANZIANO E NEL GRANDE ANZIANO



Andrea Macchi

U.O. C. di Cardiologia, UTIC ed Emodinamica

A.O. Ospedale di Circolo di Busto Arsizio (VA)

CONFLITTO DI INTERESSI

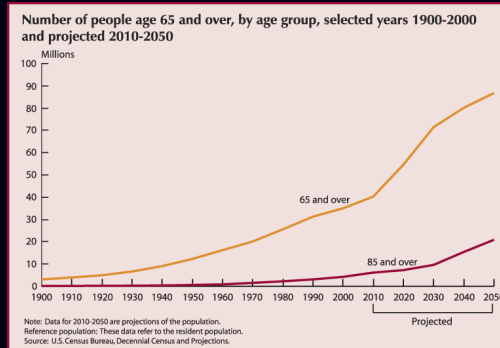
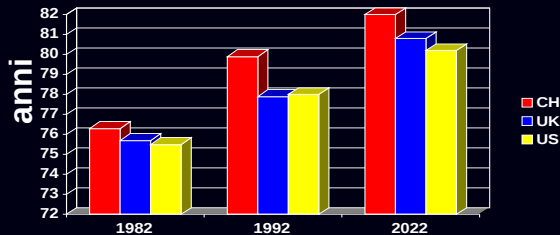
DISCLOSURES:

none

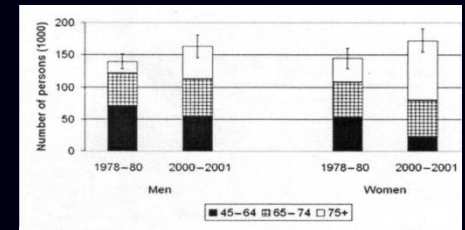
SENECTUS IPSA MORBUS EST

Eta' principale fattore di rischio CV

Aspettativa di vita a 65 anni : 17 anni,
a 80: 8 anni



Da malattia dell'uomo di mezza eta' a malattia della donna molto anziana

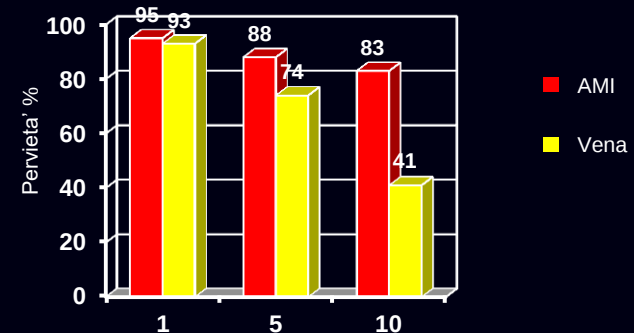


Aumento della sopravvivenza agli eventi acuti

RITA TRIAL

- Nei pazienti sottoposti a PTCA la percentuale di reintervento è del 28% nel primo anno, del 9% a due anni e del 3% dall'anno 3 all'anno 5
- Nei pazienti sottoposti a CABG la percentuale di reintervento rimane stabile al 2% per anno **ma tende ad aumentare dopo il 7° anno**

GRAFT ARTERIOSO VS GRAFT VENOSO

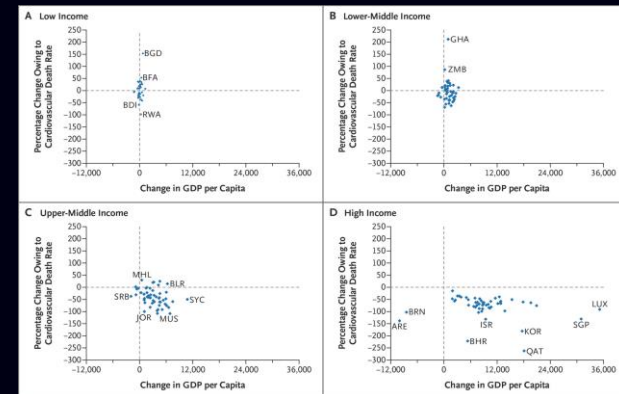
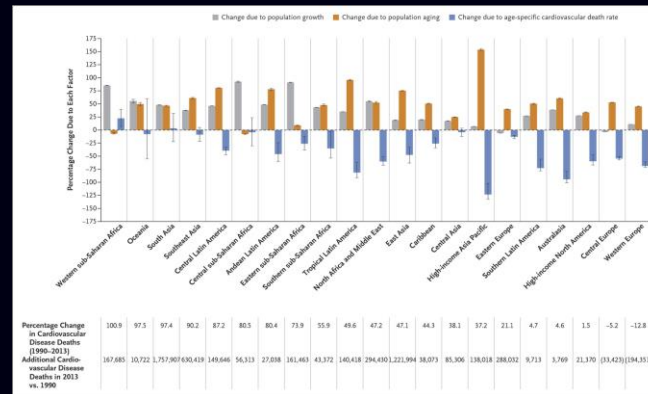
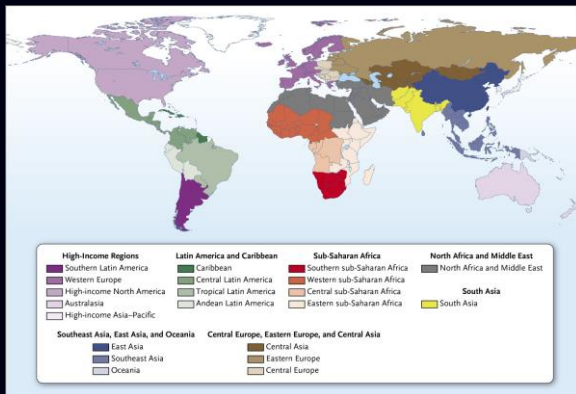


- 30% delle persone con eta' >80 anni e' affetta da coronaropatia sintomatica
- >25% popolazione >80 anni e' funzionalmente limitata dalle patologie cardiovascolari
- 50% di essi andra' incontro a morte per cardiopatia ischemica

US Government Printing Office 1989

DOVE ANDIAMO?

Global deaths from cardiovascular disease are increasing as a result of population growth, the aging of populations, and epidemiologic changes in disease.



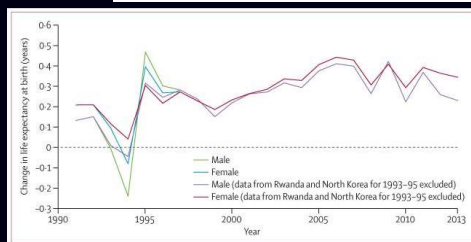
Percentage change in cardiovascular death rate owing to changes in age- sex- and cause-specific death rates, according to change in country income

The aging and growth of the population resulted in an increase in global cardiovascular deaths between 1990 and 2013, despite a decrease in age-specific death rates in most regions. Only Central and Western Europe had gains in cardiovascular health that were sufficient to offset these demographic forces.

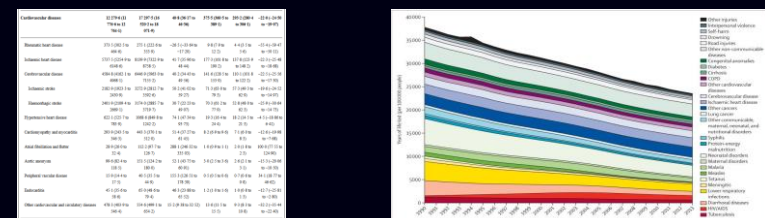
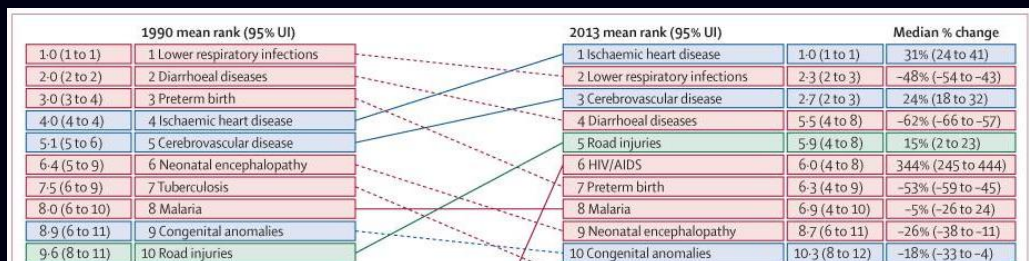
The NEW ENGLAND JOURNAL of MEDICINE

Roth GA et al. N Engl J Med 2015;372:1333-1341

Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.



Germany	IHD	Lung C	Stroke	Alzheimer's	Colorectal C	COPD	Cirrhosis	Self harm	Breast C	Pancreatic C
Greece	IHD	Stroke	Lung C	Alzheimer's	COPD	Road injuries	Colorectal C	Breast C	LRI	CKD
Iceland	IHD	Lung C	Stroke	Alzheimer's	Self harm	Colorectal C	COPD	Breast C	Prostate C	Road injuries
Ireland	IHD	Lung C	Stroke	Self harm	COPD	Colorectal C	LRI	Alzheimer's	Breast C	Congenital
Israel	IHD	Lung C	Stroke	Alzheimer's	Diabetes	Stroke	Colorectal C	Road injuries	CKD	Congenital
Italy	IHD	Stroke	Lung C	Alzheimer's	Colorectal C	COPD	Diabetes	Breast C	Cirrhosis	Road injuries
Luxembourg	IHD	Lung C	Stroke	Alzheimer's	Colorectal C	COPD	Cirrhosis	Alzheimer's	Breast C	Road injuries
Malta	IHD	Stroke	Lung C	Colorectal C	Breast C	COPD	Congenital	LRI	Pancreatic C	Diabetes
Netherlands	IHD	Lung C	Stroke	Colorectal C	COPD	Alzheimer's	Breast C	LRI	Self harm	Pancreatic C
Norway	IHD	Lung C	Stroke	Alzheimer's	Colorectal C	COPD	Self harm	LRI	Drugs	Breast C



GBD 2013 Mortality and Causes of Death Collaborators, Lancet 2015

CARDIOVASCULAR RISK MANAGEMENT IN THE ELDERLY

Clinical consequences of an ageing population

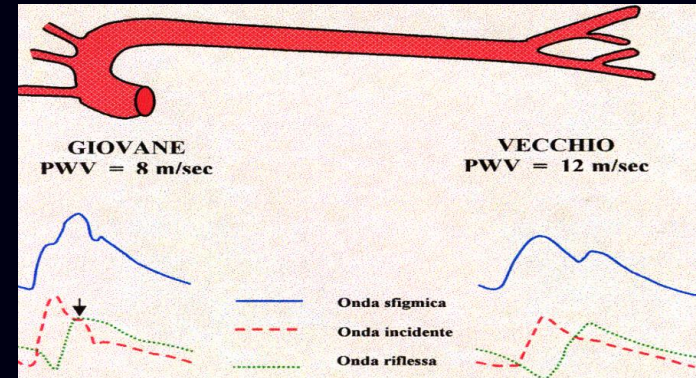
- Increased CHD
- increased stroke
- dementia
- disability
- dependency

World Population Ageing 1950-2030 (billions)

Year	Population (billions)
1950	~40
1960	~50
1970	~60
1980	~80
1990	~100
2000	~130
2010	~170
2020	~230
2030	~290

% AGED >65 YEARS

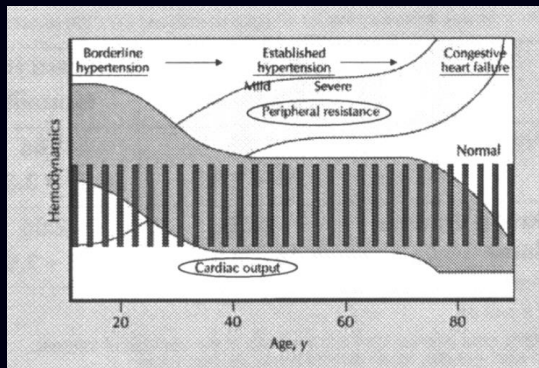
Country	2000 (%)	2020 (%)
JAP	~20	~25
BWP	~18	~18
BLU	~15	~15
FRA	~18	~18
USA	~13	~13
NL	~15	~15
UK	~14	~14
IRE	~10	~10



-
- PP (pressione differenziale)**
Rischio di eventi CV in 3 studi combinati
- 2-year risk of CV event**
- DBP (mmHg)
- EVUPIE (n= 840)
 Syst-Eur (n= 840)
 Syst-China (n= 4695)
 in stratified Cox model
- ** Standardized to mean age, male sex, previous CV complications, smoking and active treatment
- Systolic blood pressure (mmHg)

The diagram illustrates the aging heart with the following changes labeled:

- Reduced Elasticity
- Increased return waves
- Peripheral resistance increased
- Thickened Septum
- Prolonged Action Potential
- Delayed relaxation
- Mycocytes reduced
- Reduced β receptors
- Reduced diastolic filling rate



Eta' anni	PA diastolica	PA sistolica	PA media	"Pulse pressure"	
30-49	↑	↑	↑	→ ↑	R > S
50-59	→	↑	→	↑↑	R = S
> 60	↓	↑	↓→	↑↑↑↑	S > R

R = Piccole arterie di resistenza

“... even in revasc era... ischaemia does still exist!”

Quanti pazienti con angina cronica vede il MMG?

Health Search Database

550 MMG

Selezione di pazienti con diagnosi di angina e/o
almeno 2 prescrizioni di Nitrati negli ultimi 12 mesi

14.177 (nessun pregresso IM)

20-30 pazienti / MMG

Ogni mille assistiti un MMG deve aspettarsi

Patologia	Pazienti/MG
Angina pectoris	25-30
Pregresso infarto	20
Pregresso ictus cerebrale	15
Arteriopatia ostruttiva sintomatica	15-20
ISS > 20%	20
Pazienti diabetici ipertesi	66
Pazienti con sindrome metabolica	200
Pazienti con danno renale	150
Pazienti ipertesi	210

SIMGE

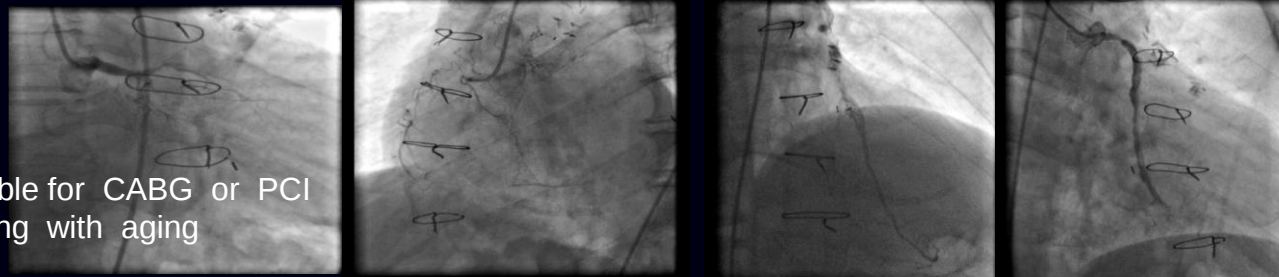
“IN THE REAL WORLD”

- Malattia distale
- Malattia di rami di secondo ordine ma a zone algogene
- Impossibilita' anatomica alla rivascolarizzazione
- Rivascolarizzazioni non complete

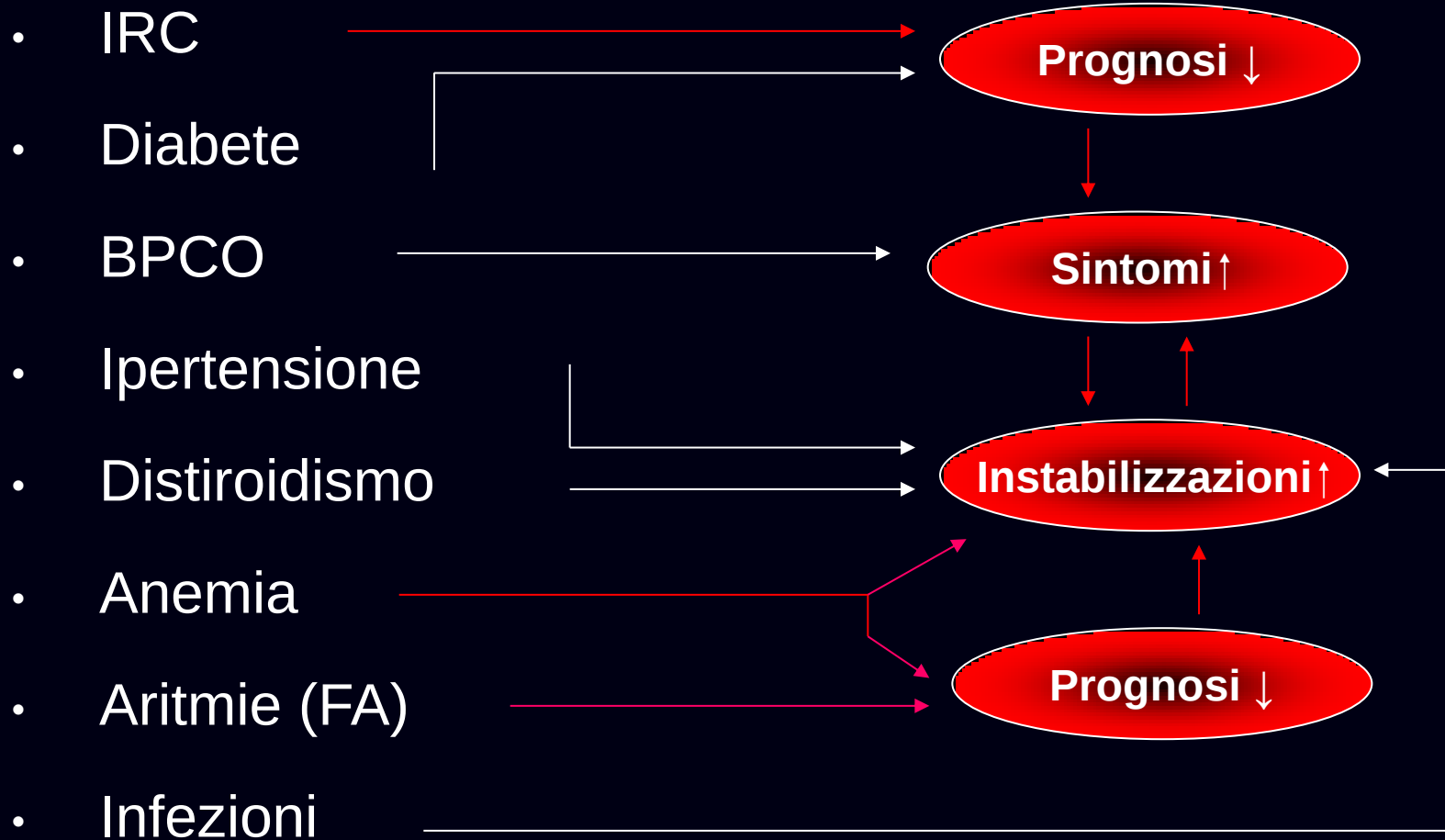


IN U.S.

- 3.2 million CAD pts
- 0.8 – 2.4 million CAD pts not amenable for CABG or PCI
- ESC data 15 % of the pts presenting with aging

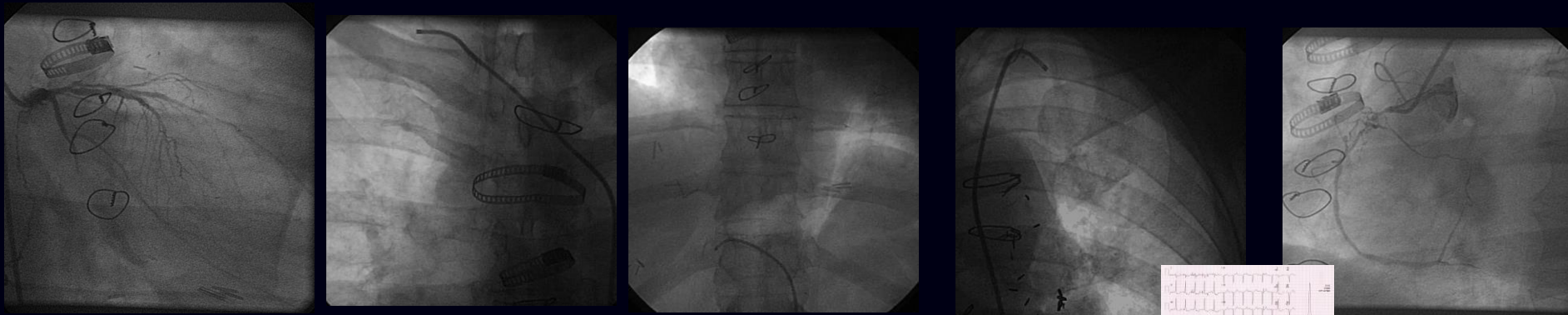


IL NOSTRO PAZIENTE CON CARDIOPATIA ISCHEMICA



“Per non parlar di” Osteoporosi e Depressione

...UNA BRUTTA STORIA DOPO CABG O PCI

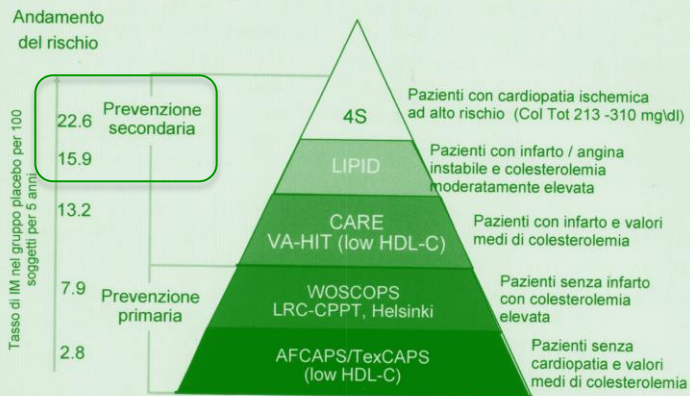


“... in revasc era...”

La **rivascolarizzazione** non e' la cura della cardiopatia ischemica ma **solo una parte del trattamento**
Solo l'aggressione dei fattori di rischio puo' prevenire la progressione della malattia aterosclerotica
Solo **stile di vita e farmaci prognostici modificano il corso della malattia**

- Modificazioni dello stile di vita
- Controllo dei valori pressori
- Antiaggregazione piastrinica
- **Trattamento della dislipidemia**
- Controllo dell'iperglicemia

RISCHIO DI UN SECONDO EVENTO VASCOLARE



Aumento del rischio vs. popolazione generale

Evento iniziale	Infarto miocardico	Ictus
Infarto miocardico	5-7 volte ¹ (inclusa la morte)	3-4 volte ² (incluso TIA)
Ictus	2-3 volte ² (inclusa angina e morte improvvisa*)	9 volte ³
Arteriopatia obliterante periferica	4 volte ⁴ (inclusi solo IM fatale e altre morti CV**)	2-3 volte ³ (incluso TIA)

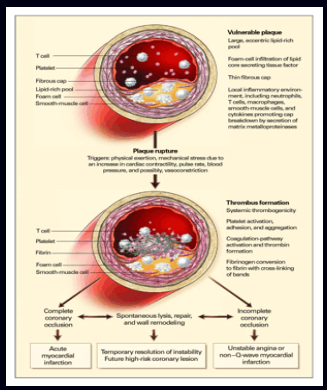
1. Adult Treatment Panel II. Circulation 1994; 89: 1333-1363.
2. Kannel WB. J Cardiovasc Risk 1994; 1: 333-339.
3. Willettingk JI, Easton JD. Arch Neurol 1992; 49: 857-863.
4. Criqui MH et al. N Engl J Med 1992; 326: 381-386.

TEST PROVOCATIVI

Informazione di tipo funzionale

PRESENZA DI STENOSI CORONARICA

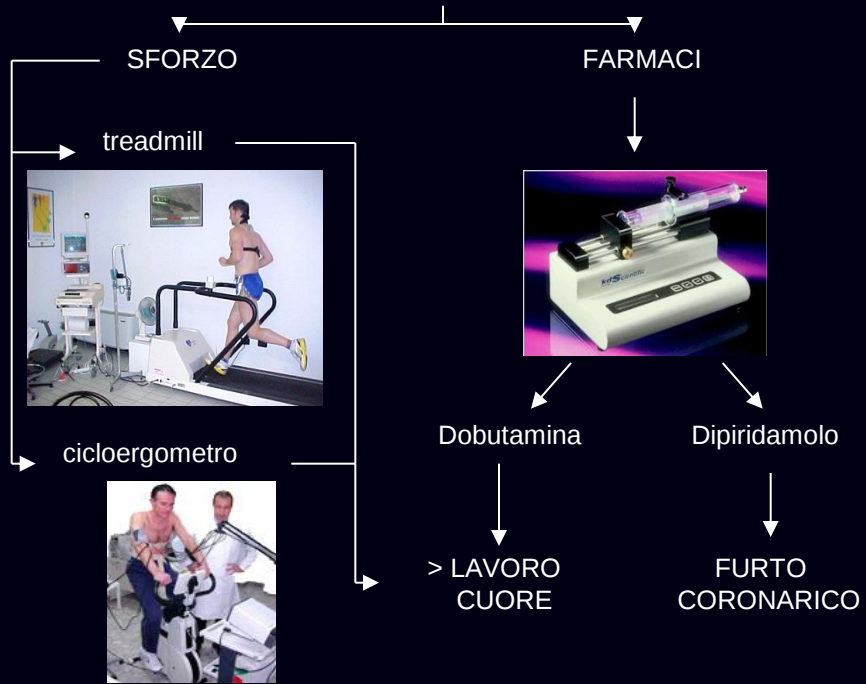
CONDIZIONI
NORMALI
↓
FLUSSO
ADEGUATO
↓
ASSENZA DI
ISCHEMIA
↓
ECG NORMALE



STRESS
↓
AUMENTO
CONSUMO DI
OSSIGENO
↓
DISCREPANZA
APPORTO E
RICHIESTA O₂
↓
ISCHEMIA

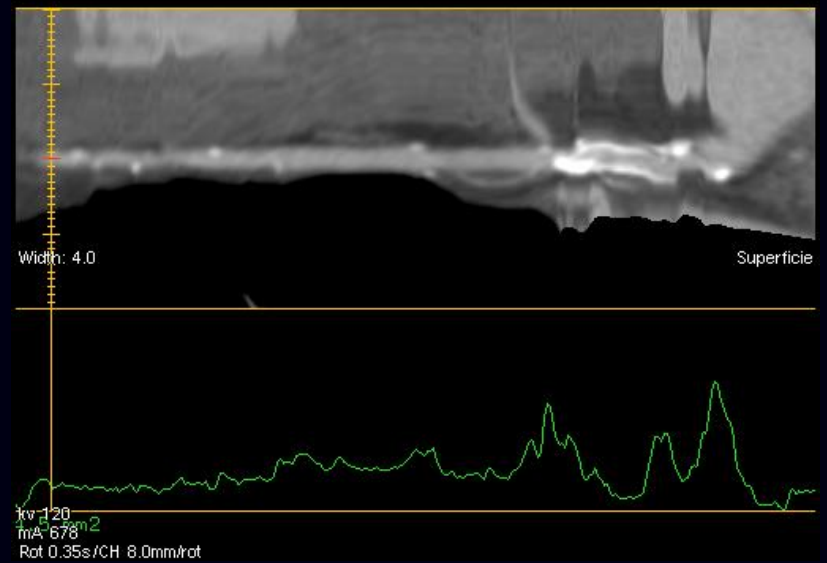
LOGICA DEI TEST PROVOCATIVI

STRESSORI



Angle: -95.0° Rfnt

LP: 102.2

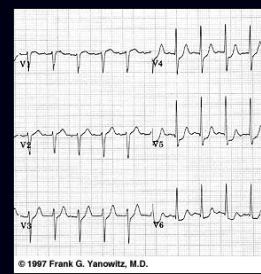


LETTORI

ECG

ECOCARDIOGRAMMA

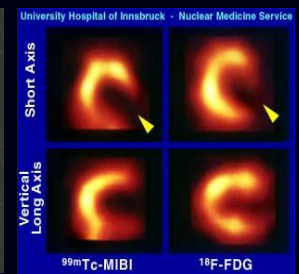
SCINTIGRAFIA



MODIFICAZIONI
del tratto ST
solitamente
sottolivellamento



RIDUZIONE
della CINESI
REGIONALE
asinerjie

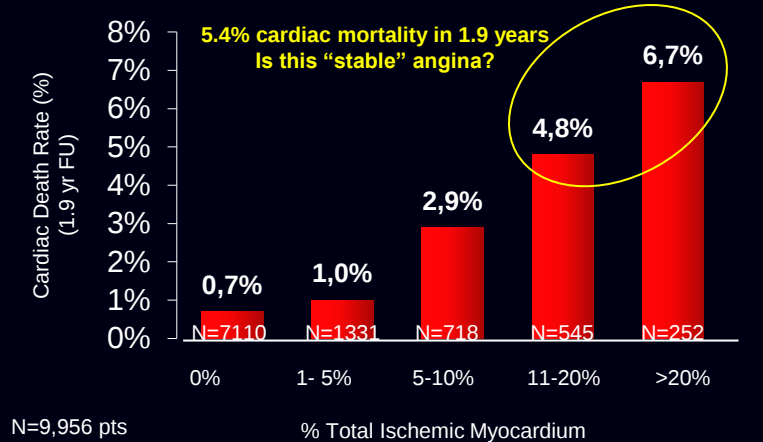


IPOPERFUSIONE

TEST di IMMAGINE

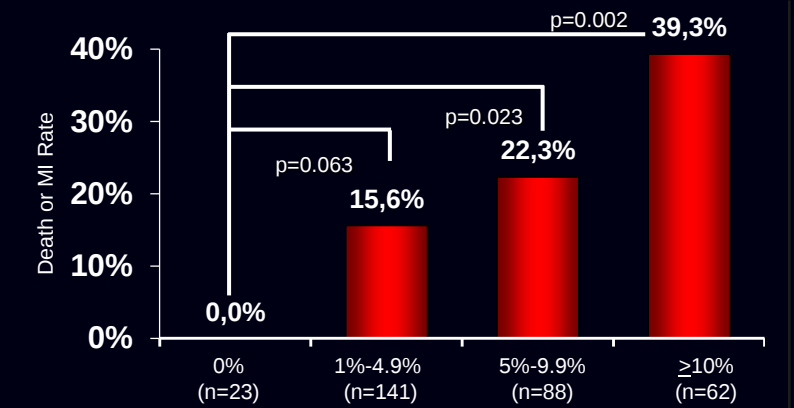
PROGNOSI "ISCHAEMIA DRIVEN"

Prognosi in funzione del "burden ischemico"



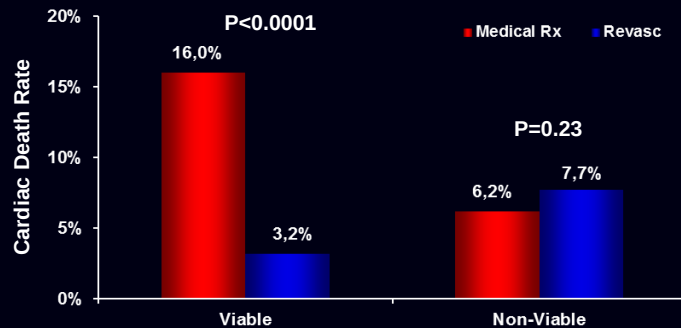
Hachamovitch et al, Circulation 2003

Prognosi in funzione dell' ischemia residua

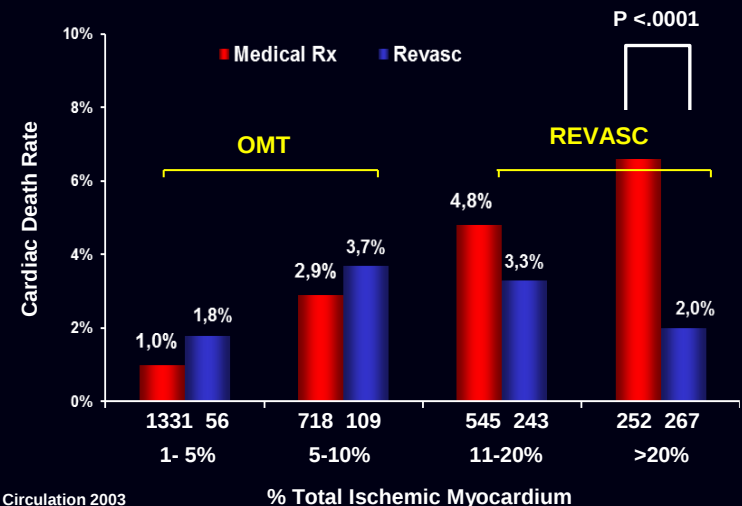


Shaw et al, AHA 2007 and Circulation 2008

FROM GUIDELINES TO MINDLINES

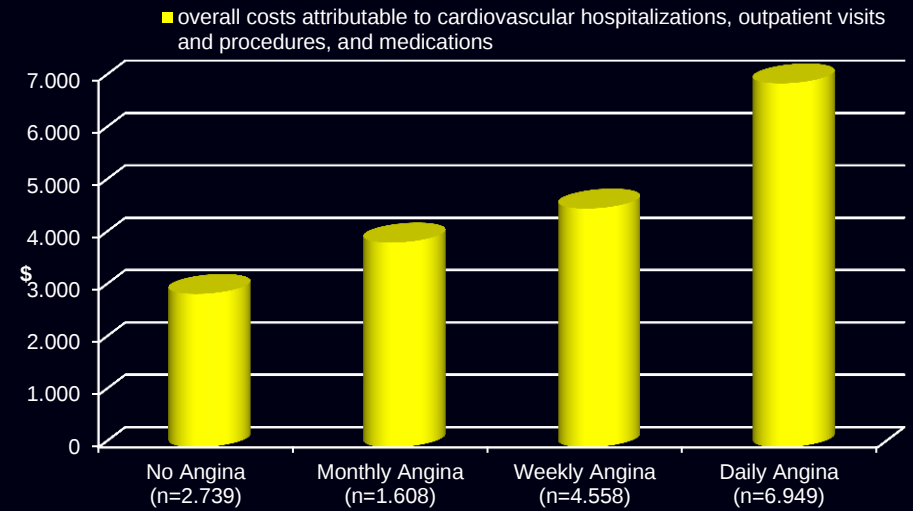
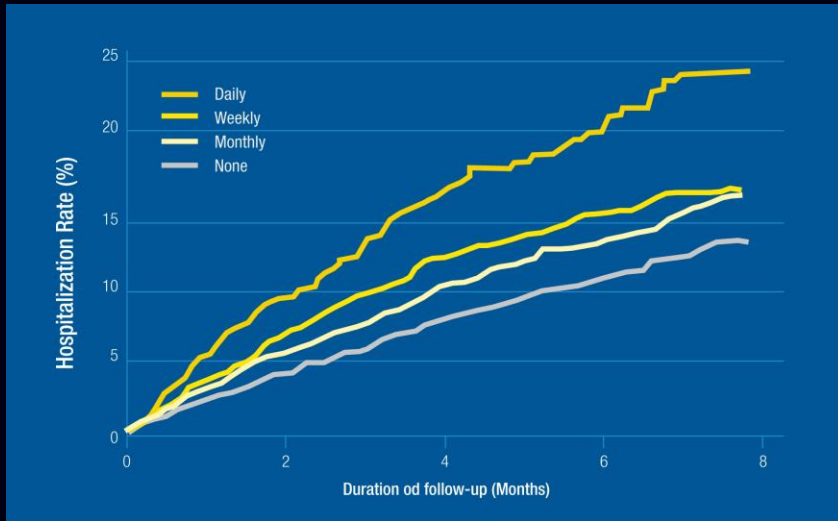


Allman KC et al, J Am Coll Cardiol 2002

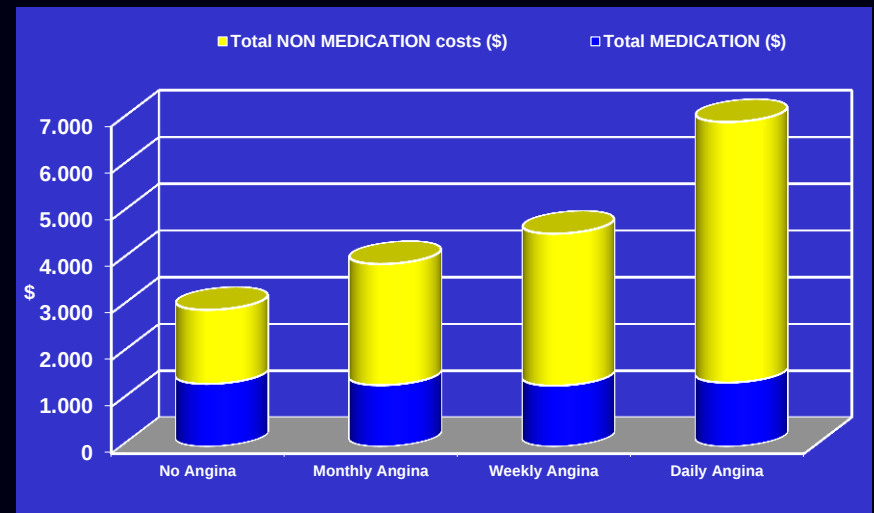
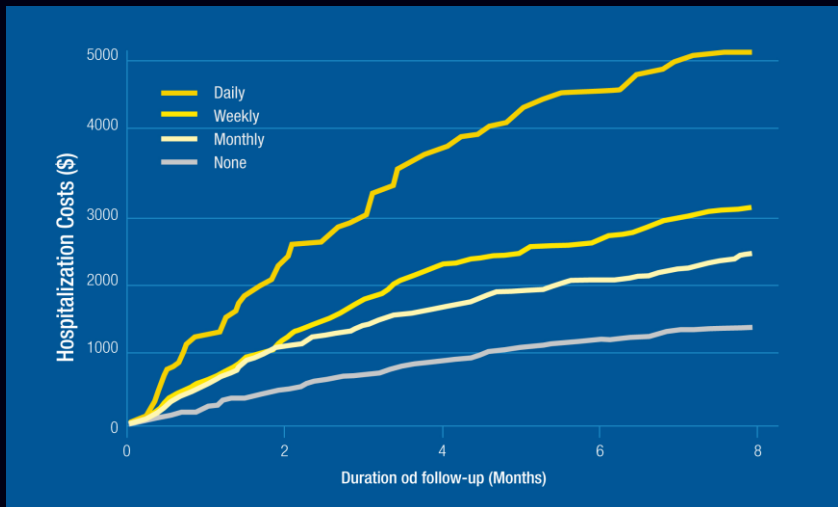


Hachamovitch et al, Circulation 2003

FREQUENZA DI ANGINA: RISCHIO DI OSPEDALIZZAZIONE ED IMPATTO ECONOMICO



MERLIN-TIMI 36 trial, 5460 pazienti ambulatoriali stabili dopo SCA, follow up 12 mesi



QUALE TRATTAMENTO PER IL PAZIENTE ANZIANO CON CARDIOPATIA ISCHEMICA?

“... l'età > 70-75 anni e' stata sempre criterio di esclusione dai grossi trial clinici”

“... with advancing patient age comes therapeutic ignorance”

Merchant FM et al, Coronary Artery Disease 2009
Abizaid AS, Am J Cardiol 2000
Wiener M et al, Am Heart J 2007
Braunwald's Heart Disease 2005
Peterson ED, Am Heart J, 1999

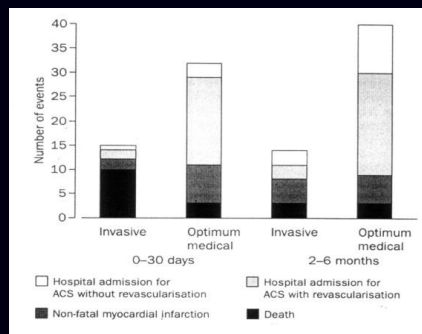
Trial Name	Enrollment Year(s)	Treatment Comparisons	Number Enrolled	Age Inclusion	Number Enrolled ≥75 yr of Age
CASS	1970s	CABG vs. medical	780	Age ≤65 yr	0
VA	1970s	CABG vs. medical	686	None	0
European					
RITA					
EAST					
GABI					
CABRI					
BARI					
ERACI					
ACME					
ARTS					
TIME		medical			

pazienti ≥ 75 anni con **angina cronica CSS II**

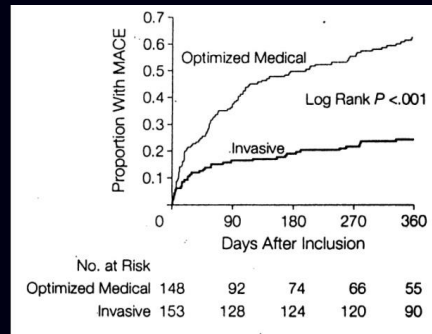
Misure che riducono le complicanze post-procedurali - sanguinamento, IRA, arizzazione
dispersione enzimatica - migliorano l'outcome dei pazienti anziani sottoposti a PCI arizzazione

Rickenbacher P, Eur Heart J 2002

TIME Trial of Invasive vs Medical therapy in Elderly patients



TIME, Lancet 2001



Pfisterer M, JAMA 2003

OUTCOME POST-PCI

successo clinico 96%
mortalita' 3.0%

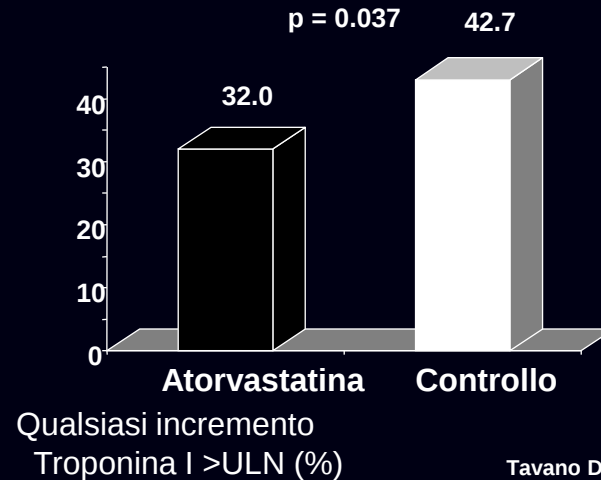
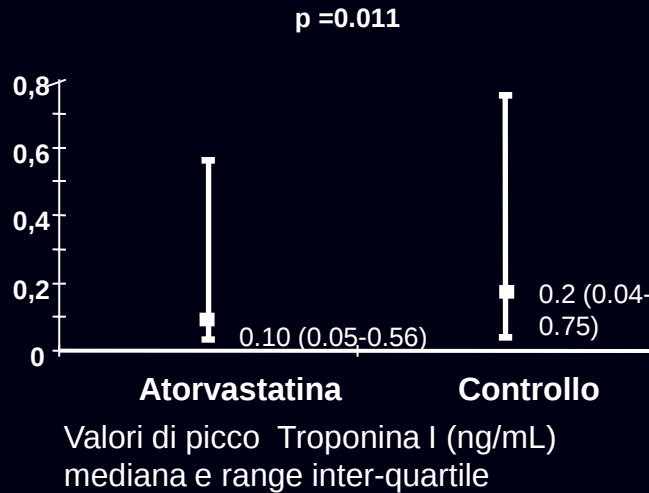
Mortalita' intraospedaliera	1.0%	0.3%	p<0.001
IMA intraospedaliero	1.4%	1.2%	n.s.
Rivascolarizz. intraosp.	2.0%	1.3%	n.s.
MACE intraospedaliere	3.8%	2.4%	p=0.01

Nonostante il maggior rischio iniziale, il trattamento invasivo e' piu' sicuro riducendo la probabilita' di un successivo intervento d'urgenza

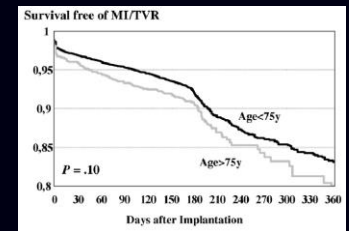
Circa il 50% dei pazienti trattati farmacologicamente va incontro ad ospedalizzazione per procedura di rivascolarizzazione miocardica

ATORVASTATINA 80 mg IL GIORNO PRIMA DELL'IMPIANTO DI STENT CORONARICO

Impatto sul danno miocardico peri-procedurale

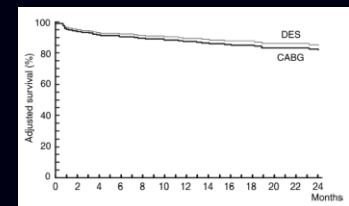


Sicurezza dei DES nei pz > 80 anni



Wierner M et al, Am Heart J 2007

CABG vs DES nel TC non protetto pz >75 anni

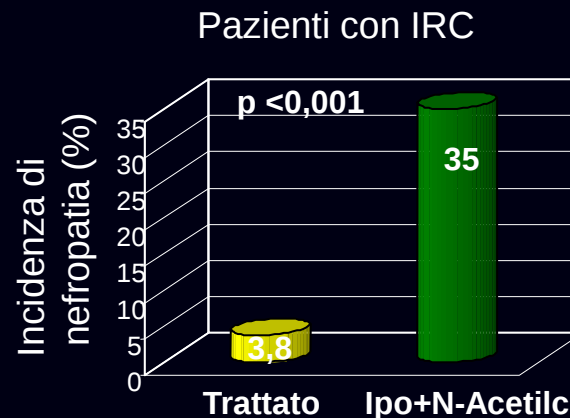
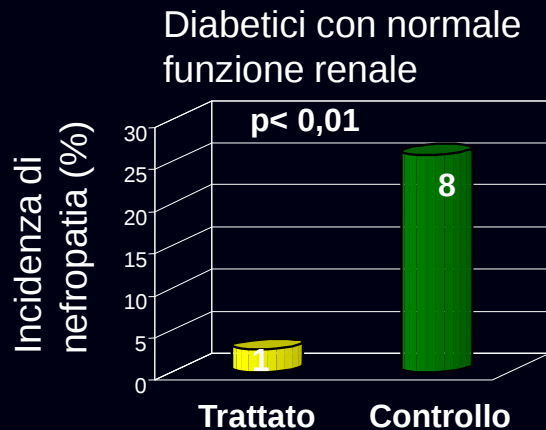


Palmerini T et al, Eur Heart J 2007

Macchi A et al, ESC 2007

PREVENZIONE DELLA NEFROPATIA DA MEZZO DI CONTRASTO

Ipotonica+bicarbonato+N-Acetilcisteina+Vit. C



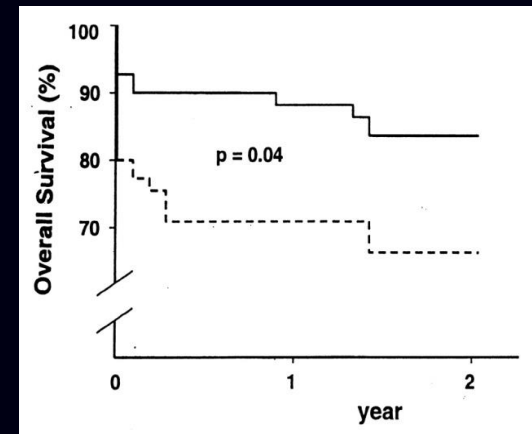
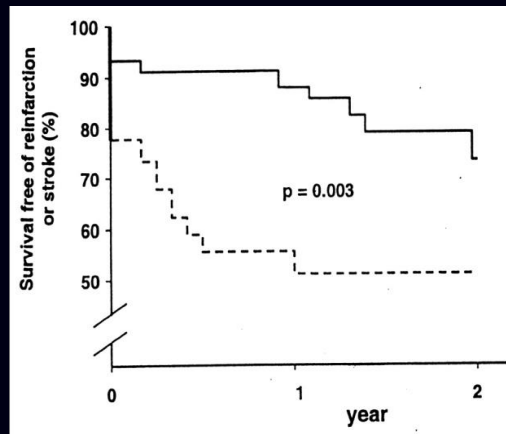
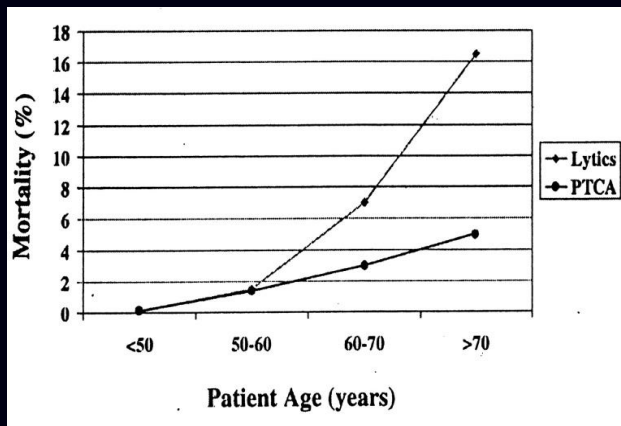
SINDROME CORONARICA ACUTA

Anziani con sindrome coronarica acuta

Coorte ad alto rischio in popolazione ad alto rischio

RIPERFUSIONE MANDATORIA

STEMI Trombolisi vs PCI



Successo PCI 90%

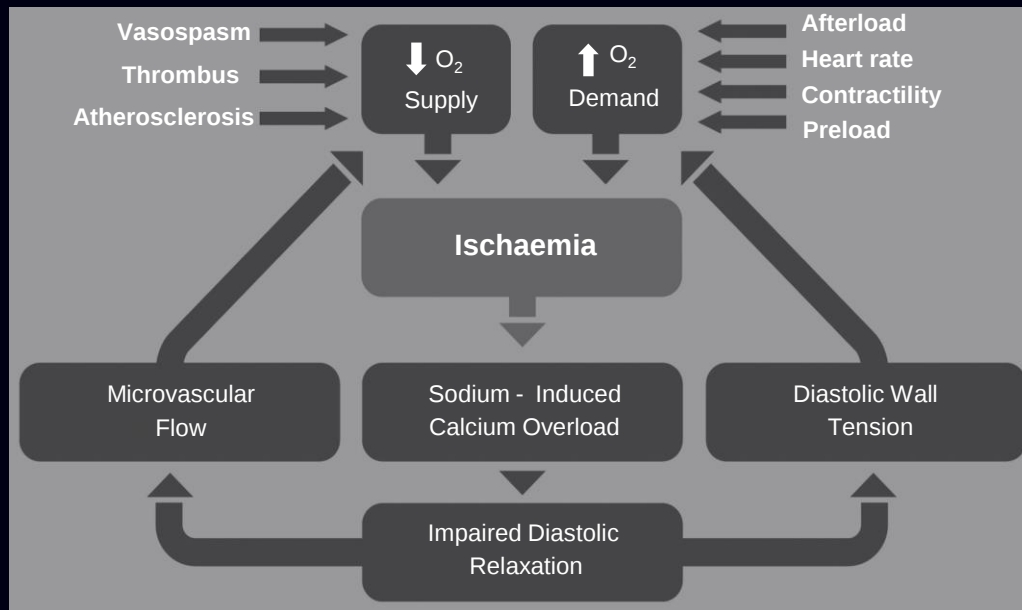
TRIANA Study (ESC 2009 Barcellona)

primary PCI piu' efficace di trombolisi: ischemia ricorrente a 30 giorni 0.8% vs 9.7% ($p < 0.001$)

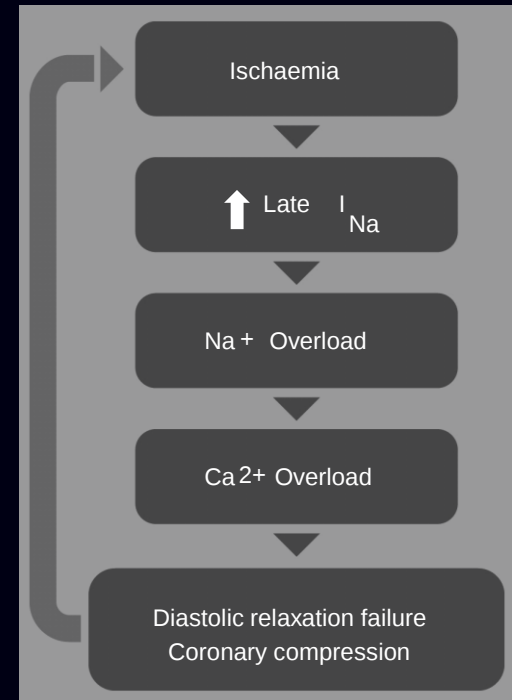
CAD - HF - ARITMIE - DIABETE

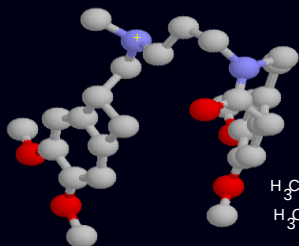
- La **cardiopatia ischemica** e' il principale fattore di rischio per la sviluppo di **scompenso cardiaco** ed entrambe queste patologie si associano con **aritmie severe atriali e ventricolari**
- Un gran numero di pazienti con CAD e' affetto da **diabete** o presenta **alterato metabolismo glicidico**

ISCHEMIA MIOCARDICA

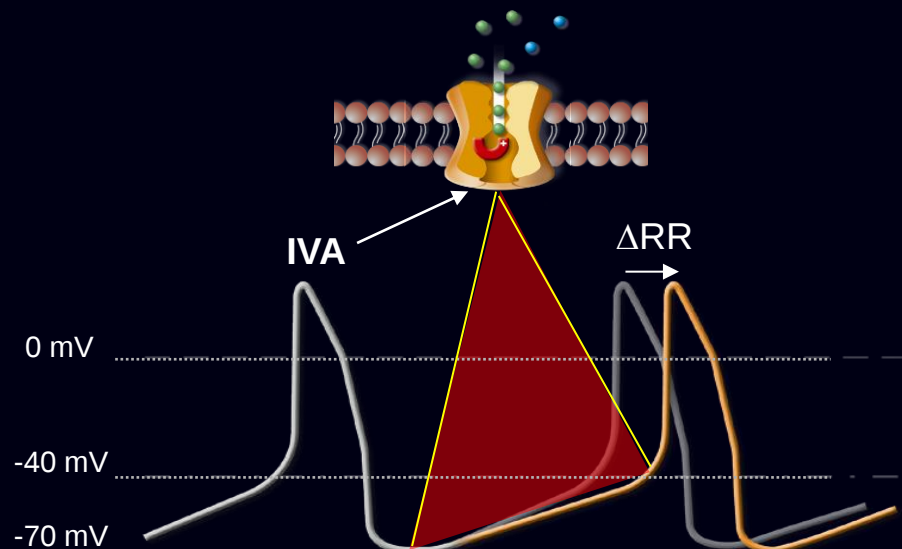


Chaitman BR, Circulation 2006
Belardinelli L et al, Eur Heart J 2004





INIBITORE SELETTIVO E SPECIFICO DEI CANALI I_f



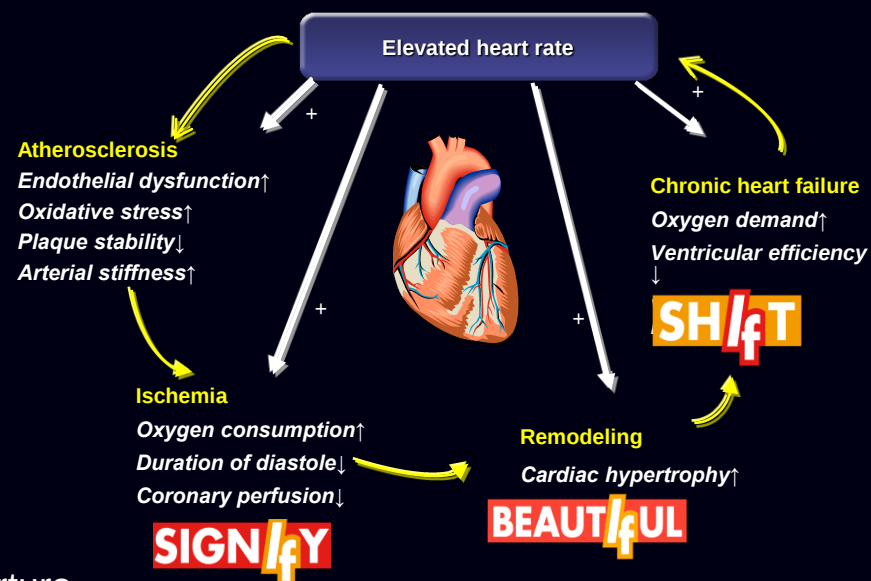
Specifico legame ai canali I_f delle cellule pacemaker
Inibizione selettiva dei canali quando sono in stato di apertura

Riduzione pura della frequenza cardiaca

Funzione cardiaca completamente preservata

Non effetto su inotropismo

CARDIOPROTECTIVE EFFECTS OF HEART RATE REDUCTION WITH IVABRADINE



INITIATIVE
ASSOCIATE I – II
REDUCTION -
ADDICTION

> 40.000 pts

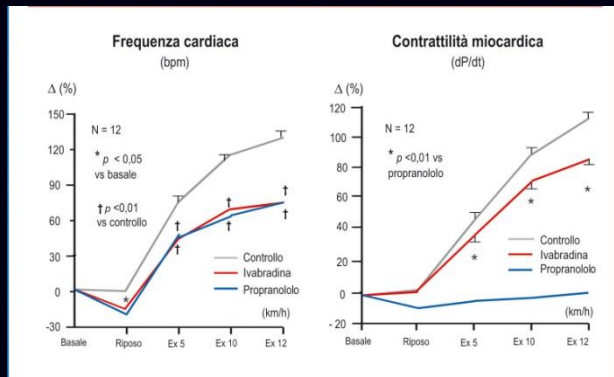
Efficacy + Safety

Non effetto sulla pressione arteriosa

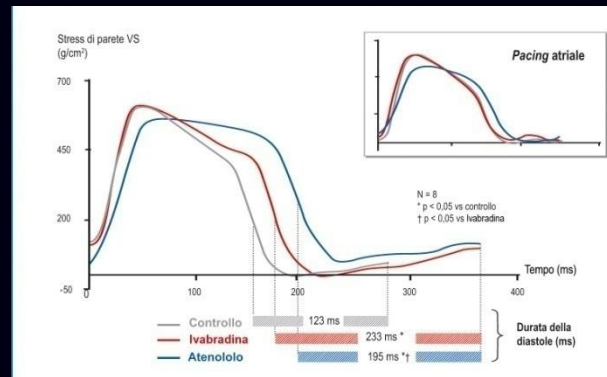
“BEYOND HR REDUCTION”

IVA vs β -B

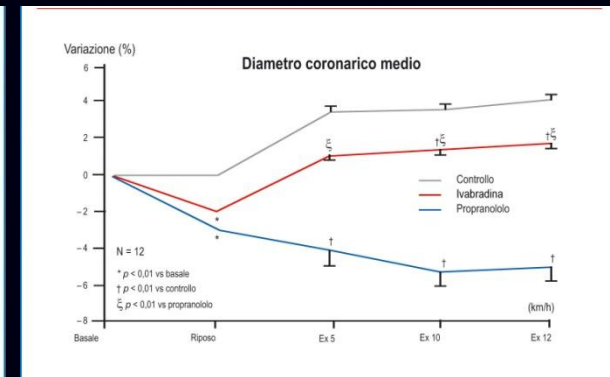
CONTRATTILITA' DA SFORZO



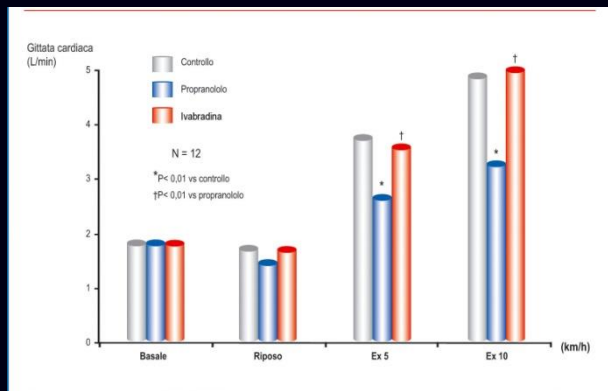
DURATA DELLA DIASTOLE



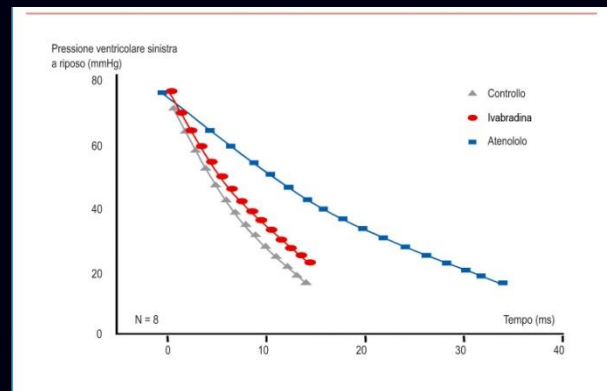
VASODILATAZIONE DA SFORZO



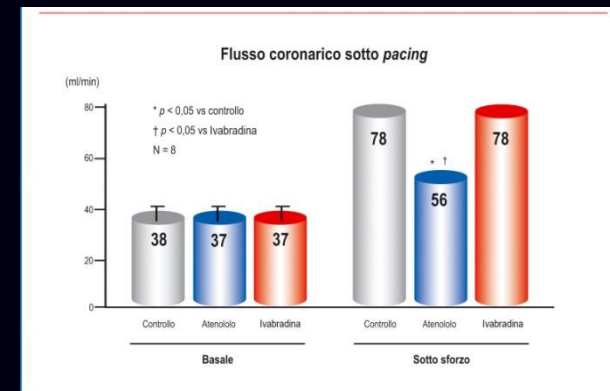
GITTATA CARDIACA DA SFORZO



RILASCIAMENTO VS



FLUSSO CORONARICO DA SFORZO

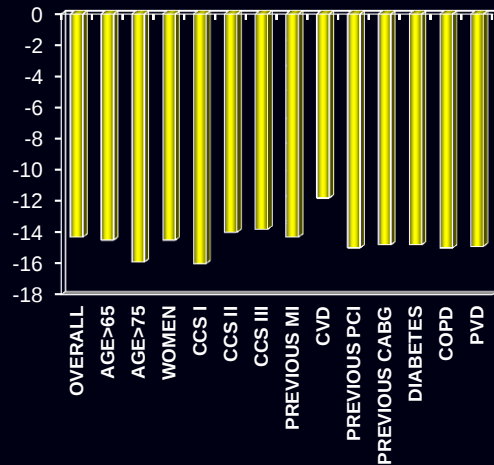


ANGINA ATTACKS, S-A NITRATE CONSUMPTION, HR

2,425 pts from 5 IVA randomized trial

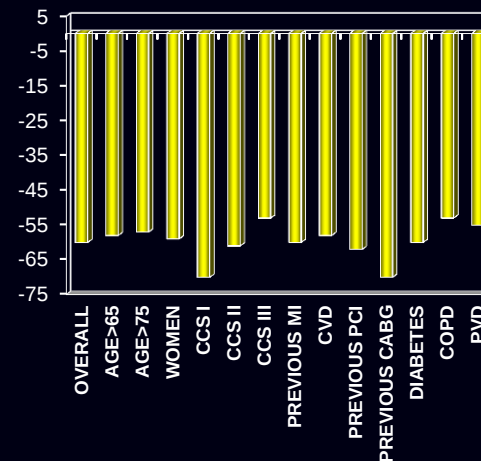
IVA reduced: angina attacks by 59.4%, nitrate consumption by 53.7%
IVA had a good safety and tolerability profile in all the subpopulations assessed

CHANGE IN HEART RATE (%)



Tendera et al, Cardiology 2009

CHANGE IN ANGINA ATTACKS (%)



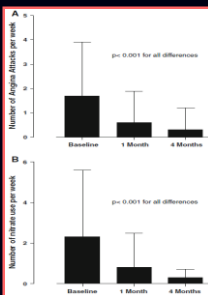
Clin Res Cardiol (2012) 101:365–373
DOI 10.1007/s00392-011-0402-4

ORIGINAL PAPER

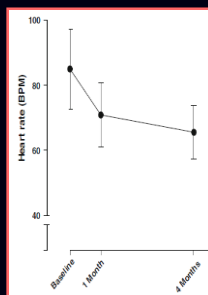
Ivabradine in combination with beta-blocker improves symptoms and quality of life in patients with stable angina pectoris: results from the ADDITIONS study

Karl Werdan · Henning Ebel ·
Sebastian Nuding · Florian Höpfner ·
Guido Hack · Ursula Müller-Werdan

2.330 pts



Medication	Patients, n (%)	Mean daily dose at baseline (mg)
Metoprolol	999 (43%)	106.5 ± 50.05
Bisoprolol	872 (37%)	7.01 ± 3.44
Nebivolol	293 (13%)	5.08 ± 1.83
Carvedilol	165 (7%)	29.6 ± 16.60
Atenolol	13 (<1%)	67.3 ± 32.89
Others	14 (<1%)	



were CCS grade I (68%). The EQ-5D index improved by 0.17 ± 0.23 ($p < 0.0001$). The overall efficacy of ivabradine was considered by the physicians as “very good” (61%) or “good” (36%) in most patients. Suspected adverse drug reactions were documented in 14 patients; none were severe.

Conclusion In daily clinical practice, combining ivabradine with beta-blocker not only reduces heart rate, number of angina attacks, and nitrate consumption, but also improves the quality of life in patients with stable angina pectoris.

Ivabradina , bloccante selettivo dei canali if, riducendo FC:

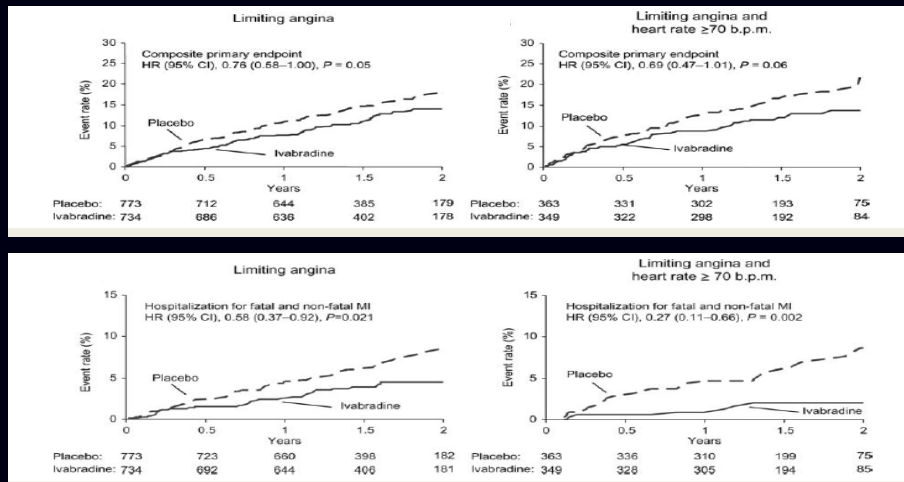
- diminuisce i marker dello stress ossidativo vascolare, migliora la funzione endoteliale e riduce la formazione della placca aterosclerotica
- **riduce** il rischio di **eventi coronarici del 22%** ($p=0.023$), il rischio di **IMA fatale e non fatale del 36%** ($p=0.001$) e le **rivascolizzazioni coronariche del 30%** ($p=0.016$) nei pazienti con FC basale ≥ 70 bpm **BEAUTifUL**

Druin A et al ,Br J Pharmacol 2008

Custodis F et al, Circulation 2008

Tardif JC, Br Med Bull 2009

BEAUTifUL Angina limitante



IVA:

nei pazienti sintomatici riduce l'incidenza di **morte CV, IMA, scompenso (-24%)** ed **ospedalizzazione per IMA fatale e non (-42%)**, indipendentemente da FC basale

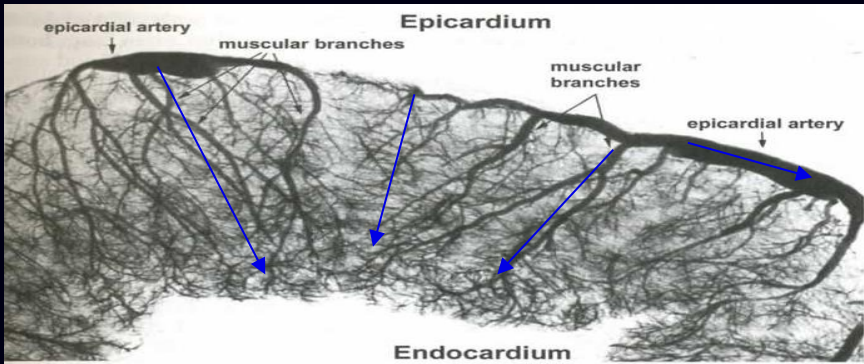
K Fox et al, Eur Heart J 2009

BEAUTifUL Safety

In pazienti con coronaropatia e ventricolo sinistro disfunzionante IVA puo' essere somministrata in piena sicurezza anche con il beta-bloccante

Fox K et al, Lancet 2008

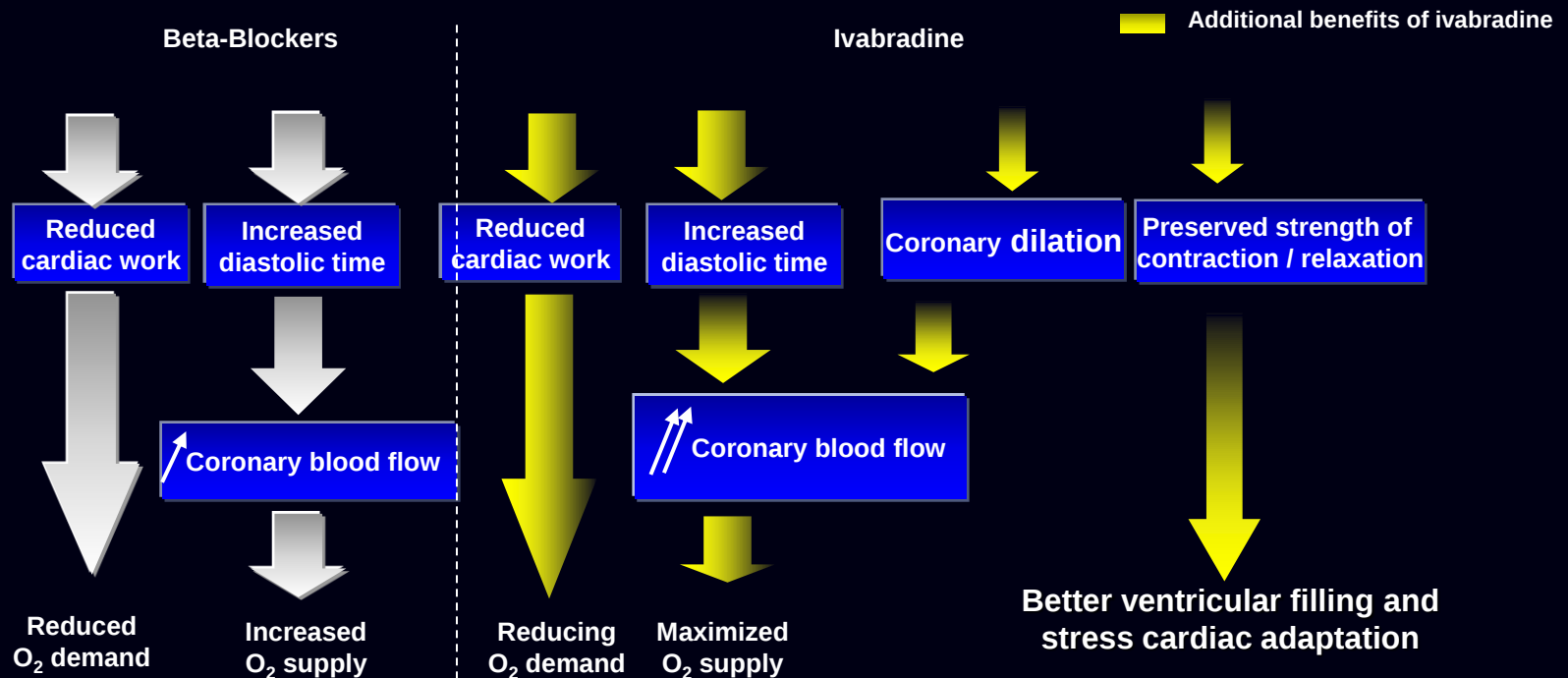
WHAT A TRIAL DOES NOT SIGNIFY



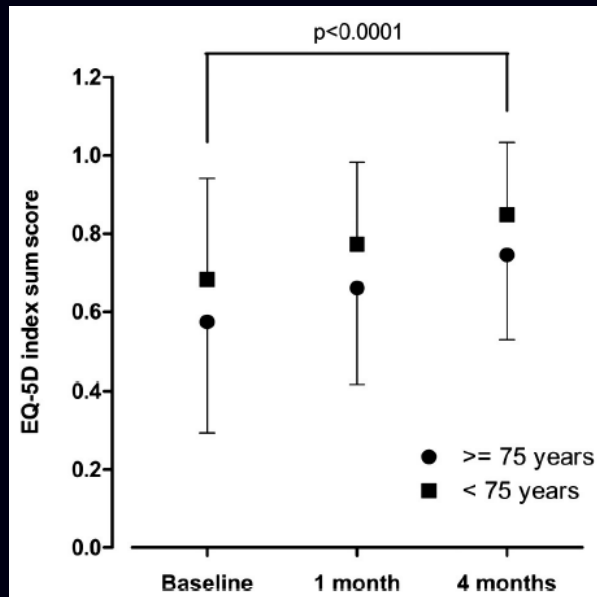
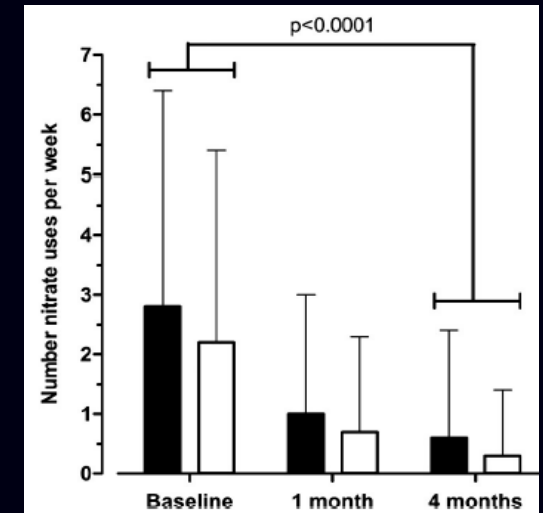
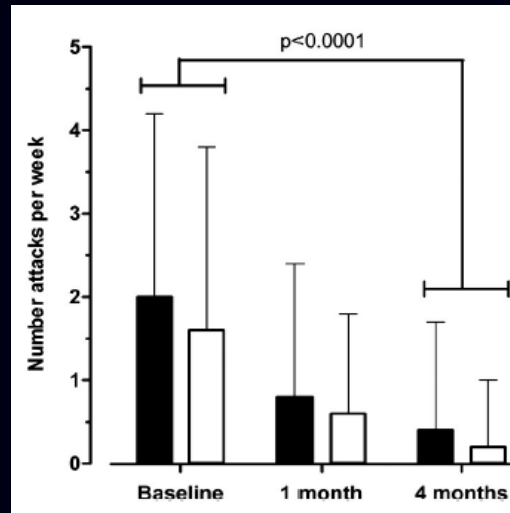
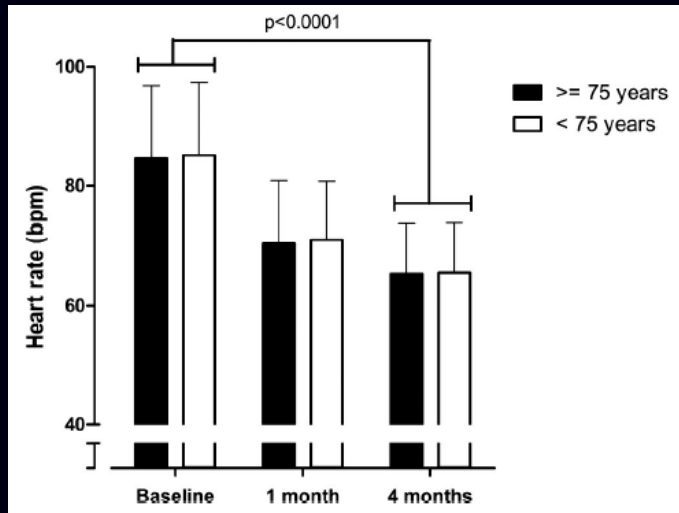
CIRCULATION OF BLOOD IN CORONARY ARTERIES

Coronary flow occurs only in diastole « An increase of 1% of diastolic time, increases blood flow by 2,6 to 6% in the subendocardium » - The difference between coronary artery pressure and LVEDP drives subendocardial perfusion

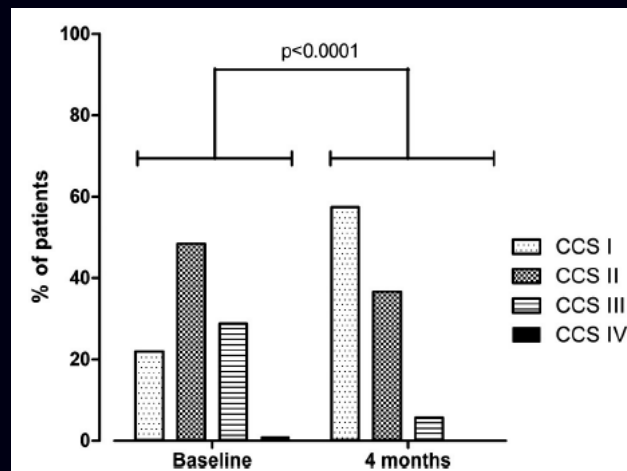
HEART RATE REDUCTION AND ISCHEMIA



Ivabradine in combination with beta-blocker reduces symptoms and improves quality of life in elderly patients with stable angina pectoris: Age-related results from the ADDITIONS study



Wider use in elderly, pts with incomplete myocardial revascularization or Total chronic occlusions or too risky business for revascularization



MIGLIORAMENTI DELLA CAPACITÀ DI ESERCIZIO E RIDUZIONE ATTACCHI DI ANGINA INDIPENDENTI DALLA PRESENZA DI DIABETE

3000 Pts

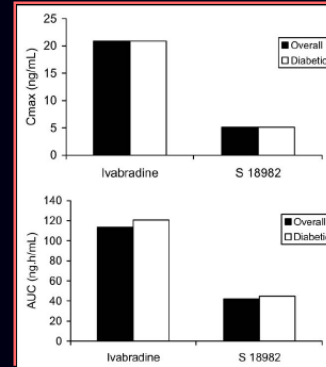
Farmacocinetica, Efficacia, Safety, Effetto sul metabolismo glicidico

Changes in frequency of angina attacks in patients with and without diabetes mellitus (DM)

Variable	Patients (n)	Baseline (attacks/wk)	Change From Baseline (attacks/wk)
No diabetes mellitus			
Ivabradine, all doses	1968	3.7 ± 6.1	-2.2 ± 4.6 (-60%)
Diabetes mellitus			
Ivabradine, all doses	457	3.3 ± 5.9	-2.0 ± 4.8 (-61%)

Exercise tolerance test (ETT) (treadmill, modified Bruce protocol) results for patients with and without diabetes mellitus (DM) in study 2

Variable	Patients (n)	Baseline (s)	Change From Baseline (s)
Total exercise duration			
No diabetes mellitus			
Ivabradine, all doses	475	602.9 ± 128.3	92.1 ± 124.0 (15%)
Diabetes mellitus			
Ivabradine, all doses	123	554.1 ± 150.5	77.9 ± 123.7 (14%)
Time to 1-mm ST-segment depression			
No diabetes mellitus			
Ivabradine, all doses	471	541.0 ± 158.4	93.5 ± 139.2 (17%)
Diabetes mellitus			
Ivabradine, all doses	123	464.6 ± 166.6	88.5 ± 150.5 (19%)
Time to angina onset			
No diabetes mellitus			
Ivabradine, all doses	474	482.1 ± 146.8	145.9 ± 150.8 (30%)
Diabetes mellitus			
Ivabradine, all doses	123	435.0 ± 144.3	129.1 ± 131.1 (30%)



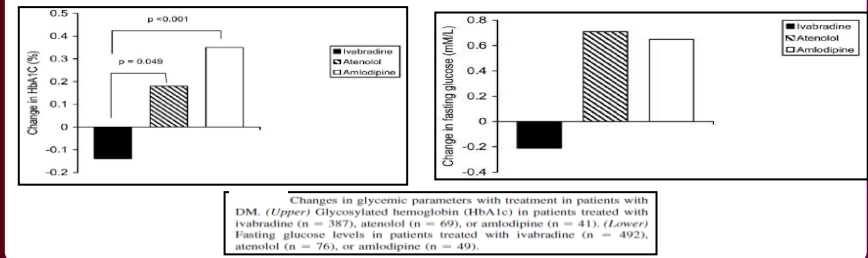
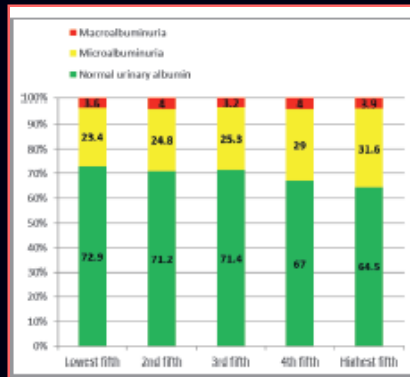
= FARMACOCINETICA

Borer et al. Am J Cardiol 2010

IVABRADINA EFFETTI SUL PROFILO GLICEMICO DEL PAZIENTE DIABETICO A CONFRONTO CON ALTRE TERAPIE

EFFETTI DELLA FREQUENZA CARDIACA SUGLI EVENTI MICROVASCOLARI

	No Events/No at Risk	Relative to Age, Sex, and Treatment	P	Falsely Adjusted	P
Major microvascular events	216/1113	1.18 (1.12-1.24)	<0.001	1.13 (1.07-1.20)	<0.001
Heart rate (b/min)					
Lowest HR (≤55 bpm)	110/588	1.00 reference		1.00 reference	
2nd HR (56-70 bpm)	184/593	1.23 (0.99-1.54)	0.07	1.27 (1.00-1.61)	0.047
3rd HR (71-75 bpm)	101/518	1.19 (0.86-1.66)	0.18	1.13 (0.80-1.61)	0.27
4th HR (76-85 bpm)	184/593	1.40 (1.16-1.67)	0.001	1.38 (1.10-1.70)	0.008
Highest HR (≥86 bpm)	240/598	1.78 (1.44-2.20)	<0.001	1.63 (1.29-2.06)	<0.001
P for trend					<0.001
P for nonlinearity					0.27
New or worsening retinopathy	25/1113	1.02 (1.16-1.30)	<0.001	1.16 (1.08-1.25)	<0.001
Heart rate (b/min)					
Lowest HR (≤55 bpm)	110/588	1.00 reference		1.00 reference	
2nd HR (56-70 bpm)	184/593	1.13 (0.86-1.50)	0.38	1.13 (0.85-1.51)	0.46
3rd HR (71-75 bpm)	110/518	1.01 (1.12-2.03)	0.97	1.44 (1.05-1.98)	0.02
4th HR (76-85 bpm)	184/593	1.67 (1.36-2.03)	<0.001	1.67 (1.29-2.16)	<0.001
Highest HR (≥86 bpm)	240/598	1.88 (1.46-2.37)	<0.001	1.72 (1.30-2.24)	<0.001
P for trend					<0.001
P for nonlinearity					0.69
New or worsening nephropathy	26/1113	1.13 (1.04-1.23)	0.003	1.11 (1.02-1.21)	0.01
Heart rate (b/min)					
Lowest HR (≤55 bpm)	110/588	1.00 reference		1.00 reference	
2nd HR (56-70 bpm)	184/593	1.24 (0.91-1.70)	0.18	1.45 (1.04-2.02)	0.03
3rd HR (71-75 bpm)	101/518	0.88 (0.65-1.21)	0.38	0.86 (0.61-1.21)	0.37
4th HR (76-85 bpm)	184/593	1.68 (1.31-2.15)	0.001	1.53 (1.10-2.10)	0.007
Highest HR (≥86 bpm)	240/598	1.80 (1.39-2.37)	0.001	1.61 (1.15-2.26)	0.006
P for trend					0.01
P for nonlinearity					0.003



11140 Pts
ADVANCE Trial

Graham S. Hillis et al Am Heart Assoc. 2012;1:e002832 doi: 10.1161/JAHA.112.002832

Conclusion—Patients with type 2 diabetes mellitus who have a higher resting heart rate experience a greater incidence of new-onset or progressive nephropathy and retinopathy.

Heart failure

Type-3 long-QT syndrome

Oxygen free radicals

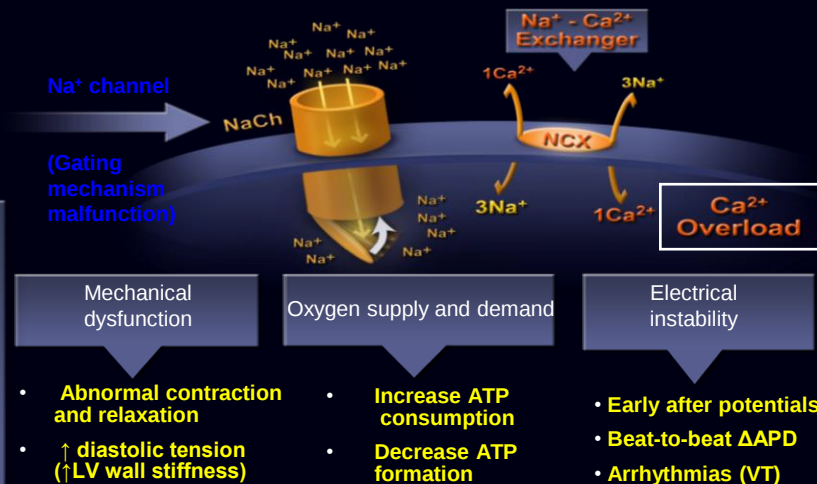
Post-MI remodeling

Ischemia

Zaza A et al, Pharm Ther 2008

Moss J et al, Cardiovasc Electrophysiol 2008

- Diseases (eg, ischemia, heart failure)
- Pathological milieu (reactive O₂ species, ischemic metabolites)
- Toxins and drugs (eg, ATX-II, etc.)

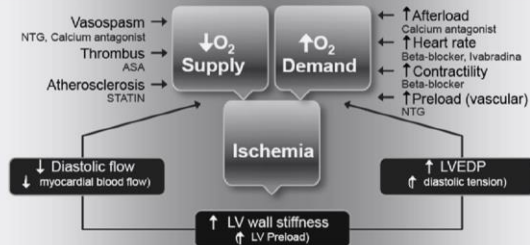


DIASTOLIC RELAXATION FAILURE INCREASES O₂ CONSUMPTION AND REDUCES O₂ SUPPLY

Acute alteration in regional lusotropic properties, the very first abnormality in “ischaemia cascade”

Tennant R and Wiggers CJ Am J Physiol 1935

CARDIOPATIA ISCHEMICA E TRATTAMENTO MEDICO



Adapted from Braunwald's Heart Disease 7th Edition 2006.

RANOLAZINE

DECREASES LATE SODIUM CURRENT

Decreases calcium overload

Improves relaxation

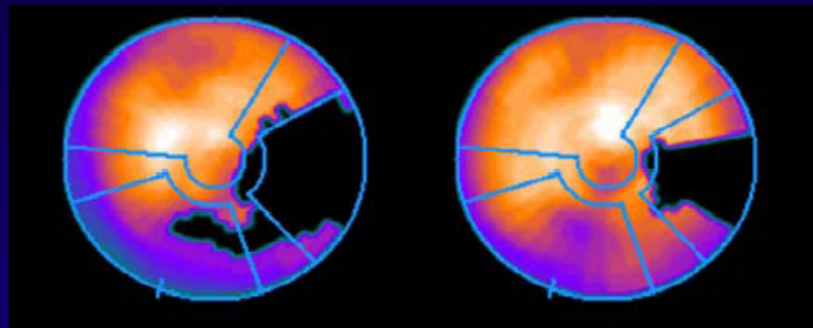
- ↓ Ca⁺⁺ transient duration
- ↓ Relaxation time
- ↑ Rate of relax

Improves electrical stability

- ↓ Prolong APD
- ↓ Afterpotential (EADs, DADs)
- ↓ Abnormal automaticity
- ↓ Disp. of repolarization

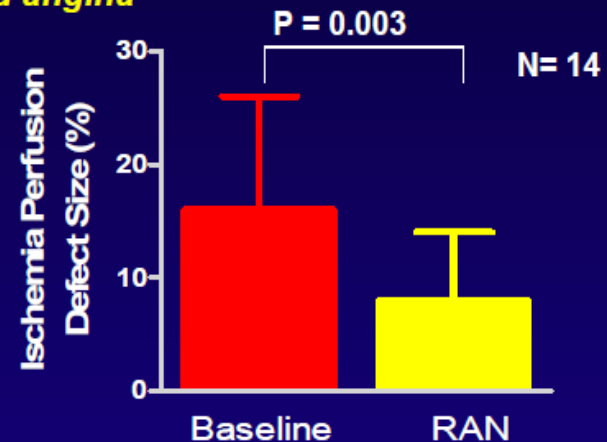
Myocardial Perfusion Imaging in Patients with Coronary Artery Disease Treated with Ranolazine

Exploratory study in 20 patients with CAD and angina



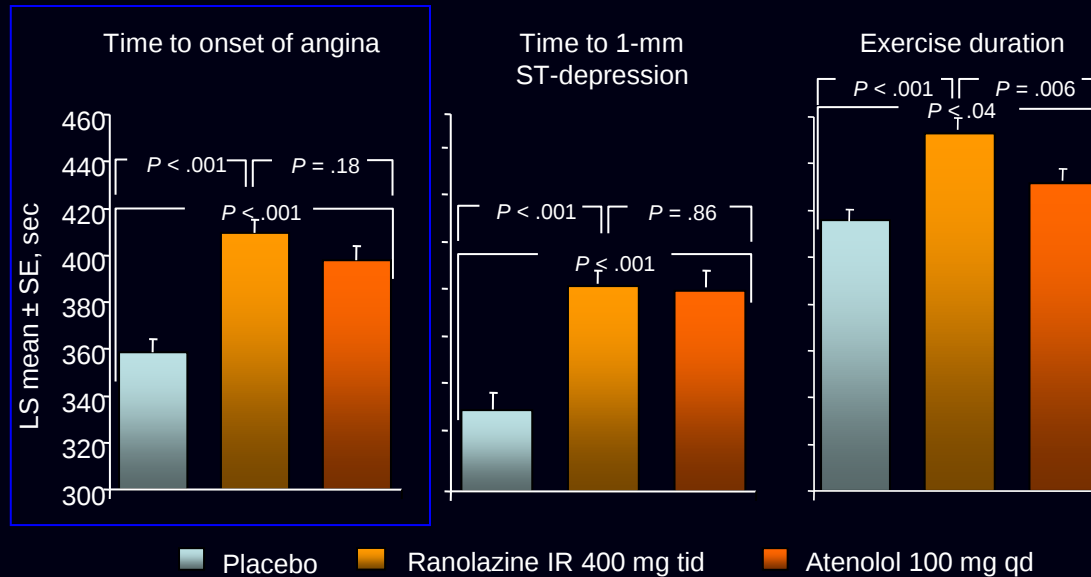
Before Ranolazine
PDS* = **25% of LV**
Peak HR = 142 bpm

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

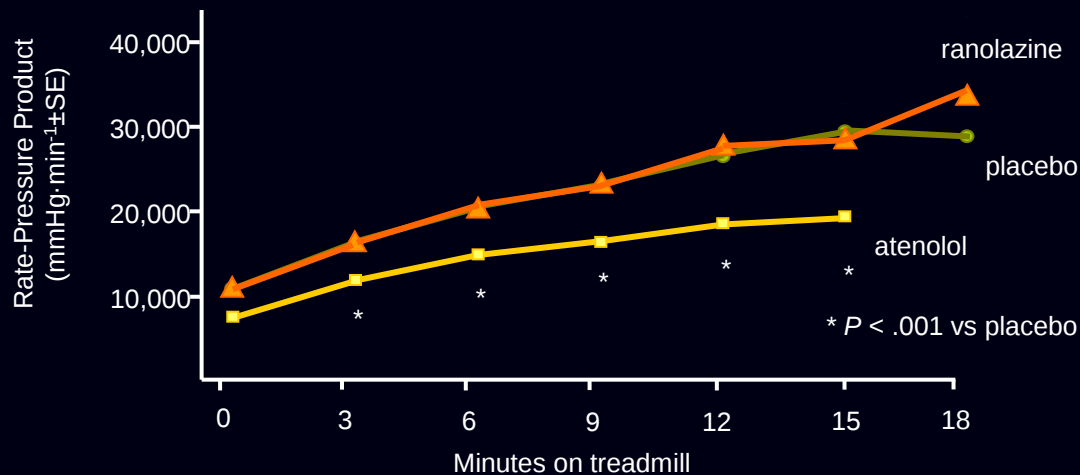


- Treadmill exercise time increased by 32 seconds ($p=0.017$, $n=20$)
- Angina reduced in 15 patients (75%) after ranolazine treatment.
- Improvement in the extent and severity of ischemia was noted in 14 patients (70%). Among these patients, ischemia PDS (% LV) decreased from 16 ± 10 to 8 ± 6 ($p=0.003$,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

RAN080: IS RANOLAZINE AS GOOD AS ATENOLOL ?



All patients analysis, N = 142

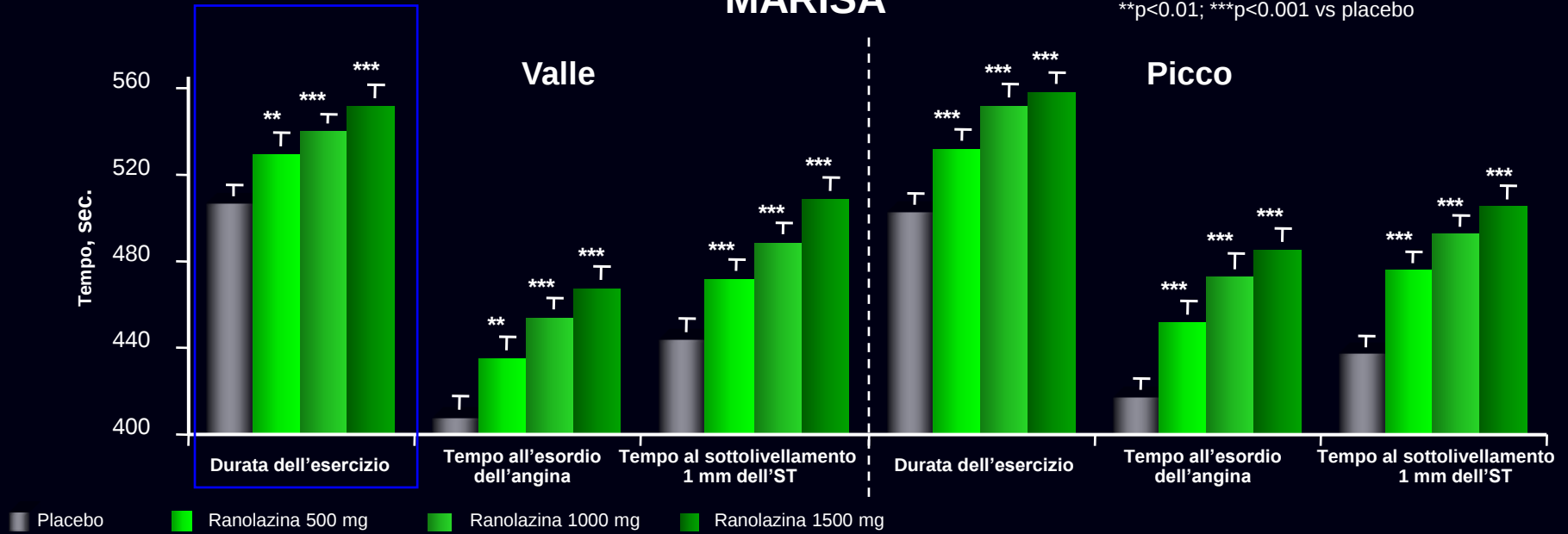


**RATE-PRESSURE
PRODUCT (RPP)**

Beta blockers blunt
exercise performance

MARISA

p<0.01; *p<0.001 vs placebo

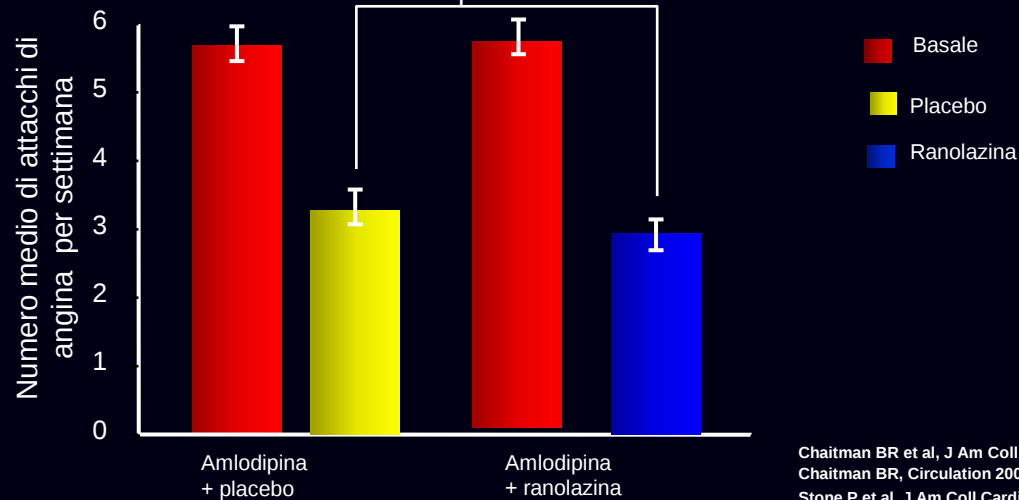


ERICA

ENDPOINT PRIMARIO: FREQUENZA ANGINA

p=0.48

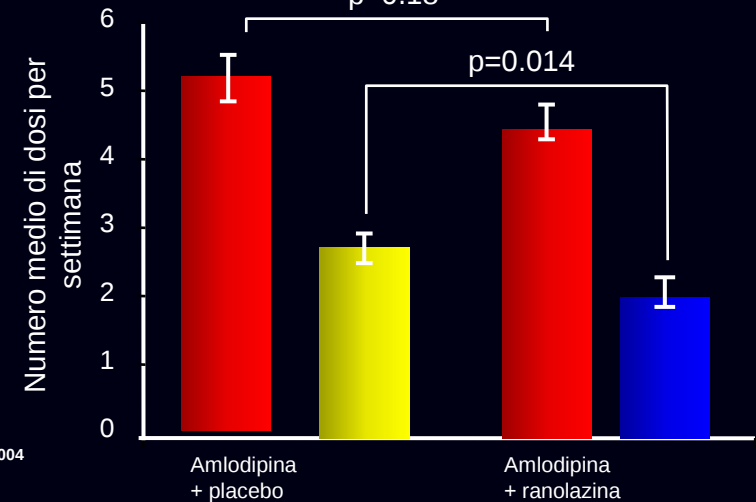
p=0.028



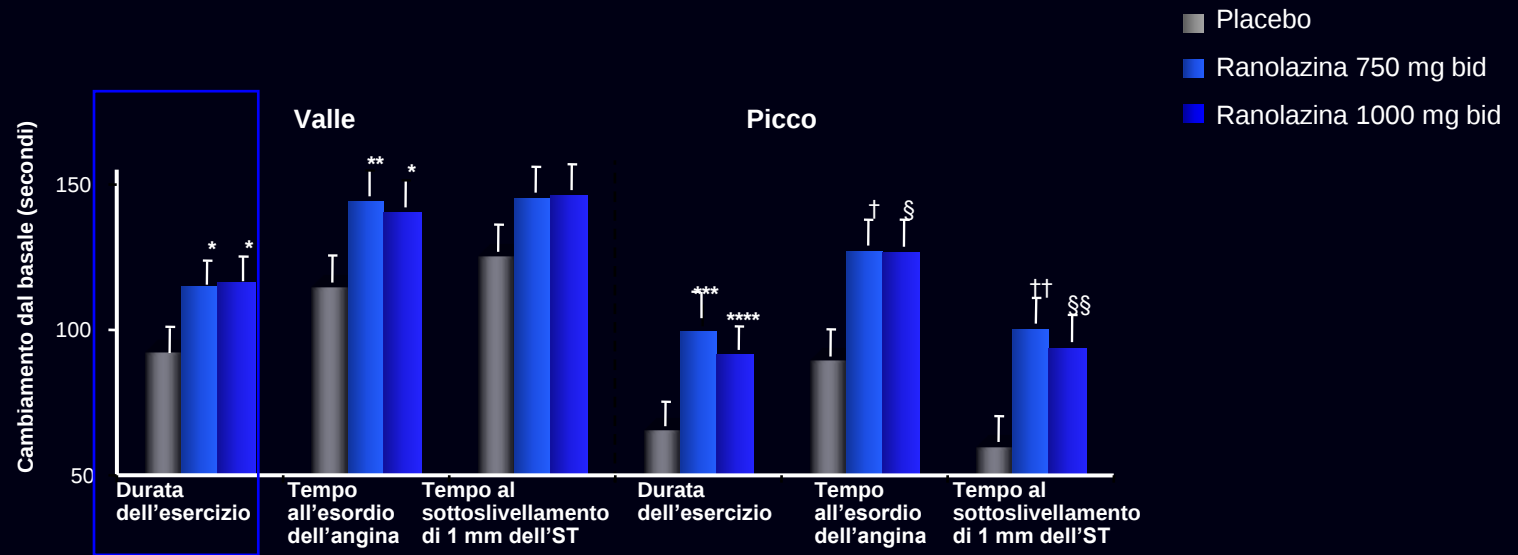
ENDPOINT SECONDARIO: CONSUMO NITRATI

p=0.18

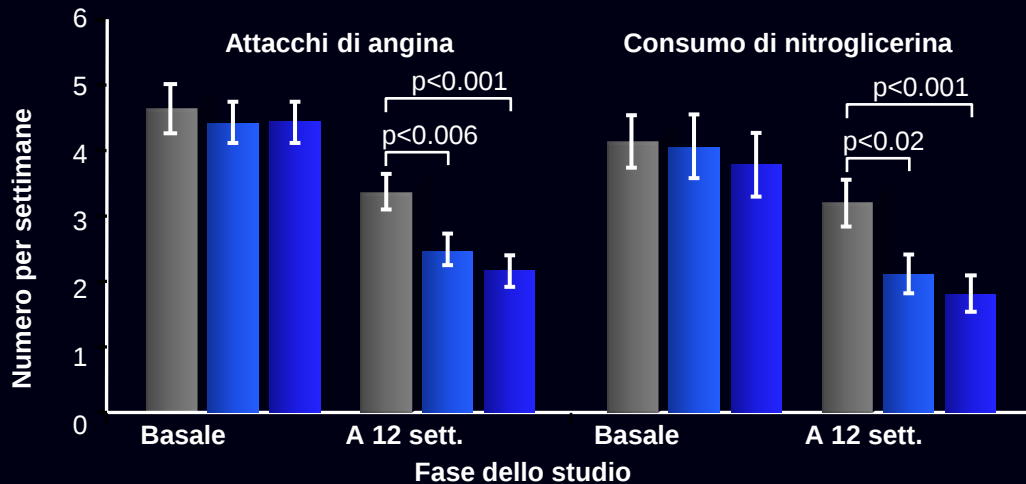
p=0.014



CARISA



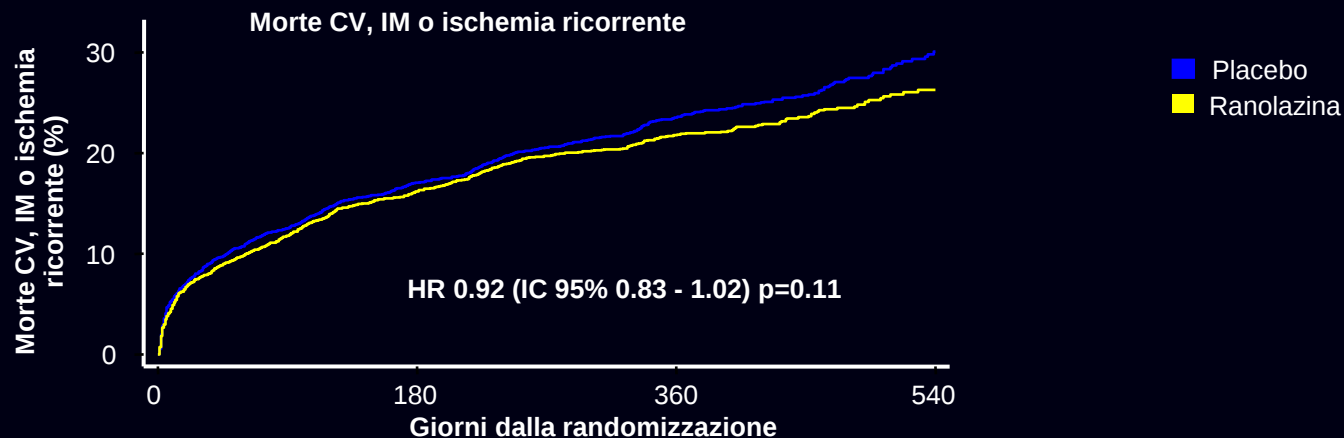
*p=0.03; **p=0.01; ***p=0.001; ****p=0.02; †p=0.002; §p=0.003; ††p<0.001; §§p=0.004 vs placebo



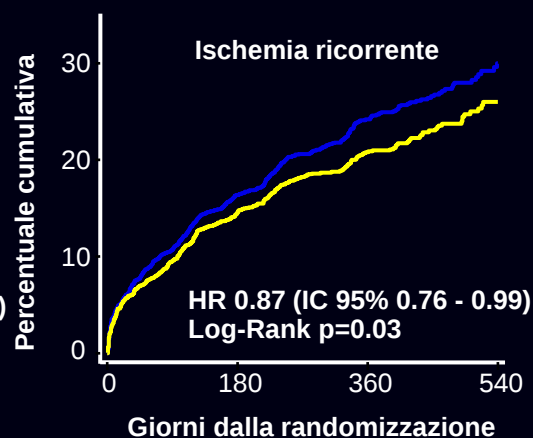
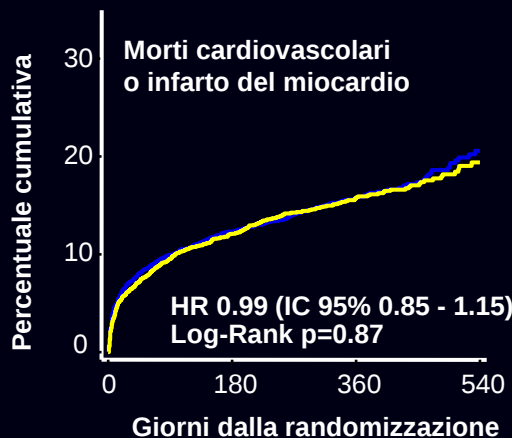
Rano vs placebo on top of OMT (diltiazem, beta-blocker, amlodipine)

MERLIN

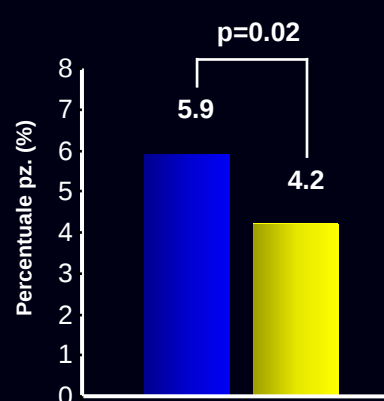
Endpoint primario: Placebo 23.5%, Ranolazina 21.8%



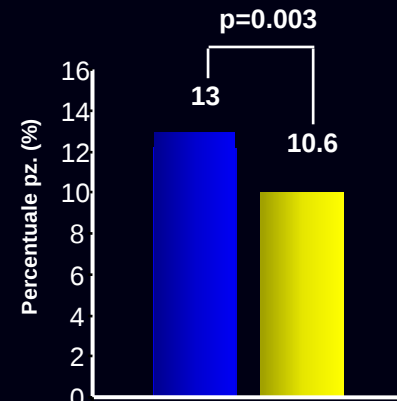
Componenti dell'endpoint primario di efficacia



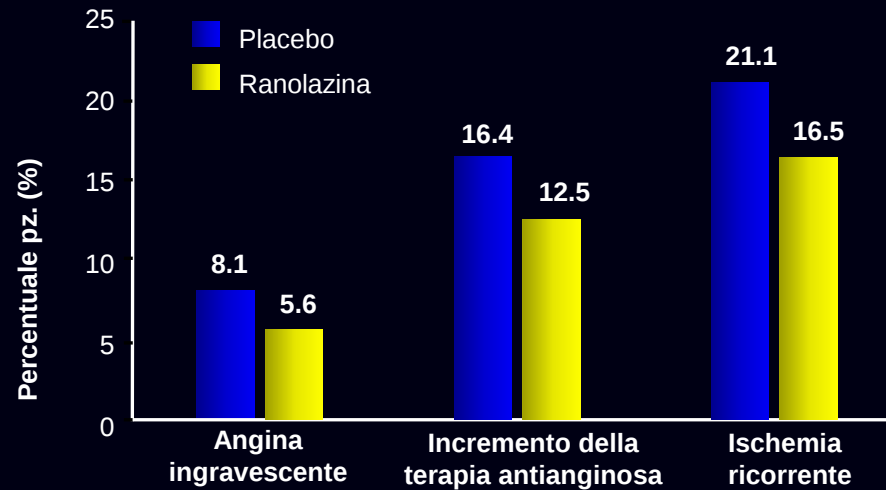
Peggioramento angina



Incremento terapia anti-anginosa



MERLIN: EFFICACIA IN PAZIENTI CON ANGINA CRONICA



Endpoint primario

morte CV, IMA, ischemia ricorrente

Ranolazina vs placebo

-14 %

p=0.017

HR 0.86 (IC 0.75-0.97)

Ischemia ricorrente

Ranolazina vs placebo

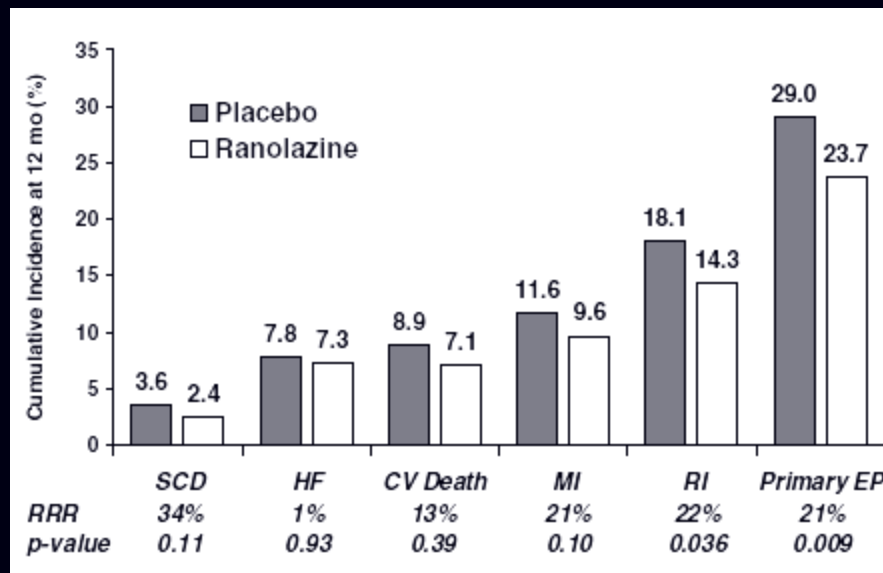
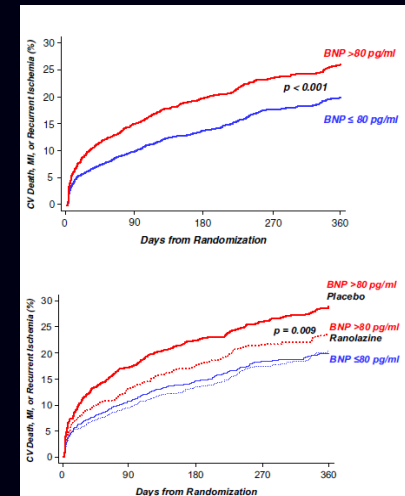
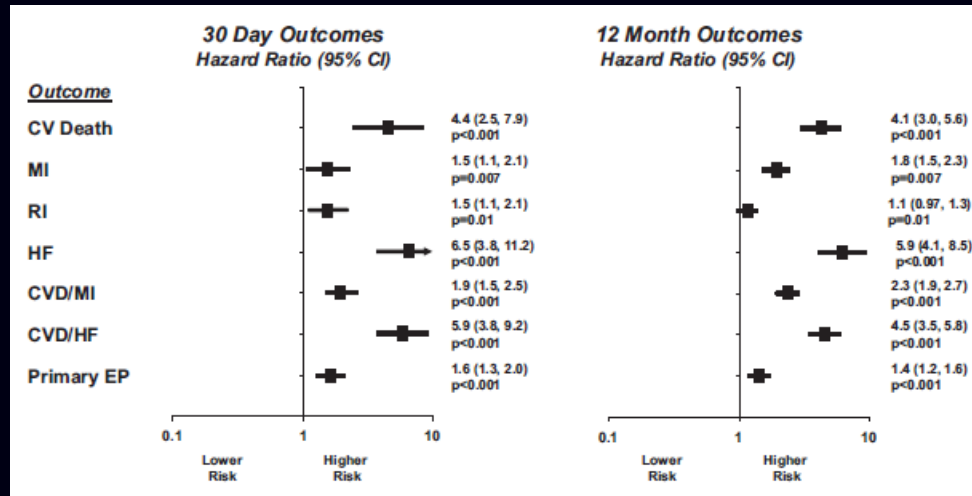
-22 %

p=0.002

HR 0.78 (IC 0.67-0.91)

RANOLAZINE - SCA - BNP > 80 pg/ml

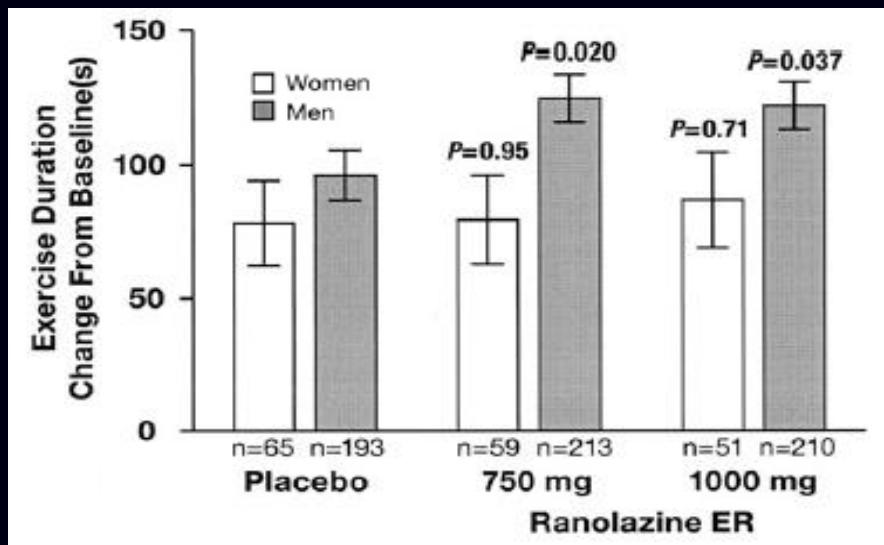
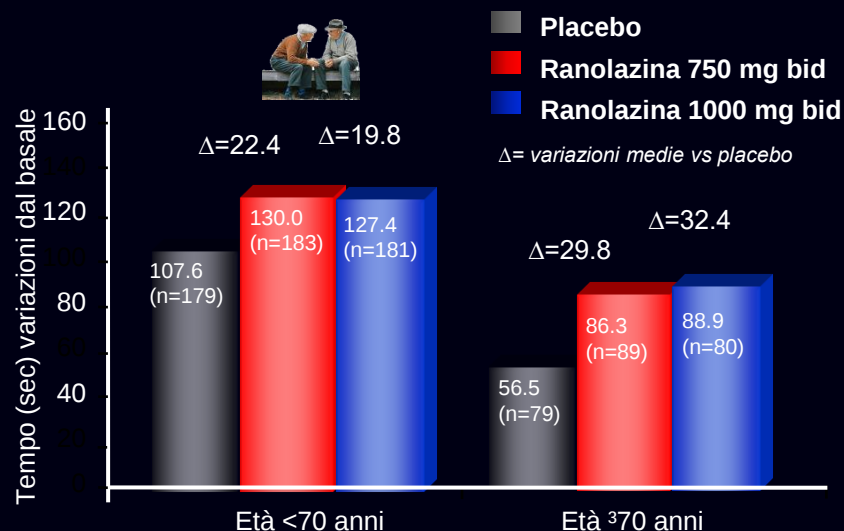
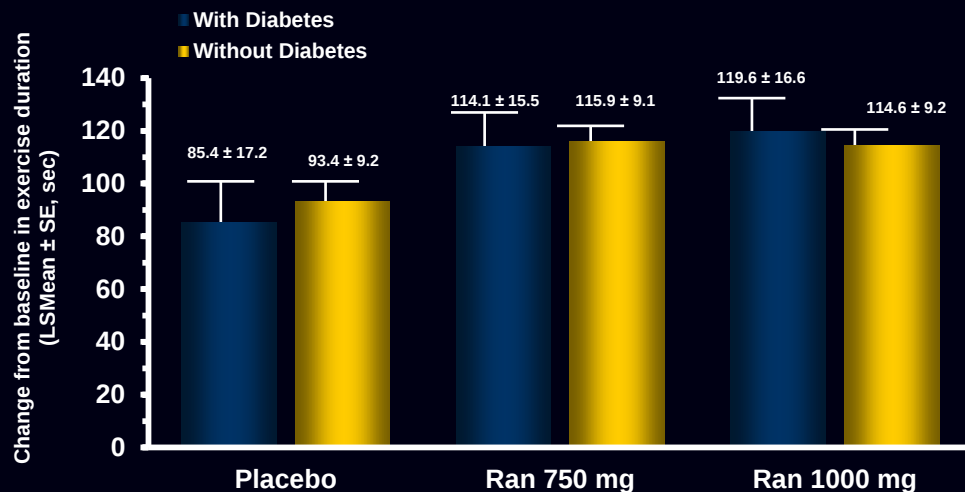
MERLIN-TIMI 36 4543 pts



Ranolazine significantly reduced (-21%) the primary end point (CV death-Mi, recurrent ischemia) p=0.009

EFFICACIA DI RANOLAZINA NEI SOTTOGRUPPI AD ALTO RISCHIO

PAZIENTI DIABETICI



Dagli studi CARISA ed ERICA aumento significativo di :

- durata dell'esercizio
- tempo all'insorgenza di angina
- tempo al sottolivellamento ST 1 mm

nei pazienti diabetici, anziani e donne

MERLIN: SAFETY AND TOLERABILITY

End point	Placebo (n = 3273)	Ranolazine (n = 3268)	Hazard ratio	P value
Death, any cause (number of patients)	175	172	0.99	.91
Sudden cardiac death (number of patients)	65	56	0.87	.43
Symptomatic documented arrhythmia (number of patients)	102	99	0.97	.84
Clinically significant arrhythmia on Holter (% of patients)	83.1%	73.1%	0.89	<.001

EVENTI AVVERSI PIÙ FREQUENTI (%)		
	Ranolazina	Placebo
Vertigini	12.4	7.4
Nausea	9.7	6.1
Stipsi	8.5	3.3

STUDIO ROLE

Ranolazine Open Label Experience 746 pz FU @ 2.8 anni

MARISA

n=168 hanno completato
e sono risultati
eleggibili per il ROLE

n=143 (85% dei pazienti
eleggibili)

CARISA

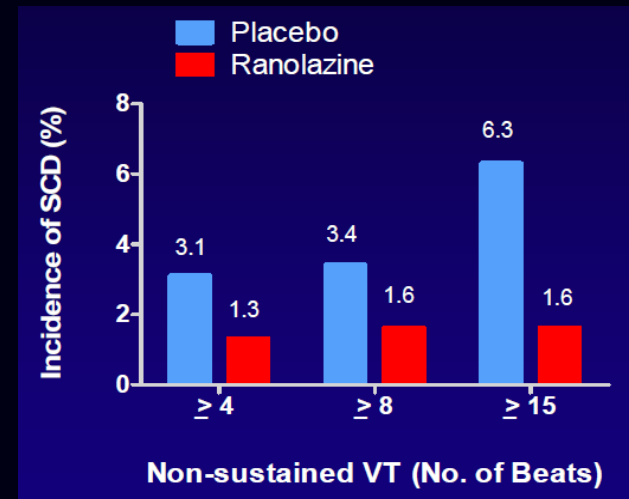
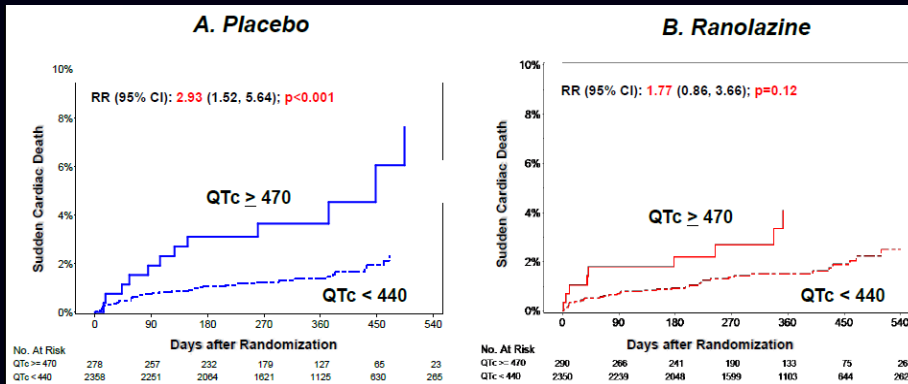
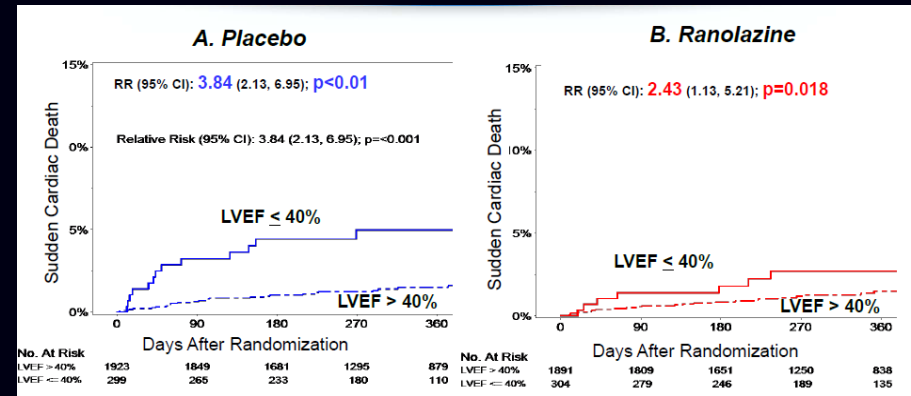
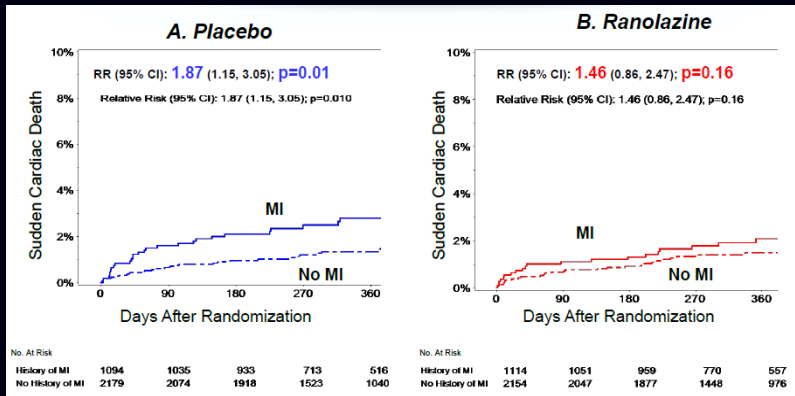
n=731 hanno completato
e sono risultati eleggibili per il ROLE

n=603 (82% dei pazienti eleggibili)

Wilson SR, et al. J Am Coll Cardiol 2009
Morrow et al, JAMA 2007

- Gli eventi avversi più comuni sono stati: **vertigini** e **stipsi**
- Riscontrati modesti allungamenti del QTc: allungamento medio di 2.4 ms
- **Nessun paziente ha interrotto lo studio per allungamento del QTc**
- Profilo di **sicurezza e tollerabilità a lungo termine** di ranolazina
- Non incremento della mortalità cardiaca a lungo termine
- L'elevata **percentuale di pazienti che hanno volontariamente deciso di continuare il trattamento open label con ranolazina**

RANOLAZINA ED EFFETTO ANTIARITMICO



Prokopczuk E et al, HR 2009
 Scirica B et al, Circulation 2007
 Scirica B et al, J Am Coll Cardiol 2009

RANOLAZINE: PILL IN THE POCKET FOR AF

AF <3HRS >48 HRS, RANOLAZINE 2000 MG P.O., SINGLE DOSE

Patient	Age/ Sex	EF%	LAD/ LAVI	AF type	Structural Heart Disease	Associated Conditions	Location of initial R dose
1	57/M	50	52/41	paroxysmal (failed D, S)	cardiomyopathy	none	home
2	77/M	60	41/36	paroxysmal	LAE, LVH	HTN	office
3	76/M	60	38/29	paroxysmal	LVH, mild MR, brad-tach syn	pacemaker	office
4	71/M	55	40/30	paroxysmal	LAE, LVH	lymphoma	hospital
5	65/F	65	38/49.4	initial episode	LAE, LVH	cinthosis, colon ca	hospital
6	68/F	60	35/56	paroxysmal (failed A, S)	LAE, LVH	HTN, OSA	home
7	81/F	60	62/41	initial episode post op	mild AS & MS moderate MR		
8	53/M	40	31/29	initial episode	Post MI		
9	83/F	65	43/42	paroxysmal	CAD, brad-tach syn, LAE, LVH Mild AS		
10	81/F	20	33/36	initial episode	CAD,		
11	72/m	40	56/42	initial episode	CAD		
12	65/m	65	46/38	paroxysmal	LVH, LAE		
13	73/M	45	40/28	initial episode	CAD, LAE Re, JWMI		
14	55/M	60	none	initial episode	CAD, limited Anterior MI	HTN	hospital
15	80/M	50	42/41	initial episode	CAD	HTN renal failure, cardiac surgery	hospital
16	70/M	60	32/30	Initial episode	LAE, LVH	stage 4 non hodkins lymphoma	hospital
17	71/M	65	39/41	initial episode	LAE, LVH, CAD	HTN, CAD	hospital
18	72/M	none	none	initial episode	none known	Stage 4 lymphoma	hospital

CONVERSION RATE 72%

Patient	Out come of 1st attempt	Current status or outcome
1	converted to NSR	chronic ranolazine for AF suppression
2	converted to NSR	continues to use ranolazine on as needed basis for AF
3	converted to NSR	continues to use ranolazine on as needed basis for AF
4	converted to NSR	recurrent AF treated with chronic amiodarone
5	converted to NSR	remains on ranolazine in NSR
6	6/7/14	remains in AF chronically having failed sotalol and amiodarone
		electrically cardioverted, maintained on ranolazine for AF prophylaxis
		treated with 1 month ranolazine
		on amiodarone for recurrent AF
		discharged on ranolazine, died 1 month later in palliative care
		electrically cardioverted, remaining in NSR
		remaining in sinus without anti -arrhythmic agents
		remaining in sinus without anti -arrhythmic agents
14	converted to NSR	remaining in sinus without anti -arrhythmic agents
15	converted to NSR	relapsed 3 weeks later and started on amiodarone
16	failed to convert	responded to DC cardioversion
17	converted to NSR	remaining in sinus without anti -arrhythmic agents
18	failed to convert	responded to DC cardioversion - died of disease in palliative care

RANO MEGLIO DI AMIODARONE NEL PREVENIRE FA POST-CABG

393 pazienti

211 Amiodarone 400 mg pre-intervento + 200 mg post

182 Ranolazina 1500 mg pre-intervento +1000 mg post

26.5 % FA nel gruppo Amiodarone

17.5 % FA nel gruppo Ranolazina

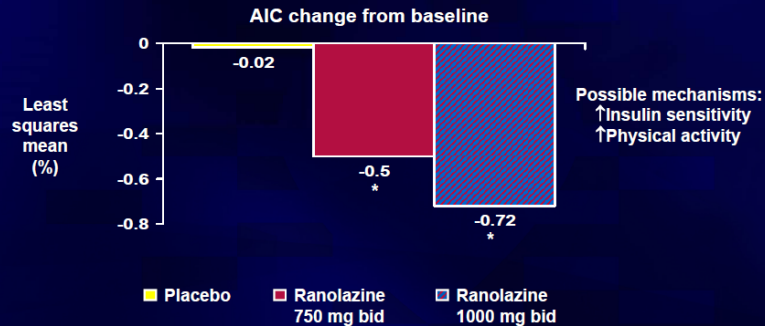
P = 0.035

Ranolazina prolunga la refrattarieta' atriale , inibisce le depolarizzazioni e l'attivit  triggerata

RANOLAZINA E METABOLISMO GLICIDICO

CARISA: Reductions in A1C (diabetes substudy)

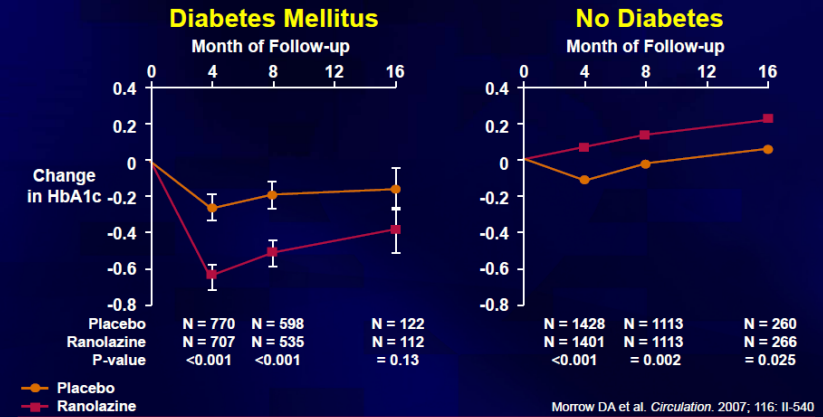
n = 131 with diabetes (n = 31 on insulin)



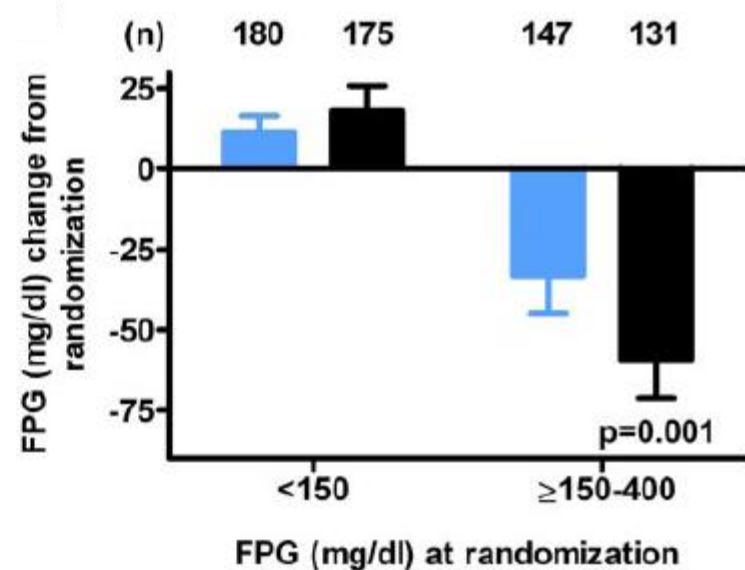
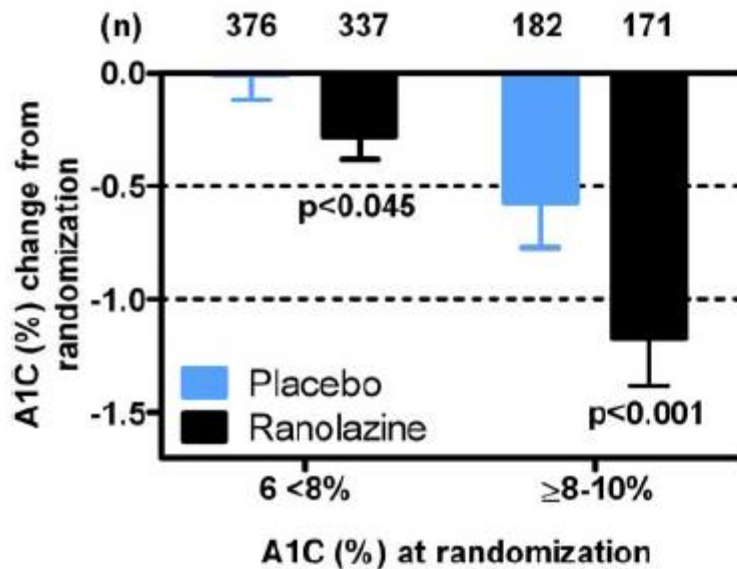
*P ≤ 0.008 vs placebo

Cooper-DeHoff R, Pepine CJ. *Eur Heart J.* 2006;27:5-6.
Timmis AD et al. *Eur Heart J.* 2006;27:42-8.

MERLIN-TIMI 36: Effect of ranolazine on HbA1c



Morrow DA et al. *Circulation.* 2007; 116: II-540



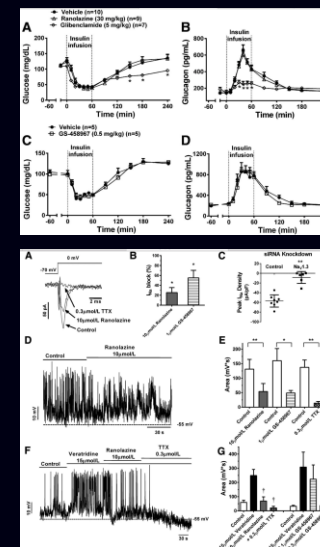
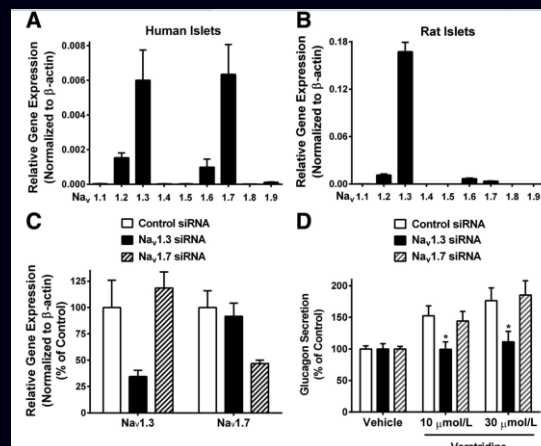
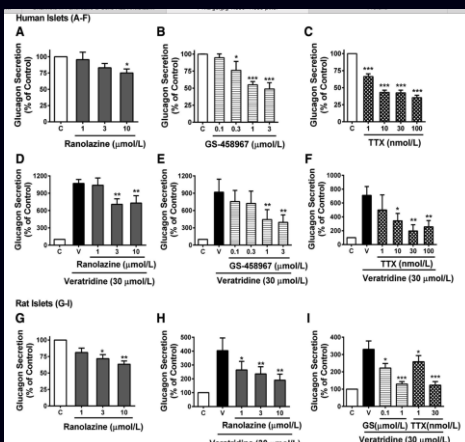
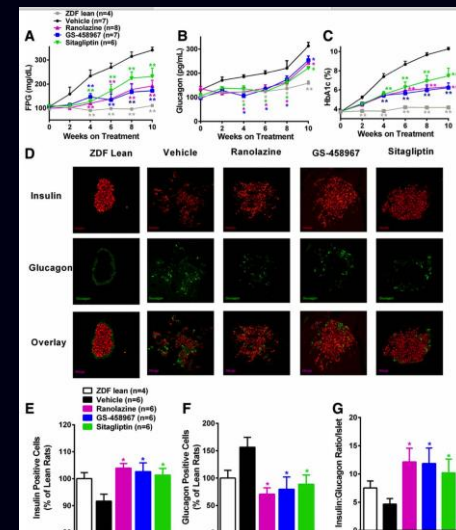
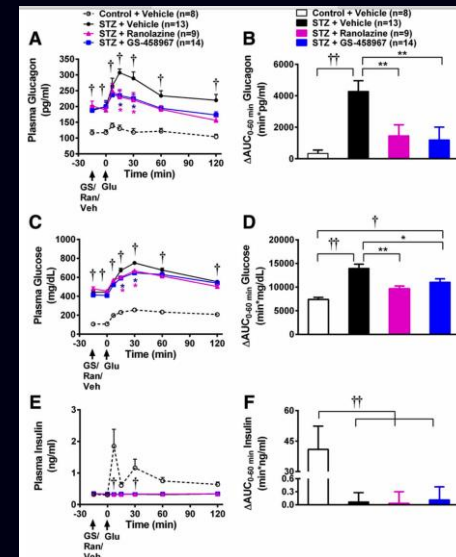
Blockade of Na⁺ Channels in Pancreatic α -Cells Has Antidiabetic Effects

Pancreatic α -cells express voltage-gated Na⁺ channels (NaChs), which support the generation of electrical activity leading to an increase in intracellular calcium, and cause exocytosis of glucagon.

ranolazine, via blockade of NaChs in pancreatic α -cells, inhibits their electrical activity and reduces glucagon release.

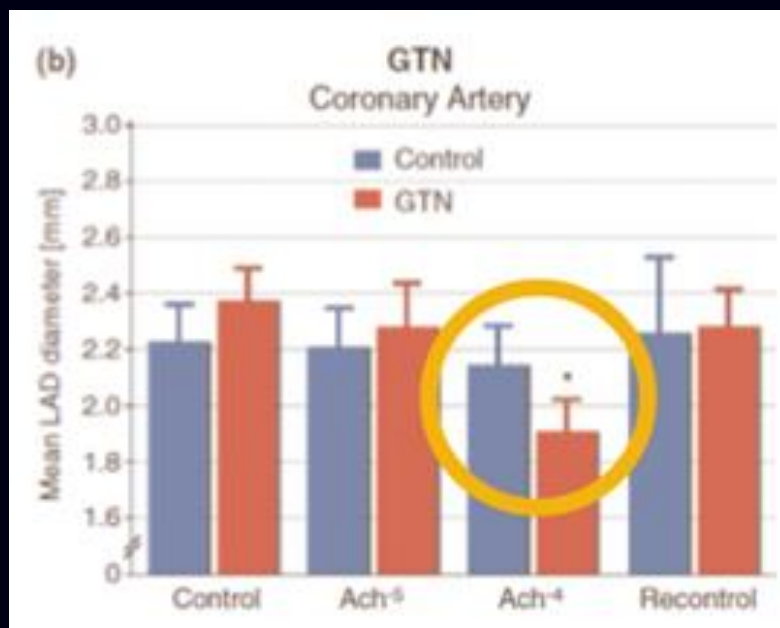
glucose-lowering effects of ranolazine are due to the blockade of NaChs.

EFFETTO ANTIDIABETICO DI RANO



Nitrate therapy and nitrate tolerance in patients with coronary artery disease

Thomas Münzel and Tommaso Gori



Prolonged exposure to organic nitrates induces tolerance, sympathetic activation, and endothelial dysfunction in patients with cardiovascular disease

Nitrate-induced endothelial dysfunction, human studies

RIABILITAZIONE E TERAPIA

1. Il mio pz 80enne con IMA ha fumato per decenni. Perché dovrebbe smettere?

Riduzione mortalità 25-50%, meta' nel primo anno

Riduzione di mortalità $\geq$ a quella ottenuta con ASA, β -blocc, ACE-I. Houston TK et al, Am J Med 2005

2. I pz anziani hanno abitudini radicate. Modificazione di dieta e stile di vita hanno senso?

Uomini e donne di età 70-90 anni hanno una riduzione di mortalità per tutte le cause e CV $> 50\%$ con dieta e abitudini sane di vita. Knoop KTB et al, JAMA 2004

3. Gli anziani sono spesso malnutriti. E' importante la sindrome metabolica?

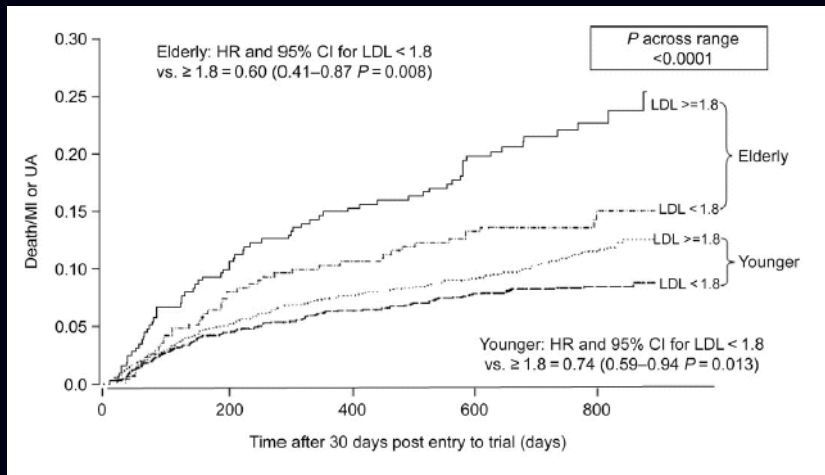
Il 40% degli anziani ha sindrome metabolica. Dislipidemia, ipertensione, insulino-resistenza danno di per se' rischio e si potenziano. Lavie CJ, Am J Geriatr Cardiol 2004

4. Il mio 75enne infartuato riferisce fatica e paura a muoversi. Puo' e come iniziare attivita' fisica?

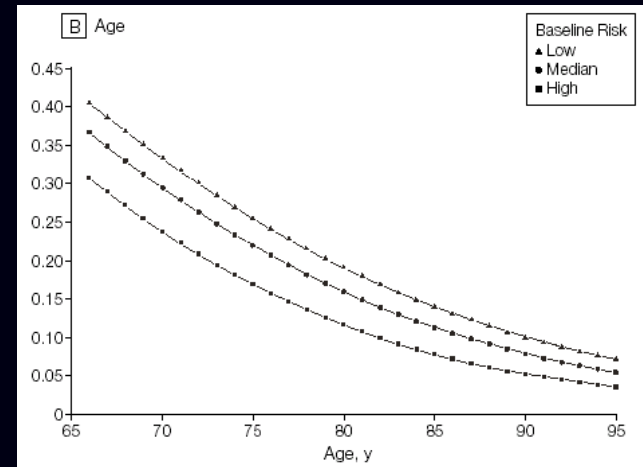
Riferire ad una riabilitazione cardiologica permette di iniziare attivita' fisica e ridurre il rischio CV. La capacita' funzionale e sintomi esercizio-relati migliorano dopo 12 settimane. Attivita' fisica impatto su obesita', ipertensione, dislipidemia e insulino-R. Williams MA et al, Circulation 2002

5. Le statine sono costose e potenzialmente pericolose in associazione multifarmaco. Il beneficio vale il costo ed il rischio?

La riduzione LDL con statina riduce nell'anziano gli eventi CV come nel giovane ed il beneficio e' evidente dopo un anno di trattamento; concomitante riduzione del rischio di stroke. Le statine sono sicure, ben tollerate e con minimi effetti collaterali negli anziani. **PROSPER Study, Lancet 2002** **Grundy SM et al, Circulation 2004**



Ray KK et al, Eur Heart J 2006



Ko DT, JAMA 2004

GRAZIE PER L'ATTENZIONE



amacchi@aobusto.it

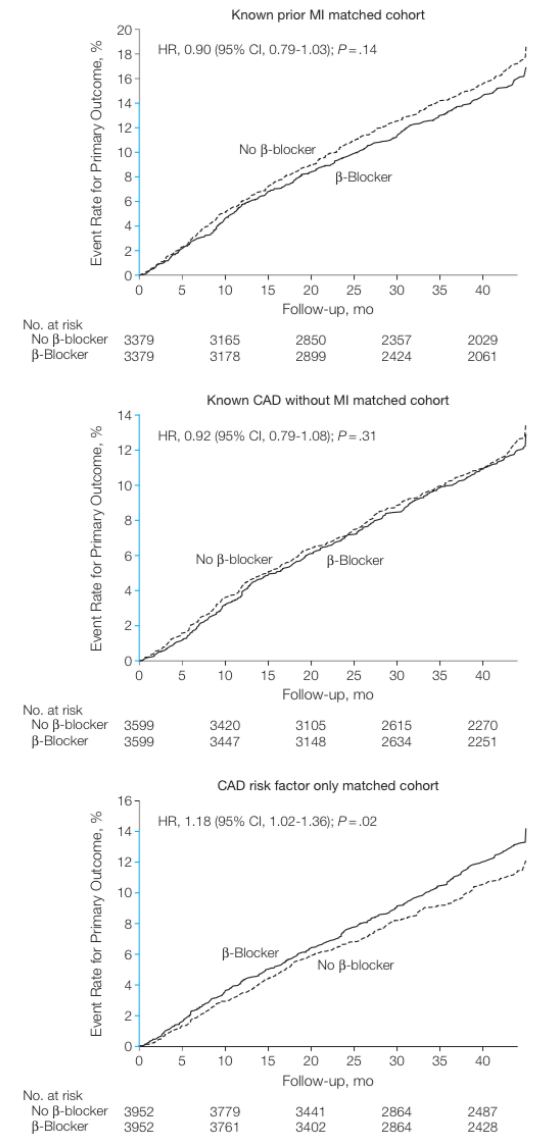
BELIEVE IT OR NOT

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

β -Blocker Use and Clinical Outcomes in Stable Outpatients With and Without Coronary Artery Disease

Effects of Angiotensin-Converting Enzyme Inhibitors and Beta Blockers on Clinical Outcomes in Patients With and Without Coronary Artery Obstructions at Angiography
(from a Register-Based Cohort Study on Acute Coronary Syndromes)

Effetto prognostico del β -bloccante solo nel breve periodo post-IMA



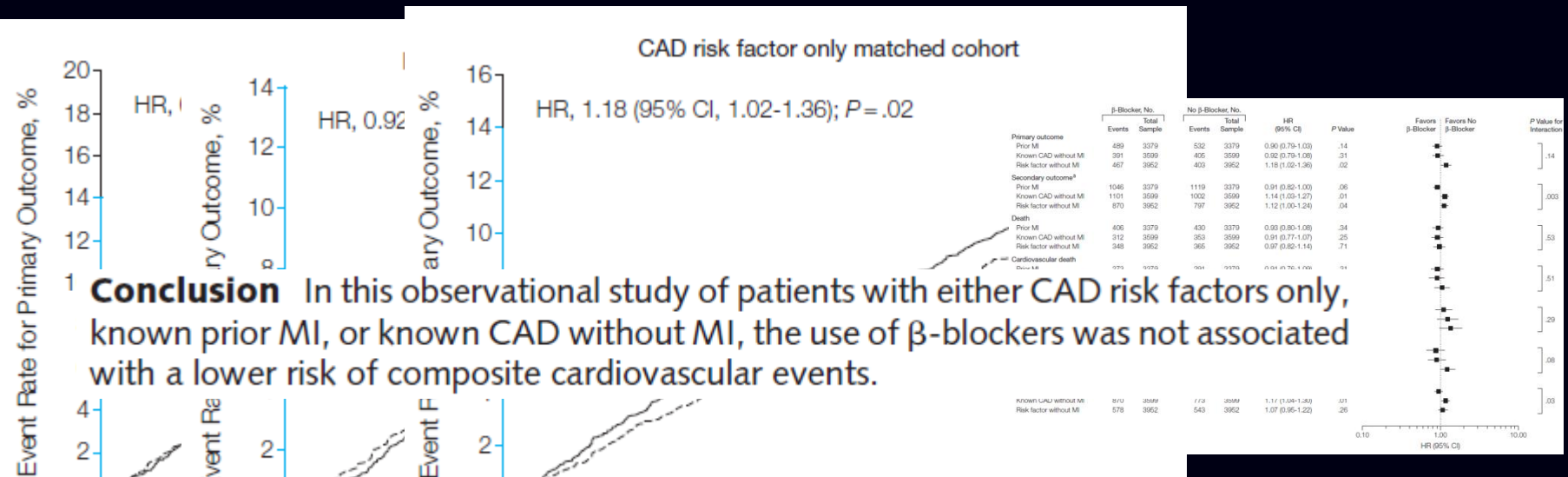
Andersson C et al, J Am Coll Cardiol 2014
Bangalore S et al, JAMA 2012
Manfrini O et al, Am J Cardiol 2014

βB - CAD - PROGNOSI

Effects of Angiotensin-Converting Enzyme Inhibitors and Beta Blockers on Clinical Outcomes in Patients With and Without Coronary Artery Obstructions at Angiography (from a Register-Based Cohort Study on Acute Coronary Syndromes)

Manfrini O et al , Am J Cardiol 2014

mortality. In conclusion, ACE-inhibitor therapy seems to be an effective first-line treatment for preventing the occurrence of mortality in patients with nonobstructive CAD © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:1628–1633)



CONCLUSIONS Use of beta-blockers among patients with new-onset CHD was associated with a lower risk of cardiac events only among patients with a recent MI. (J Am Coll Cardiol 2014;64:247-52) © 2014 by the American College of Cardiology Foundation.

Andersson C et al , J Am Coll Cardiol 2014

Bangalore S et al , JAMA 2012

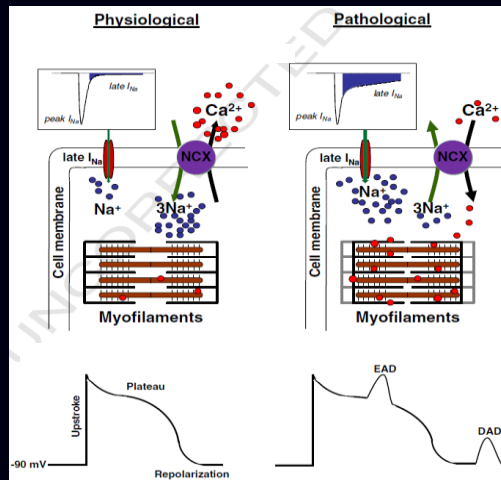
TAKE HOME POINTS

CAD - HF - ARITMIE - DIABETE

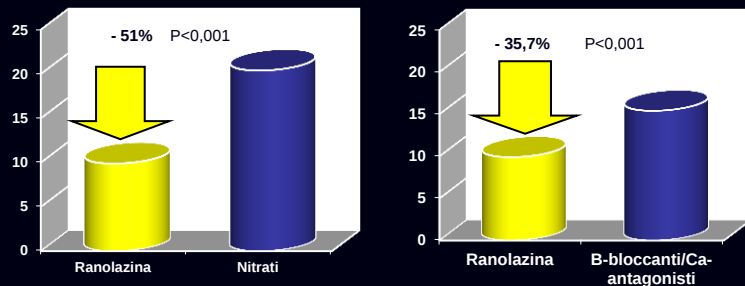
UNIQUE MODE OF ACTION OF RANOLAZINE

Composto con potente azione antiischemica ed antianginosa, con proprieta' antaritmiche, effetto sulla disfunzione diastolica/sistolica e che migliora il metabolismo glicidico

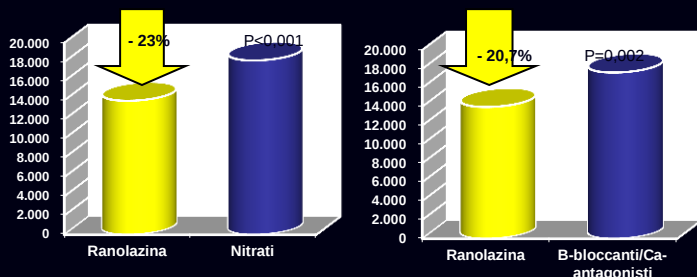
Sossala S, Maier LS, Pharmacol Therapeutics 2011



PERCENTUALE DI RIVASCOLARIZZAZIONE



COSTI TOTALI DI CURA (\$)



Costs and Clinical Outcomes Associated with Use of Ranolazine for Treatment of Angina

4.545 angina pts

CONCLUSIONS: Adding ranolazine to the treatment regimen of patients with poorly controlled angina was associated with lower rates of revascularization and lower total costs of care than for comparable patients, differences both statistically and clinically relevant.