58 Congresso SIGG

Mcentro Congressi Lingotto di Torino
27/11/2013 - 30/11/2013

SIMPOSIO
"SCOMPENSO CARDIACO ACUTO E COMORBILITÀ NELL'ANZIANO"

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Abete P, MD, PhD

Dipartimento di Scienze Mediche Traslazionali
Università di Napoli Federico II

July 8, 1871.] *THE BRITISH MEDICAL JOURNAL*

THE HASTINGS PRIZE ESSAY,
1870.

ON DIGITALIS: ITS MODE OF ACTION AND ITS USE.*

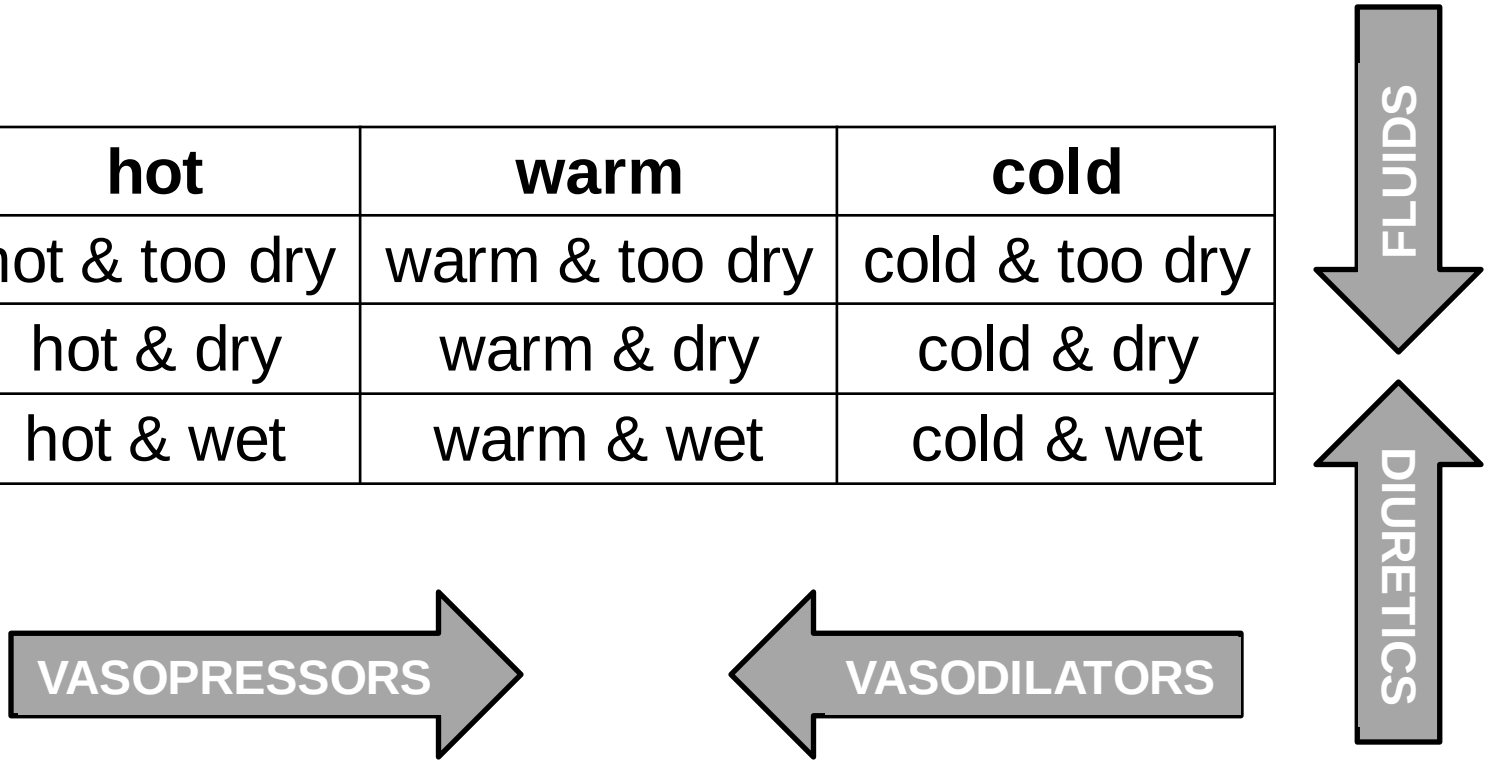
By J. MILNER FOTHERGILL, M.D.,
Senior Resident Medical Officer to the Public Dispensary, Leeds.

Digitalis' mystery

…since 1870

Hemodynamic profiles of acute heart failure

hot	warm	cold
hot & too dry	warm & too dry	cold & too dry
hot & dry	warm & dry	cold & dry
hot & wet	warm & wet	cold & wet

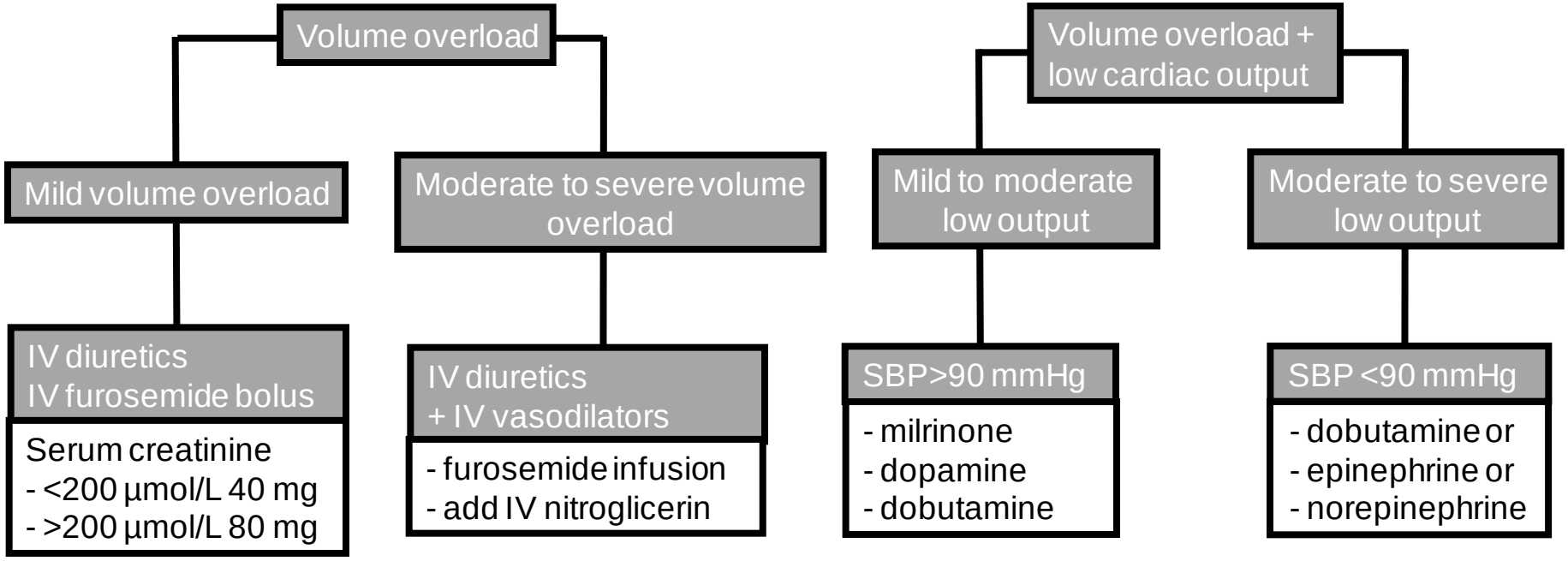


1) “dry” describes volume depletion, which is accompanied by low central venous pressure and poor skin turgor: patients are treated with fluids.
2) “wet” describes volume overload, which is usually accompanied by elevated jugular venous pressure, edema, and rales: patients are treated by removing excess

Liu SS et al., Am J Med 2013

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

ACUTE HEART FAILURE, treatment initiated based on symptoms and signs



Howlett JG, Can J Cardiol 2011

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

ACUTE HEART FAILURE, treatment initiated based on symptoms and signs

Volume overload

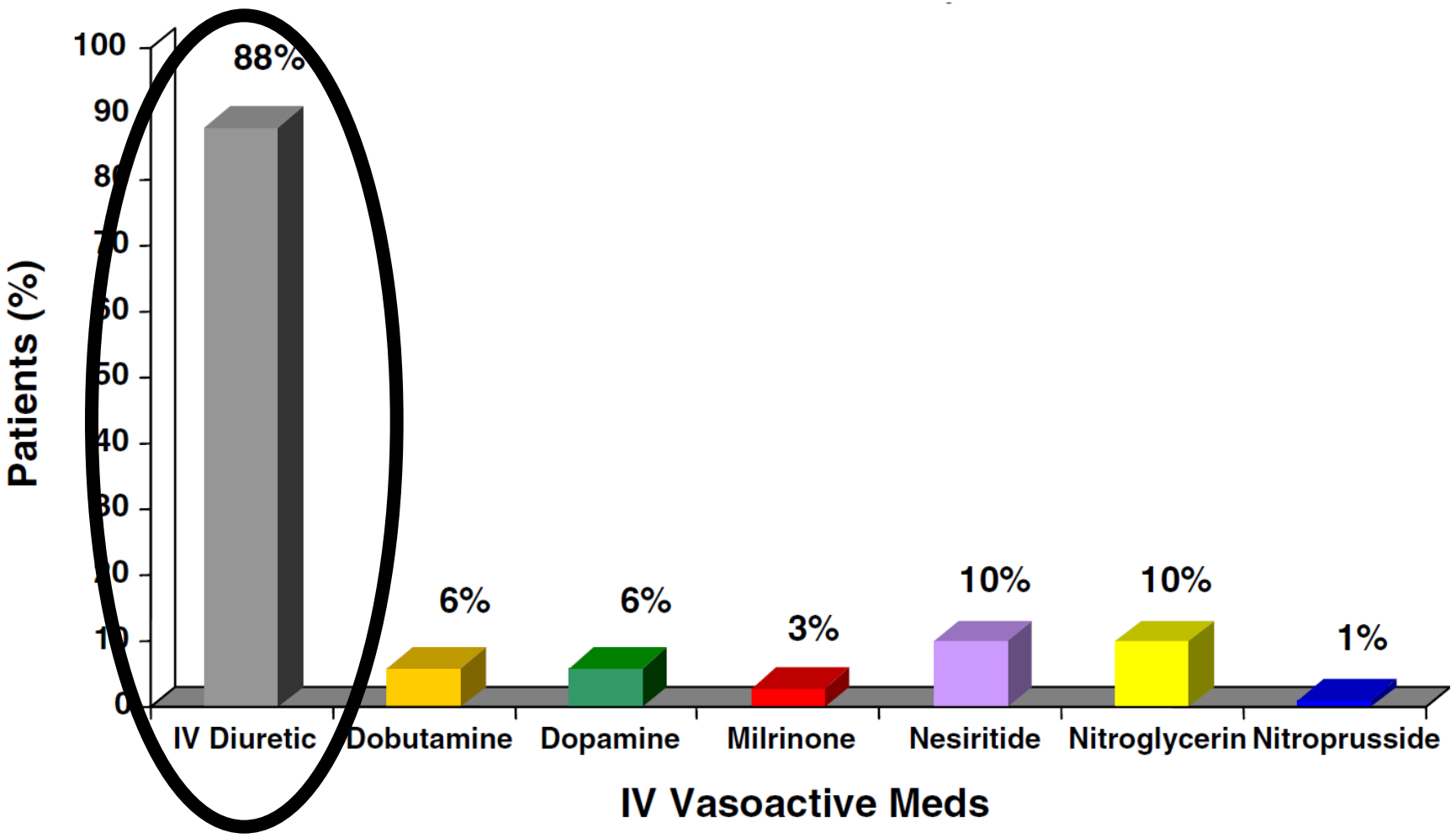
MILD volume overload

IV diuretics
IV furosemide bolus

Serum creatinine
- <200 µmol/L 40 mg
- >200 µmol/L 80 mg

Howlett JG, Can J Cardiol 2011

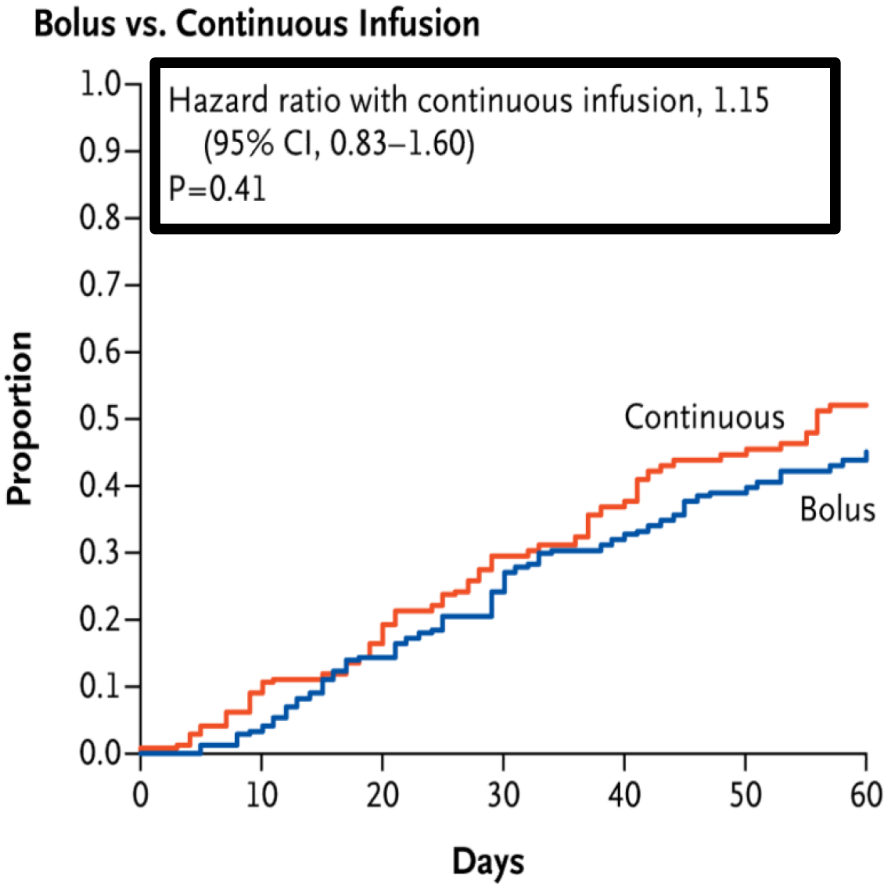
Most commonly used I.V. medications in acute decompensated heart failure

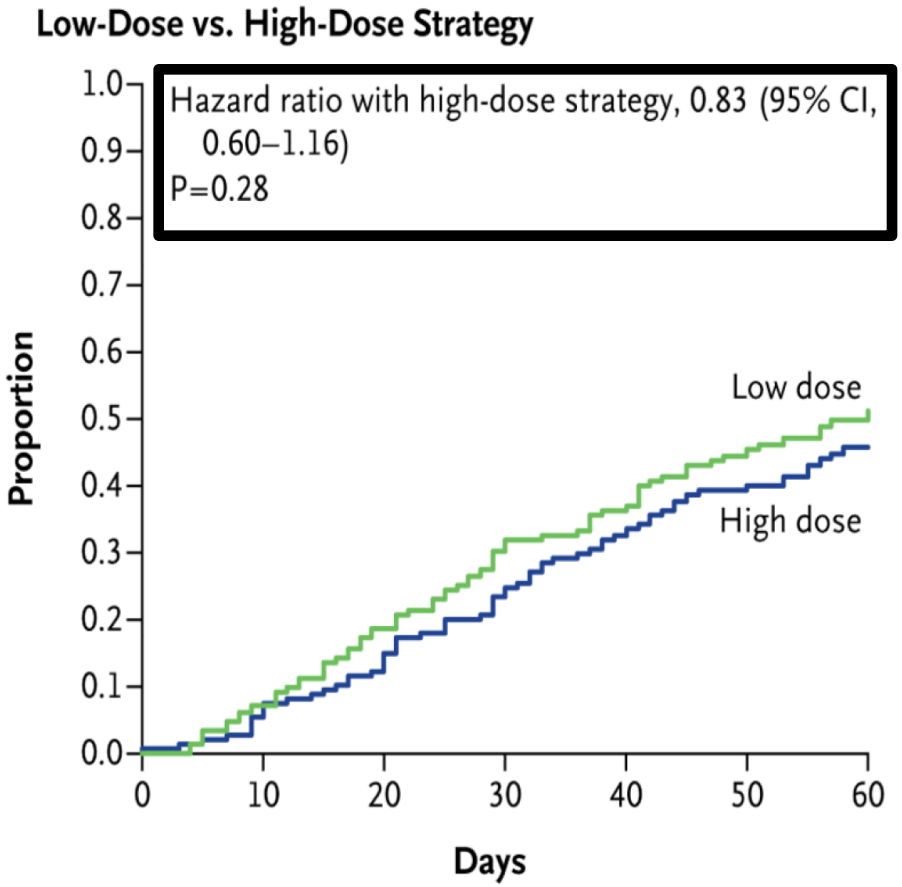


Iyengar S & Abraham WT, Hear Failure Review 2007

Kaplan–Meier Curves for the Clinical Composite End Point of Death,Rehospitalization, or Emergency Department Visit

Diuretic Optimization Strategies Evaluation (DOSE) trial



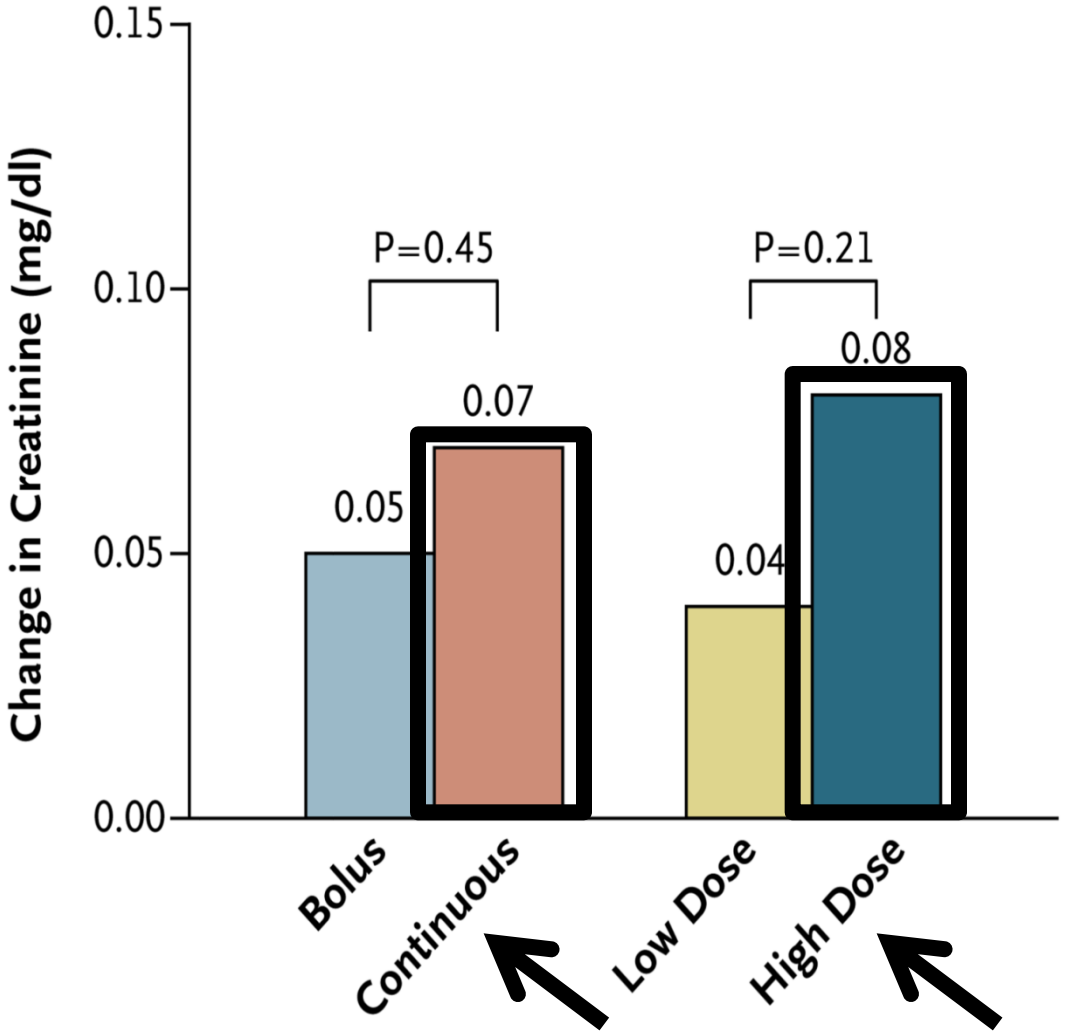


Felker GM et al., N Engl J Med. 2011

Mean Change in Serum Creatinine Level

Diuretic Optimization Strategies Evaluation (DOSE) trial

Age, y	***Bolus***
	66.2±13.2
	Continuous
	66.2±13.9
	Low dose
	65.8±14.1
	High dose
	65.9±13.3



Felker GM et al., N Engl J Med. 2011

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

The NEW ENGLAND JOURNAL of MEDICINE

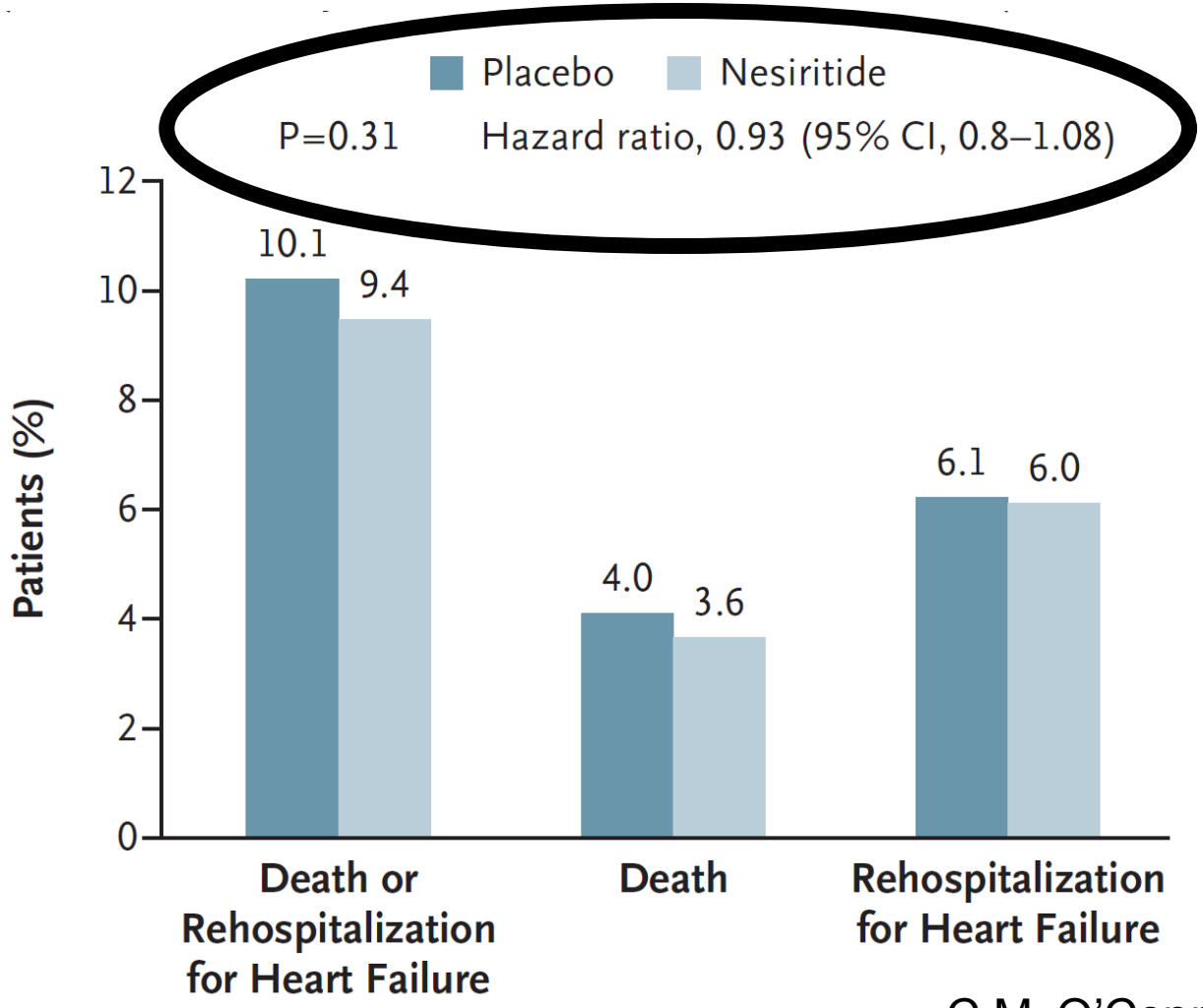
ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

"NESIRITIDE", a recombinant B-type natriuretic peptide (BNP) with vasodilatory properties

Effect of Nesiritide in patients with acute decompensated heart failure

Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF)

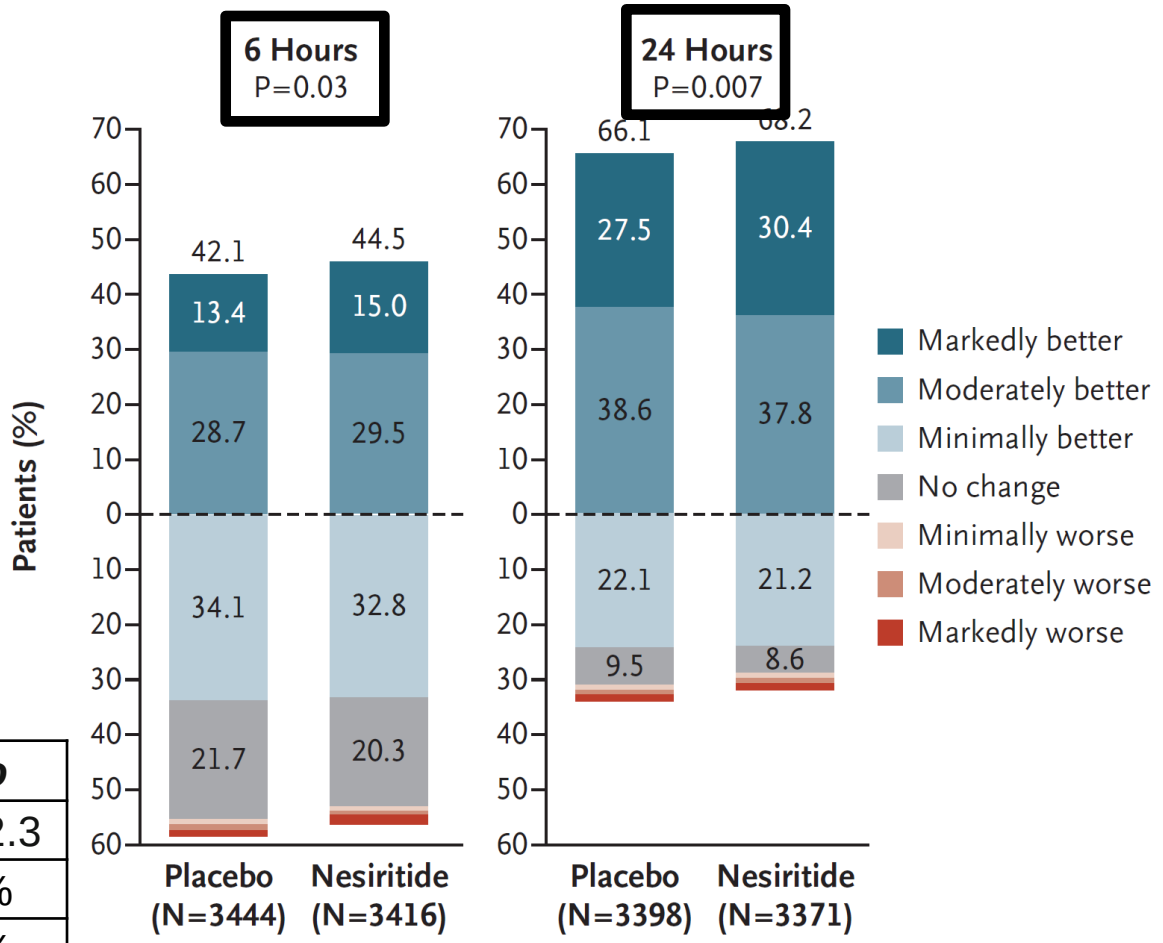


C.M. O'Connor, NEJM 2011

Effect of Nesiritide in patients with acute decompensated heart failure

Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF)

Self-assessed change in dyspnea



	Nesiritide	*Placebo*
Age, y	67.9±11.2	68.1±12.3
LVEF <40%	80.8 %	79.5 %
LVEF ≥40%	19.2 %	20.5 %

C.M. O'Connor, NEJM 2011

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

SIMPOSIO

"SCOMPENSO CARDIACO ACUTO E COMORBILITÀ NELL'ANZIANO"

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

EUROPEAN SOCIETY OF CARDIOLOGY®

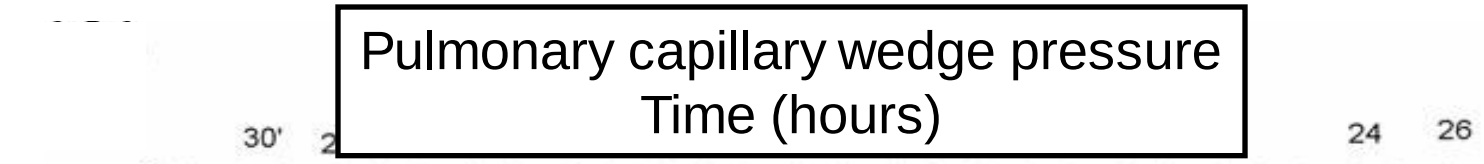
European Heart Journal (2006) **27**, 2823–2832
doi:10.1093/eurheartj/ehl337

Clinical research
Heart failure/cardiomyopathy

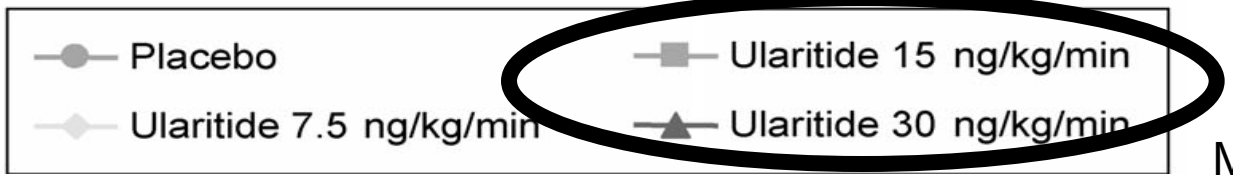
Haemodynamic and clinical effects of ularitide in decompensated heart failure

"ULARITIDE" is the chemically synthesized form of urodilatin - a human, natriuretic peptide that is produced in the kidneys and induces natriuresis

Haemodynamic and clinical effects of “ularitide” in decompensated heart failure



Trial of Ularitide’s Efficacy and Safety in Patients With Acute Heart Failure (TRUE-AHF) is an *ongoing phase III* randomized clinical trial designed to evaluate the role of ularitide as an intravenous infusion in addition to conventional therapy in 2116 patients.



Mitrovic V, Eur Heart J 2006

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

ACUTE HEART FAILURE, treatment initiated based on symptoms and signs

Volume overload

MODERATE to SEVERE volume overload

IV diuretics
+ IV vasodilators

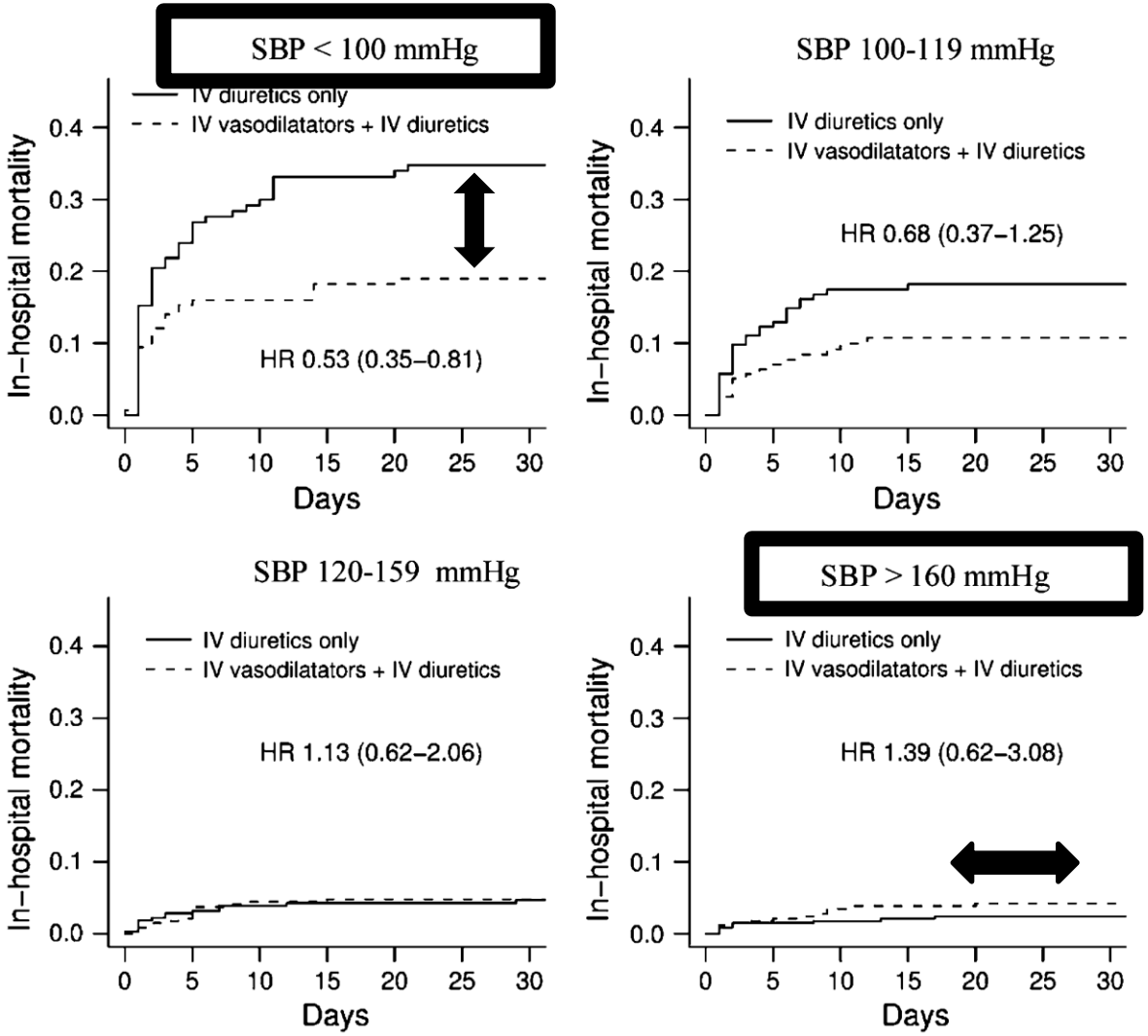
- consider furosemide infusion
- add IV nitroglicerin starting at 5-10 µg/kg/min

Howlett JG, Can J Cardiol 2011

Short-term survival by treatment among patients hospitalized with acute heart failure

ALARM-HF registry

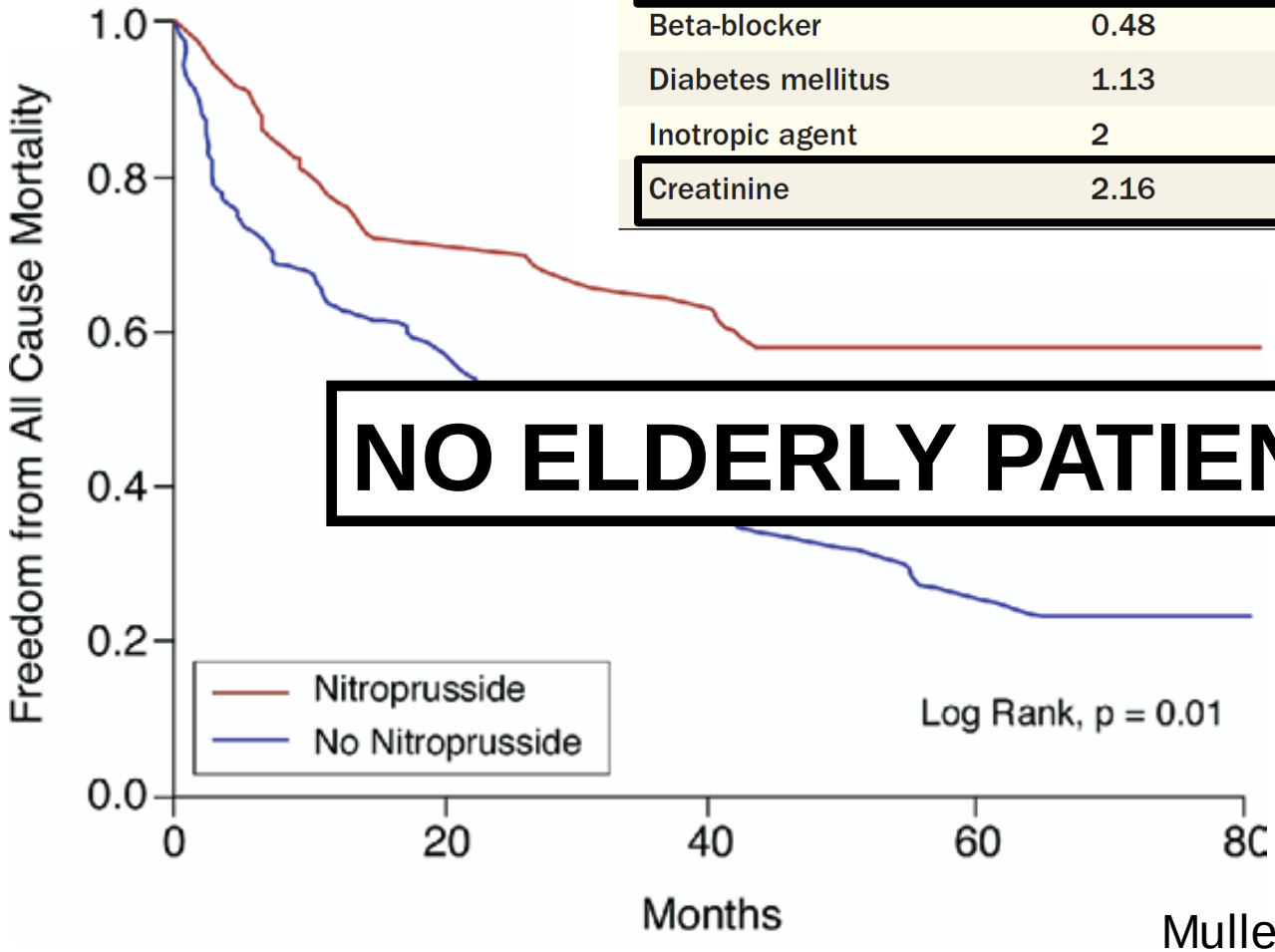
Age (years)	Vasodilators + diuretics (n=1805)	Diuretics alone (n=2362)
16–45	2.7 %	5.6 %
46–60	21.2 %	19.0 %
61–70	**31.5 %**	**27.8 %**
71–80	**31.2 %**	**30.0 %**
>80	13.4 %	17.5 %



Mebazaa A ET AL., Intens Care Med 2011

Sodium nitroprusside for advanced low-output heart failure

	Hazard Ratio	95% Confidence Interval	p Value
Sodium nitroprusside	0.54	0.33–0.88	0.015
Beta-blocker	0.48	0.29–0.78	0.03
Diabetes mellitus	1.13	0.62–2.07	0.7
Inotropic agent	2	1.36–3.6	0.01
Creatinine	2.16	1.56–3.24	0.001



age=55±11

NO ELDERLY PATIENTS !

age=55±11

Mullens W et al., JACC 2008

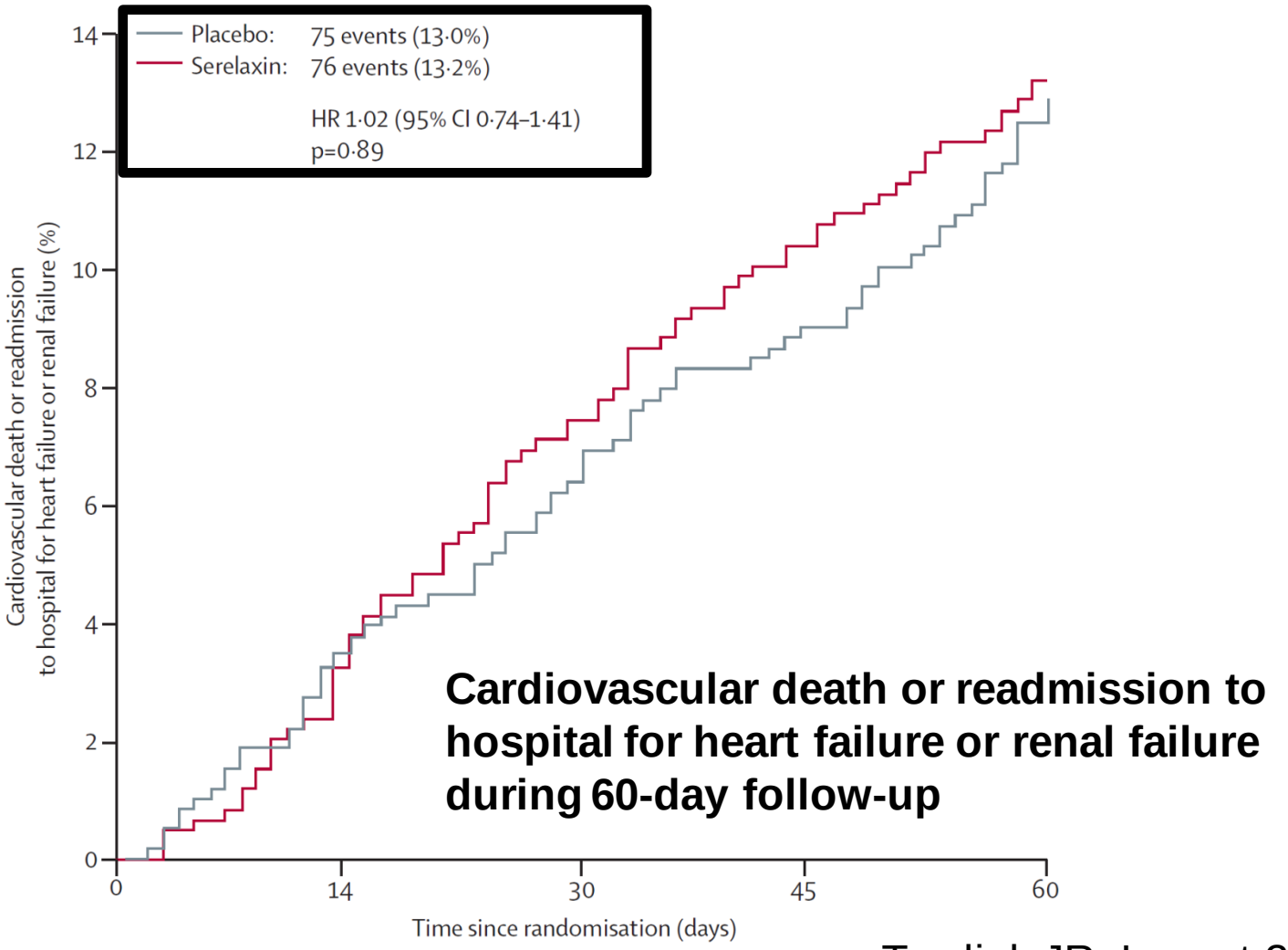
"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial — THE LANCET

"SERELAXIN" is recombinant human relaxin-2, a peptide that regulates maternal adaptations to pregnancy with several eff ects increased arterial compliance, cardiac output, and renal blood flow

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure

RELAX-AHF: a randomised, placebo-controlled trial



Cardiovascular death or readmission to hospital for heart failure or renal failure during 60-day follow-up

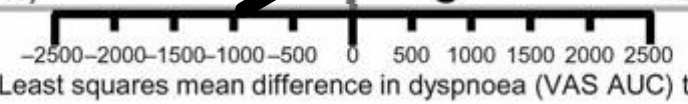
Teerlink JR, Lancet 2013

Effects of serelaxin in “subgroups” of patients with acute heart failure

RELAX-AHF: a randomised, placebo-controlled trial

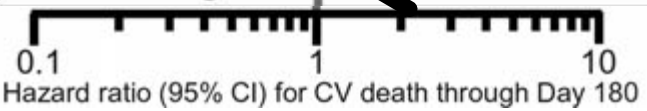
Dyspnoea Visual Analogue Scale

Subgroup		Placebo Mean (SD)	Serelaxin Mean (SD)	LS mean difference Estimate (95%CI)
Age	<65 years	2325.0 (3210.1)	2634.7 (2582.5)	309.7 (–381.4, 1000.8)
	≥65 years	2303.5 (3051.7)	2795.8 (2591.9)	492.3 (119.1, 865.6)
	<75 years	2483.5 (3042.2)	2675.7 (2482.0)	192.2 (–259.6, 644.0)
	≥75 years	2124.9 (3117.8)	2850.3 (2710.5)	725.4 (249.1, 1201.6)



Cardiovascular death through Day 180

Subgroup		Placebo *n/N* (K–M%)	Serelaxin *n/N* (K–M%)	Hazard ratio Estimate (95%CI)
Age	<65 years	9/119 (7.6)	9/145 (6.3)	0.82 (0.33, 2.07)
	≥65 years	45/461 (9.9)	25/436 (5.8)	0.58 (0.35, 0.94)
	<75 years	18/296 (6.1)	20/315 (6.5)	1.05 (0.55, 1.98)
	≥75 years	36/284 (12.9)	14/266 (5.3)	0.40 (0.22, 0.74)



Metra M et al., Eur Heart J 2013

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

The NEW ENGLAND JOURNAL of MEDICINE

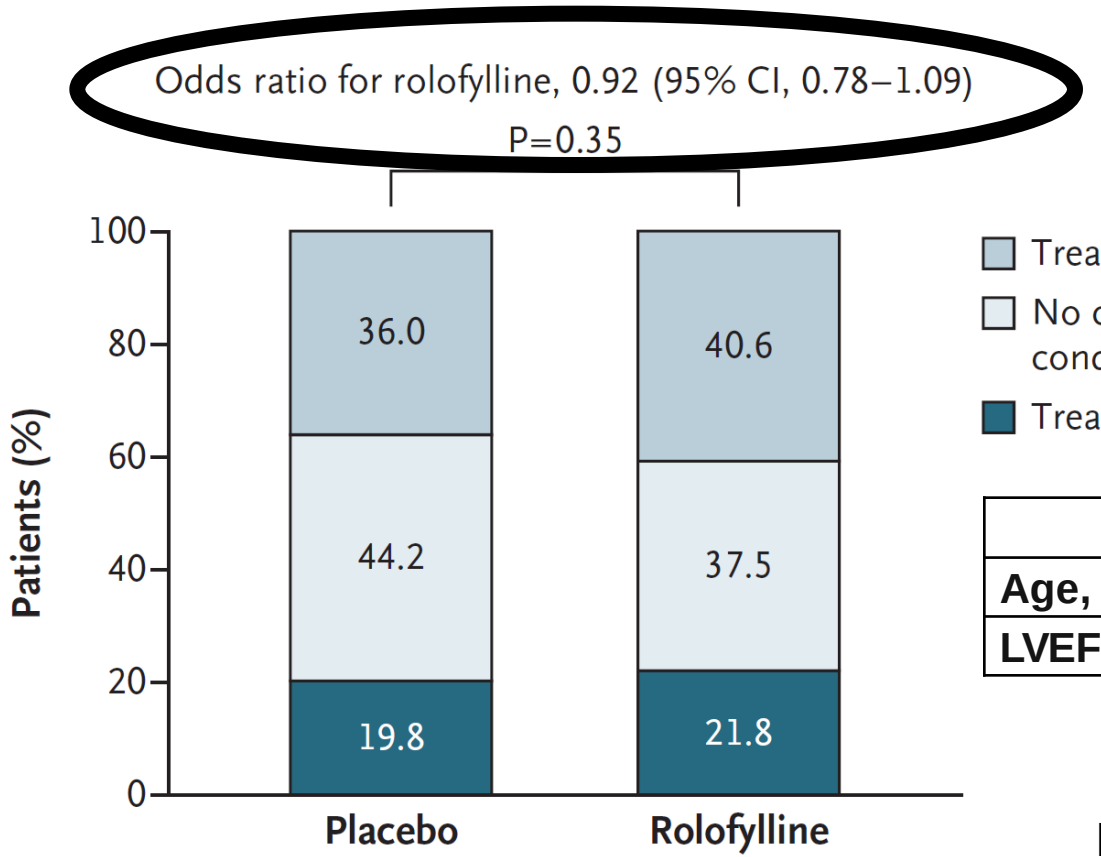
ORIGINAL ARTICLE

Rolofylline, an Adenosine A_1–Receptor Antagonist, in Acute Heart Failure

"ROLOFYLLINE" is adenosine A_1 antagonist acting by preserving the GFR, enhance sodium excretion and improve diuretic responsiveness.

Distribution of the primary composite end point in the rolofylline and placebo groups

PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment)



	Rolofylline	*Placebo*
Age, y	70.2±11.7	70.2±11.5
LVEF %	32.3	32.5

Massie BM et al., NEJM 2010

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

SIMPOSIO

"SCOMPENSO CARDIACO ACUTO E COMORBILITÀ NELL'ANZIANO"

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Cardiovasc Drugs Ther
DOI 10.1007/s10557-013-6491-8

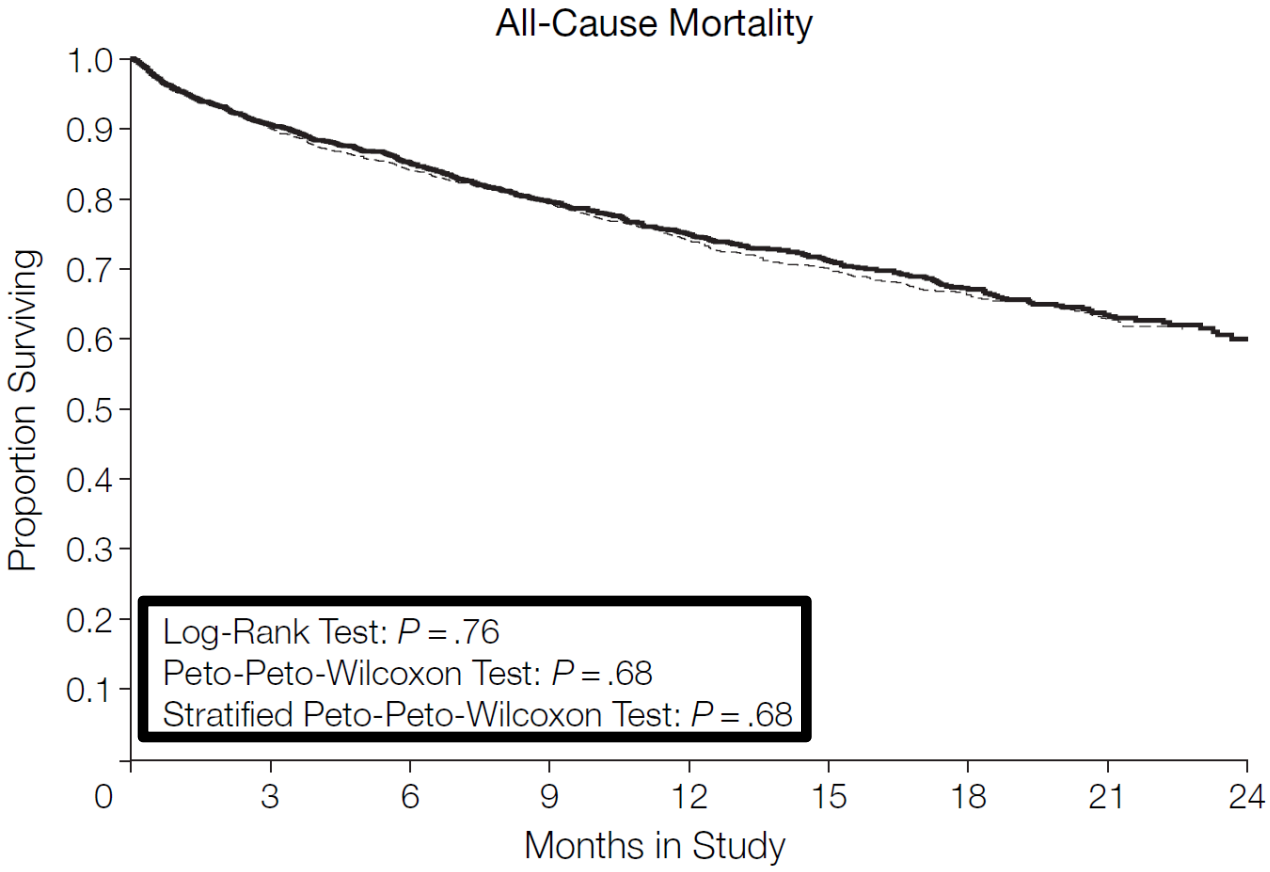
ORIGINAL ARTICLE

Clinical Effectiveness of Tolvaptan in Patients with Acute Decompensated Heart Failure and Renal Failure: Design and Rationale of the AQUAMARINE Study

"TOLVAPTAN" is an oral, once-daily, vasopressin-2 receptor antagonist. It achieves urine output without decreasing renal blood flow in heart failure patients

Effects of Oral Tolvaptan in patients hospitalized for worsening heart failure

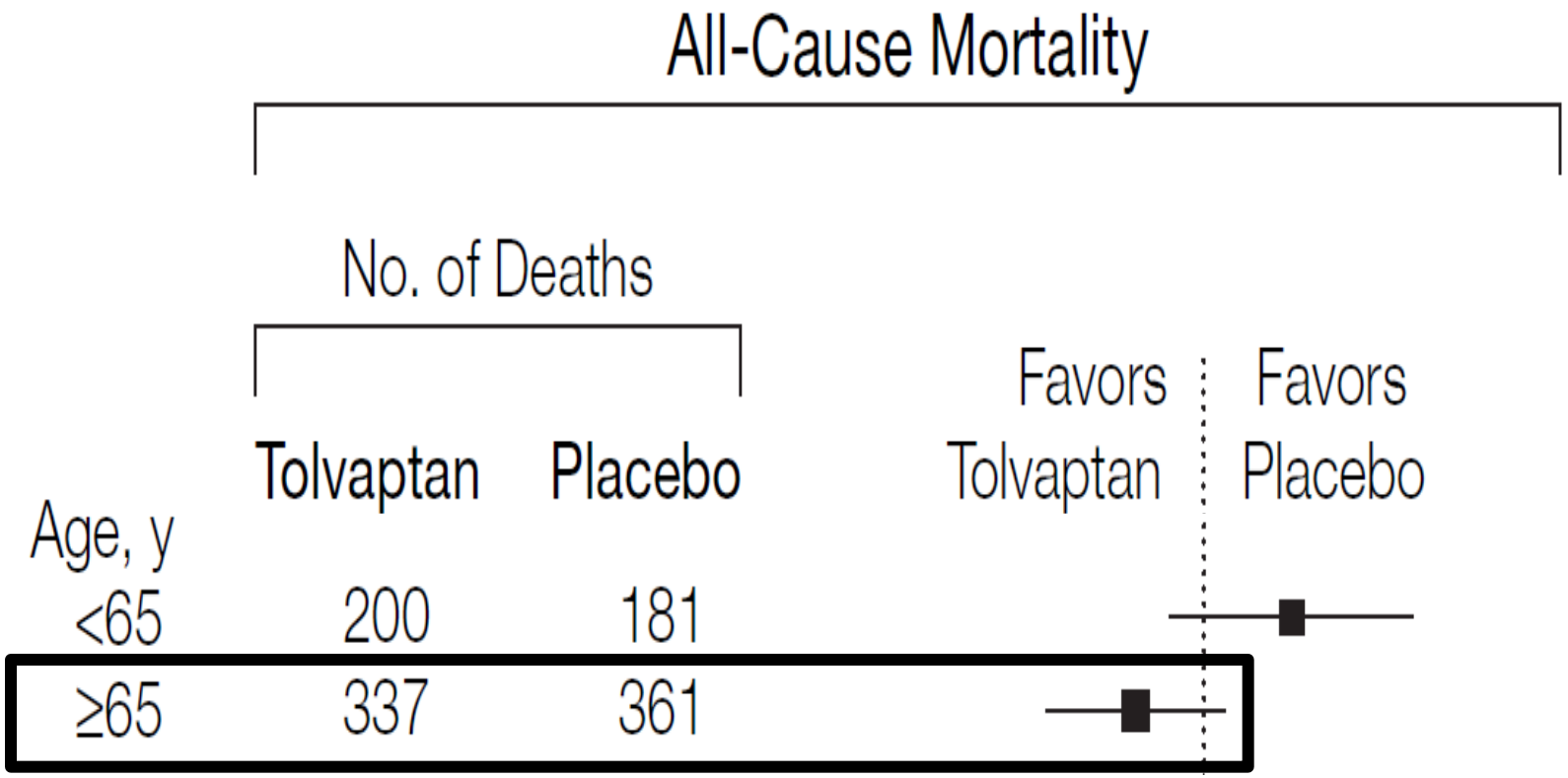
The EVEREST Outcome Trial



Konstam MA et al., JAMA 2007

Effects of Oral Tolvaptan in patients hospitalized for worsening heart failure

The EVEREST Outcome Trial



Konstam MA et al., JAMA 2007

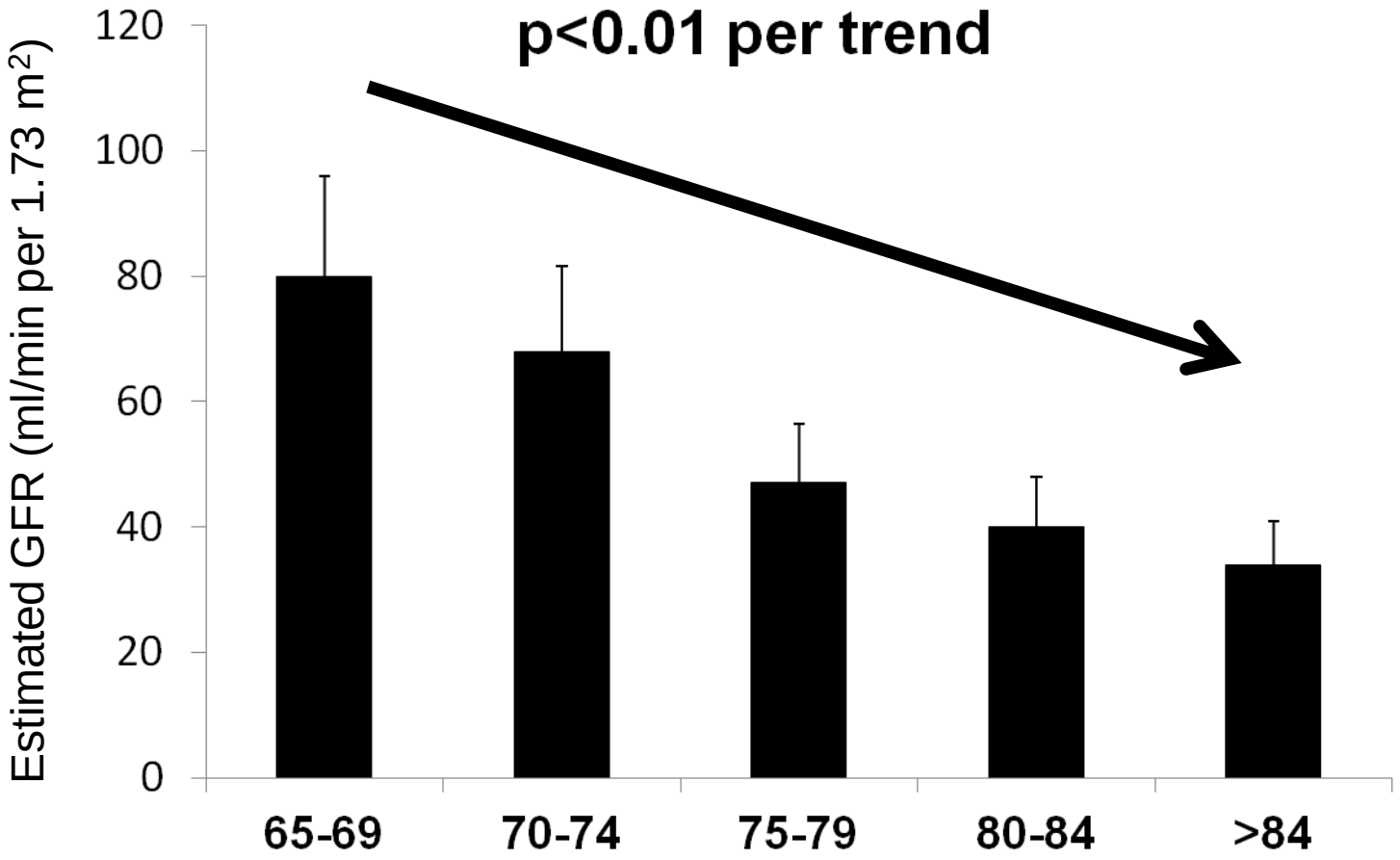
DIURETICS and VASODILATORS
main drug interactions and main side effect

DRUG	MAIN DRUG INTERACTIONS	MAIN SIDE EFFECTS
Furosemide	Non-steroidal anti-inflammatory drugs. Co-administration of angiotensin-converting enzyme inhibitors (ACEI)	***Hypotension, renal failure,*** hypokalemia, hypocalcemia, hypomagnesemia, hyperuricemia, metabolic alkalosis, hyperglycemia, and hyperparathyroidism, orthostatic
Nitrates	Phosphodiesterase type 5 inhibitors (PDE5-I), such as sildenafil.	***Hypotension***, brady- and tachyarrhythmias, injection site irritation, headache.
Nitroprusside	PDE5-I (eg, sildenafil).	***Hypotension***, brady- and tachyarrhythmias, metabolic acidosis
Nesiritide	Co-administration with ACEIs can lead to hypotension.	***Hypotension***, nausea, dizziness, headache, and arrhythmias.

Majure DT et al., Curr Treat OptI Cardiovasc 2011

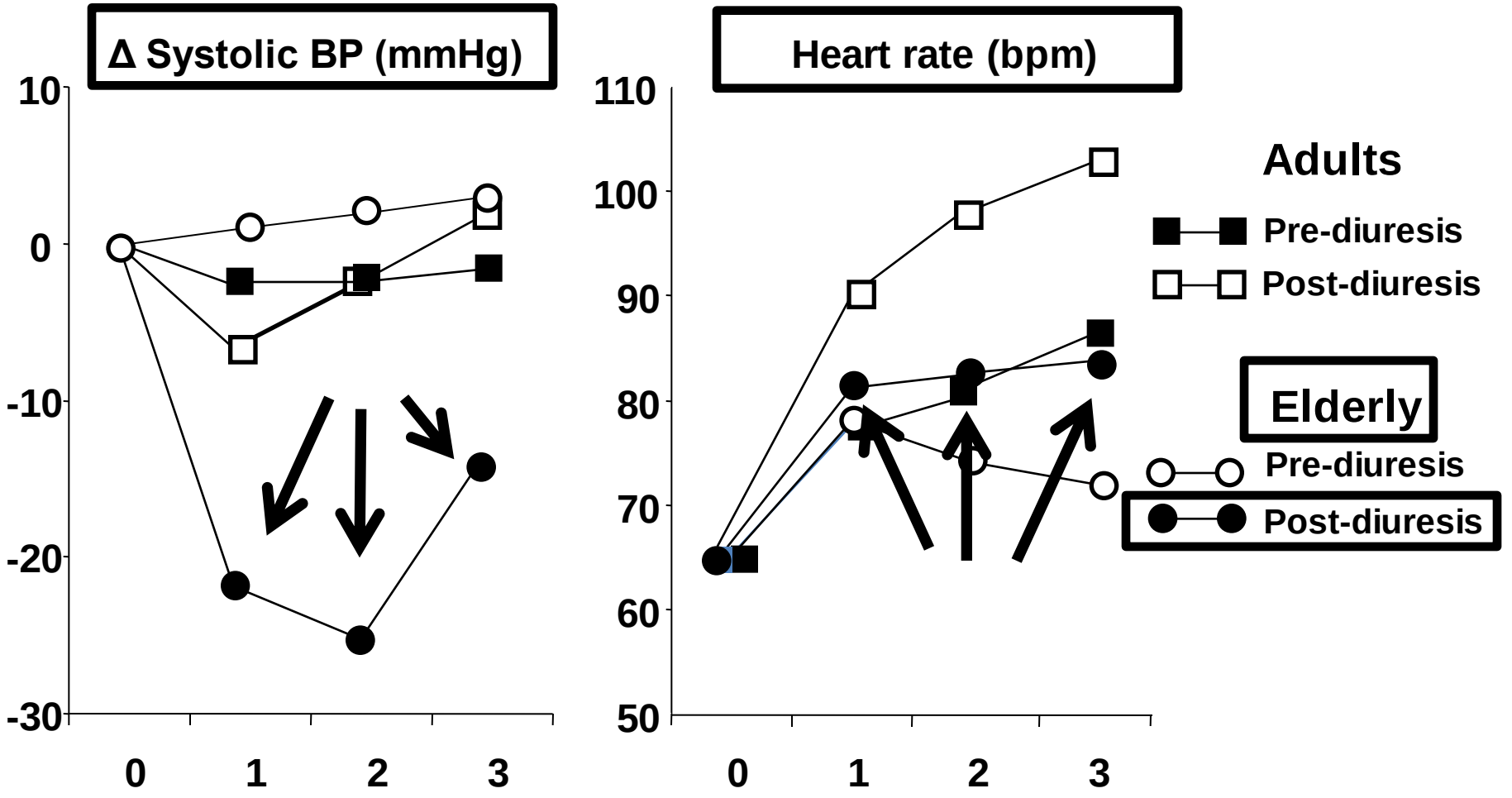
The Aging kidney

"Osservatorio Geriatrico Campano"



Abete P et al, Heart Failure Review 2013

Effects of "*age*" and sodium depletion on cardiovascular response during orthostatism



Abete P et al., J Clin Geriatr Gerontol 2013

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

ACUTE HEART FAILURE, treatment initiated based on symptoms and signs

Volume overload + low cardiac output

MILD to MODERATE low output

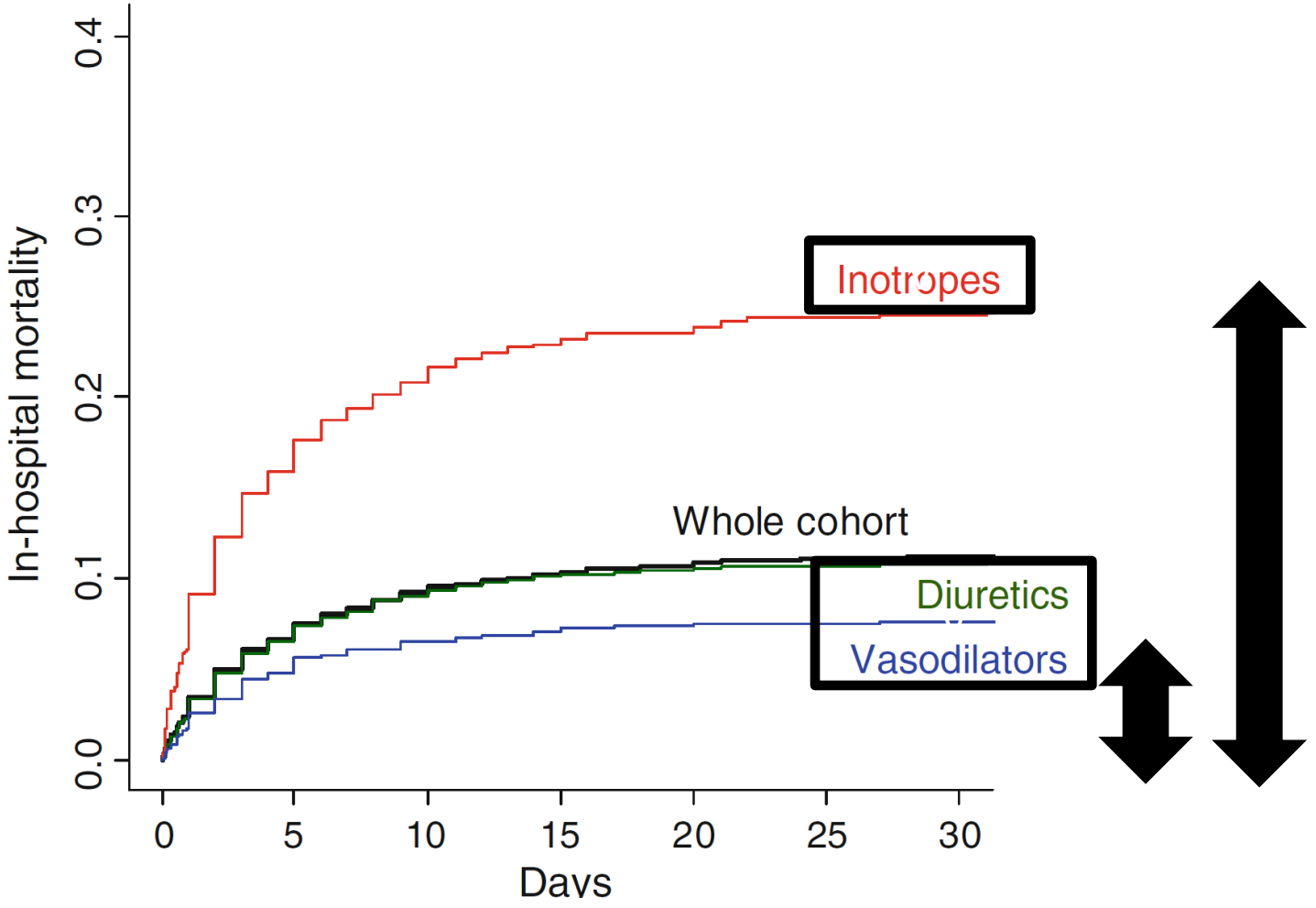
Systolic Blood Pressure >90 mmHg

- milrinone 0.275 µg/kg/min or
- dopamine
- dobutamine

Howlett JG, Can J Cardiol 2011

Short-term survival by treatment among patients hospitalized with acute heart failure

ALARM-HF registry



Mebazaa A et al., Intens Care Med 2011

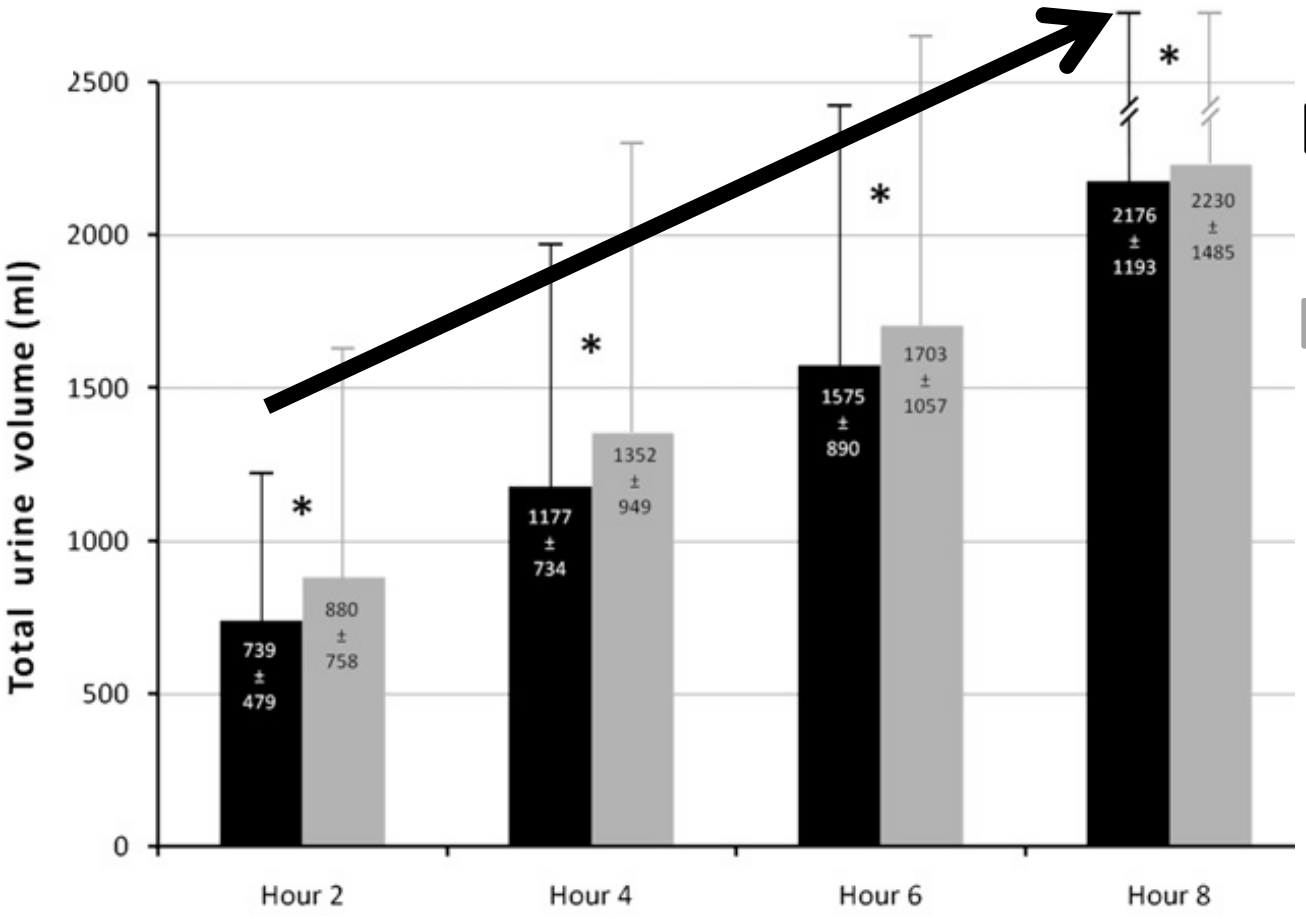
Old inotropic agents

Agent	Mechanism	Class of Recomendation
Dobutamine	Predominant $\beta_1$ar agonist with β_2-AR and α_1-AR agonist properties	IIa- B
Dopamine	DA_1-D2, (<2µg/kg/min) β_1-AR, α_1-AR agonist (2-5µg/kg/min)	IIb – C
MiIrinone/enoximone	PDE-I	IIb – B

Metra M et al., Progress in Cardiovasc Diseases, 2011

Impact of Dopamine Infusion on Renal Function in Hospitalized Heart Failure Patients

Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial



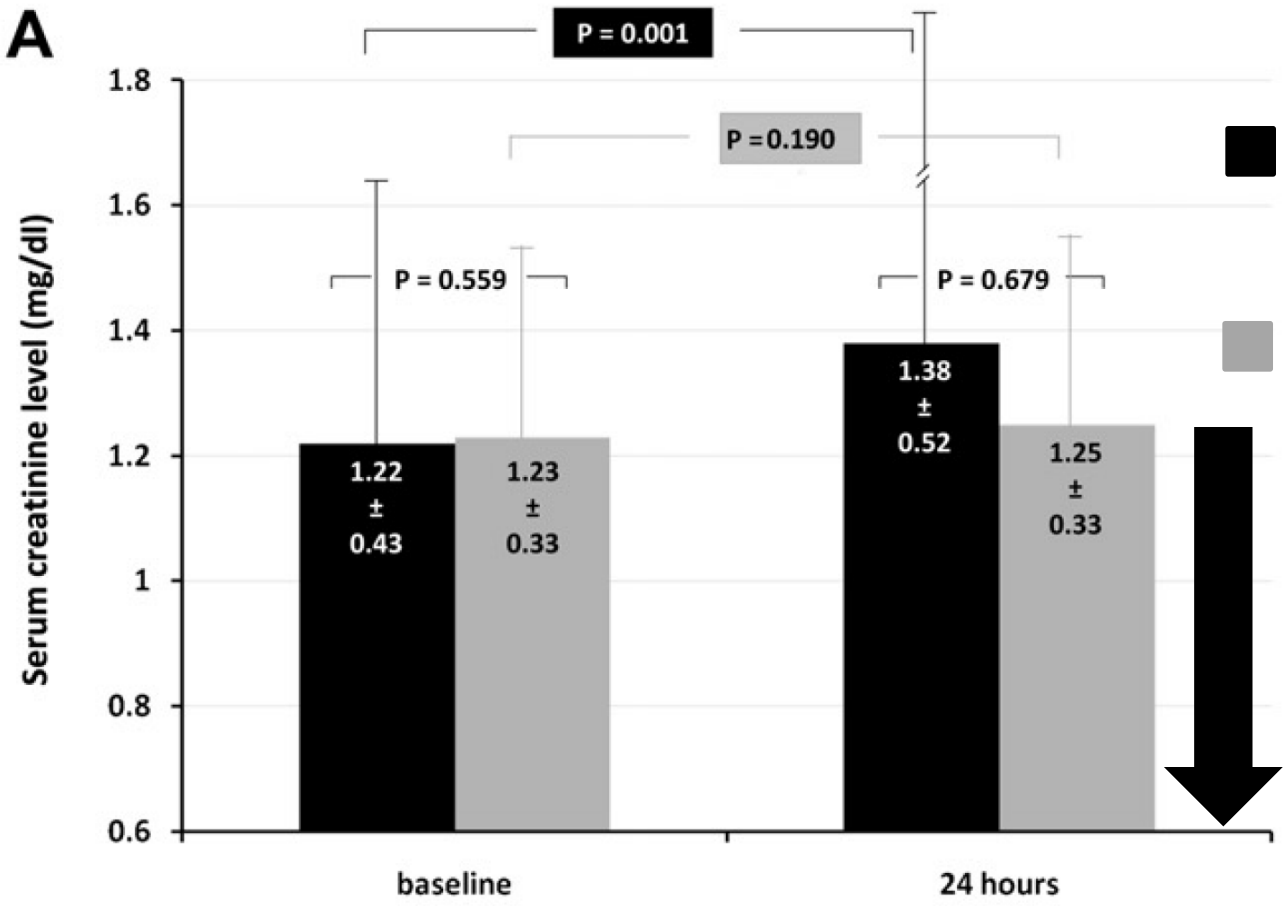
high-dose furosemide group
age 74.1±11.7

low-dose furosemide + low-dose dopamine group
age 77.4±10.7

Giamouzis G et al., ,J Cardiac Fail 2010

Impact of Dopamine Infusion on Renal Function in Hospitalized Heart Failure Patients

Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial



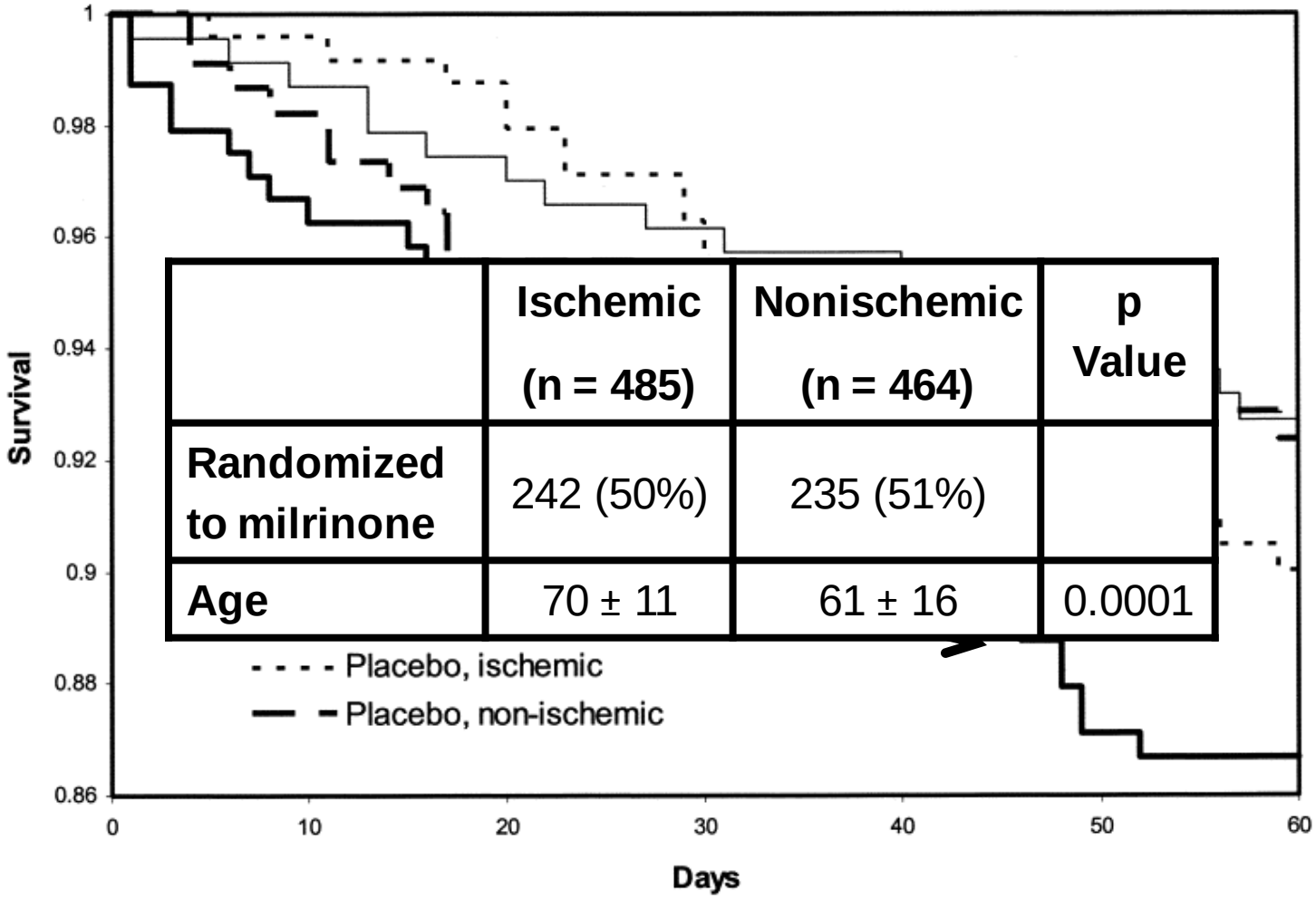
high-dose furosemide group
age 74.1±11.7

low-dose furosemide + low-dose dopamine group
age 77.4±10.7

Giamouzis G et al., J Cardiac Fail 2010

Heart failure etiology and response to “milrinone” in decompensated heart failure

OPTIME-CHF study



	Ischemic (n = 485)	Nonischemic (n = 464)	p Value
Randomized to milrinone	242 (50%)	235 (51%)	
Age	70 ± 11	61 ± 16	0.0001

Flker GM et al , JACC 2003

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

ACUTE HEART FAILURE, treatment initiated based on symptoms and signs

Volume overload + low cardiac output

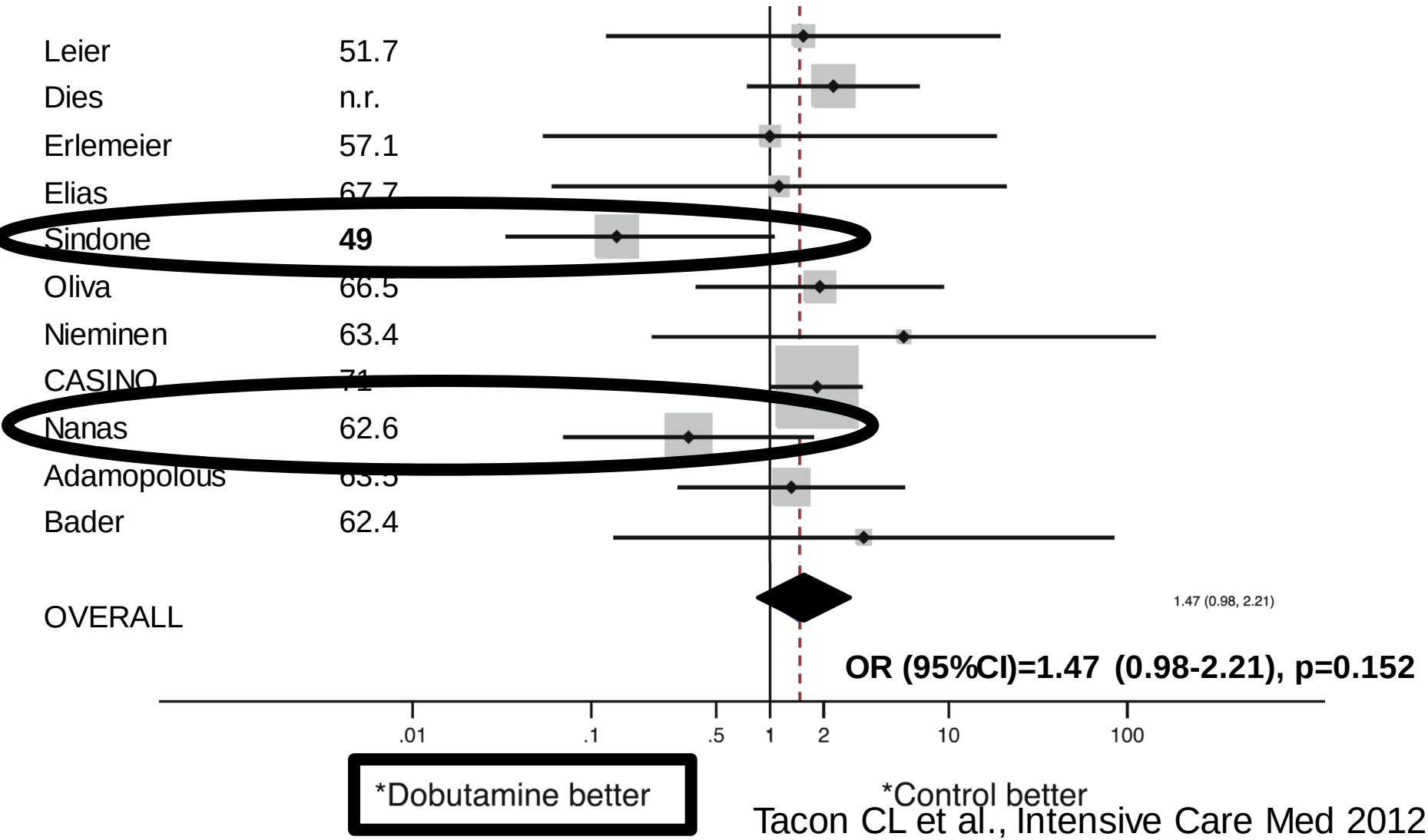
MODERATE to SEVERE low output

Systolic Blood Pressure <90 mmHg

- dobutamine 2.5 µg/kg/min or
- epinephrine/norepinephrine (vasopressors)

Howlett JG, Can J Cardiol 2011

Dobutamine for patients with severe heart failure: a meta-analysis of randomised controlled trials



Tacon CL et al., Intensive Care Med 2012

NEW INOTROPIC AGENTS

AGENT	EXAMPLE	MECHANISM
Calcium sensitizers	**Levosimendan**	calcium sensitization of the contractile proteins and opening of adenosine triphosphate (ATP)–dependent K+ channels
Cardiac myosin activators	**Omecamtiv mecarbil**	Increasing the probability of the transition from a weakly actin-bound to a strongly actin-bound, force-producing state.
Na+/K+-ATPase inhibitors	**Istaroxime**	Inhibition of Na+/K+-ATPase and SERCA2 Activation

Metra M et al., Progress in Cardiovasc Diseases, 2011

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

SIMPOSIO

"SCOMPENSO CARDIACO ACUTO E COMORBILITÀ NELL'ANZIANO"

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

JACC: Heart Failure
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Vol. 1, No. 2, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2012.12.004

CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

"LEVOSIMENDAN" is a calcium sensitizer of the contractile proteins and opening of adenosine triphosphate (ATP)–dependent K+ channels

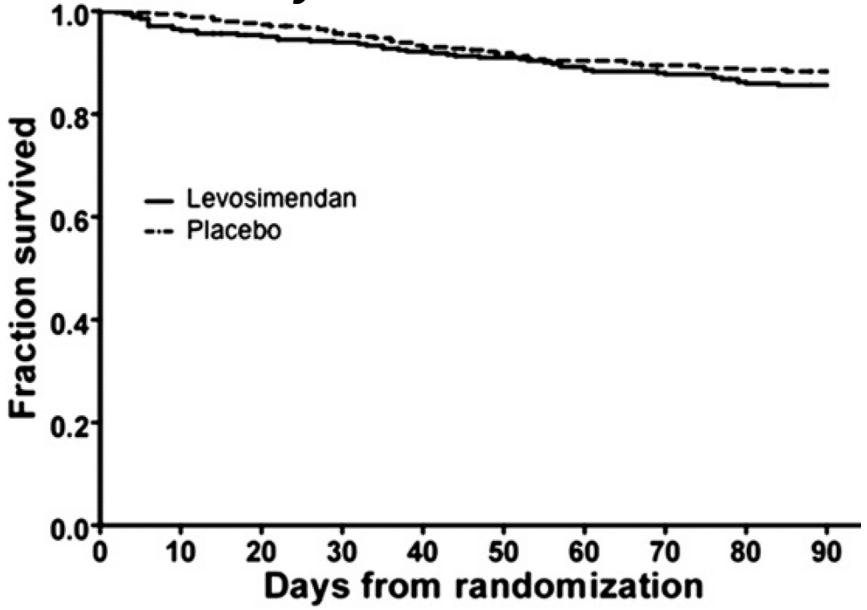
Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

REVIVE

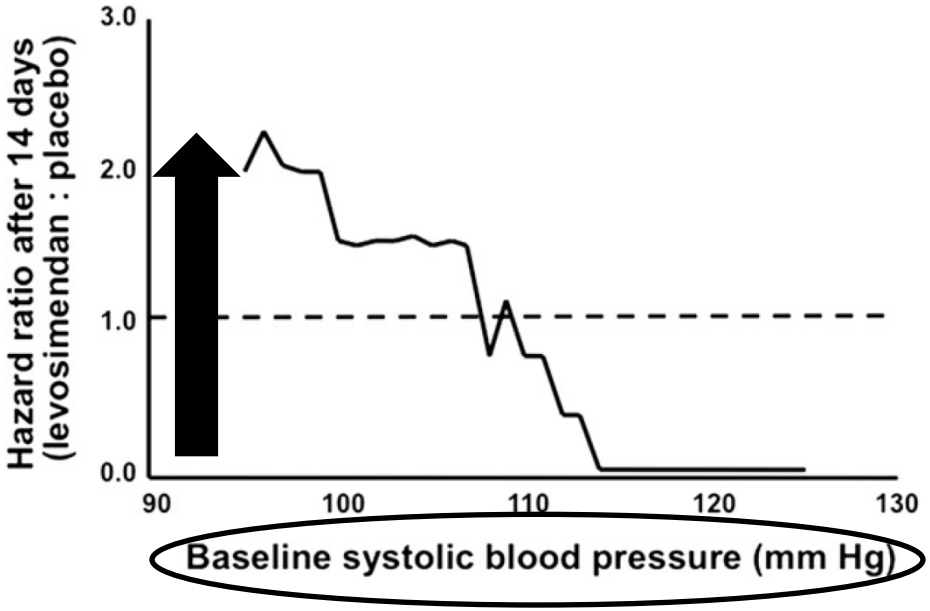
(Randomized EValuation of Intravenous LeVosimendan Efficacy I and II)

	Levosimendan	***Placebo***
REVIVE I	59±15 yr	58±15 yr
REVIVE II	64±15 yr	63±15 yr

Time to Death for Any Reason During First 90 Days After Randomization



Hazard Ratio for All-Cause Mortality



Packer M et al., JACC Heart Failure 2013

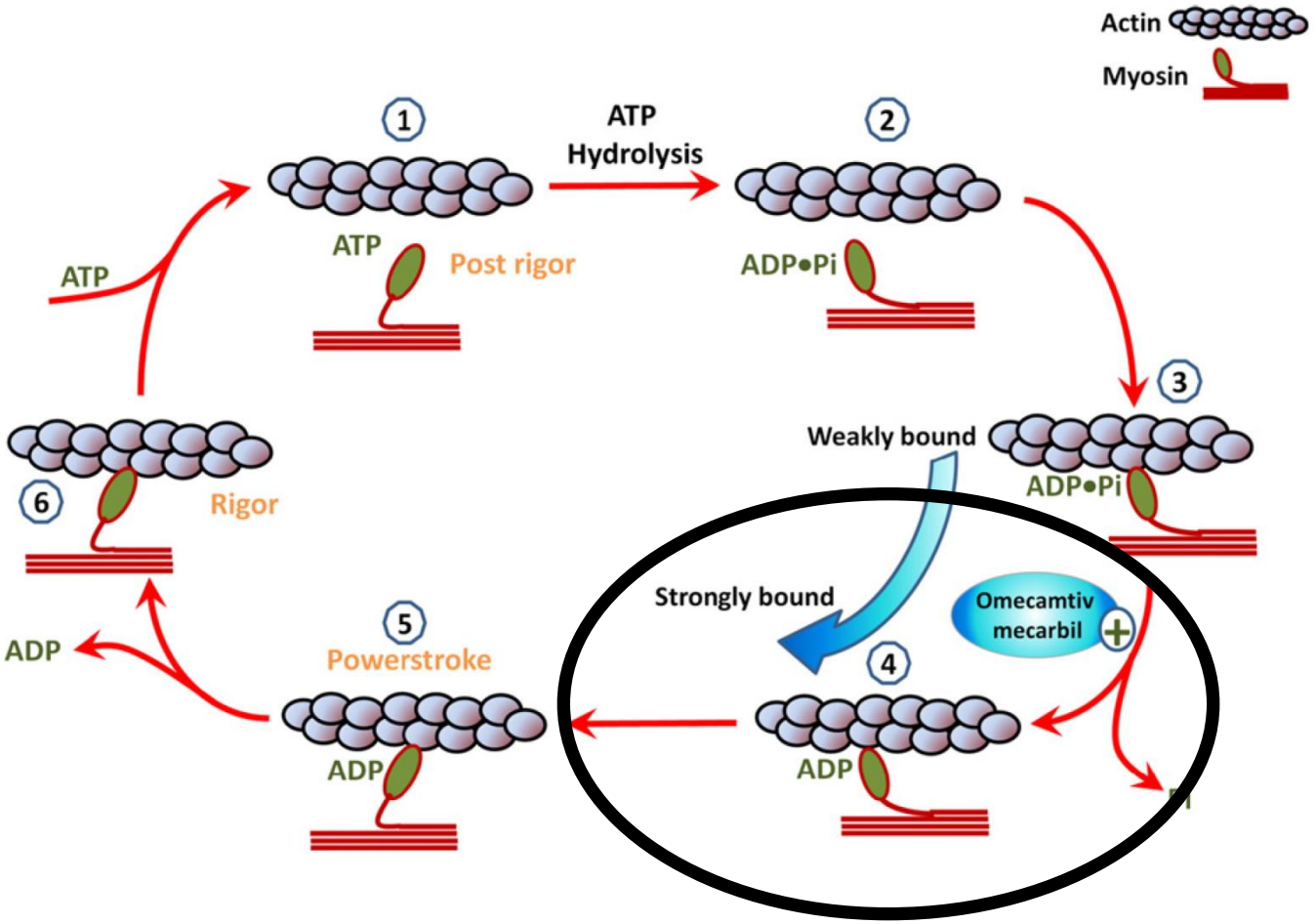
"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study THE LANCET

"OMECANTIV-MECARBIL" increases the probability of the transition from a weakly actin-bound to a strongly actin-bound, force-producing state

Effect of “omecamtiv mecarbil” on the cross-bridge cycle of cardiac muscle

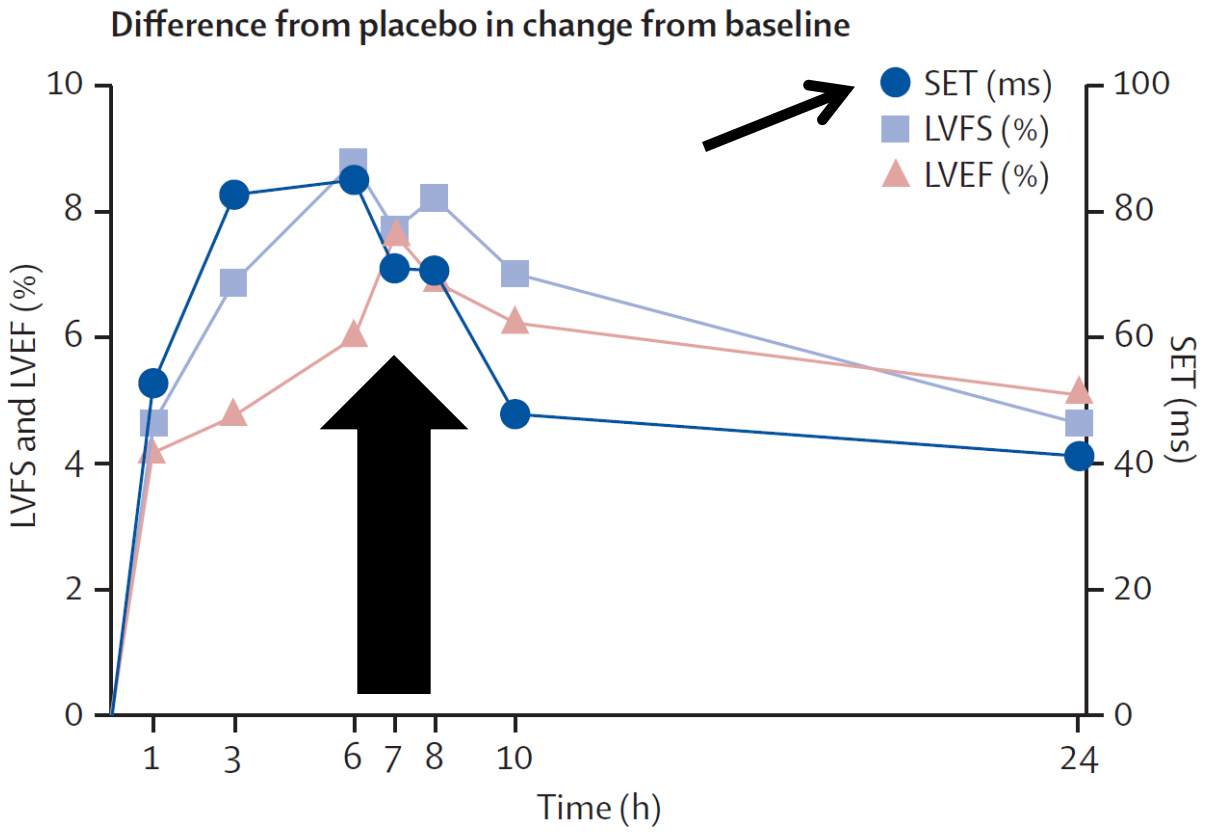
Omecamtiv mecarbil increases the actin-dependent phosphate release (step 4 in the figure), leading to an acceleration of the transition rate from the weakly bound myosin to the actin filament to the strongly bound force-producing state



Aronson D & Krum H. Pharmacology & Therapeutics 2012

Dose-dependent augmentation of cardiac function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

Change in selected echocardiogram variables over time (omecamtiv mecarbil 0·5 mg/kg per h)



SET=systolic ejection time
LVFS=left ventricular fractional shortening
LVEF=leftventricular ejection fraction

Teerlink JR , Lancet 2011

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

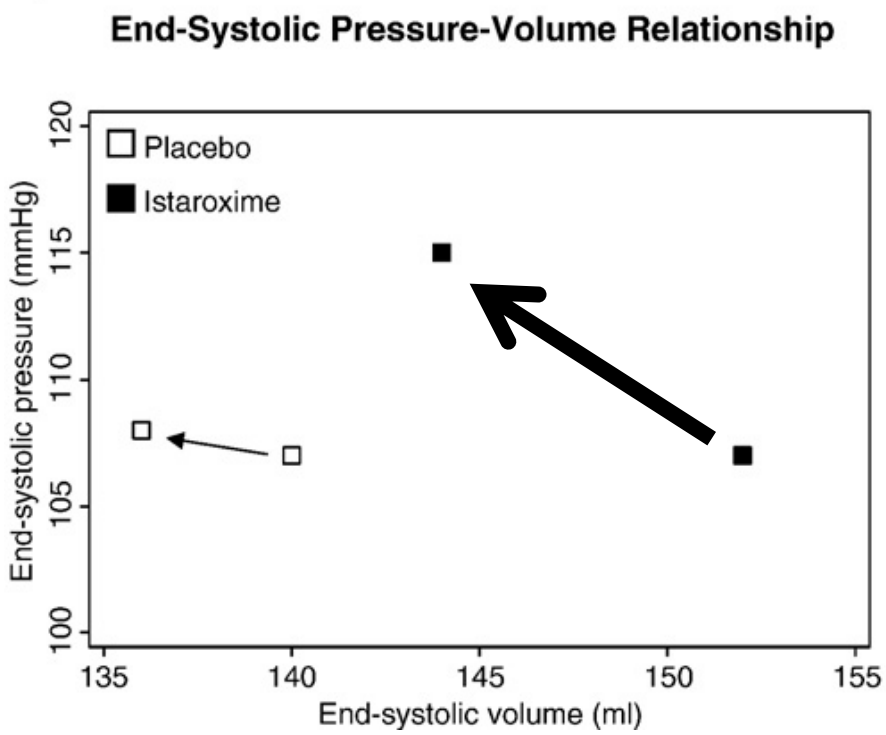
Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: Results from the *H*emodynamic, Ech*o*cardiographic, and Neu*r*ohormonal Effects of *I*staroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Co*n*trolled Trial in Patients Hospitalized with *H*eart *F*ailure (HORIZON-HF) trial

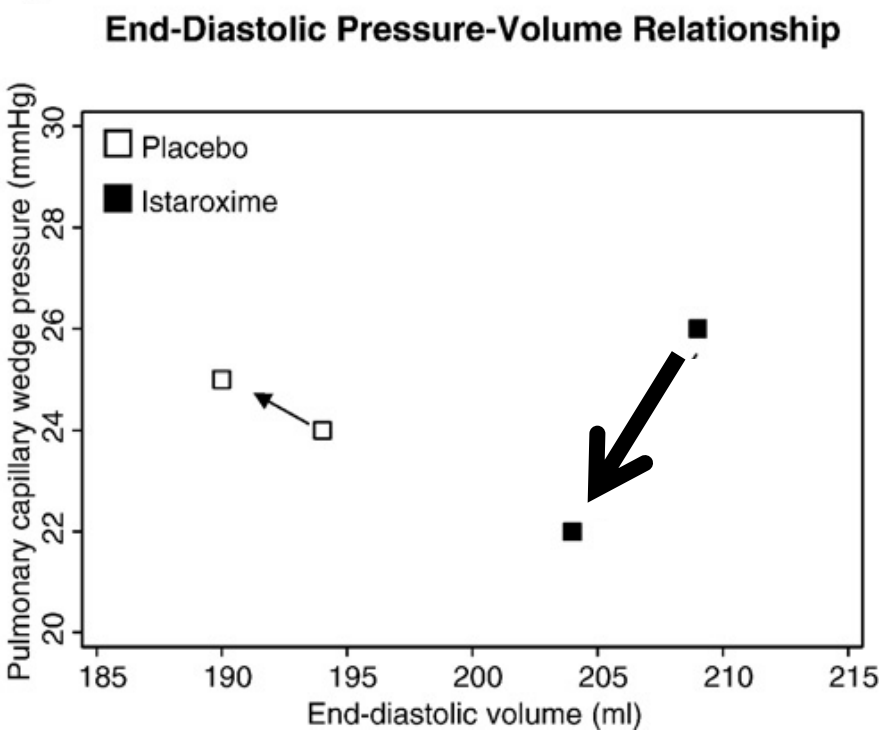
Am Heart J 2009

"ISTAROXIME" acts by Na+/K+-ATPase inhibition and SERCA2 Activation

Effects of Istaroxime, a novel intravenous inotropic and lusitropic agent

a randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) trial





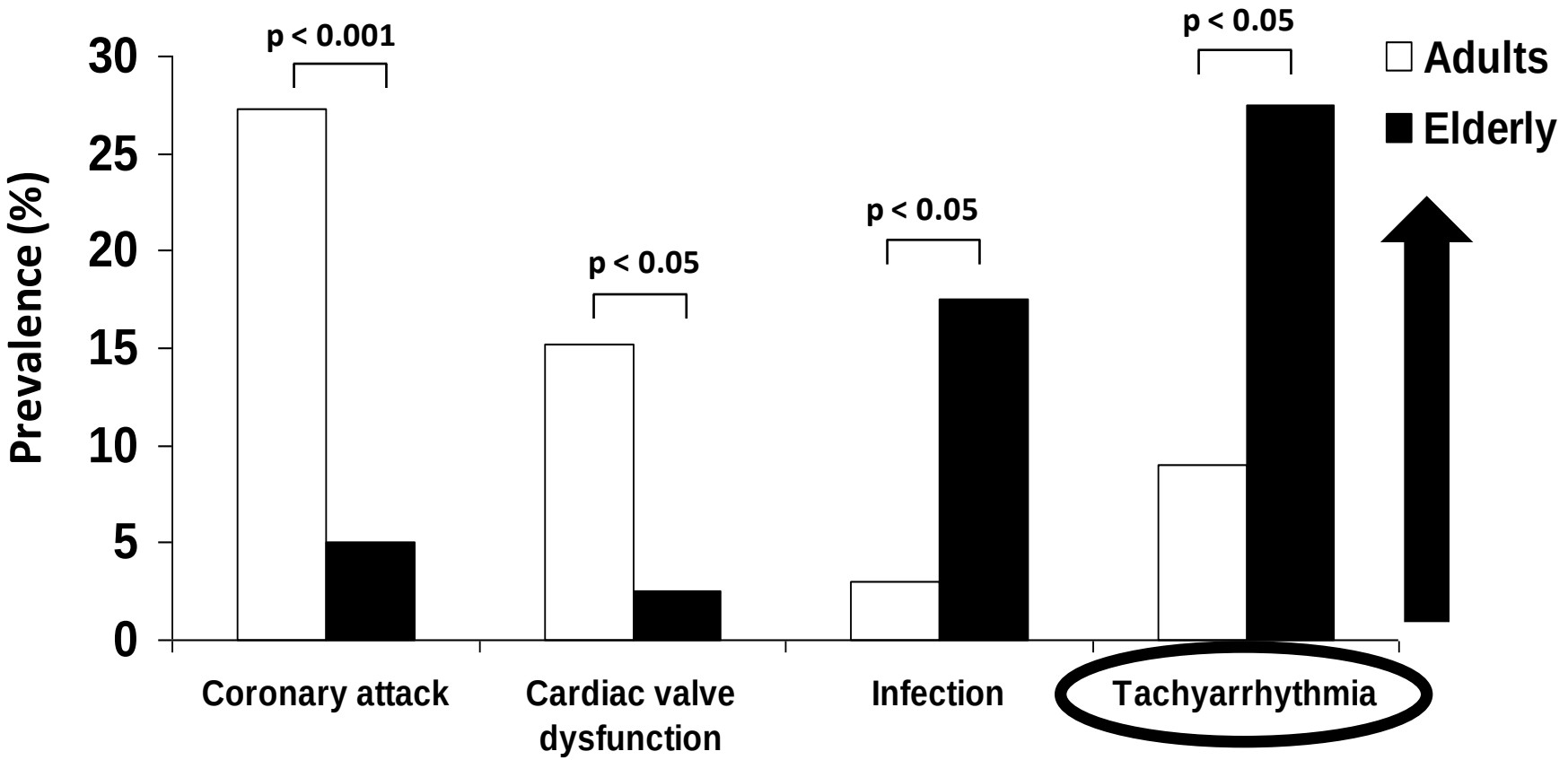
	Istaroximine	***Placebo***
Age (years)	55±11 yr	57±10 yr
Systolic BP (mmHg)	117±12	114±15

Shah SJ et al. , Am Heart J 2009

INOTROPES- VASOPRESSORS
main drug interactions and main side effect

DRUG	MAIN DRUG INTERACTIONS	MAIN SIDE EFFECTS
Dopamine	Entacapone, ergotamine, phenytoin, linezolid, phenelzine.	**Tachyarrhythmias,** hypertension, chest pain, injection site reaction following infiltration.
Dobutamine	Beta-blockers, linezolid, and sympathomimetics.	**Tachyarrhythmias**, hypotension, and headache. Rarely eosinophilic myocarditis and peripheral eosinophilia.
Milrinone	Anagrelide.	**Tachyarrhythmias**, hypotension, and headache.
Levosimendan	None. Co-administration with other vasoactive drugs can potentiate hypotension.	**Ventricular tachycardia**, hypotension, nausea, and headache.

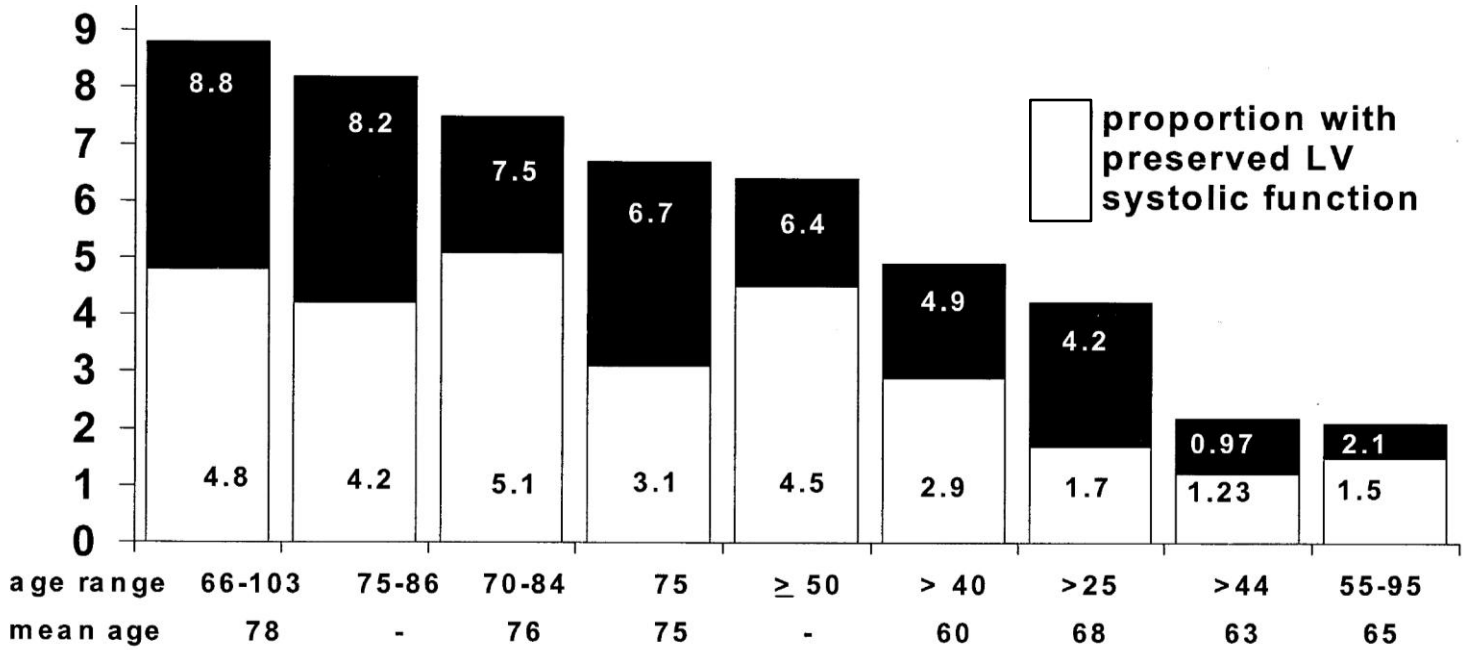
Precipitating factors of chronic heart failure in adult and elderly patients. Are they different?



Abete P et al., JAGS 2013

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

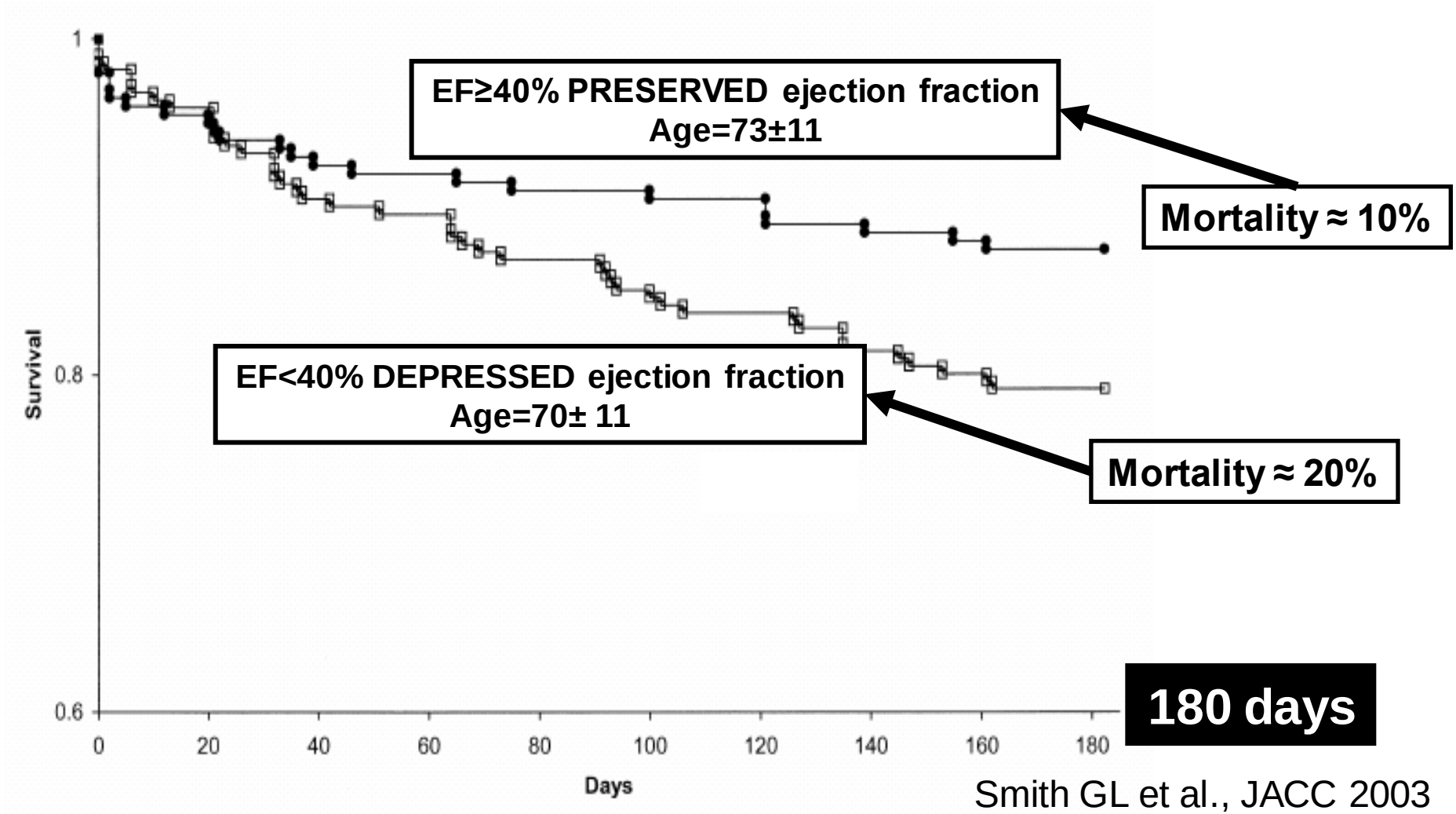
Age-related increase of prevalence of heart failure with *"preserved" left ventricular systolic function*



≈50%

Hogg K et al., JACC 2004

Mortality in heart failure patients with “depressed” and “preserved” ejection fraction

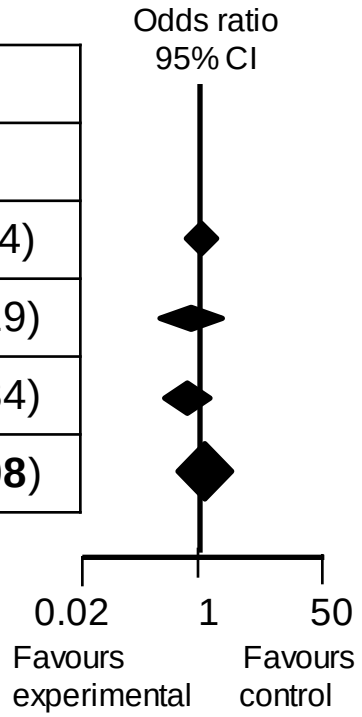


Smith GL et al., JACC 2003

Pharmacotherapy of heartfailure with normal ejection fraction (HFNEF) - a systematic review

All-cause mortality after sensitivity analysis

	Experimental		Control		Odds ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	
ACE inhibitors or ARBs	447	4001	449	3996	0.99 (0.96-1.14)
β-adrenoceptor blockers	136	399	168	402	0.60 (0.31, 1.19)
Digoxin	115	492	116	496	1.00 (0.74, 1.34)
TOTAL	698	4892	733	4894	**0.93 (0.79, 1.08**)



POOR RESULTS !

Rajagopalan S et al., Br J Pharmcol 2011

NEW AGENTS AFFECTING *"DIASTOLIC FUNCTION"*

AGENT	EXAMPLE	MECHANISM
"If" current inhibitor	**Ivabradine**	It reduces heart rate by directly affecting sinus node pacemaker
"Late" sodium current inhibitor	**Ranolazine**	It affects the sodium-dependent calcium channels by altering the intracellular sodium level and therefore it prevents calcium overload
Ryanodine receptor stabilizers	**JTV-519 (K201), S107, S44121**	Stabilization of RyR2 by improving binding of calstabin2 to RyR2

Metra M et al., Progress in Cardiovasc Diseases, 2011

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

SIMPOSIO

"SCOMPENSO CARDIACO ACUTO E COMORBILITÀ NELL'ANZIANO"

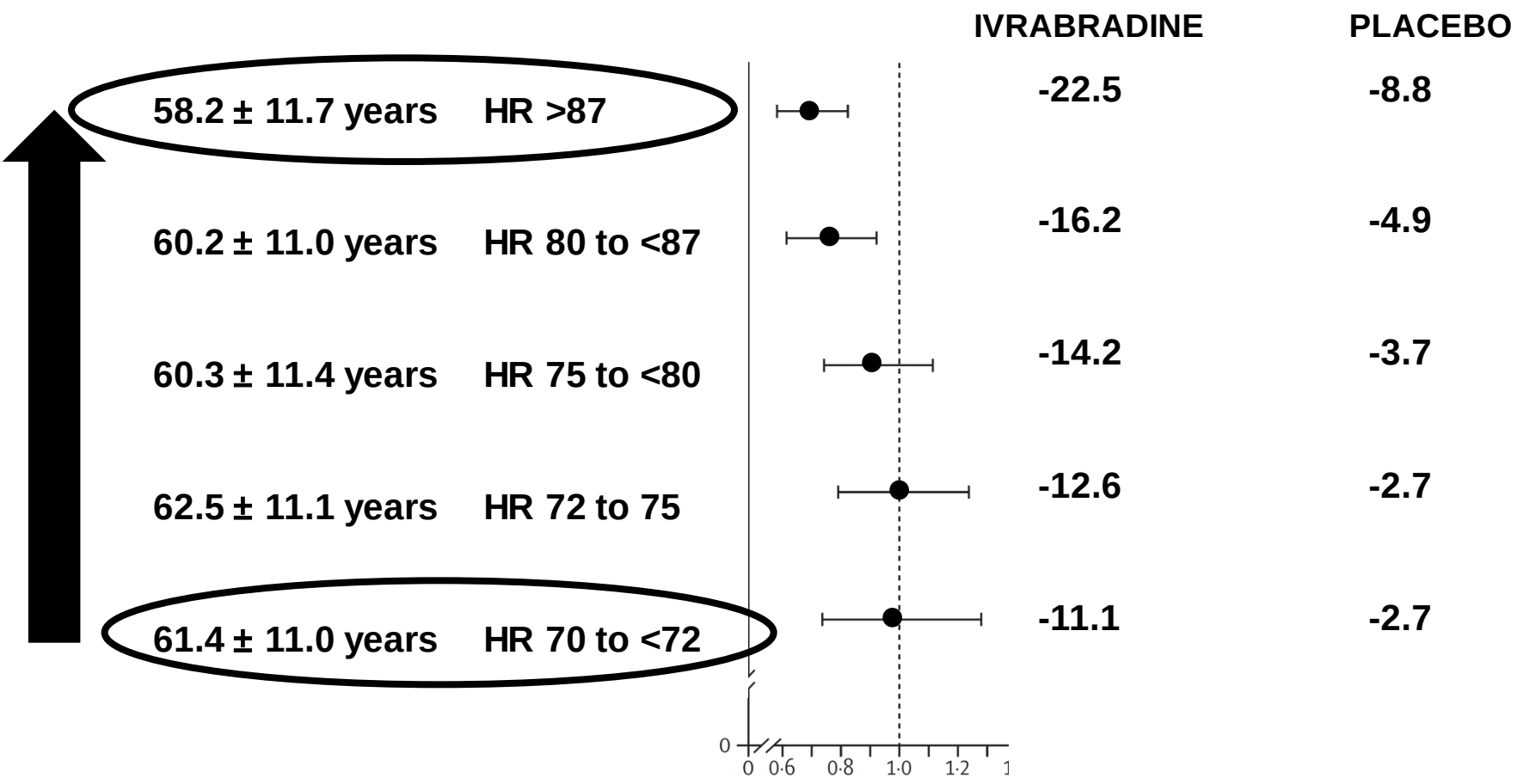
"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial THE LANCET

"IVABRADINE" slows the heart by selective "*If current*" inhibition and, unlike β blockers, has no known cardiovascular eff ects other than heart-rate reduction.

Effect of “Ivabradine” compared with placebo on cardiovascular death or hospital admission for worsening heart failure

At 28 days, heart rate (bpm) change from baseline



Böhm M, et al., Lancet 2011

"Il trattamento farmacologico tra farmaci vecchi e nuovi"

Clinical Investigations

Ranolazine for the Treatment of Heart Failure With Preserved Ejection Fraction: Background, Aims, and Design of the RALI-DHF Study

Clin. Cardiol. 34, 7, 426–432 (2011)

"RANOLAZINE" affects the "sodium-dependent calcium channels" by altering the intracellular sodium level and therefore it prevents "calcium overload".

ACC.12
61st Annual Scientific Session & Expo
ACC-i2 with TCT innovation in intervention

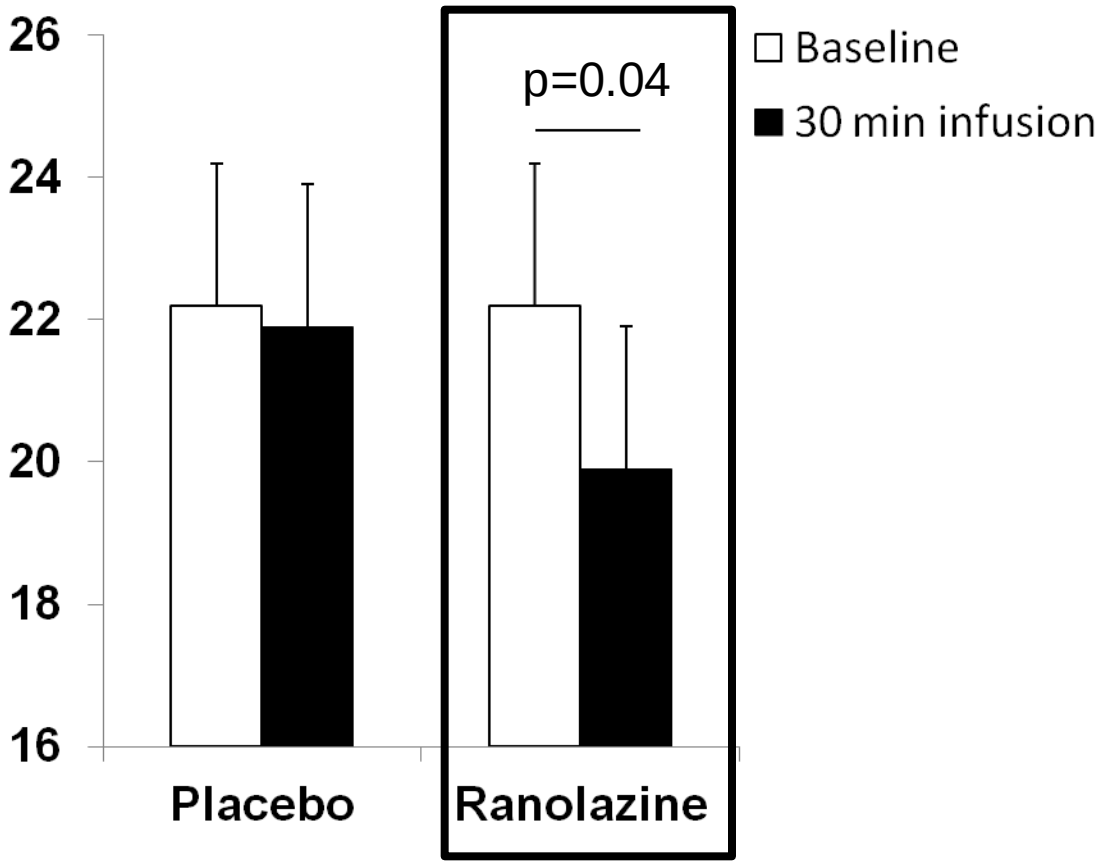
E865
JACC March 27, 2012
Volume 59, Issue 13

Heart Failure

RANOLAZINE FOR THE TREATMENT OF DIASTOLIC HEART FAILURE IN PATIENTS WITH PRESERVED EJECTION FRACTION: RESULTS FROM THE RALI-DHF STUDY

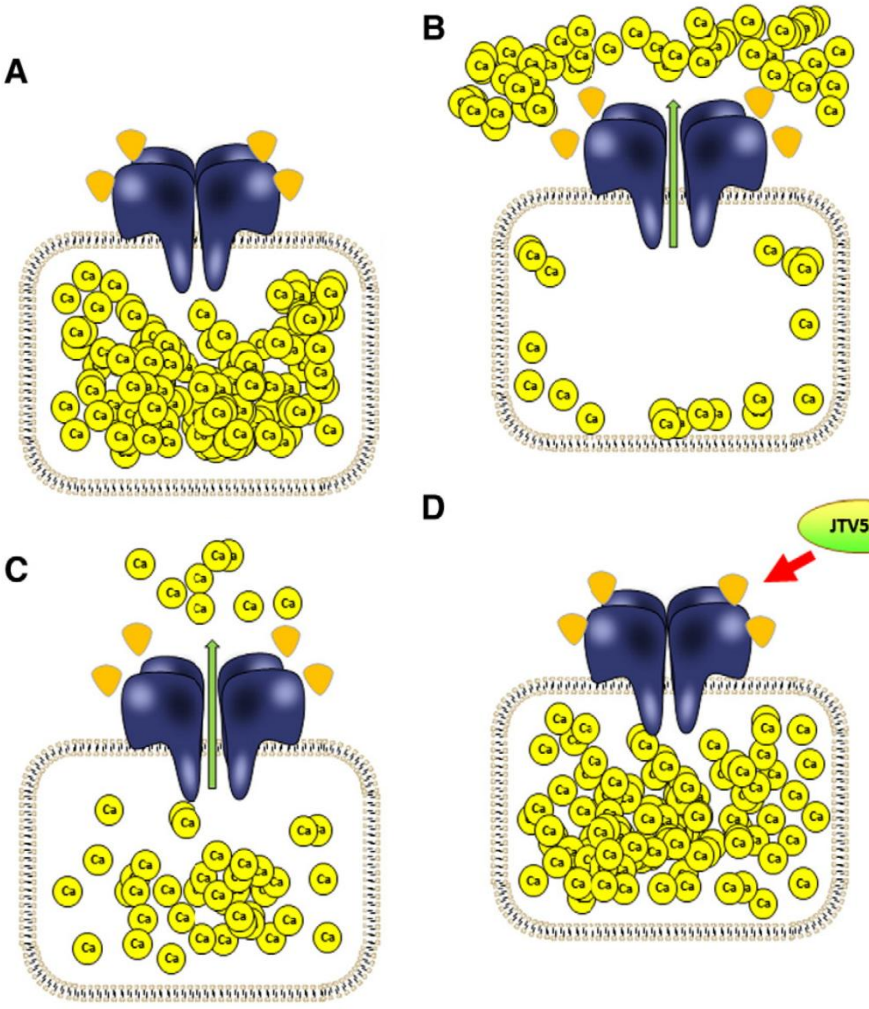
ACC Oral Contributions
McCormick Place South, S406b
Sunday, March 25, 2012, Noon-12:15 p.m.

Left ventricular end-diastolic pressure, mmHg



Treatment of SR Ca^{2+} leak in HF with "RYANODINE RECEPTOR STABILIZERS"

Normal conditions



Activation the RyR2 opens and the Ca^{2+} concentration cytoplasm rises for normal contraction

In heart failure, Ca^{2+} leaks out through the channel, resulting reduced Ca^{2+} release to the cytosol for normal contraction

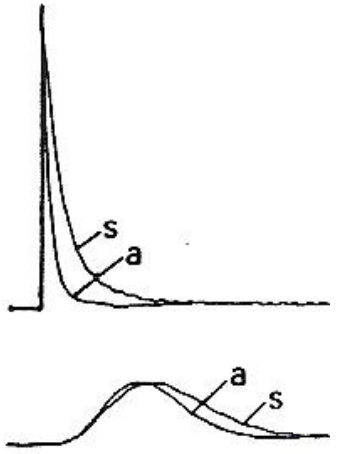
JTV519 (and other ryanodine receptor stabilizers) increases the binding affinity of calstabin2 for RyR2 thereby reducing Ca^{2+} leak.

Aronson D & Krum H. Pharmacology & Therapeutics 2012

“Calcium overload” is exagerated in *senescent* cardiac muscle

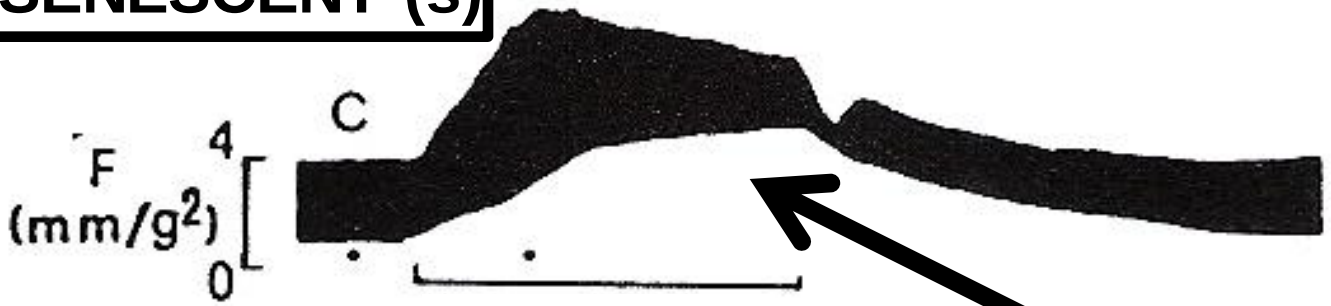
ADULT (a)

High $[Ca]_o$

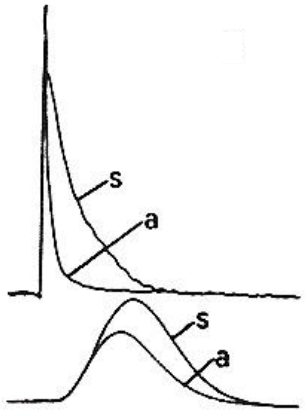


Control

SENESCENT (s)



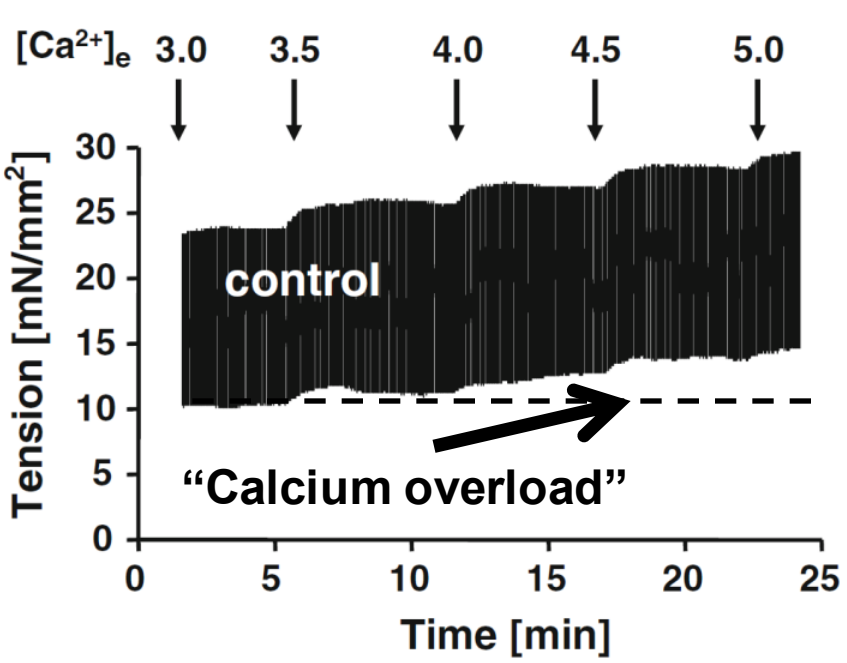
High $[Ca]_o$ **“Calcium overload”**

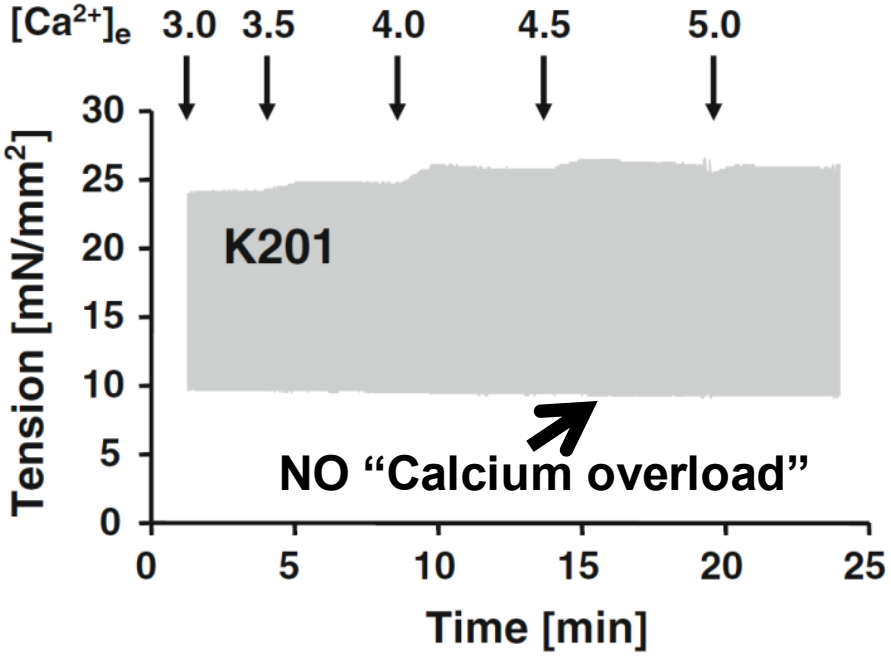


High $[Ca]_o$

Abete P et al., J Gerontol 1996

K201 improves contractile performance of human failing myocardium via reduction of "*calcium overload*"





Toischer K et al., Basic Res 2010

Take home messages (1)

- Therapeutic algorhytm involves *vasodilators* and *diuretics*, and *inotropics* and *vasopressors* in patients with decompensated heart failure with **volume overload and/or low cardiac output**, respectively;

- *New diuretics, vasodilator and inotropic drugs* have been utilized in acute decompensated heart failure **with poor results**;

- In *age-related subgroups analysis*, encouraging results are obtained. Thus, **specific trials in the elderly are necessary**.

Take home messages (2)

- Moreover , *hypotension, renal failure and tachyarrythmias* should be monitored, **especially in the elderly.**

- At this moment, therapy for *heart failure with preserved ejection fraction* **is not defined**.

- Great interest for new drugs acting against *"calcium overload"* that is **exaggerated in the aging heart.**