



TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION



SESSION III: HOT SESSION
NEW THERAPIES AND NEW TREATMENTS

P. Marino (Novara)

Part I Heart failure and diastolic dysfunction: new evidences

Heart failure and diastolic dysfunction: new evidences

IV joint meeting with Mayo Clinic
Torino 20-21 Novembre 2008

Prof. Paolo Marino

*Direttore, Cardiologia Clinica e Dipartimento
Cardiovascolare*

*Università del Piemonte Orientale
“A.Avogadro”*

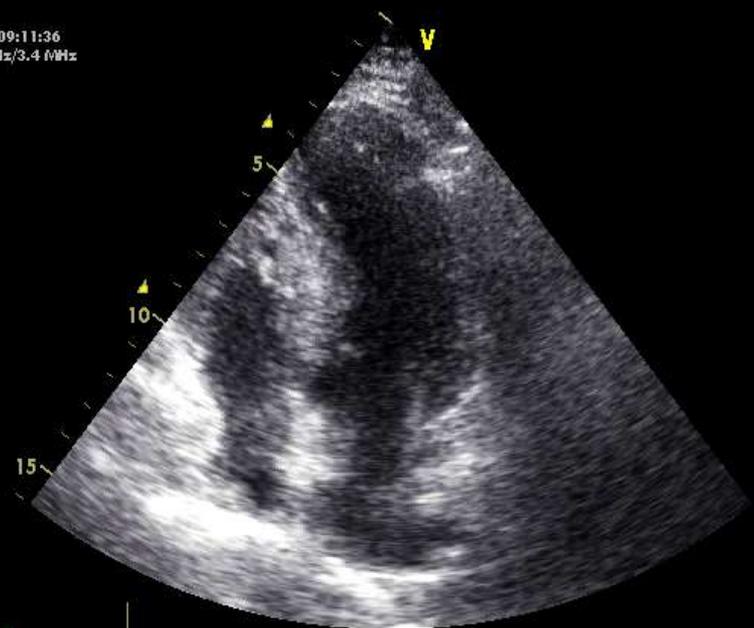
*Azienda Ospedaliera-Universitaria “Maggiore
della Carità”, Novara*

Fisiopatologia dello scompenso

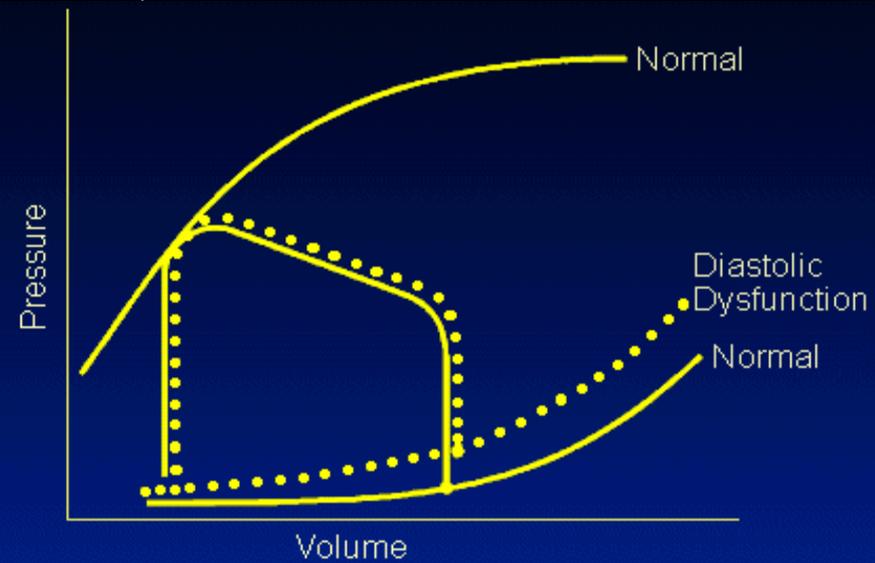
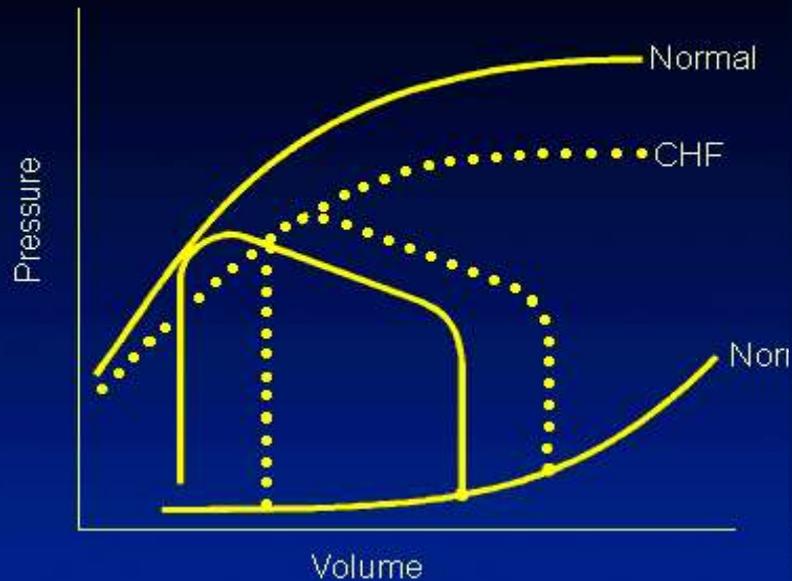
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86
HR



Consumo d'ossigeno durante esercizio massimale e sottomassimale in soggetti normali e pazienti con disfunzione sistolica o diastolica (modificato da Kitzman et al, JAMA 2002)

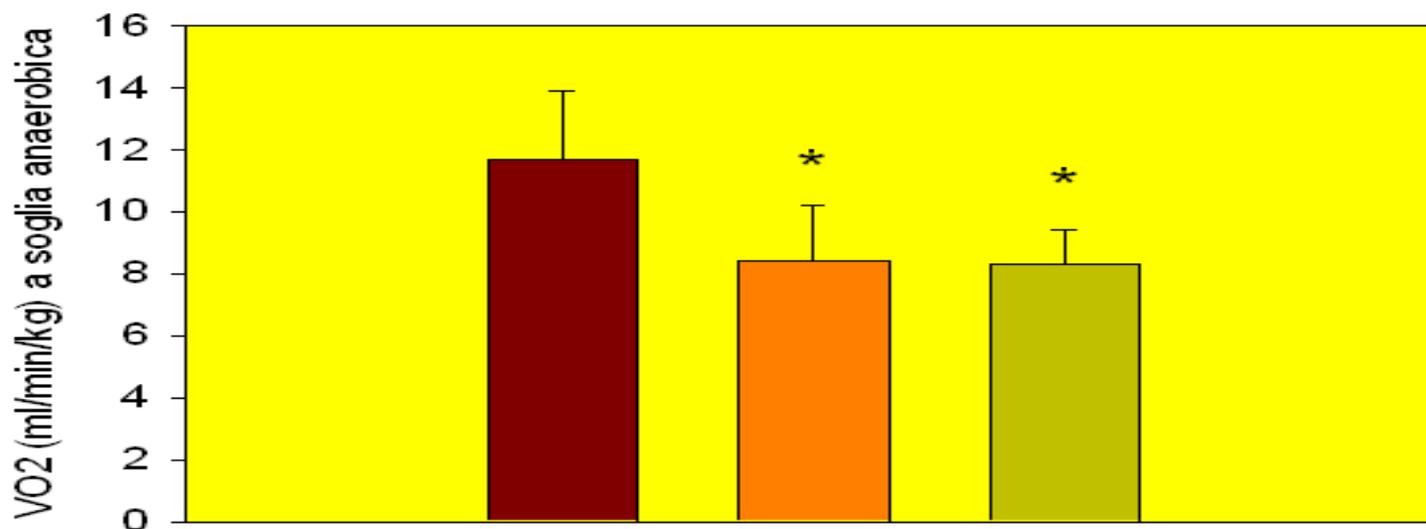
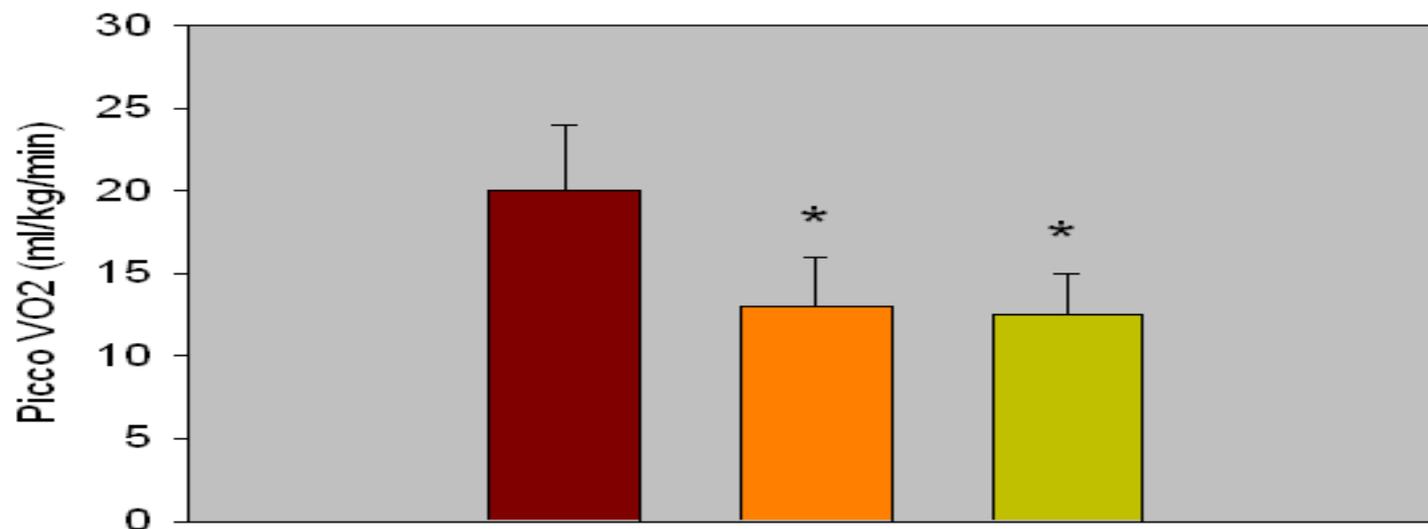


Table: comparison of clinical features of SHF and HFNEF

	<u>HF with reduced EF (SHF)</u>	<u>HF with normal EF (HFNEF)</u>
gender	M>F	F>M
age	50-60 years	60-70 years
aetiology	Myocardial infarction; idiopathic DCM	Hypertension ± diabetes; Atrial fibrillation Transient ischaemia
Clinical progress	Persistent HF	Often episodic HF
Ventricular remodeling (increased LV volumes)	+++	0
LVH	+/-	+++
Dyssynchrony	common	? less common
Mitral inflow pattern	RFP or ARP	ARP
Peak mitral annular systolic velocity	Markedly reduced	Moderately reduced
Peak mitral annular early diastolic velocity	Markedly reduced	Moderately reduced
LA pressure	raised	raised
LA volume	increased	increased

DCM= dilated cardiomyopathy; HF= heart failure; RFP= restrictive filling pattern; ARP= abnormal relaxation pattern.

Heart failure: a single or two syndromes ?

Heart failure presents and evolves as a single syndrome with HFNEF preceding HFREF

Heart failure presents and evolves as two syndromes: one with concentric LV remodeling and mainly diastolic LV dysfunction (DHF) and one with eccentric LV remodeling and combined systolo-diastolic dysfunction (SHF).

Arguments:

- Unimodal distribution of LVEF in HF trials
- Continuous decline of TDI LV long axis shortening velocity (S) from HFNEF to HFREF
- Progression to eccentric LV remodeling in hypertensive heart disease especially in African and Asian populations
- Progression to eccentric LV remodeling in end-stage hypertrophic cardiomyopathy

Arguments:

- Presence of concentric LV remodeling in DHF and eccentric LV remodeling in SHF
- Distinct myocardial ultrastructure with prominent cardiomyocyte hypertrophy in DHF and reduced myofibrillar density in SHF
- Higher in-vitro cardiomyocyte resting tension in DHF
- Distinct isoform shifts of the cytoskeletal protein titin
- Distinct expression pattern of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases
- Prognostic improvement under current heart failure therapy in SHF but not in DHF

“How to diagnose diastolic heart failure”, EHJ 2007



I PRESERVE TRIAL

Irbesartan in Heart Failure with Preserved EF

BACKGROUND: Approximately 50% of HF pts have preserved EF ($\geq 45\%$) (HFPEF). HFPEF primarily affects women and the elderly & is frequently associated hypertension.

PURPOSE: To determine whether treatment with the ARB Irbesartan reduces mortality & morbidity in HFPEF pts.

DESIGN: Randomized, double-blind, placebo-controlled trial of 4,128 pts with follow-up till 1,440 primary endpoints occurred.

Primary Endpoint: All cause mortality & protocol-specified CV hospitalizations (for HF, MI, stroke, arrhythmia).

Secondary Endpoints:

- HF death or hospitalization
- QOL (Minnesota)
- Death, MI or stroke
- CV death

RESULTS:

All cause mortality & CV Hosp: HR (95% CI = 0.95 (0.86 – 1.05) p = 0.35

CV Mortality: HR (95% CI = 1.02 (0.87 – 1.19) p = 0.85

HF Death or Hospitalization: HR (95% CI = 1.01 (0.88 – 1.16) p = 0.89

Conclusion: Irbesartan was safe & well tolerated but did not meet its primary & secondary endpoints.

I-PRESERVE: Entry Criteria

Age ≥ 60 years
Current HF symptoms
LVEF ≥ 0.45

NYHA class II - IV

- CHF hosp. ≤ 6 months

NYHA Class III/IV

- CXR congestion
- ECG (LVH, LBBB)
- Echo (LVH, LAE)

Key Exclusions: SBP > 160 mm Hg; prior EF $< 40\%$; ACS or stroke $\leq 3m$; hypertrophic or restrictive CM, pericardial or valvular disease; significant co-morbidities: pulmonary disease, creatinine > 2.5 , Hb < 11

Only 1/3 pts could enter on an ACEI



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I-PRESERVE: Outcomes

- Primary endpoint: All cause mortality and protocol-specified CV hospitalizations (for heart failure, MI, unstable angina, stroke, ventricular or atrial arrhythmia).
- Secondary endpoints:
 - All cause mortality
 - CV death
 - HF death or HF hospitalization
 - CV death, MI or stroke
 - QoL (MLwHF) at 6 months
 - Change in NT-proBNP levels at 6 months



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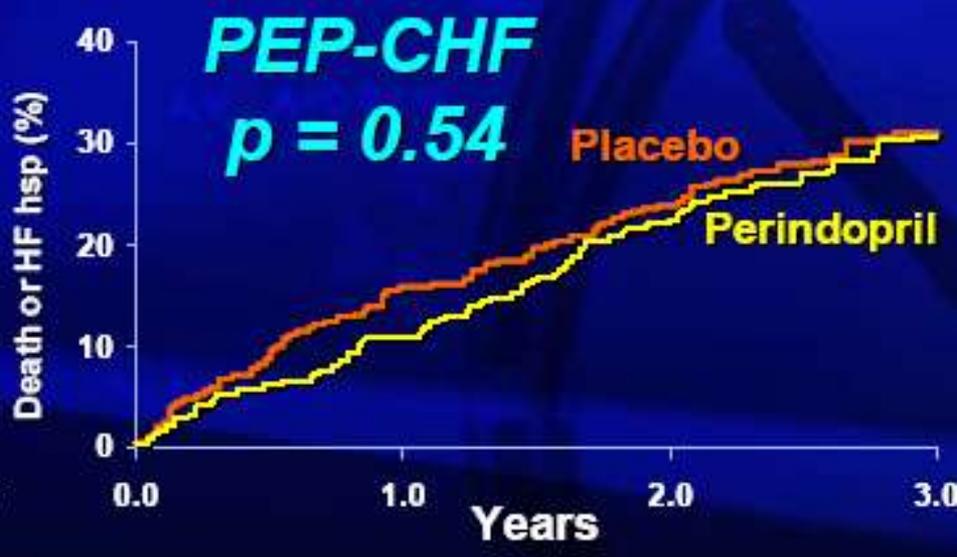
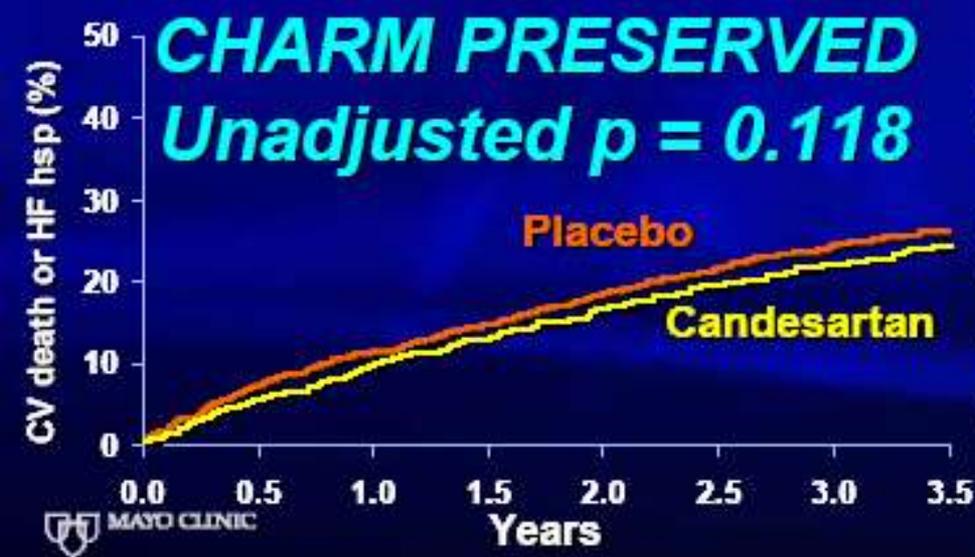
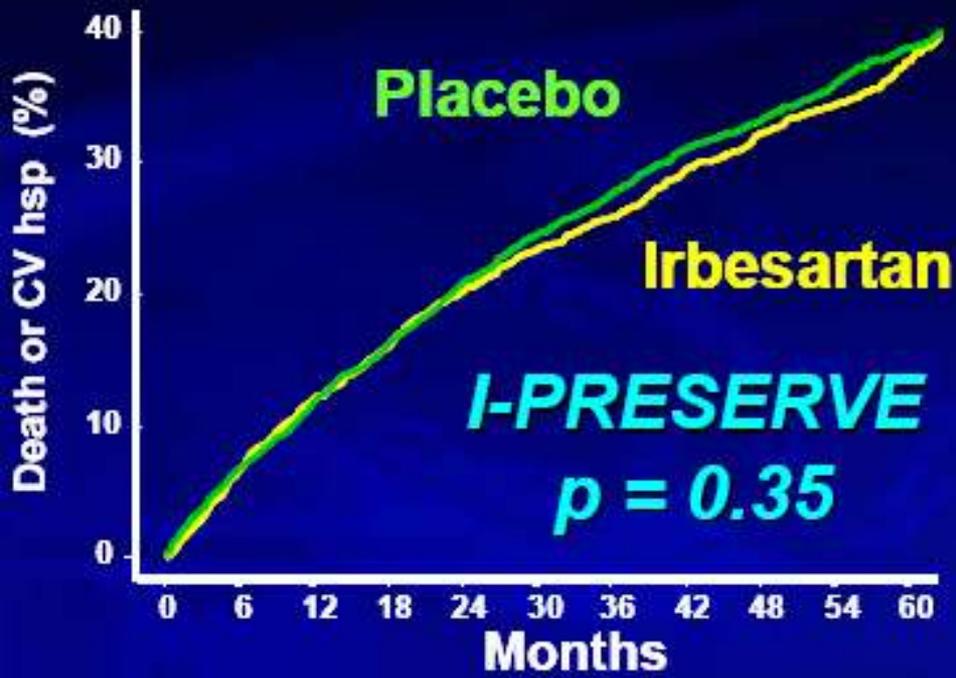
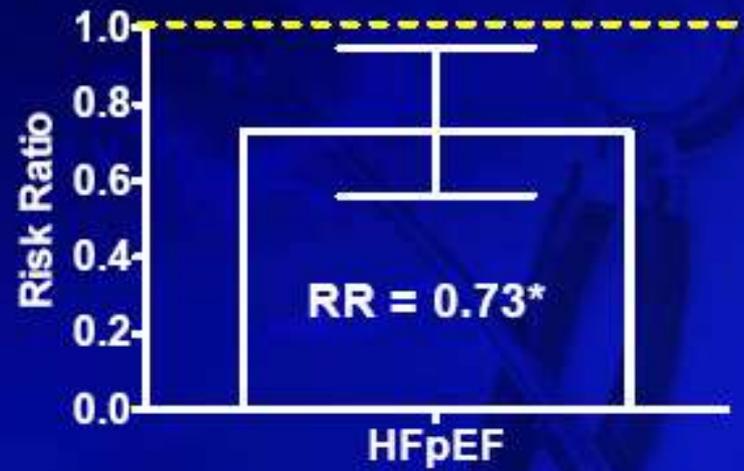
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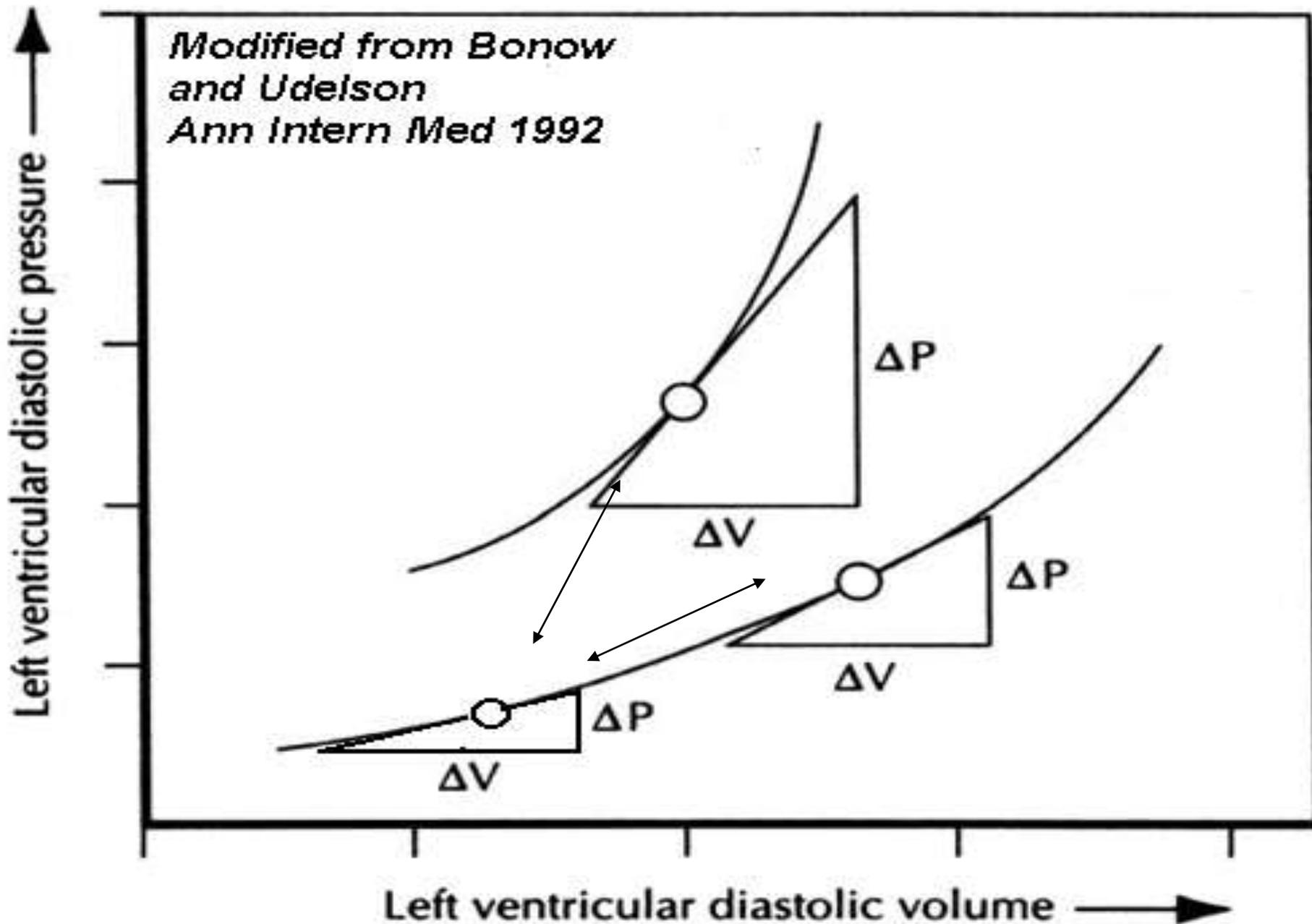
ALLHAT_{AHA} 2006

Prevention of HFpEF in Hypertensives
Chlorthalidone vs Lisinopril

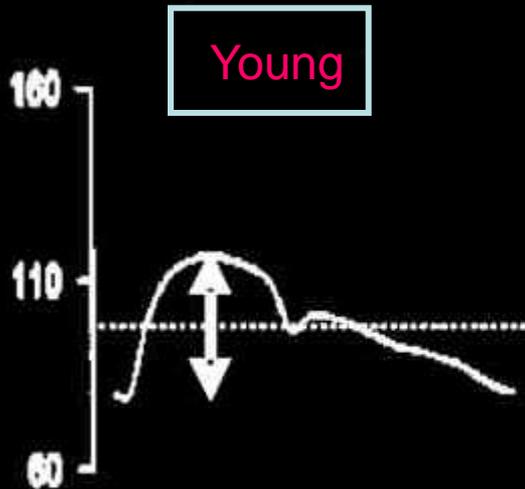
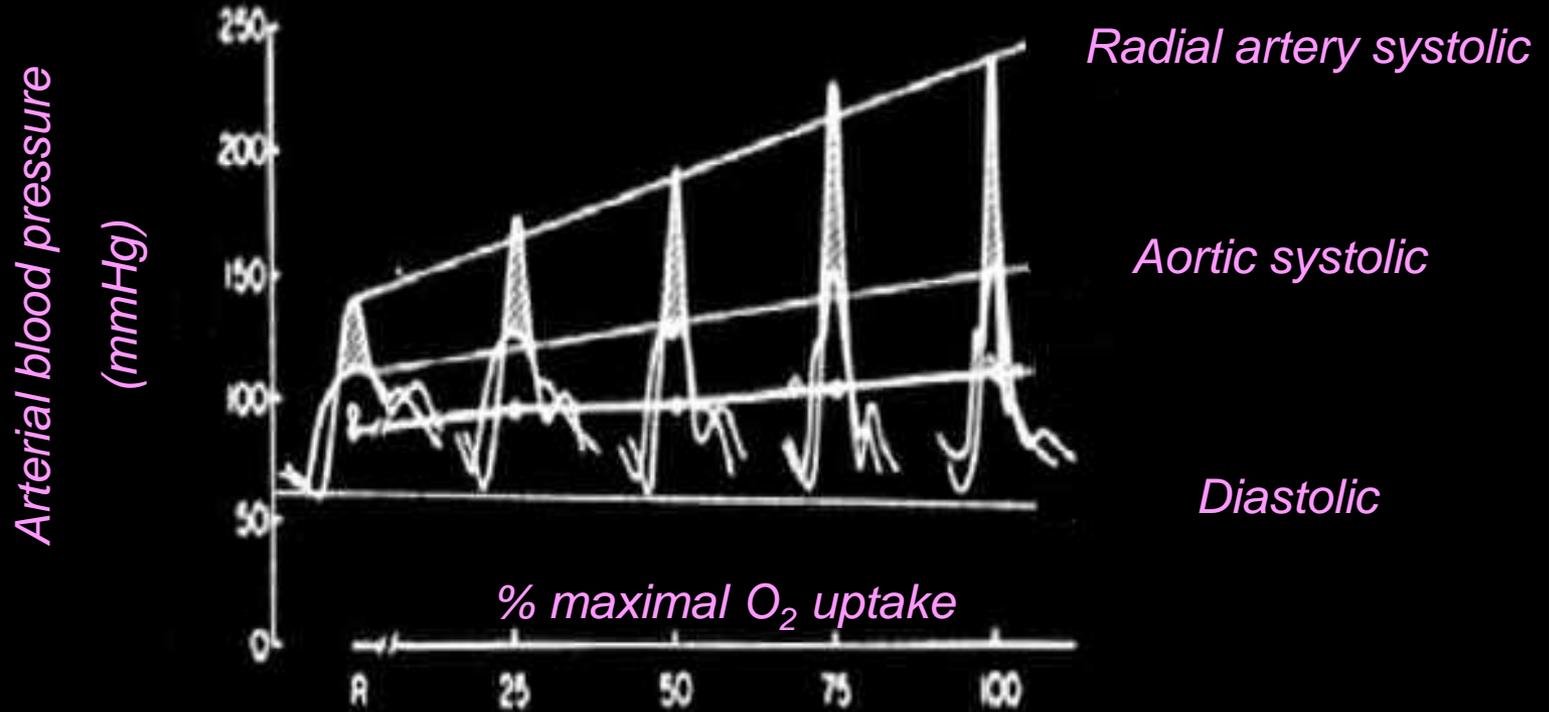


	Obs Study	Obs Study	CHARM HFpEF	PEP-CHF	I-PRESERVE
Age (yrs)	75		67	75	72
♀ %	60		40	56	60
MI %	25		44	27	24
HTN %	> 80		64	79	88
SBP mmHg	132		136	140	136
Follow up	1 yr	5 yr	3 yr	2 yr	4.5 yr
All-cause mortality*	≈ 20%	55%	16%	12.4%	21%
HF Admit*	≈ 20%		18%	17%	16.3%

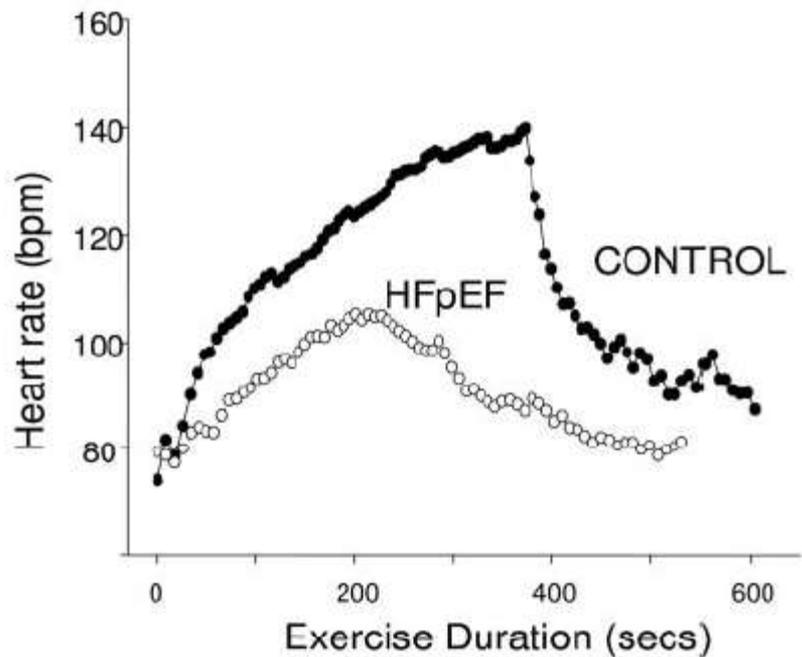
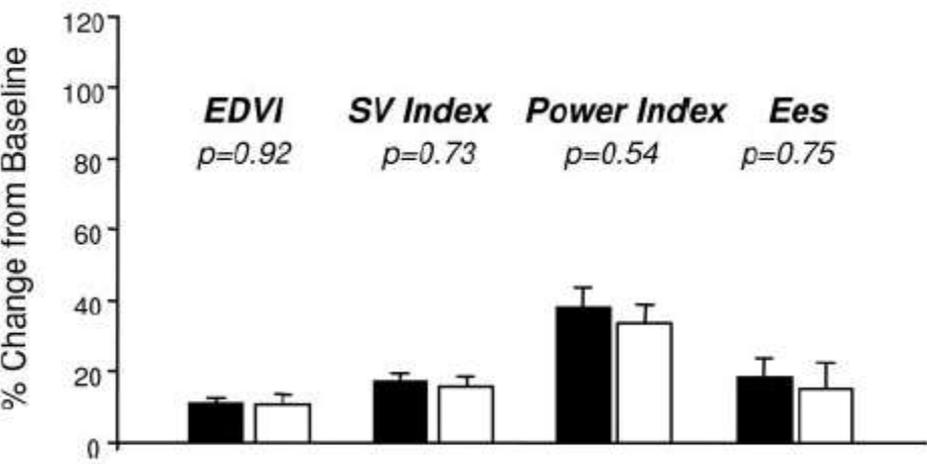
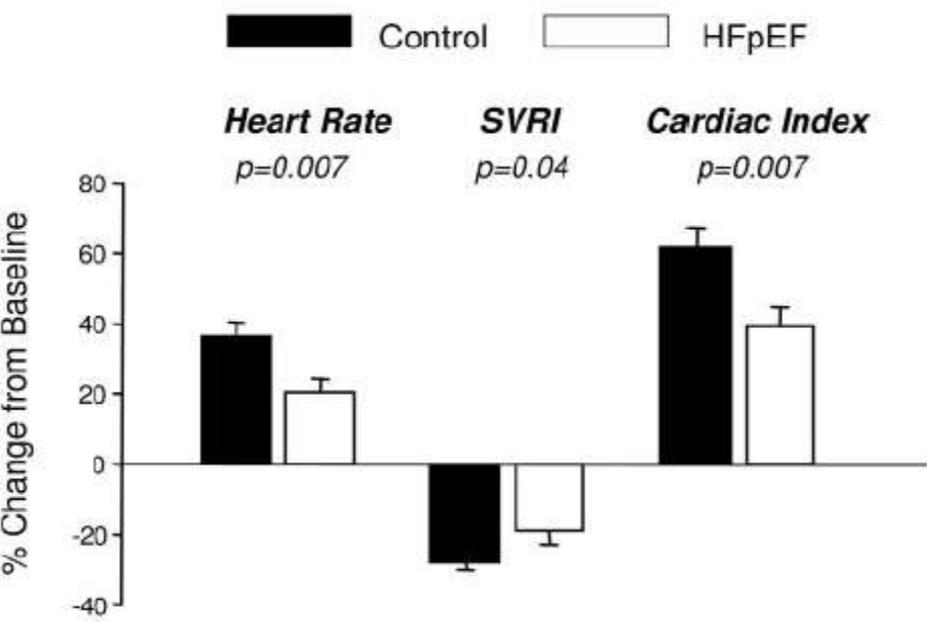
C'era una volta la compliance ventricolare sinistra....



INFLUENCE of EXERCISE on ARTERIAL PULSE PRESSURE



Risposta cardiovascolare, a bassi ed equivalenti livelli di esercizio, in soggetti con disfunzione diastolica rispetto a gruppo di controllo



Borlaug et al, Circulation 2006

- 10:45 **5884 Cardiovascular Reserve Function in Heart Failure with Preserved Ejection Fraction: Systolic versus Diastolic Determinants**
Barry A. Borlaug, The Mayo Clinic, Rochester, MN
Margaret M. Redfield, The Mayo Clinic, Rochester, MN
- 11:00 **5885 Impacts of Renal Insufficiency on the Prevalence of Heart Failure With Preserved Ejection Fraction in Hypertensive Patients**
Tomohito Ohtani, Osaka Univ of Graduate Sch, Suita, Japan
Kazuhiro Yamamoto, Osaka Univ of Graduate Sch, Suita, Japan
- 11:15 **5886 Diastolic Heart Failure and Sleep Disordered Breathing - a Prevalence Study**
Thomas Bitter, Dept of Cardiology, Heart and Diabetes Ctr North Rhine-Westphalia, Ruhr Univ Bochum, Bad Oeynhausen, Germany
Olaf Oldenburg, Dept of Cardiology, Heart and Diabetes Ctr North Rhine-Westphalia, Ruhr Univ Bochum, Bad Oeynhausen, Germany
- 11:30 **5887 Abnormal Cardiac High Energy Phosphate Metabolism and Impaired Diastolic Function after Mt Everest: A Reversible Model of Early Heart Failure?**
Cameron J Holloway, The Univ of Oxford, Oxford, United Kingdom
Kieran Clarke, The Univ of Oxford, Oxford, United Kingdom [Click to zoom out](#)
- 11:45 **5888 The Oxygen Uptake Efficiency Slope is Reduced in Older Patients with Heart Failure and a Normal Ejection Fraction**
Ross Arena, Virginia Commonwealth Univ, Richmond, VA
Dalane Kitzman, Wake Forest Univ Health Sciences, Winston-Salem, NC

AOS.56.1

Diastolic Heart Failure: Diagnosis, Mechanisms and Comorbidities

Abstract Oral Session

La Nouvelle AB

9:00 AM - 12:00 NOON

Moderator:

5878 Dalane Kitzman, Winston-Salem, NC

9:00 5879 Diagnostic Approach to Heart Failure with Normal Ejection Fraction in the Community
Carolyn S P Lam, Mayo Clinic & Fndn, Rochester, MN
Margaret M Redfield, Mayo Clinic & Fndn, Rochester, MN

9:15 5880 Serum Resistin Concentrations and Risk of New Onset Heart Failure in the Elderly
Javed Butler, Emory Univ, Atlanta, GA

9:30 5881 Influence Of Cardiac Inflammation And Extracellular Matrix Regulation On Diastolic Dysfunction In Patients With Heart Failure With Normal Ejection Fraction
Dirk Westermann, Charite, Berlin, Germany
Carsten Tschöpe, Charite, Berlin, Germany

9:45 5882 Myocardial Contractile Dysfunction in Heart Failure with Preserved Ejection Fraction
Barry A. Borlaug, The Mayo Clinic, Rochester, MN
Margaret M. Redfield, The Mayo Clinic, Rochester, MN

10:00 5883 Role of Myocardial Lymphangiogenesis in Hypertensive Heart Failure
Ryosuke Nishio, Kyoto Univ Hosp, Kyoto, Japan
Akira Matsumori, Kyoto Univ Graduate Sch of Med, Kyoto, Japan

10:15 Intermission

Conclusioni

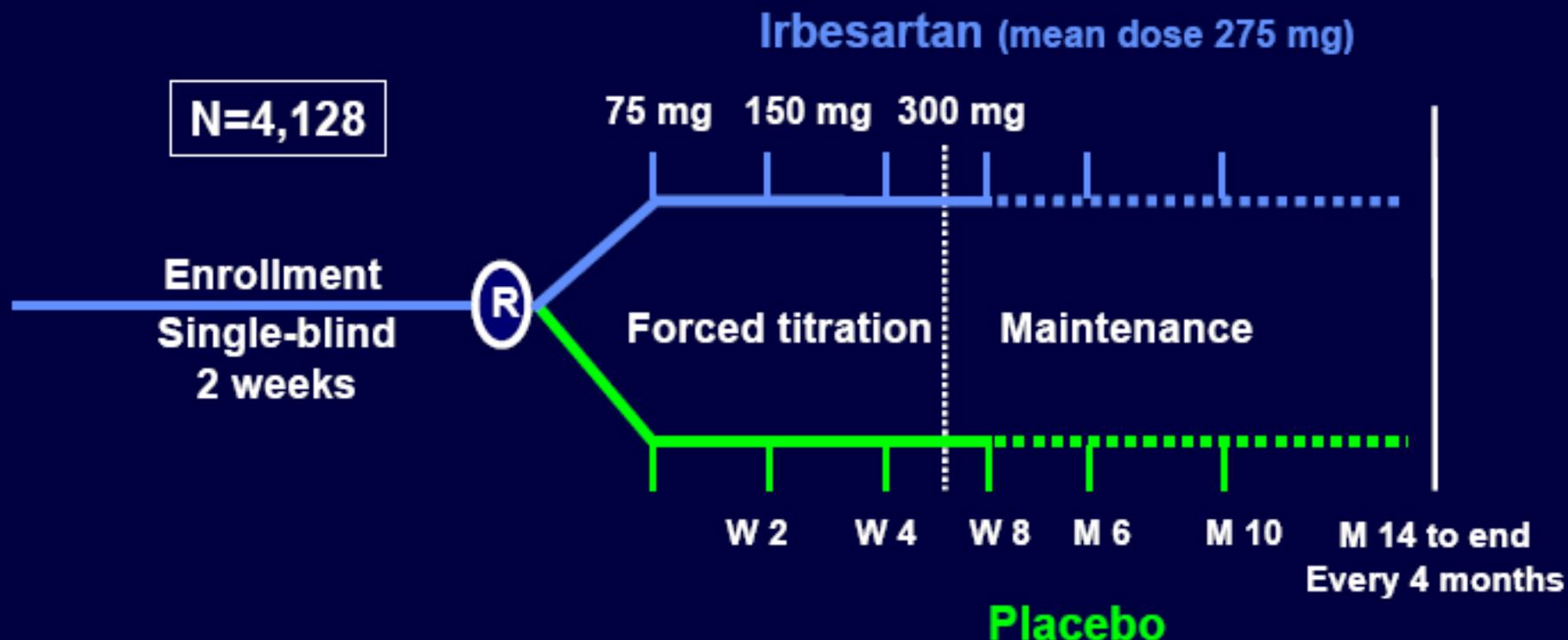
La limitazione funzionale del paziente con disfunzione diastolica, originariamente attribuita unicamente alle alterazioni delle caratteristiche ventricolari diastoliche, riconosce nel progressivo invecchiamento del letto vascolare, nell'imperfetto accoppiamento ventricolo-vascolare e, da ultimo, nell'incompetenza cronotropa possibili concause, che meritano di essere attentamente valutate quando si analizzino pazienti appartenenti a tale entità sindromica.

I-PRESERVE: Objectives

- To determine whether treatment with the angiotensin receptor blocker irbesartan reduces mortality and morbidity in patients with HF-PEF.
- To better define the characteristics, natural history, and prognosis of heart failure in this population.

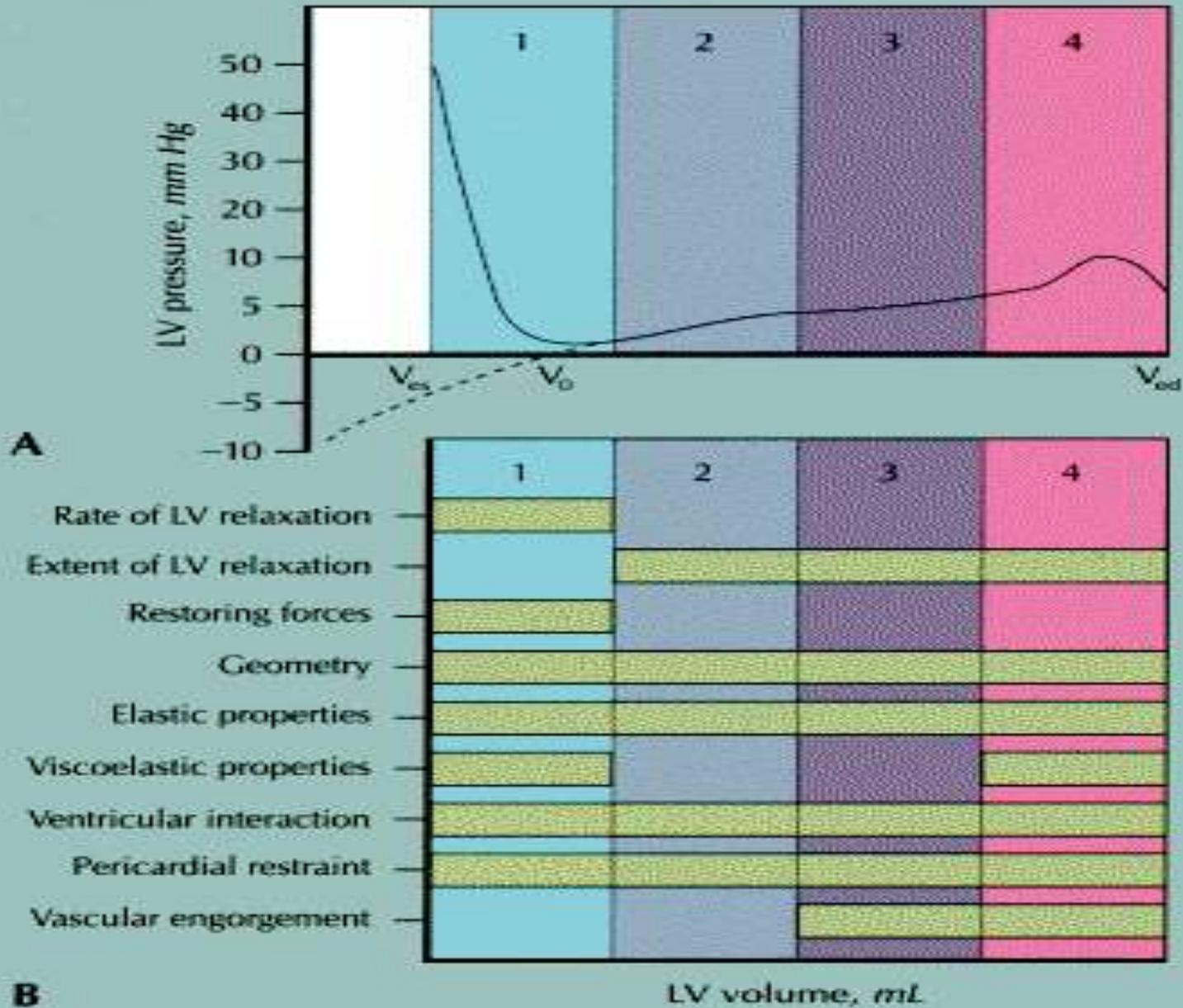
I-PRESERVE: Study Design

Randomized, double-blind, placebo controlled trial



Follow-up continued until 1,440 primary endpoints occurred

Factors affecting diastole



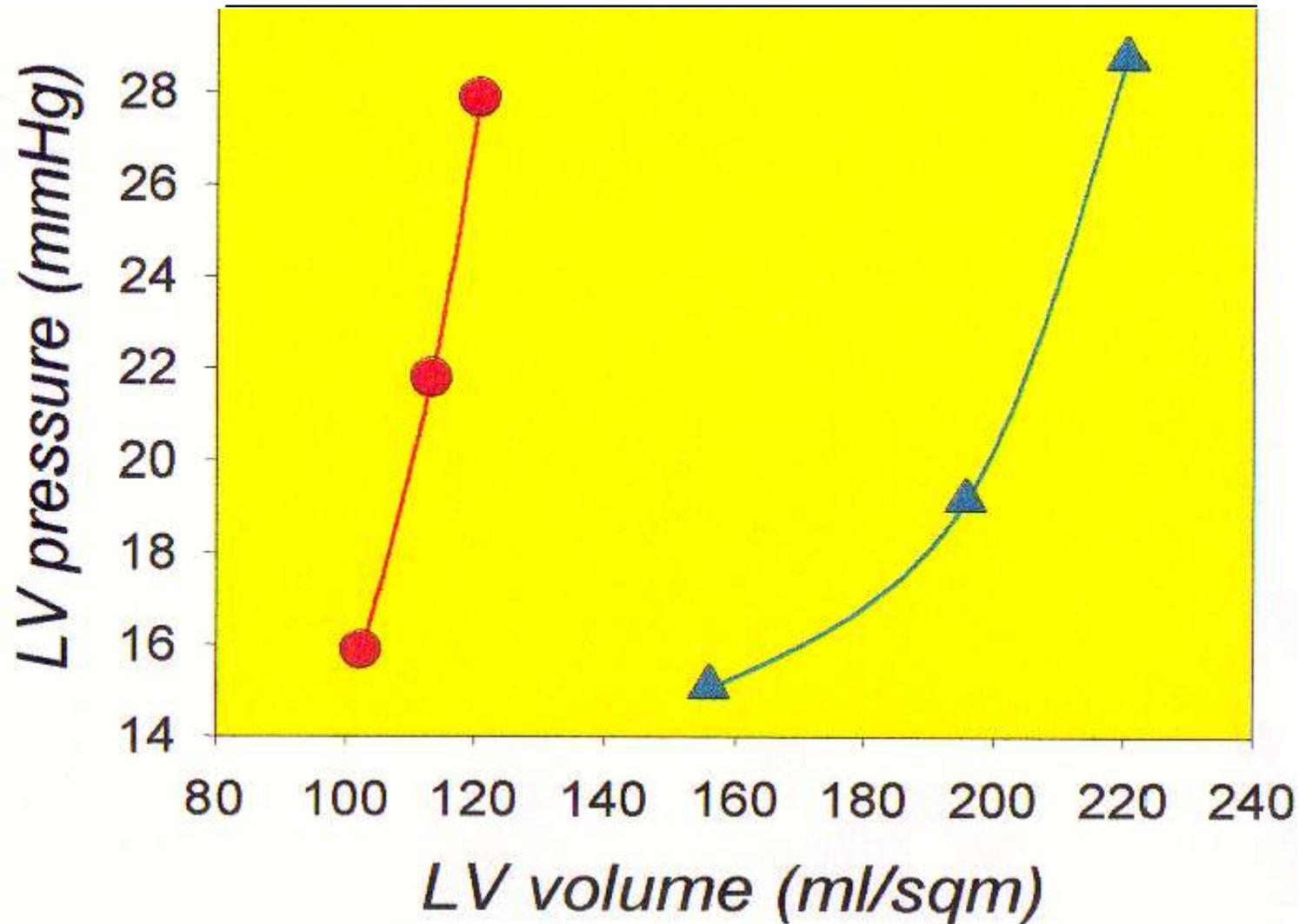
I-PRESERVE: Patient Characteristics

	Cohort & Epidemiological <u>Studies</u>	I-PRESERVE <u>(n=4,128)</u>
Age, yr	75	72
Women	65-70%	60%
EF	60%	59%
Hypertension hx	80-90%	88%
Prior MI	<20%	23%
Atrial fibrillation	20-30%	29%
Diabetes	20-30%	27%

C'era una volta la compliance ventricolare sinistra....

Insufficienza diastolica

Insufficienza sistolica



I-PRESERVE: Baseline Characteristics (i)

	Placebo (N = 2061)	Irbesartan (N = 2067)
Age (Mean – yr)	72 ± 7	72 ± 7
≥75 yrs (%)	35	34
Female sex (%)	61	59
Race - White (%)	93	94
NYHA class (%) II/III/IV	22/76/3	21/77/3
Ischemic etiology (%)	24	26
Hypertensive etiology (%)	63	64
Hypertension Hx (%)	88	89
Myocardial infarction Hx (%)	23	24
Atrial Fibrillation Hx (%)	29	29
Diabetes Mellitus Hx (%)	27	28

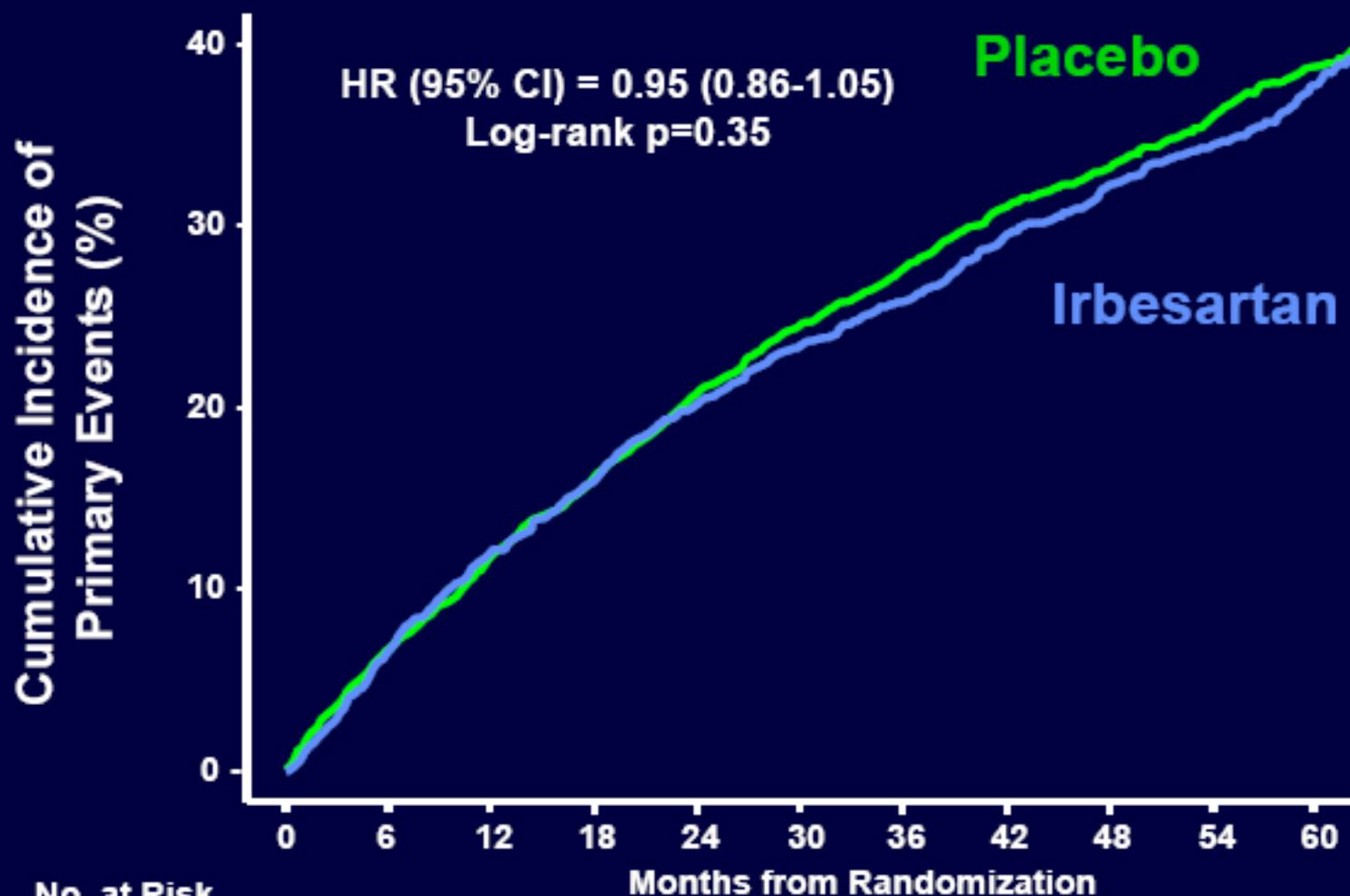
I-PRESERVE: Baseline Characteristics (ii)

Clinical measurements	Placebo (N = 2061)	Irbesartan (N = 2067)
Systolic BP, mm Hg	136 ± 15	137 ± 15
Diastolic BP, mm Hg	79 ± 9	79 ± 9
Body Mass Index, kg/m ²	29.6 ± 5.3	29.7 ± 5.3
QoL MLwHF score (median, IQ range)	42 (28 – 58)	42 (27 – 58)
Laboratory measurements		
EF	0.60 ± 0.09	0.59 ± 0.09
ECG - LVH (%)	30	31
Hemoglobin, g/dL	14 ± 2	14 ± 2
Creatinine, mg/dL	1.0 ± 0.34	1.0 ± 0.32
eGFR, ml/min/1.73m ²	72 ± 22	73 ± 23
NT-proBNP, pg/ml (median, IQ range)	320 (131 – 946)	360 (139 – 987)

Mean ± sd unless otherwise stated

I-PRESERVE: Primary Endpoint

Death or protocol specified CV hospitalization
(Mean follow-up 49.5 months)



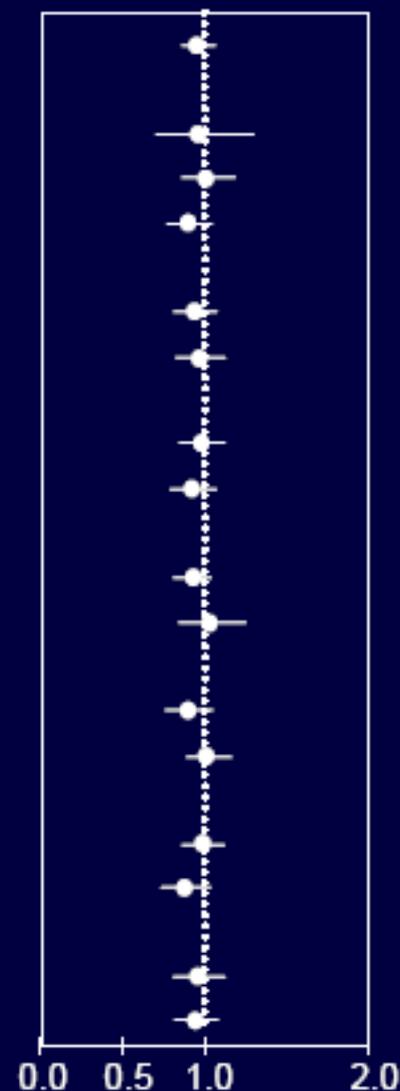
No. at Risk

Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

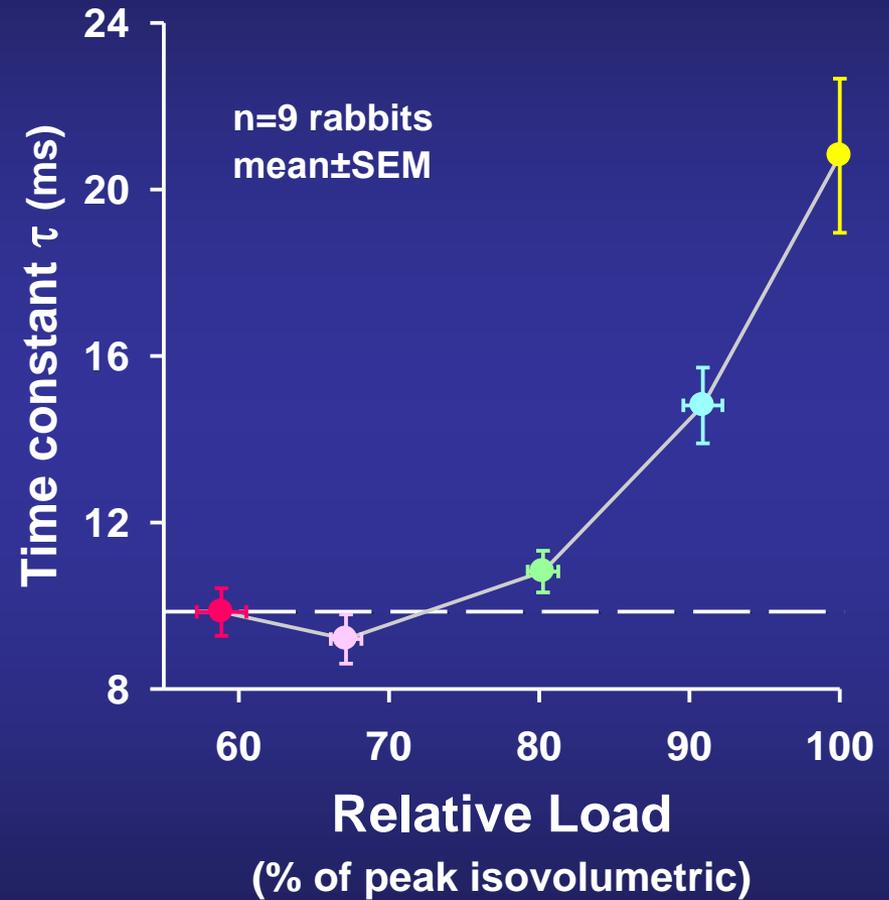
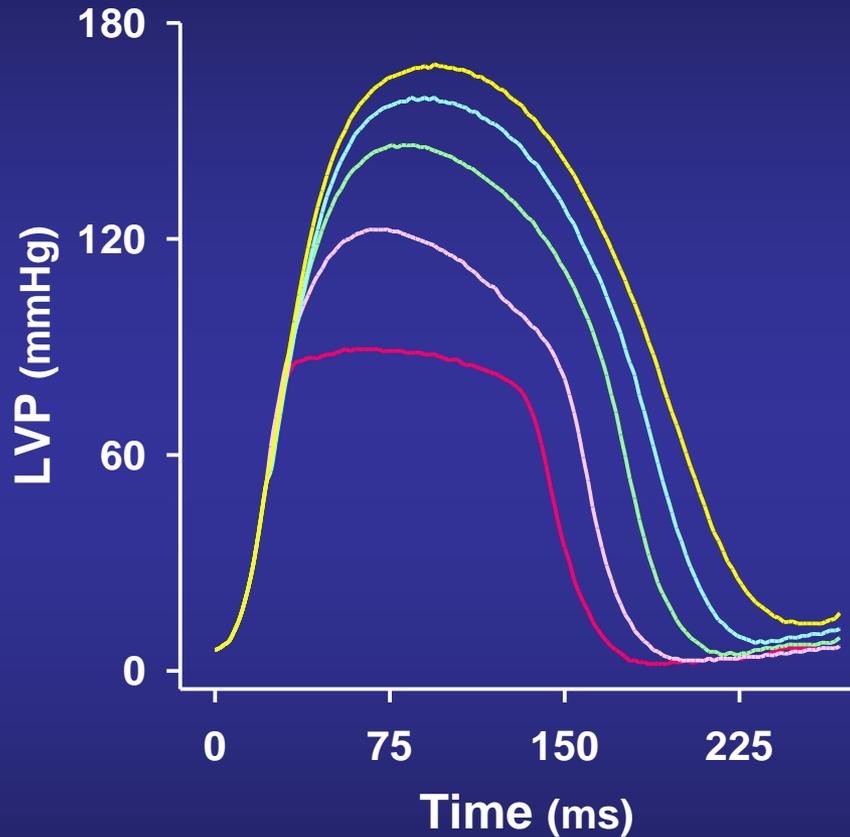
I-PRESERVE: Primary Endpoint subgroup analyses

Time to First Primary Event by Baseline Subgroup

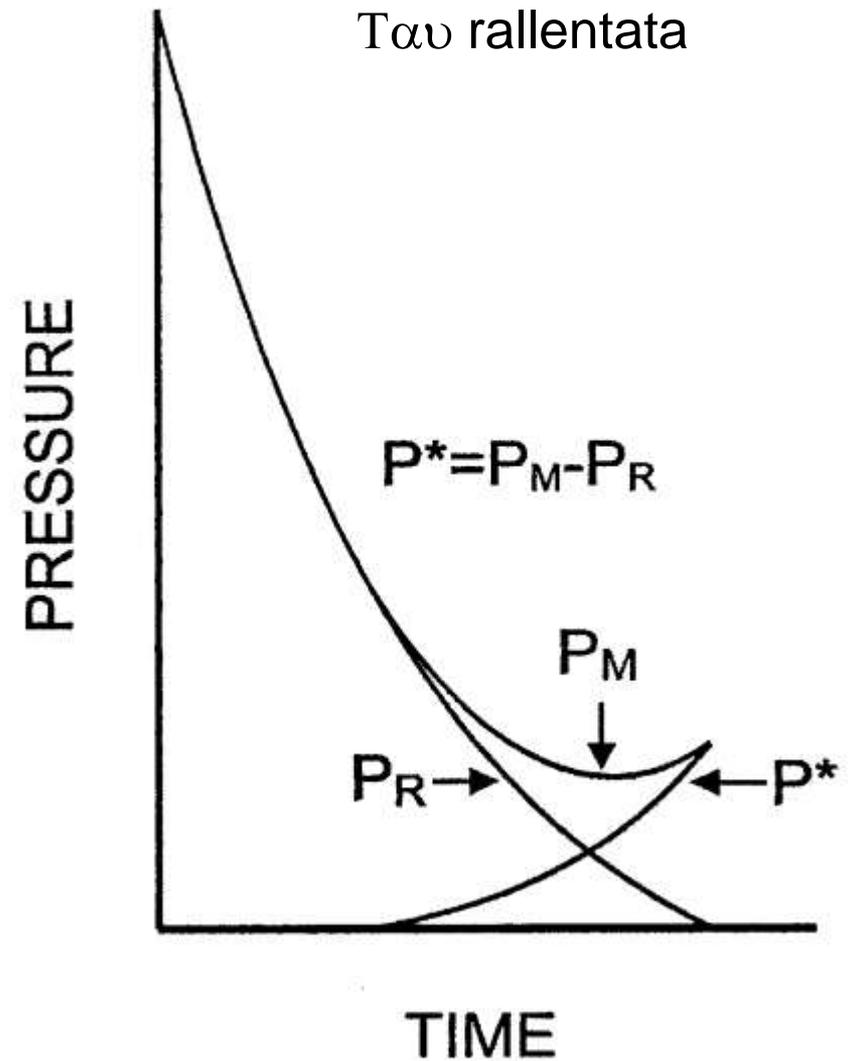
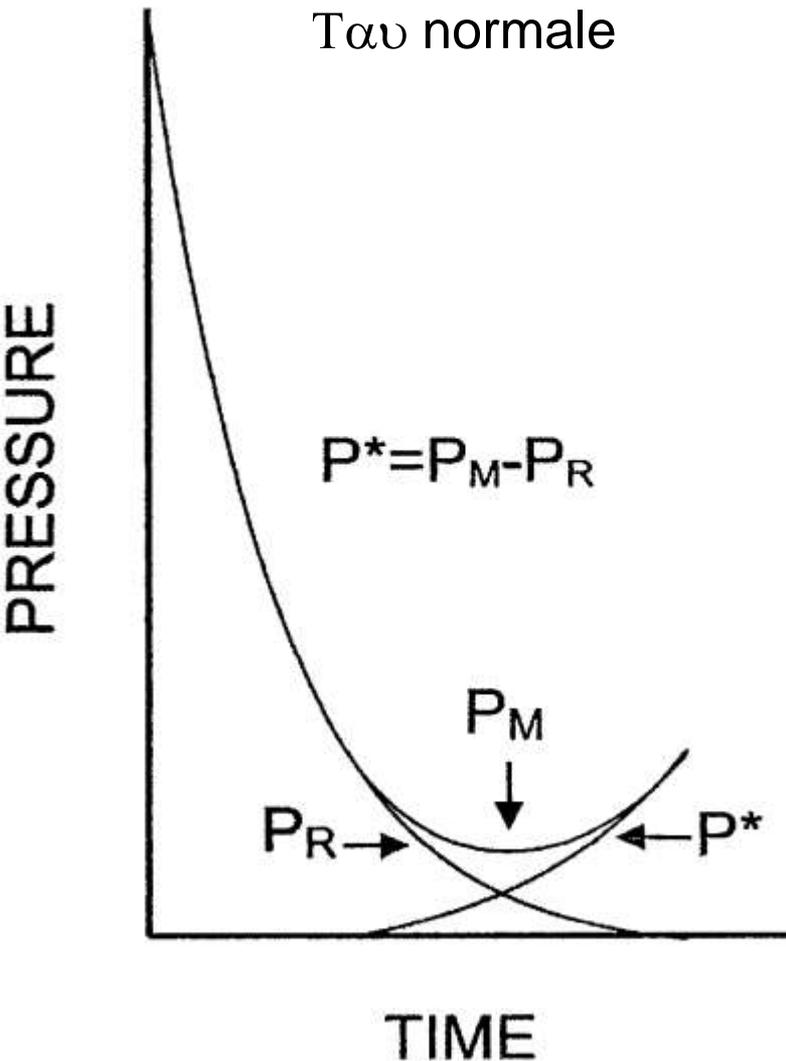
<u>Baseline Subgroup</u>	<u>Irbesartan</u>	<u>Placebo</u>
ALL PATIENTS	742/2067 (36%)	763/2061 (37%)
Age Group		
< 65	86/376 (23%)	86/364 (24%)
65-75	331/994 (33%)	322/981 (33%)
>= 75	325/697 (47%)	355/716 (50%)
Sex		
Female	392/1228 (32%)	420/1263 (33%)
Male	350/839 (42%)	343/798 (43%)
Ejection Fraction		
<= 59	433/1054 (41%)	423/1027 (41%)
> 59	309/1011 (31%)	339/1033 (33%)
ACEi		
No	529/1529 (35%)	566/1551 (36%)
Yes	213/538 (40%)	197/510 (39%)
Beta-blocker		
No	299/842 (36%)	336/859 (39%)
Yes	443/1125 (36%)	427/1202 (36%)
Diabetes		
No	491/1495 (33%)	494/1496 (33%)
Yes	25/570 (44%)	269/564 (48%)
Hosp. for HF within 6 Months		
No	323/1157 (28%)	334/1155 (29%)
Yes	419/910 (46%)	429/906 (47%)



“Carico” e rilascio ventricolare



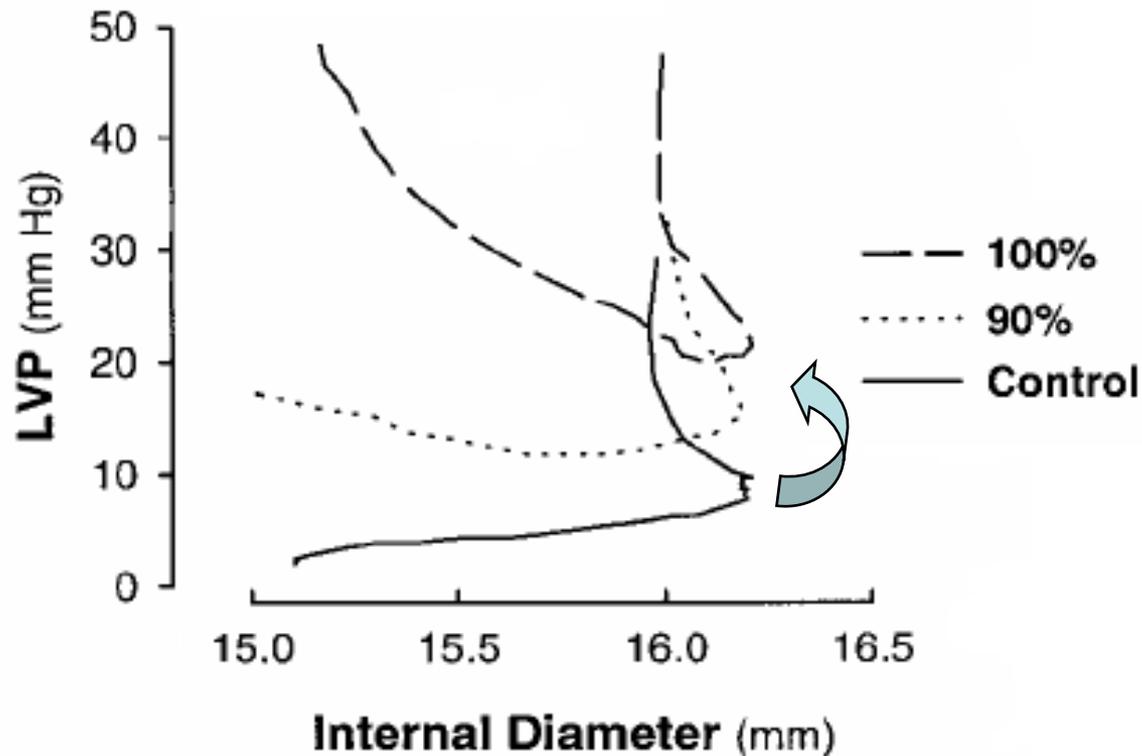
Effetto del prolungamento della fase di rilasciamento ventricolare sulla pressione diastolica ventricolare sx



Load as an acute determinant of end-diastolic pressure-volume relation

ADELINO F. LEITE-MOREIRA AND JORGE CORREIA-PINTO

Department of Physiology, Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal



Hotline Editorial

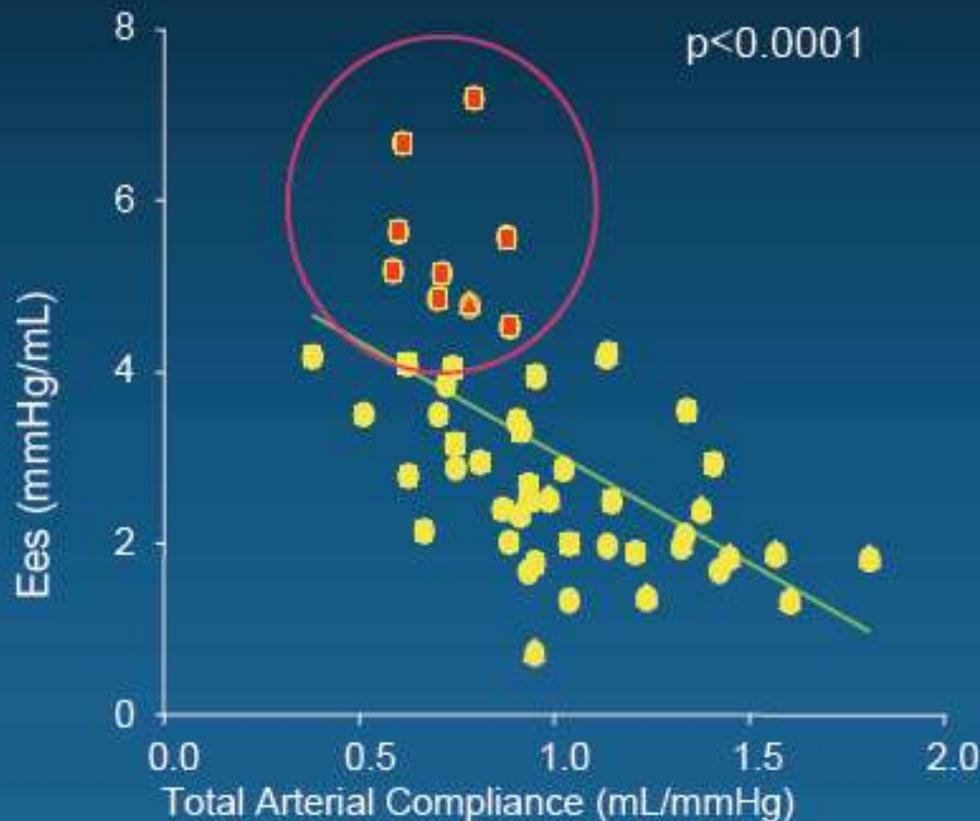
During Acute Pulmonary Edema
Blood pressure, 240/144 mm Hg



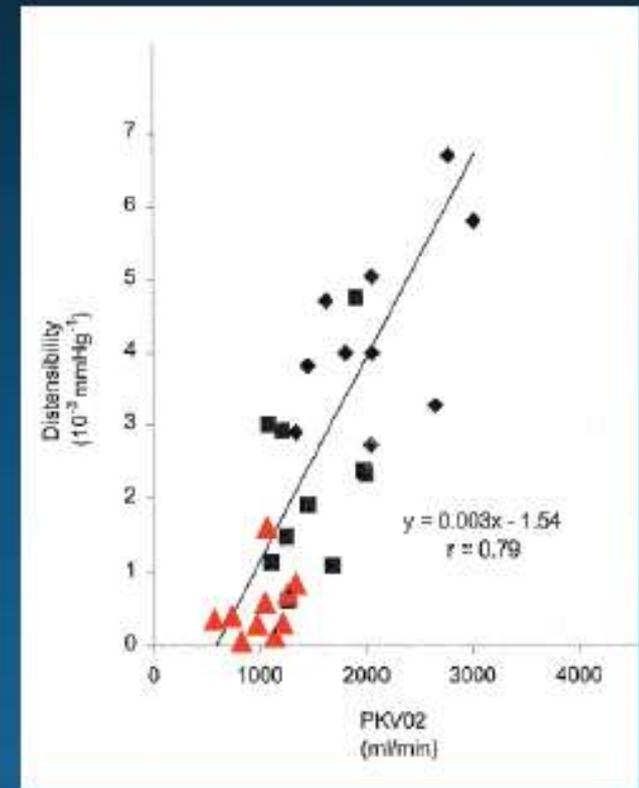
After Treatment
Blood pressure, 149/75 mm Hg



Reduced arterial compliance - correlates with increased ventricular systolic stiffening and diminished exercise capacity

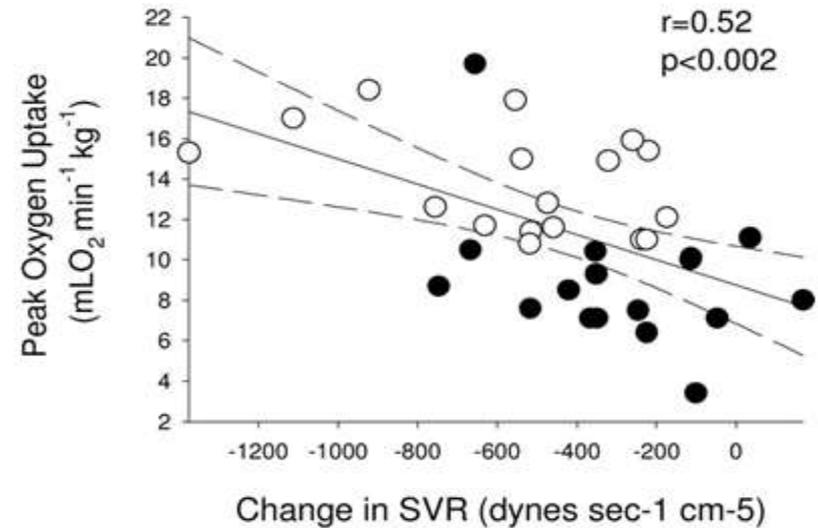
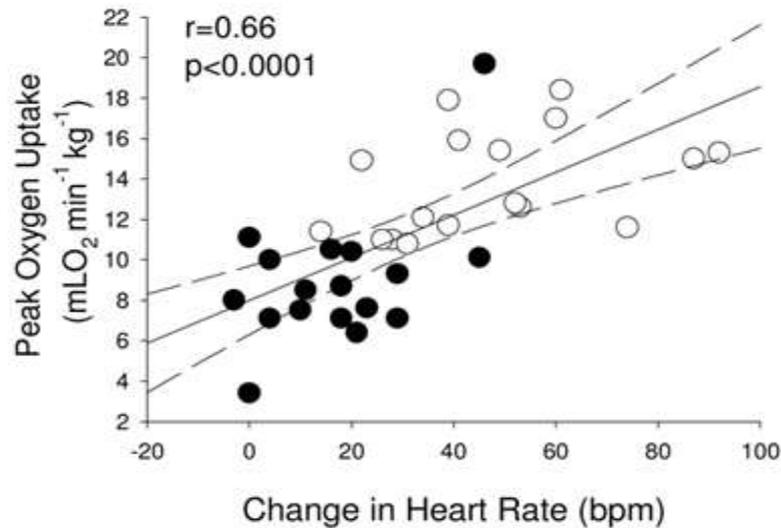


Kawaguchi et al. Circ. 2003;107:714



Hundley et al. JACC. 2001;38:976

Consumo di O₂, risposta cronotropa e vasodilatatoria rispetto a variazioni del volume e riempimento ventricolare



■ Control □ HFpEF

Borlaug et al, Circulation 2006

