

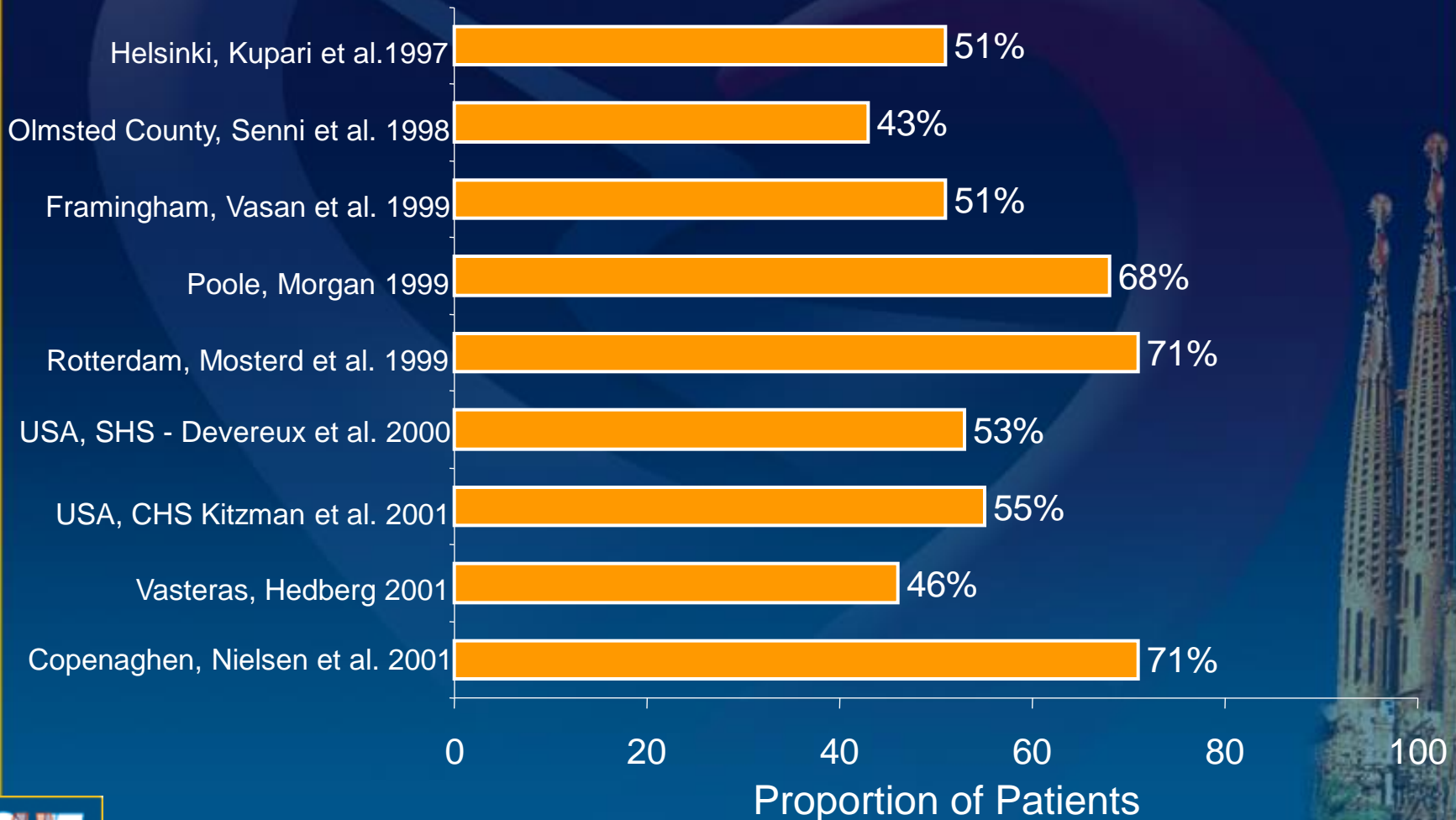
What options to Treat Diastolic Dysfunction

Marco Metra

Associate Professor of Cardiology

University of Brescia (Italy)

Prevalence of Normal LV Systolic Function in Epidemiological Studies of Heart Failure

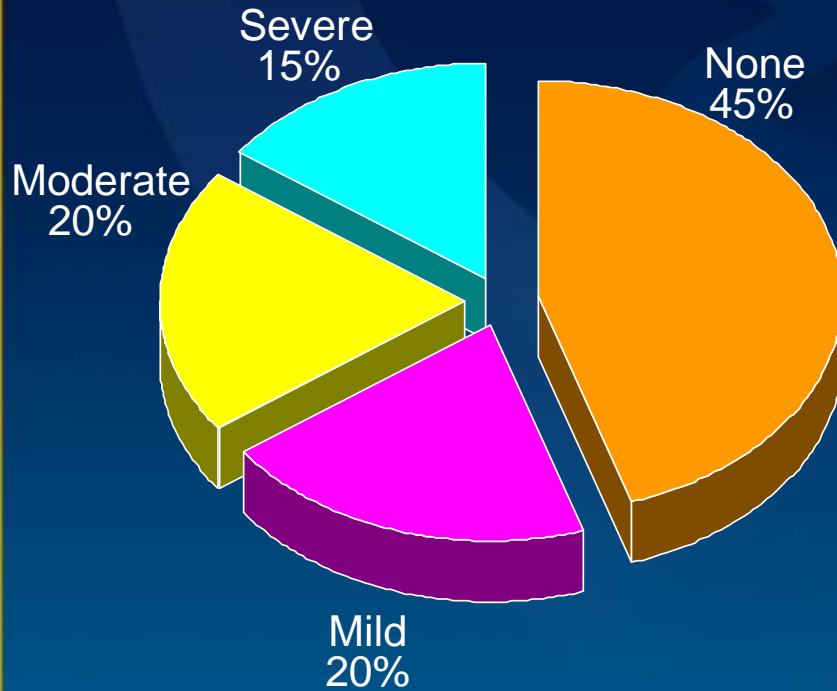


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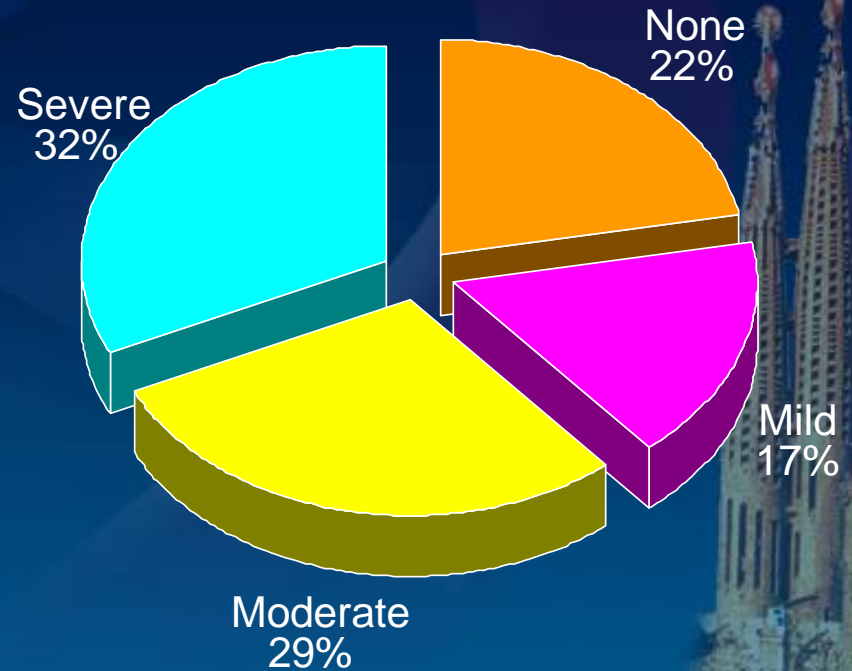
Distribution of the Severity of LV Systolic Dysfunction by Echo Assessment. Results from the EuroHeart Failure Survey:

115 hospitals 24 European countries during a 6 weeks period

Women (n = 2607)



Men (n = 2607)

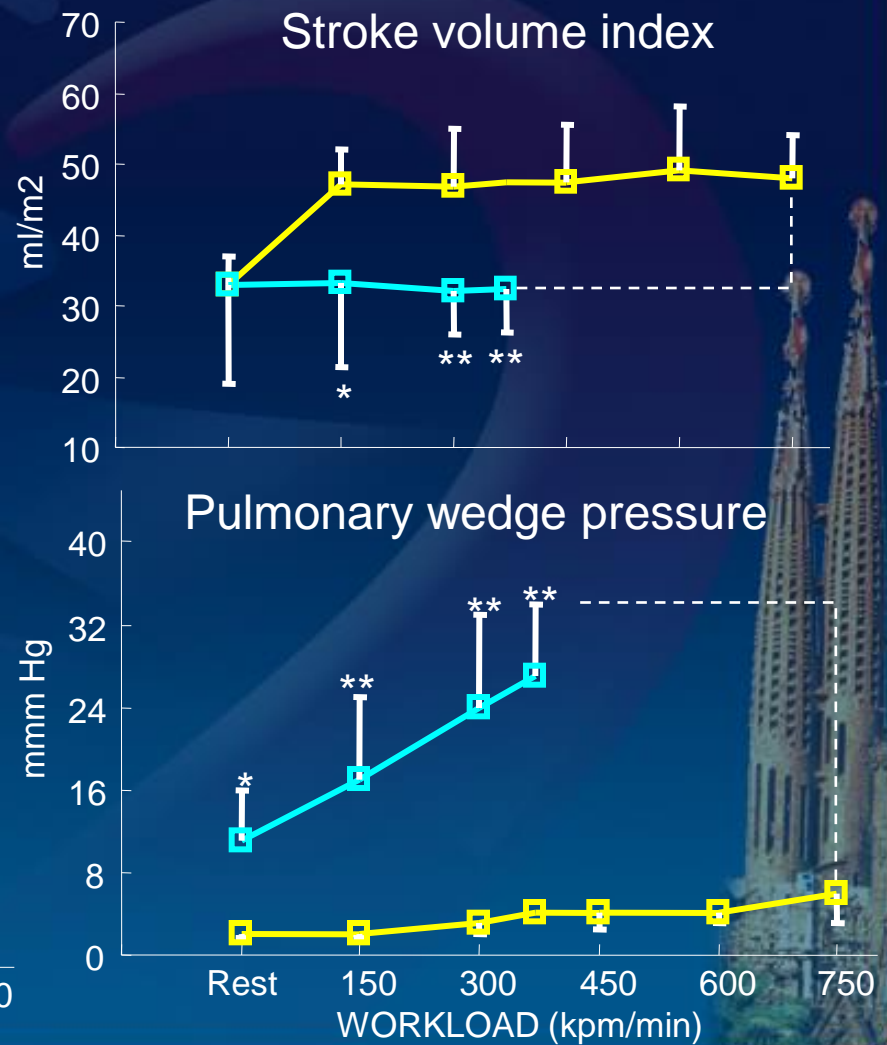
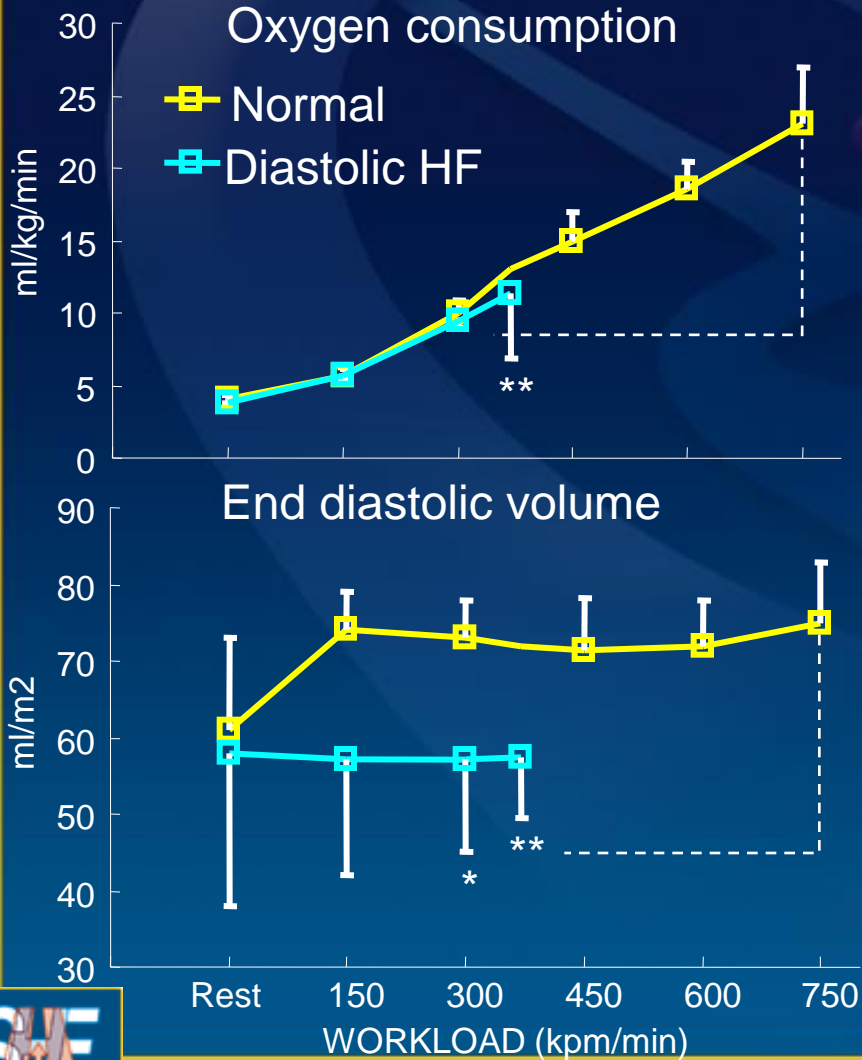


Diastolic Dysfunction: Why (and What) to Treat ?

- Clinical significance
 - Symptoms
 - Prognosis

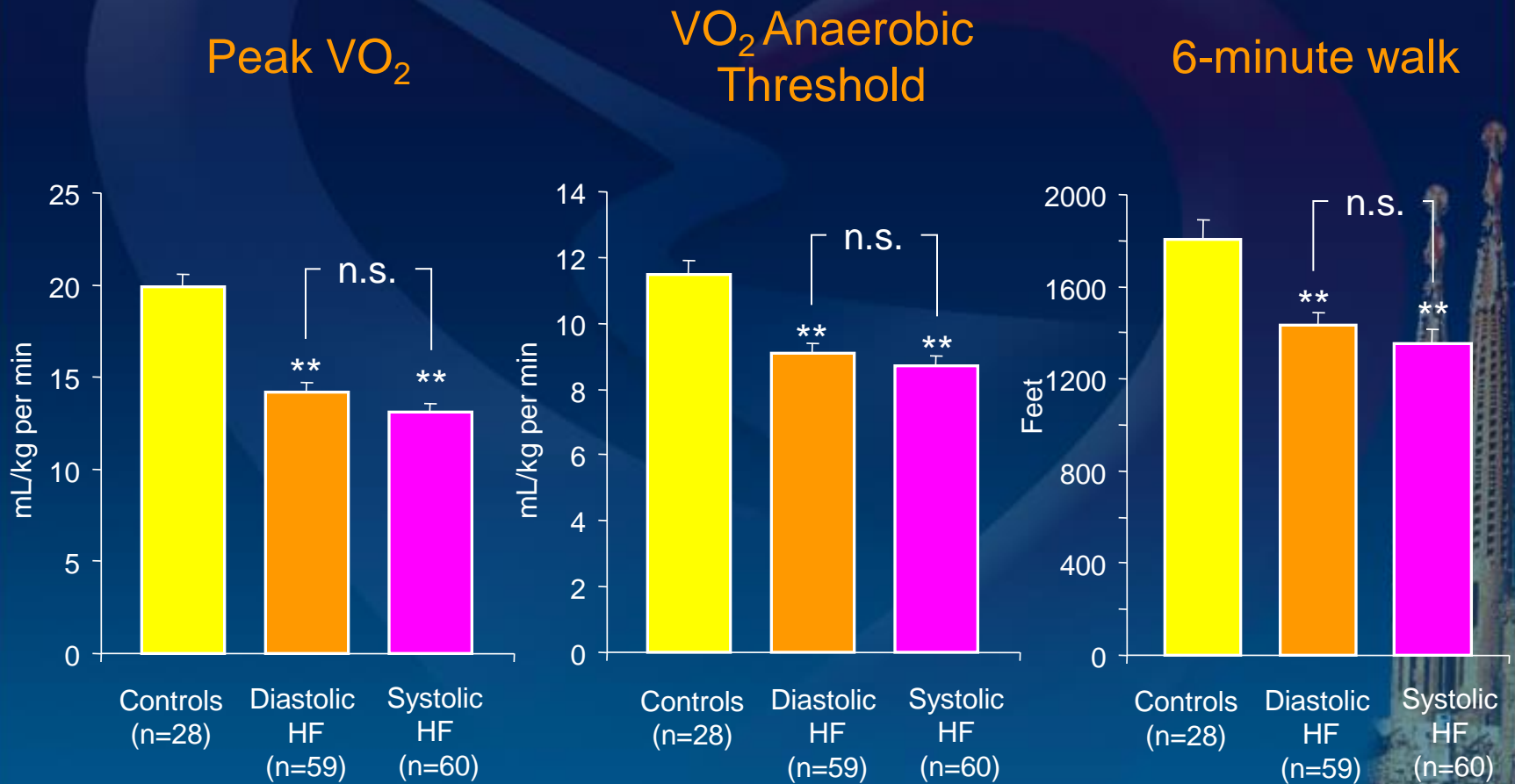
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Failure of the Frank-Starling Mechanism as a Cause of Exercise Intolerance in Diastolic CHF

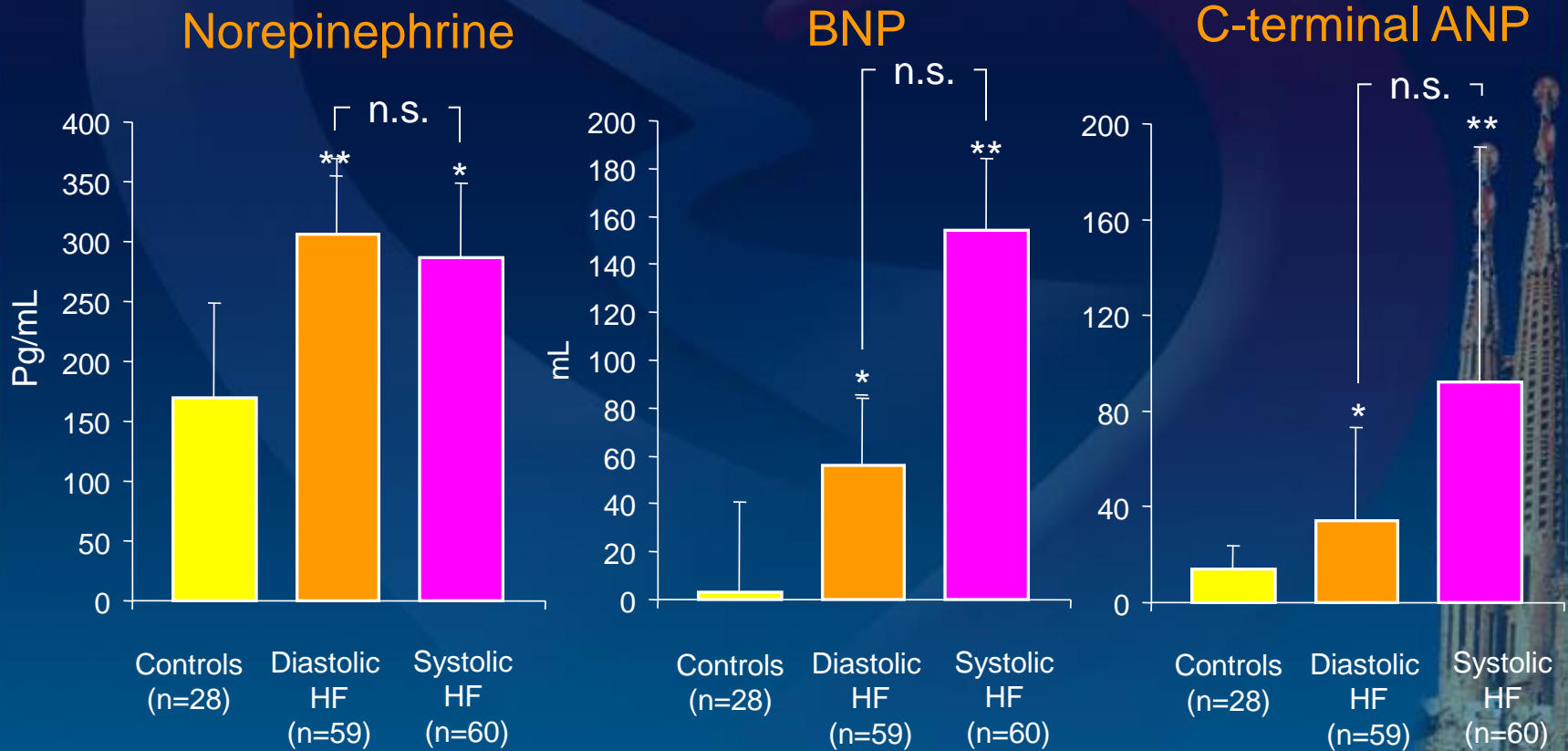


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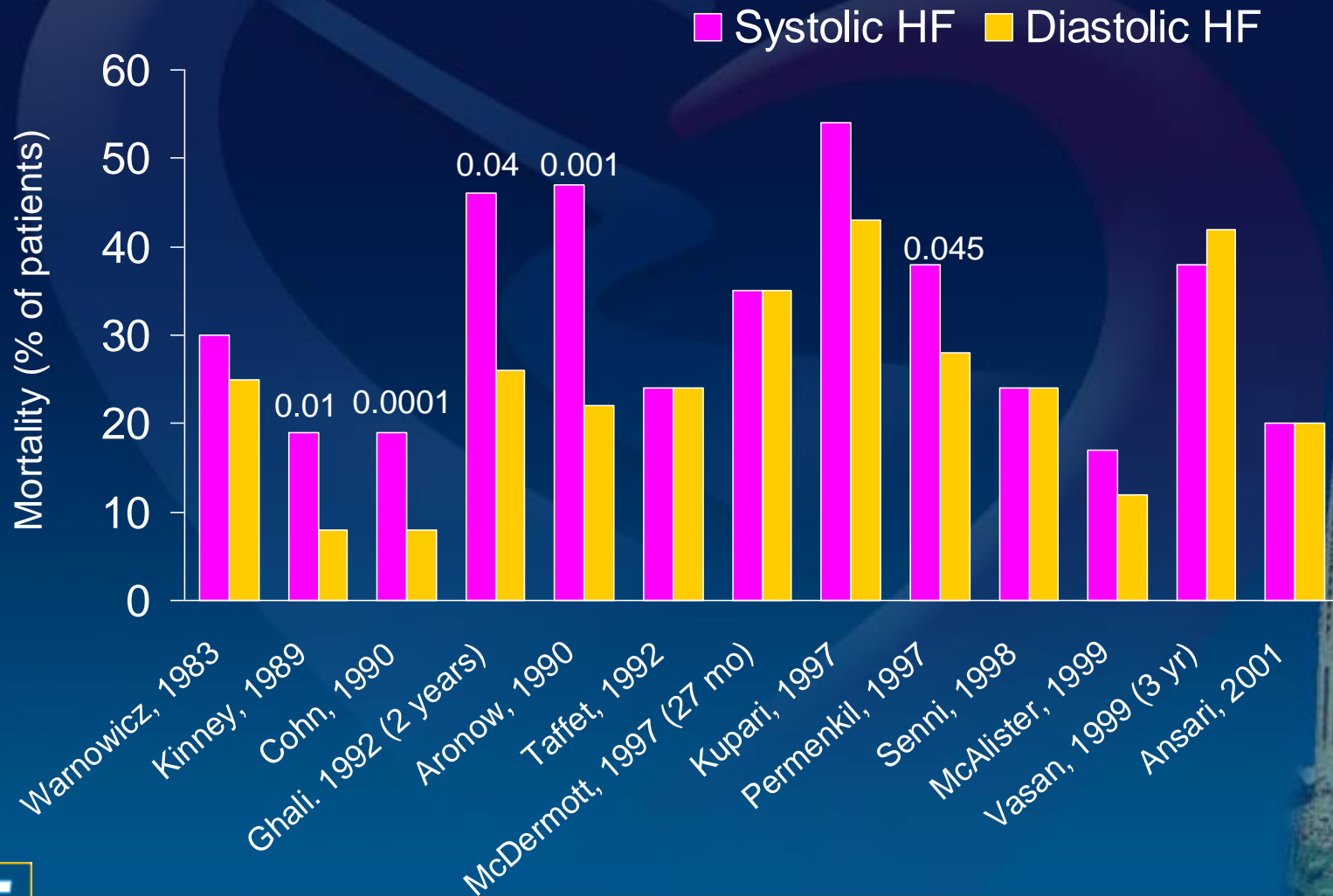
Functional Capacity in Isolated Diastolic Heart Failure in Comparison to Systolic Heart Failure



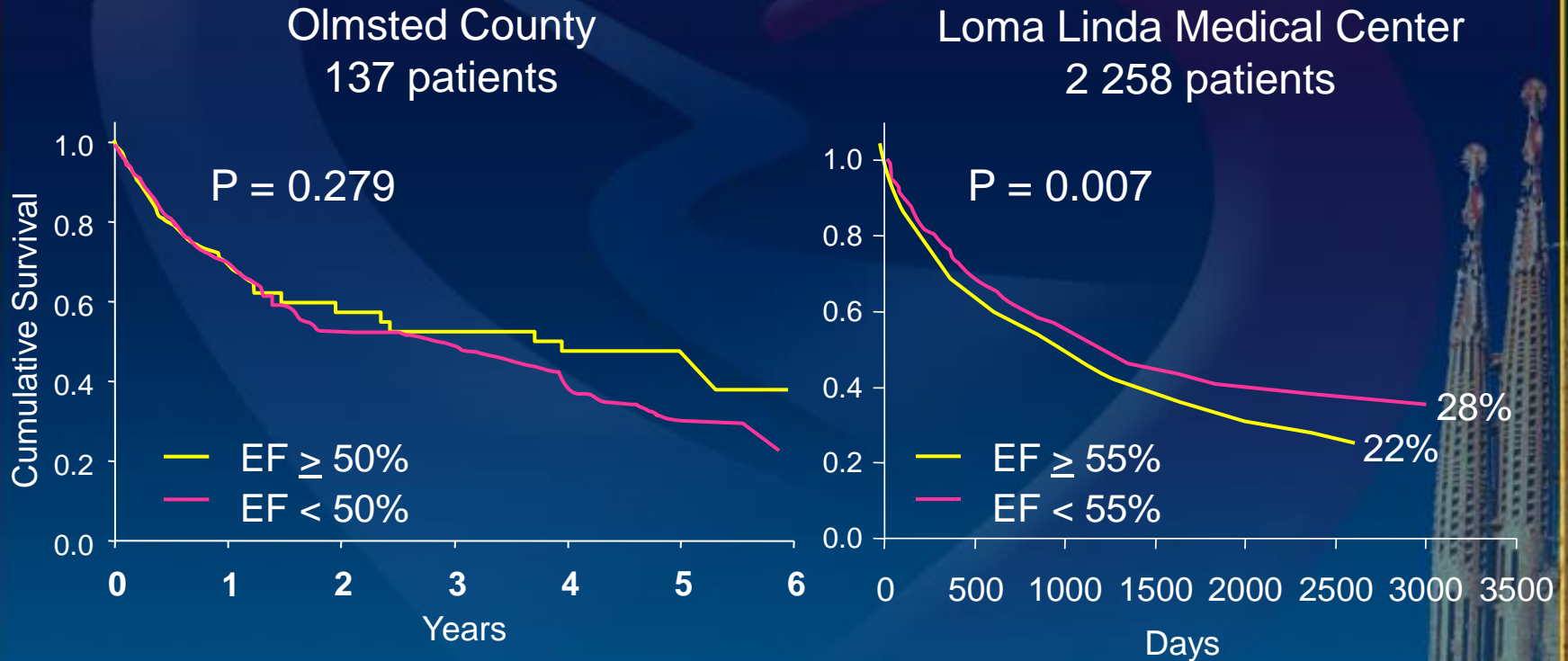
7 Plasma Neurohumoral Activation in Isolated Diastolic Heart Failure in Comparison to Systolic Heart Failure



Annual Mortality in the Patients with Systolic and Diastolic LV Dysfunction



Survival of Patients with Heart Failure and Normal or Low LV Ejection Fraction



Diastolic Heart Failure

- Clinical significance
 - Symptoms
 - Prognosis
- **Diagnosis ?**
- Therapeutic options ?

Evidences of Diastolic Dysfunction: ESC Guidelines on Diastolic Heart Failure

- **Slow isovolumic LV relaxation**
 - LV $dP/dt_{\min} < 1100$ mmHg/sec
 - Prolonged isovolumic relaxation time
 - < 30 ys, > 92 ms
 - 30-50 years, > 100 msec
 - > 50 years, > 105 msec
 - $\tau > 48$ msec
- **Slow early LV filling**
 - Peak filling rate < 160 ml/sec/m²
 - Prolonged EDV corrected PFR
 - < 30 ys, < 2 EDV/sec
 - 30-50 years, < 1.8 EDV/sec
 - > 50 years, < 1.6 EDV/sec
 - Reduced E/A and protodiastolic deceleration time
 - < 50 years, < 1.0 and > 220 msec
 - > 50 years, < 0.5 and > 280 msec
 - Increased ratio of systolic / diastolic PV flow velocities
 - < 50 years, > 1.5
 - > 50 years, > 2.5
- **Reduced LV diastolic distensibility**
 - LV end diastolic pressure > 16 mm Hg
 - Mean pulmonary wedge pressure > 12 mm Hg
 - Pulmonary venous atrial flow velocity > 35 cm/sec
 - PV atrial flow velocity duration $>$ mitral atrial flow velocity duration + 30 sec
 - Ratio of atrial wave to total signal excursion on the ACG > 0.20
- **Increased LV chamber or muscle stiffness**
 - Constant of LV chamber stiffness > 0.27
 - Constant of muscle stiffness > 16

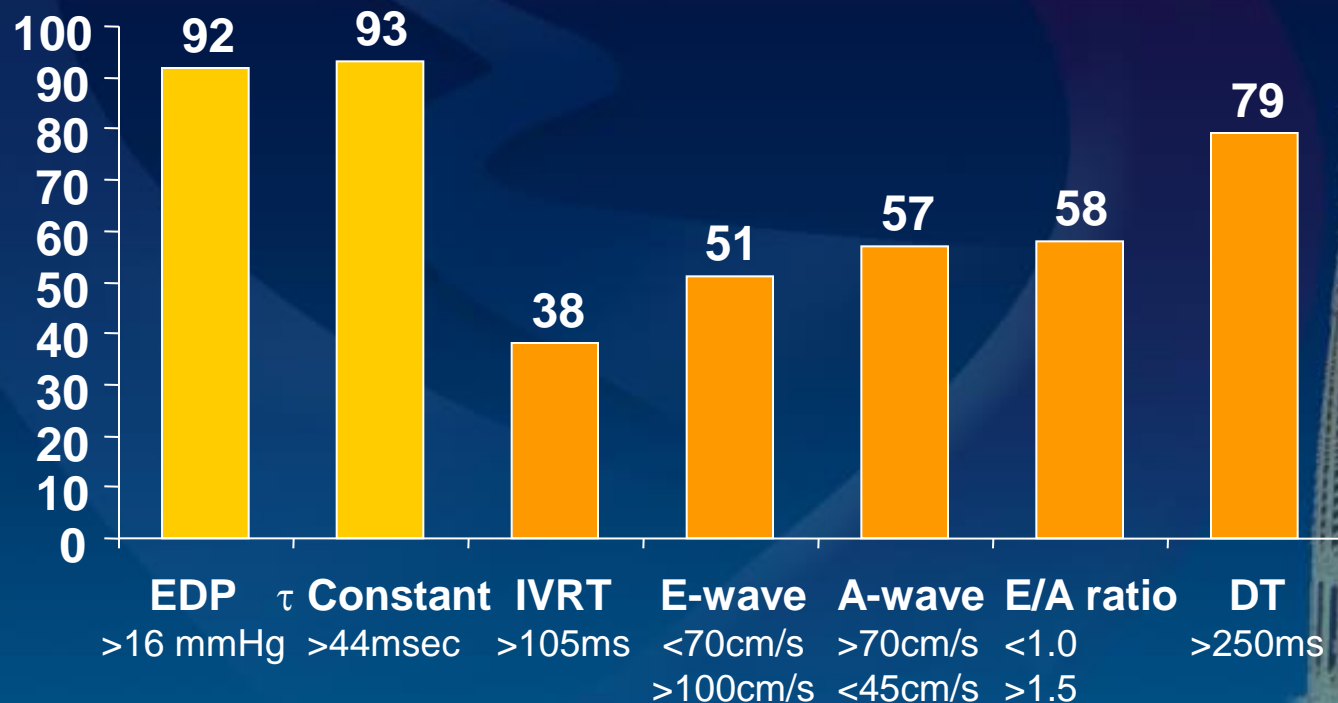
Diastolic Heart Failure (DHF)

- **Definite**
 - Symptoms and signs of heart failure
 - Evidence of normal LV systolic function ($LVEF \geq 50\%$)
 - Evidence of LV diastolic dysfunction ($\uparrow LVEDP / \downarrow \rightarrow LVEDV$)
- **Probable**
 - Symptoms and signs of heart failure
 - Evidence of normal LV systolic function ($LVEF \geq 50\%$)
in proximity (<72 hours) of the CHF event
 - Evidence of diastolic dysfunction not required
- **Possible**
 - Symptoms and signs of heart failure
 - Evidence of normal LV systolic function ($LVEF \geq 50\%$)
at > 72 hours from the CHF event
 - Evidence of diastolic dysfunction not required

13 Diastolic Heart Failure with a Normal Ejection Fraction Is measurement of diastolic function necessary?

Cath and Echo in 63 pts. With CHF Hx, LVH, normal LVEF

% with abnormal values

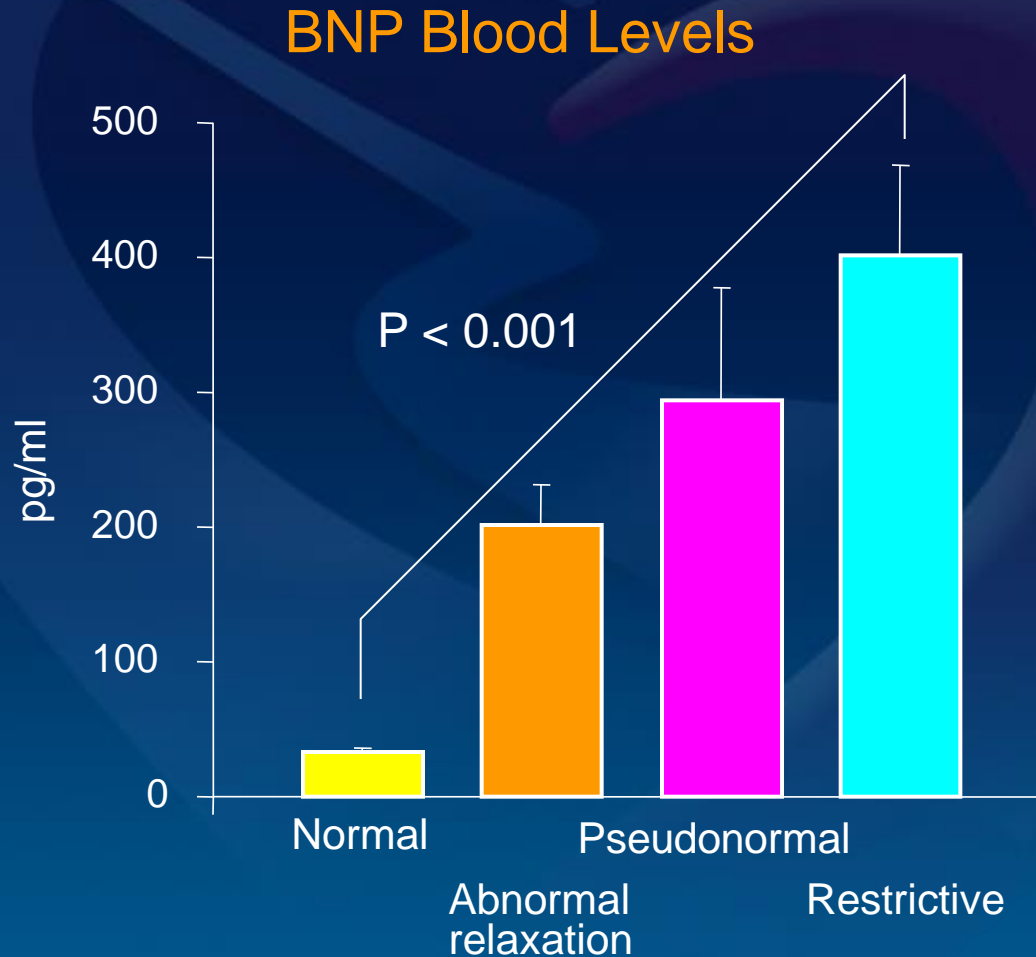


The diagnosis of diastolic heart failure can be made without measurement of diastolic function if two criteria are present:

1. Symptoms and signs of heart failure;
2. LVEF > 50%



Utility of BNP in Detecting Diastolic Dysfunction Comparison with Doppler Velocity Recordings in 294 patients



Diastolic Heart Failure

- Clinical significance
 - Symptoms
 - Prognosis
- Diagnosis?
- Therapeutic options?

Two Goals in the Management of Heart Failure

- **Stabilize the patient**
 - Make the patient feel better
- **Stabilize the disease**
 - Keep the patient alive, out of the hospital, and feeling better

Treatment of Chronic LV Diastolic Dysfunction

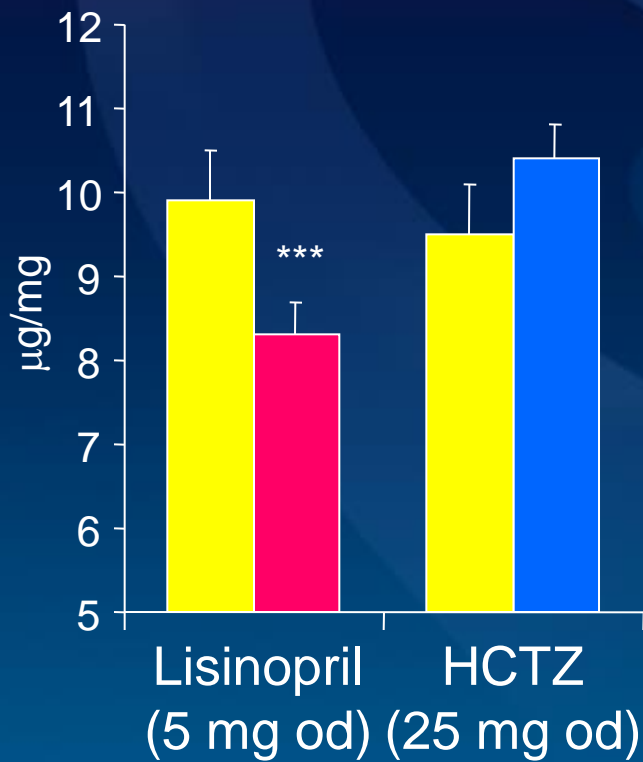
- **Symptoms targeted**
 - ↓ pulmonary venous pressure
 - Salt restriction, diuretics, nitrates...
 - Restore / maintain atrial contraction / Reduce the heart rate
 - β -blockers, verapamil, diltiazem
 - RF ablation and pacing
- **Disease targeted**
 - Myocardial ischemia
 - Nitrates, β -blockers, calcium antagonists, PTCA...
 - Tachycardia / atrial fibrillation
 - Hypertension
 - LV hypertrophy and fibrosis
 - ACE-I, aldosterone antagonists, Ca^{++} antagonists, β -blockers
- **Mechanisms targeted (myocardial / extramyocardial / intra- / extracellular)**
 - Ca^{++} antagonists (HCM)
 - NO donors (?)

Potentially Useful Effects of the ACE Inhibitors and AT₁ Receptor Blockers in the Treatment of Diastolic Heart Failure

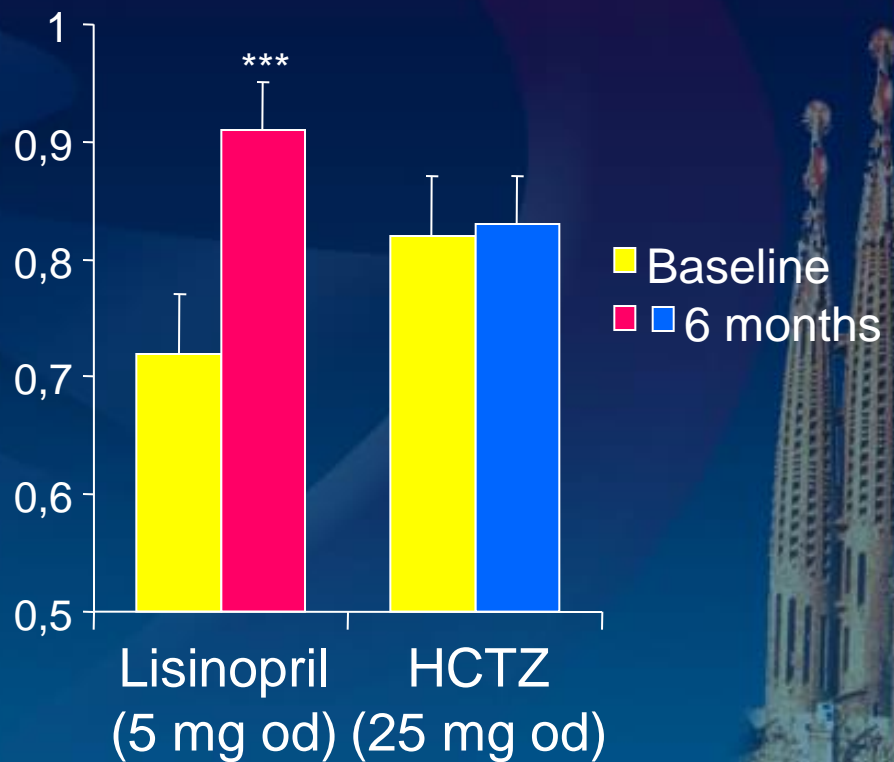
- Positive lusitropic effect
- Regression of myocardial hypertrophy
- Reduction of myocardial fibrosis
- Control of hypertension
- Prevention of myocardial ischemia

ACE-Inhibitor Mediated Regression of Myocardial Fibrosis in Patients with Hypertensive Heart Disease

Myocardial fibrosis (Hy-Pro concentration)

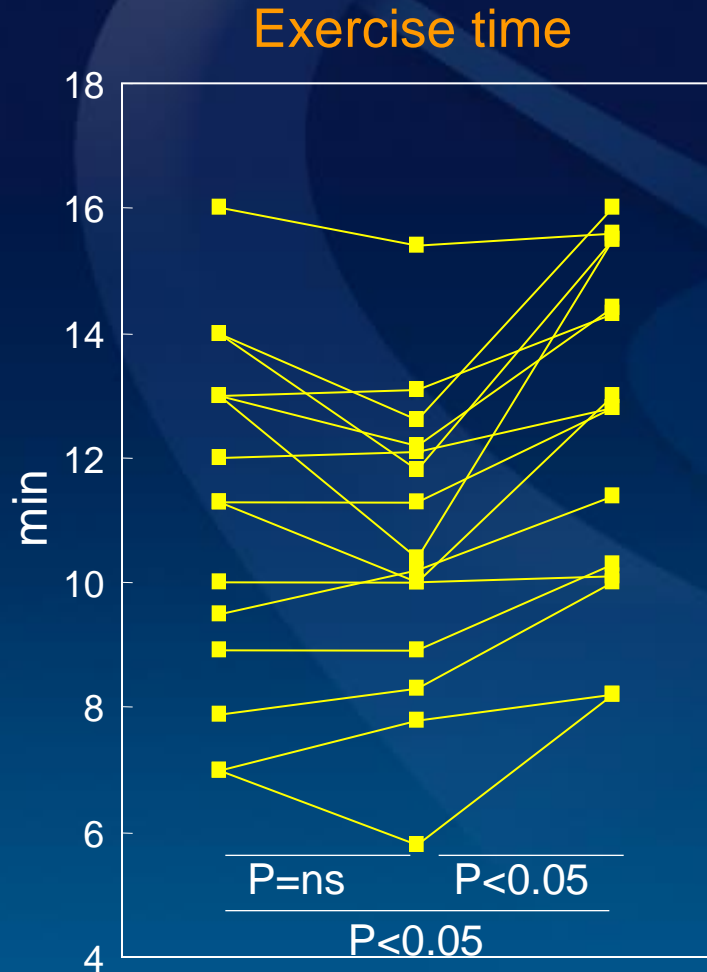


Diastolic function (E/A ratio)

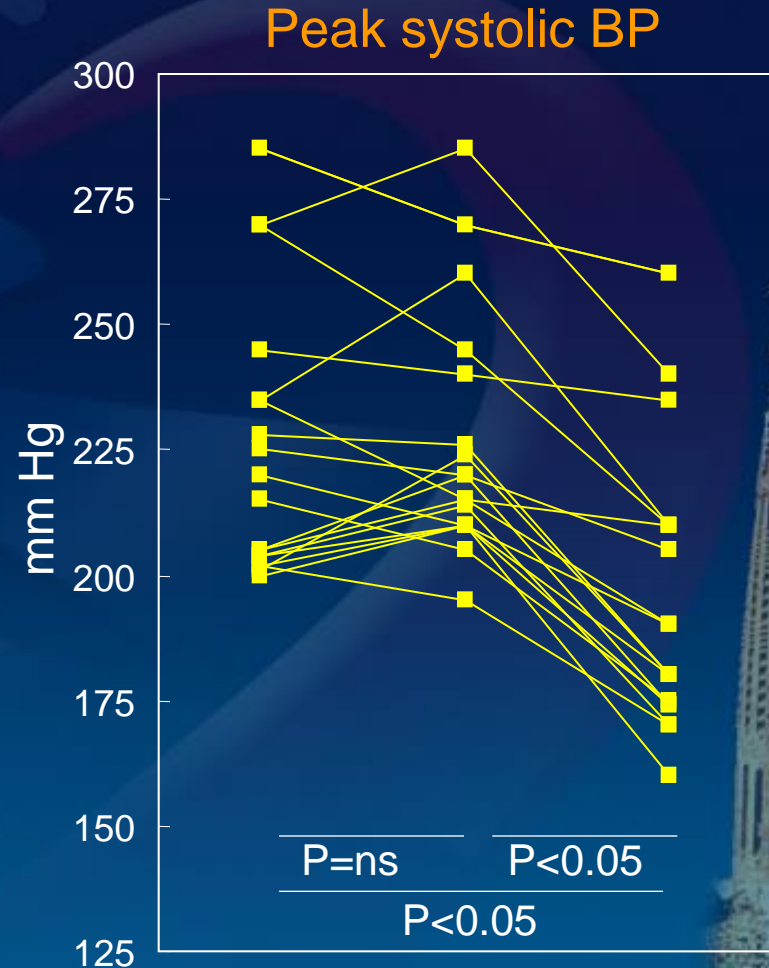


(Brilla et al., Circulation 2000; 102:1388)

Losartan Improves Exercise Tolerance in Patients with Diastolic Dysfunction and a Hypertensive Response to Exercise



Baseline Placebo Losartan



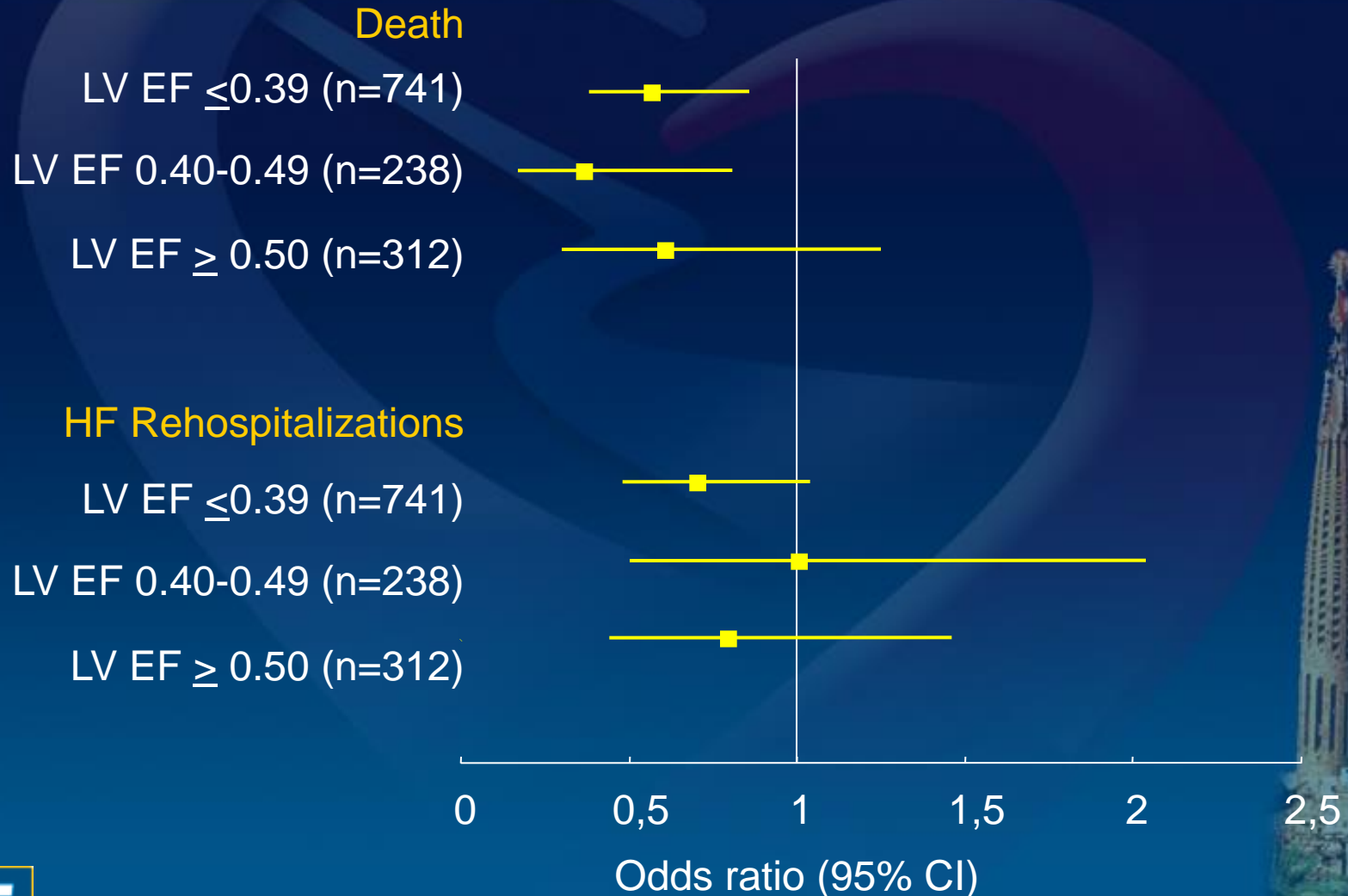
Baseline Placebo Losartan

Effects of Losartan (50 mg OD for 2 weeks) on Echo-Doppler Measures of LV Performance

	Baseline	Placebo	Losartan
Mitral E/A	0.75±0.13	0.87±0.22	0.85±0.14
E Deceleration time (ms)	197±31	186±47	205±35
IVRT (ms)	89±22	79±19	81±17
LV EF	62±9	60±10	69±10
LV EDV (ml)	87±26	92±36	82±22

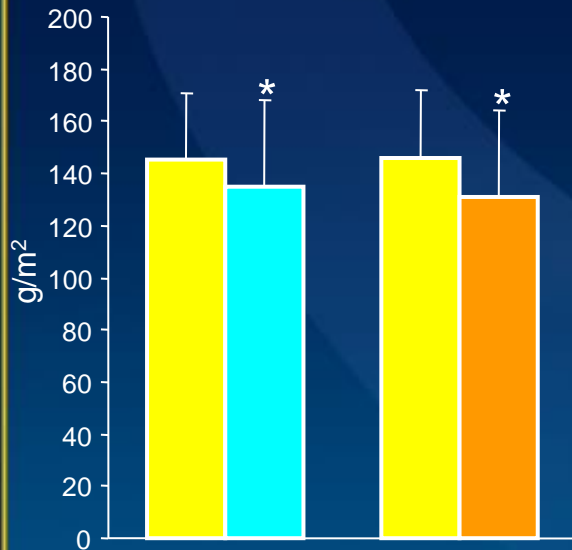
(Warner et al, JACC 1999;33:1567)

The Use of ACE Inhibitors is Not Associated with an Improved Prognosis in the Patients with Heart Failure and Preserved LV Systolic Function



Aldosterone Antagonists Improve LV Diastolic Function in Hypertension

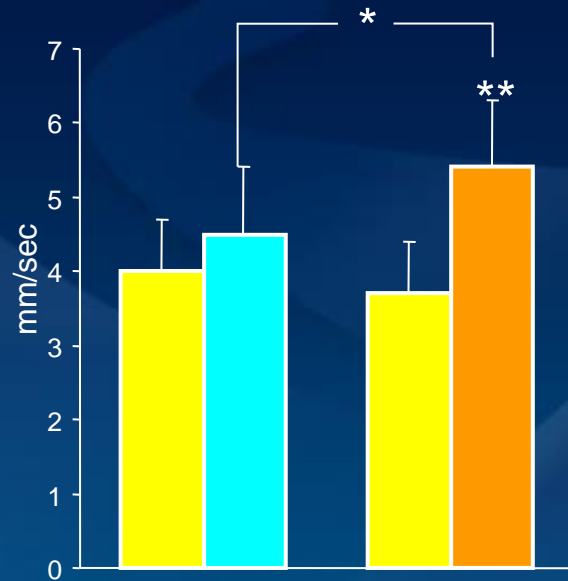
LV Mass Index



Control Canrenone

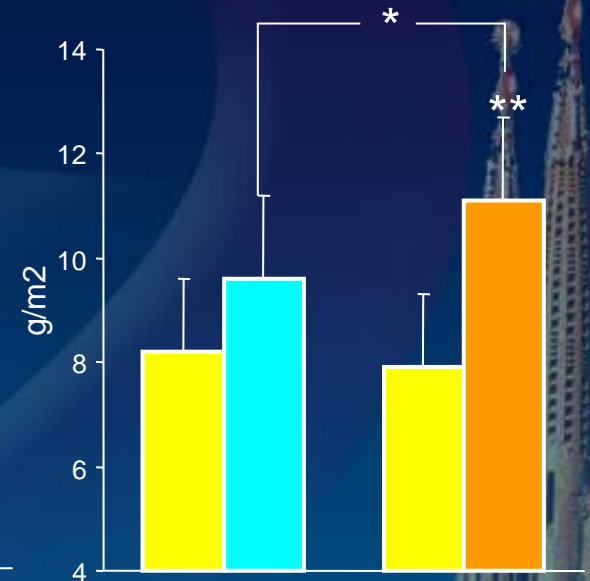
■ Baseline ■ 6 months

Peak LV Diameter Lengthening Rate



Control Canrenone

Peak LV Posterior Wall Thinning Rate



Control Canrenone

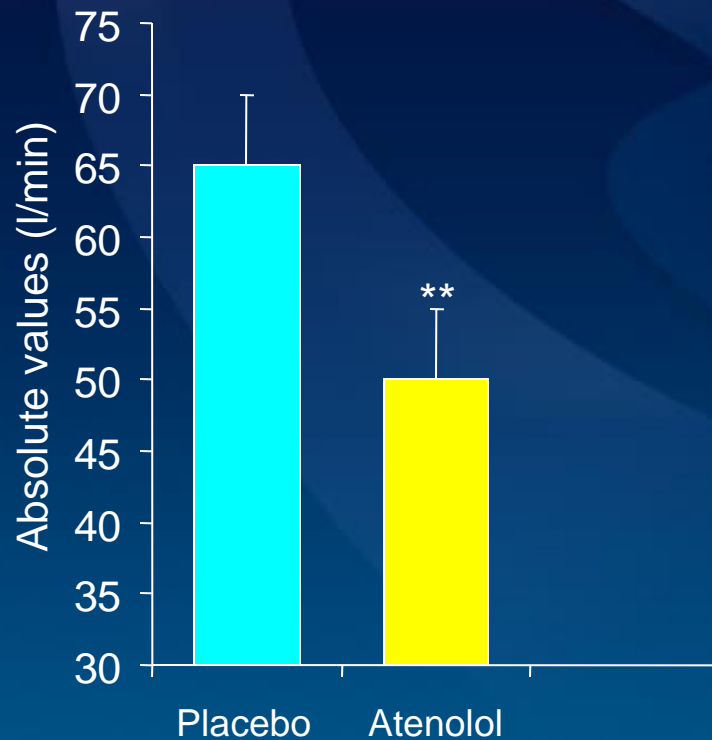
Beta-blockers in the Treatment of Diastolic Heart Failure

- **Short-term effects**
 - Negative lusitropic
- **Long-term effects**
 - Negative chronotropic
 - Anti-ischemic
 - Anti-hypertensive
 - Regression of systolic dysfunction
 - No favorable direct effect

Effects of Atenolol and Nebivolol on Exercise Tolerance

Normal subjects

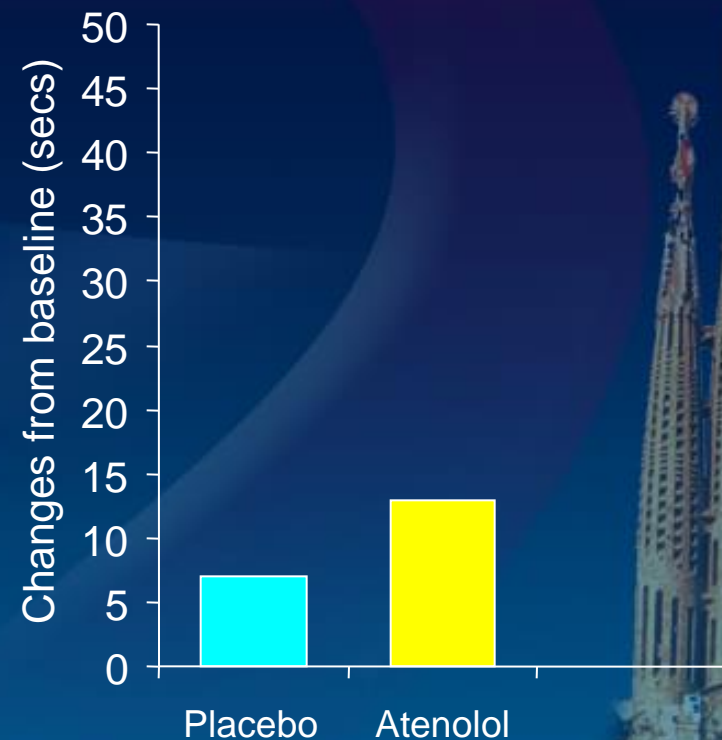
Submaximal endurance time



Van Bortel et al., *Cardiovasc Drugs Ther* 1992; 6:239

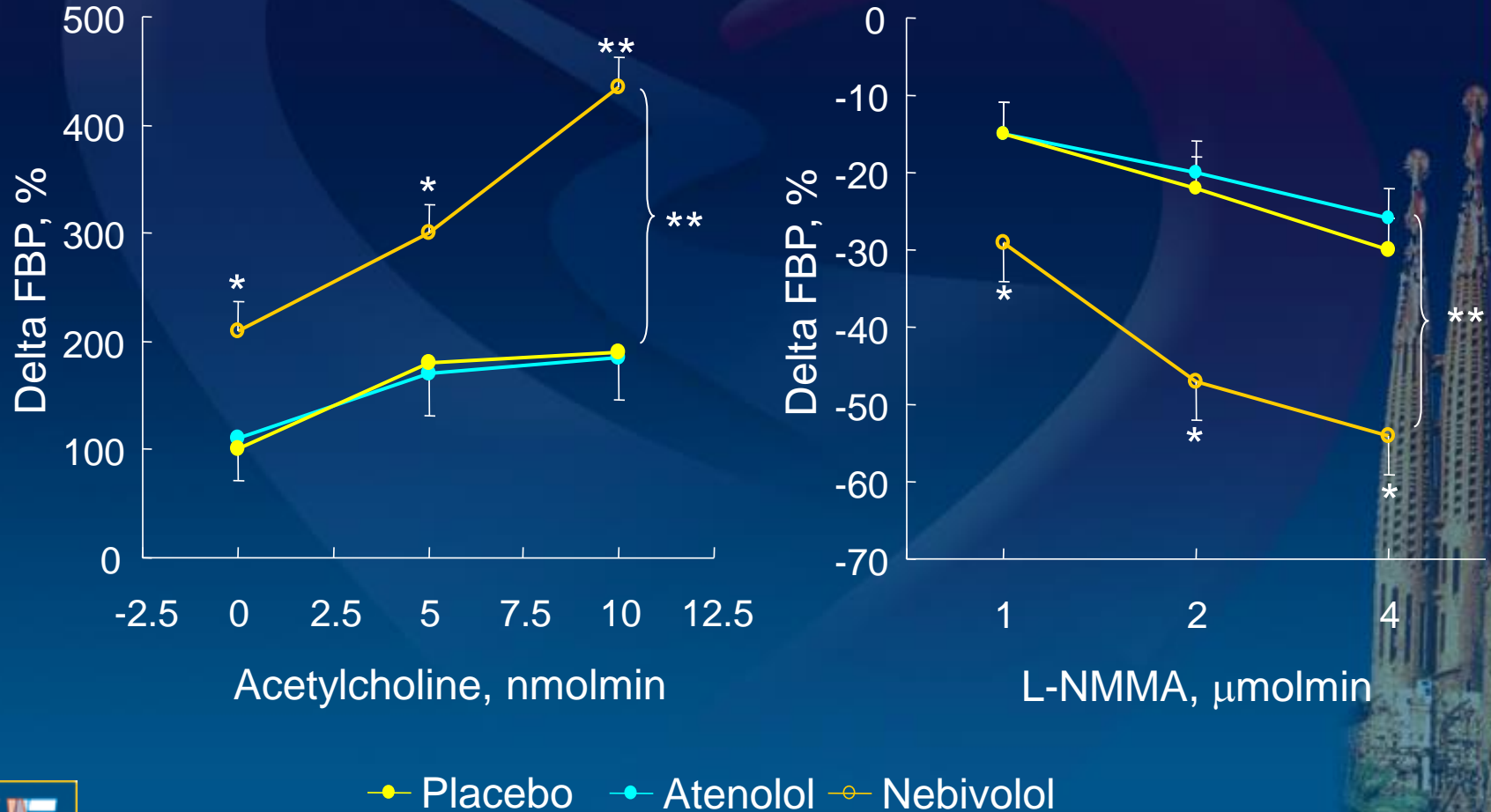
LV Systolic Dysfunction

Maximal exercise duration



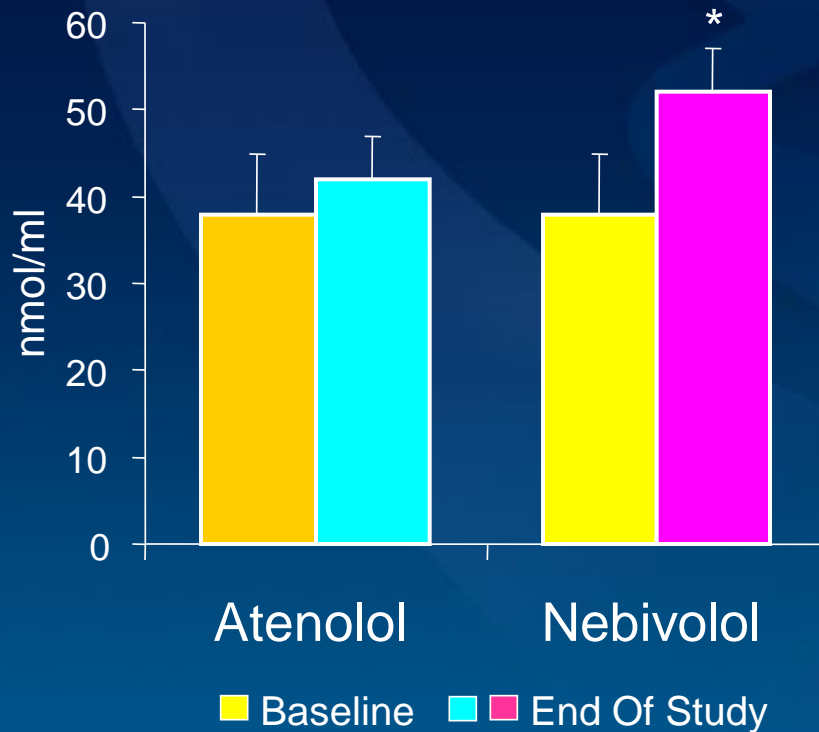
Rousseau et al., *J Cardiac Fail* 1996; 2:15

Nebivolol Reverses Endothelial Dysfunction in Essential Hypertension

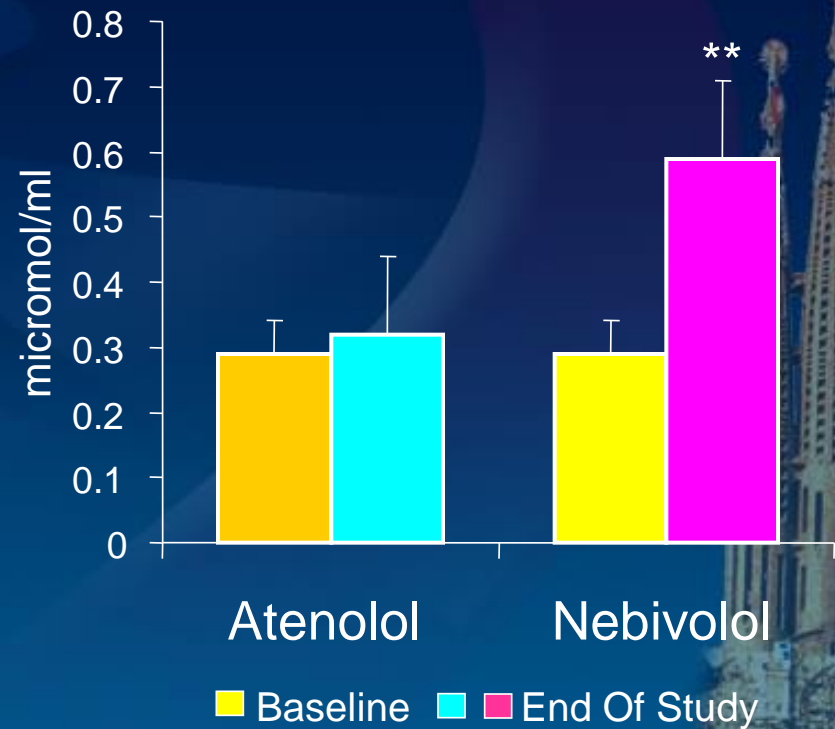


Beneficial Effects of Nebivolol on the NO-pathway in Essential Hypertensive Patients

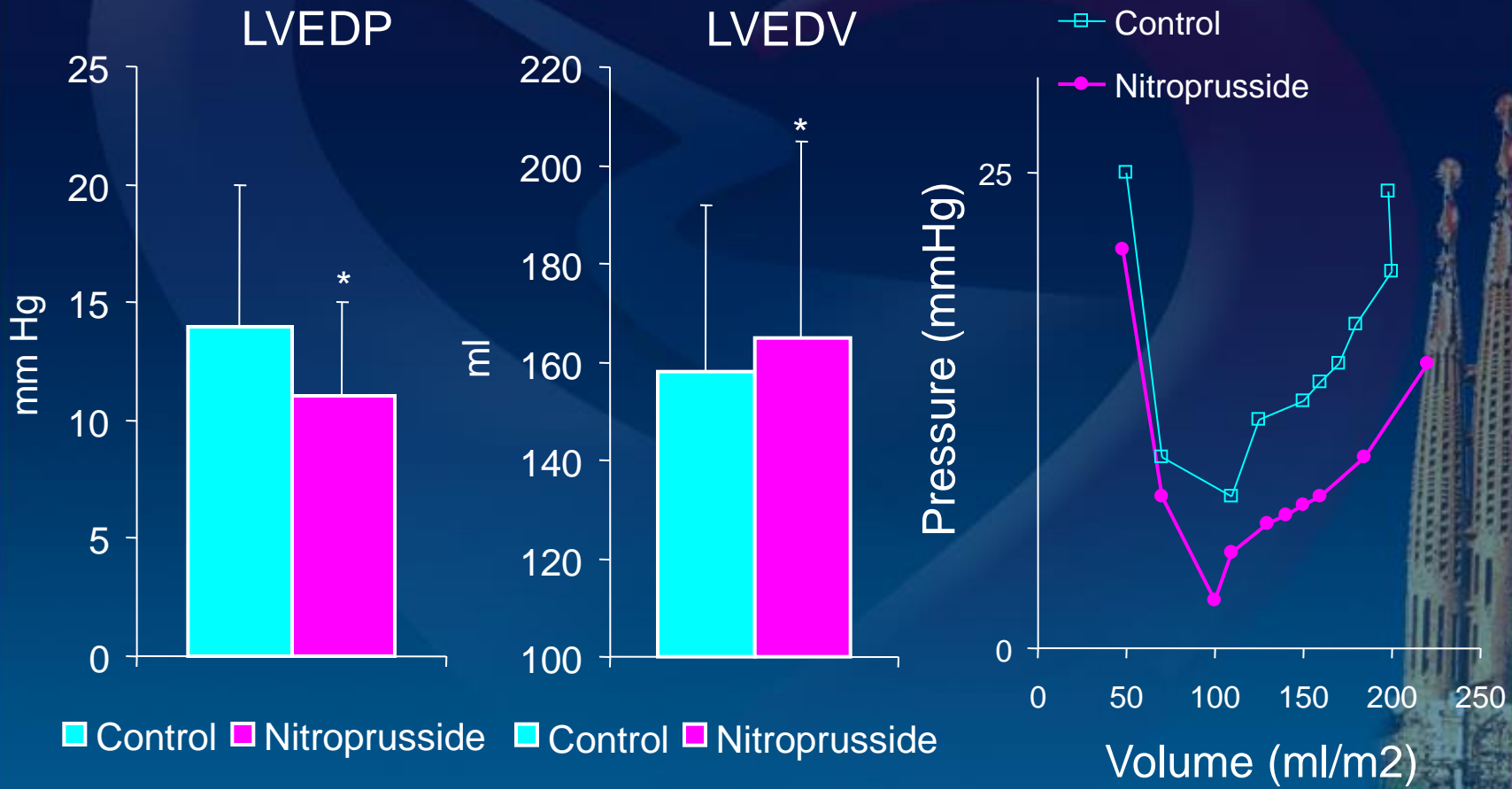
Plasma Nitrate Levels



Urinary Nitrate Levels

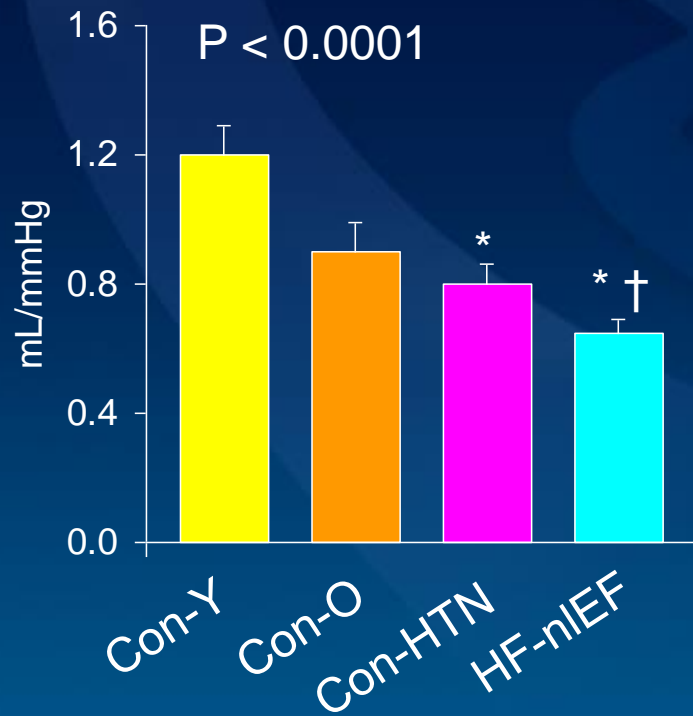


Acute Effects of NO on LV Relaxation in Humans. Assessment by Bicoronary Sodium Nitroprusside Infusion

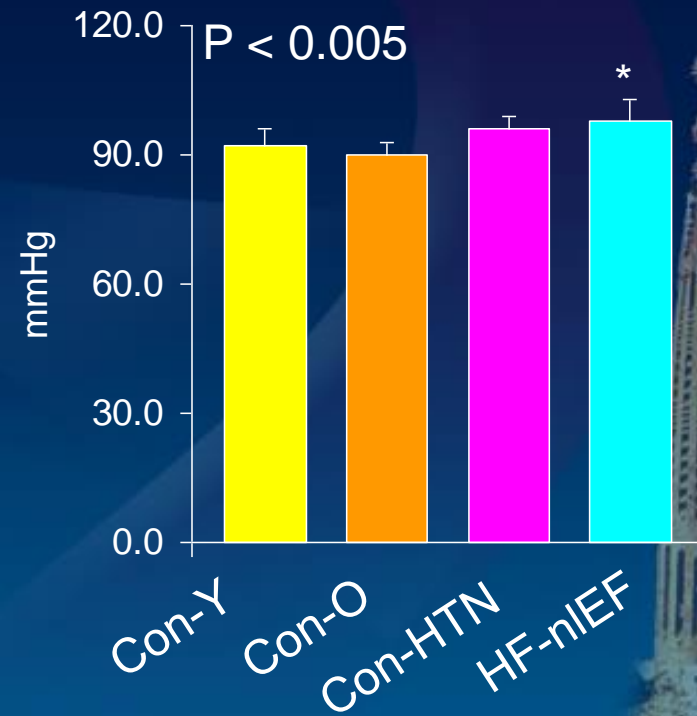


Combined Arterial and Ventricular Stiffening in Patients with Heart Failure and Preserved Ejection Fraction

Total Arterial Compliance

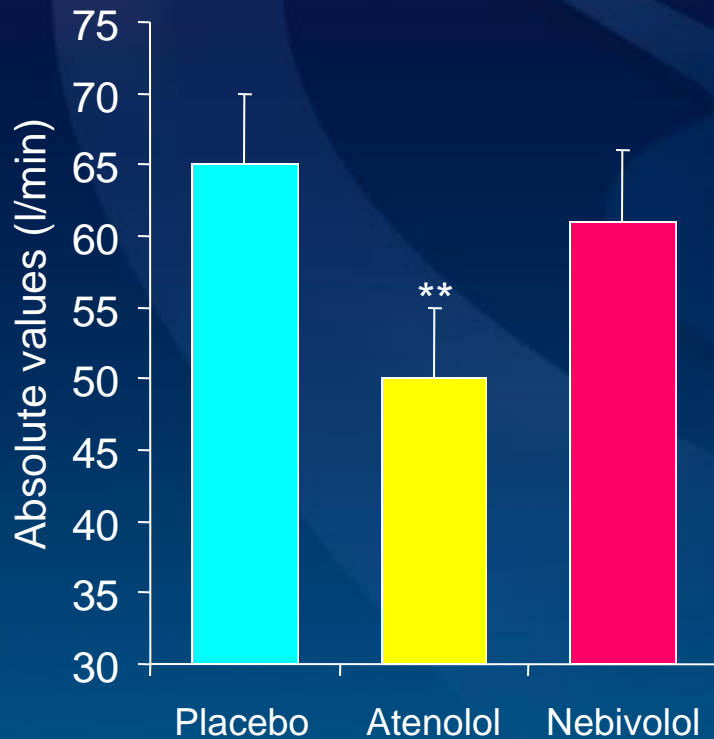


Mean Blood Pressure

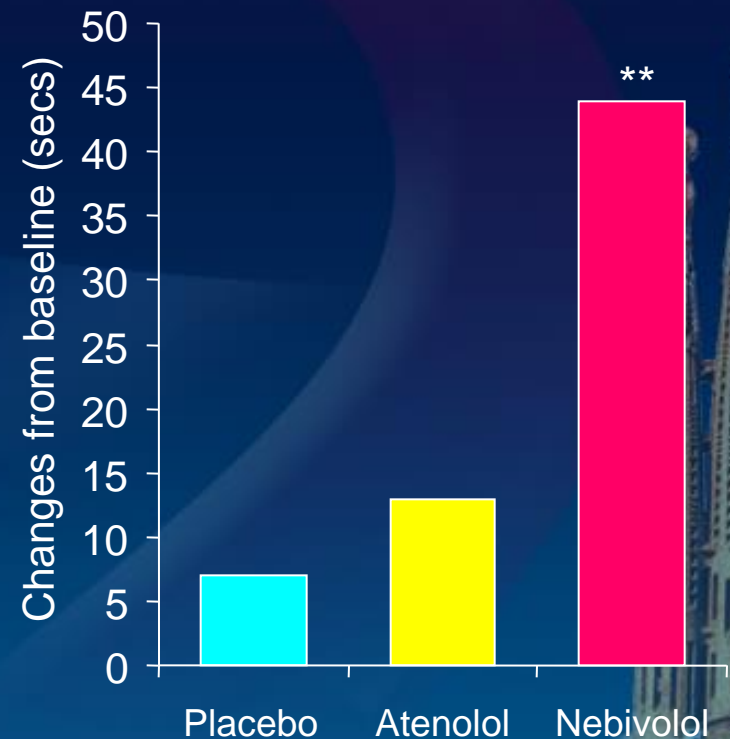


Effects of Atenolol and Nebivolol on Exercise Tolerance

Normal subjects
Submaximal endurance time



LV Systolic Dysfunction
Maximal exercise duration



Van Bortel et al., Cardiovasc Drugs Ther 1992; 6:239

Rousseau et al., J Cardiac Fail 1996; 2:15

Aim of the Study

- Compare the effects of atenolol and nebivolol in the patients with
 - Essential hypertension
 - LV hypertrophy
 - LV diastolic dysfunction
 - Symptoms of heart failure
- End-points
 - Primary
 - Peak exercise pulmonary wedge pressure
 - Secondary
 - Other resting and exercise hemodynamic parameters
 - Maximal exercise tolerance

Trial design

30 study patients

- NYHA class II-III; Peak $\text{VO}_2 < 25 \text{ ml/kg/min}$
- LV EF $> 50\%$; LV EDD $> 32 \text{ mm/m}^2$; E/A Ratio < 1
- PWP $> 12 \text{ mm Hg}$ at rest or $> 20 \text{ mmHg}$ during exercise
- No CAD, VHD, CHD, AF,
SBP > 200 or DBP $> 100 \text{ mmHg}$,
Concomitant diseases or contraindication to BB

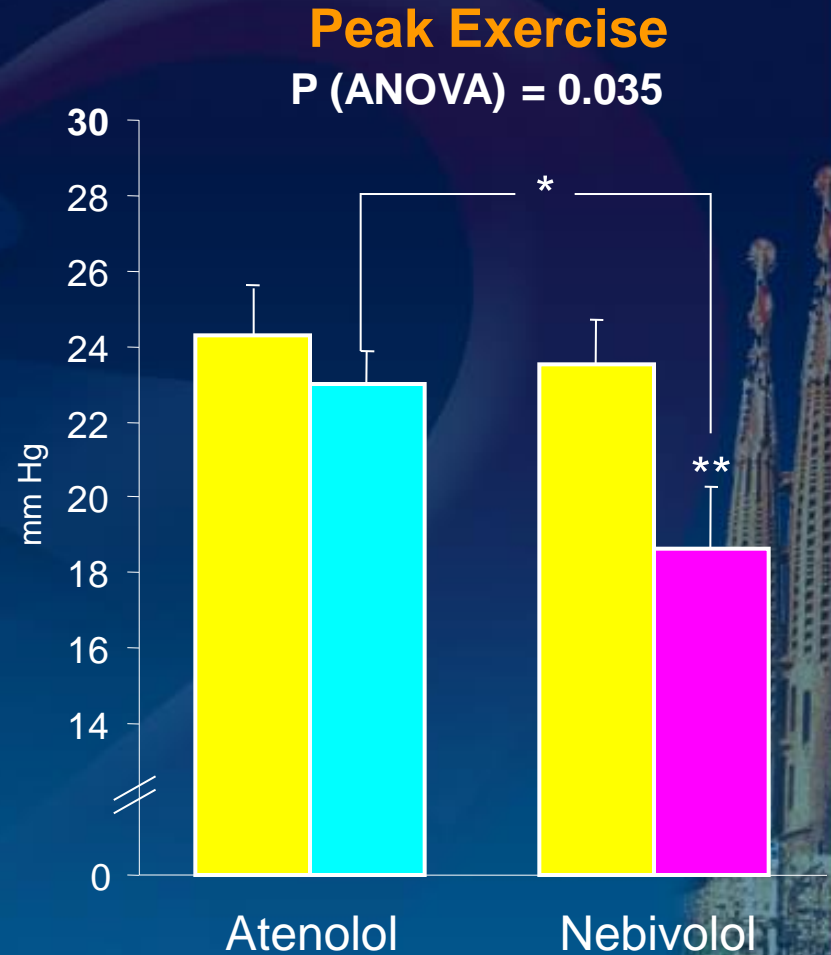
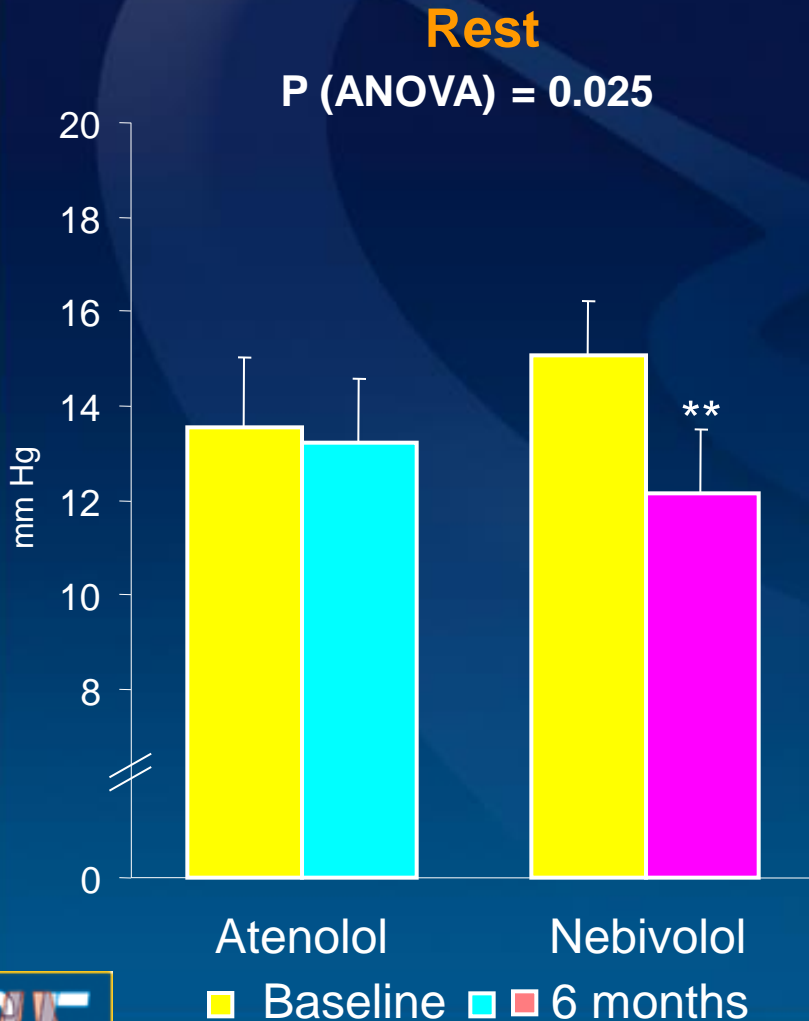
1:1 randomization

Atenolol,
50 → 100 mg/day

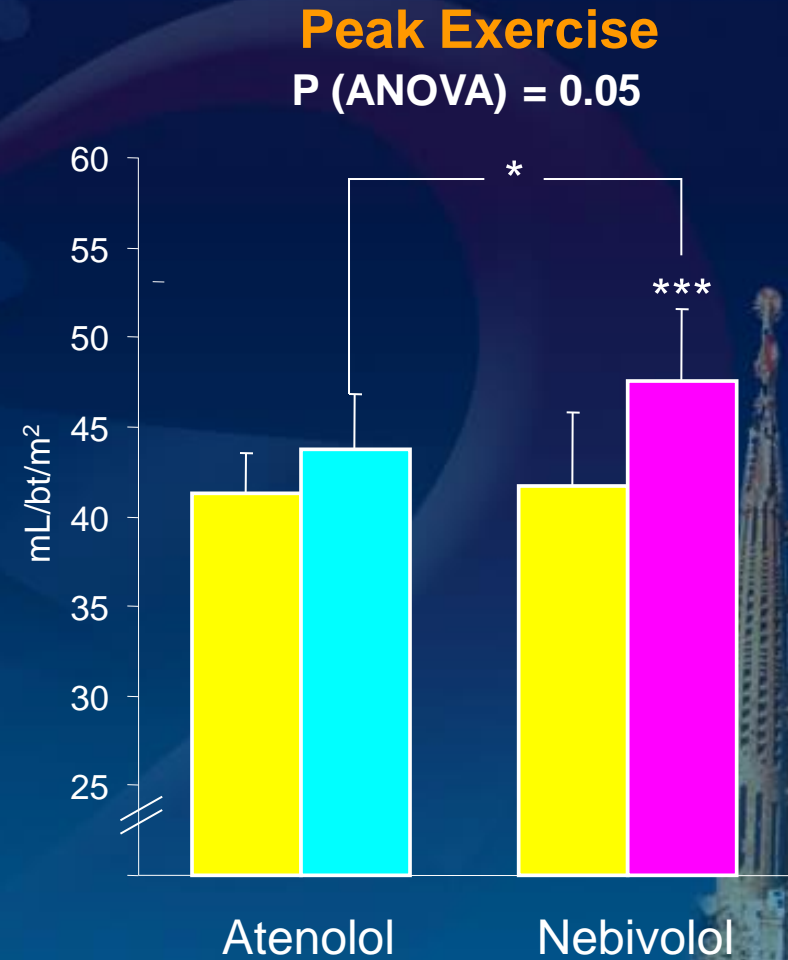
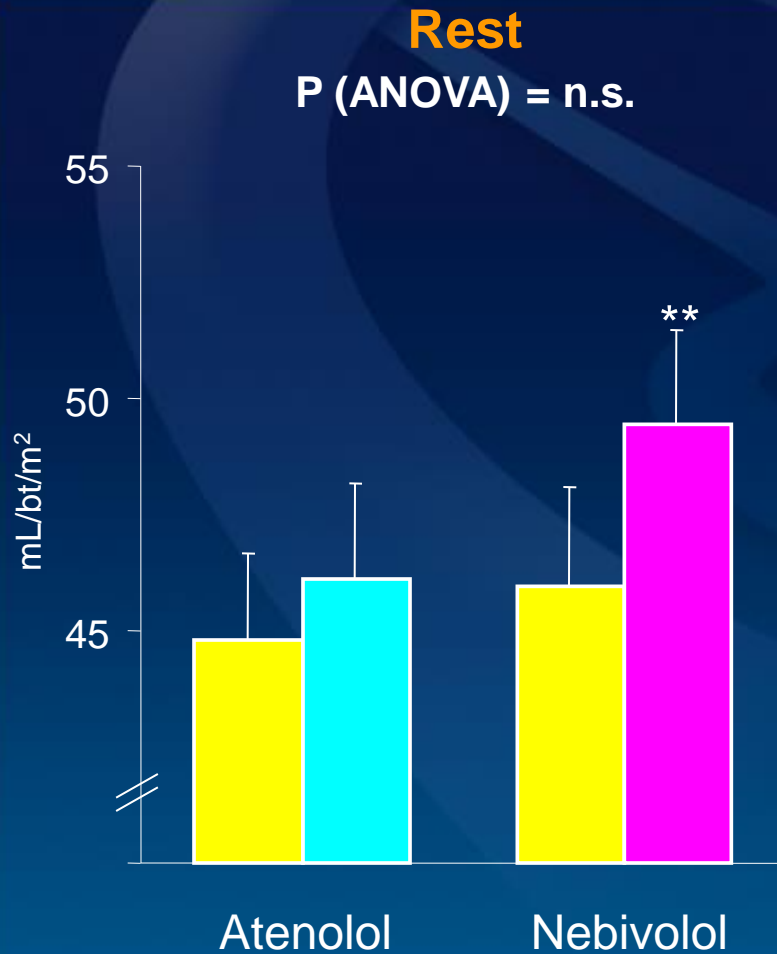
Nebivolol,
2.5 → 5 mg/day

Clinical and hemodynamic reassessment
after 6 months (26 patients)

Primary End-point Results: Effects on the Pulmonary Wedge Pressure

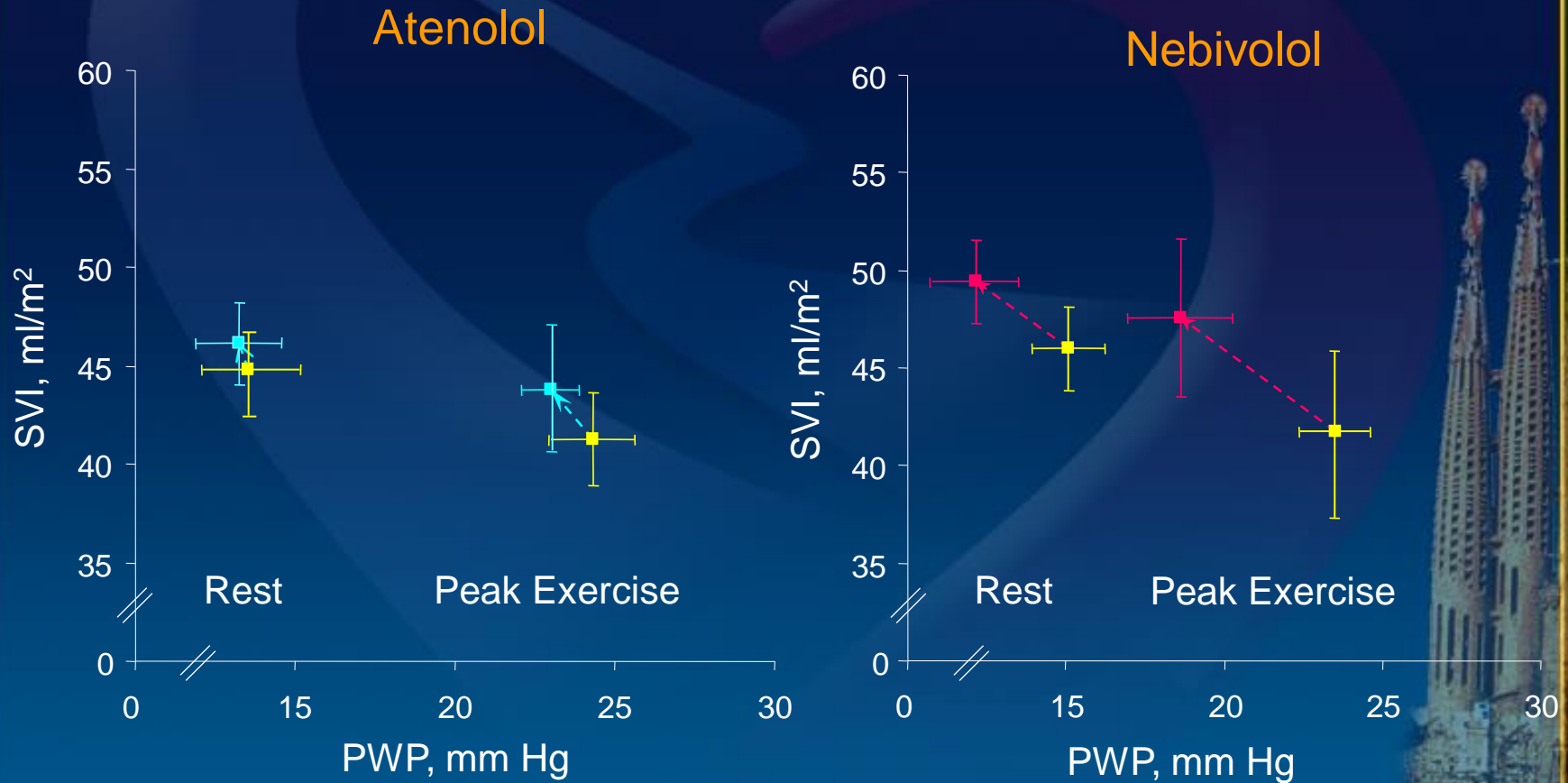


Secondary End-points: Effects on the Stroke Volume Index

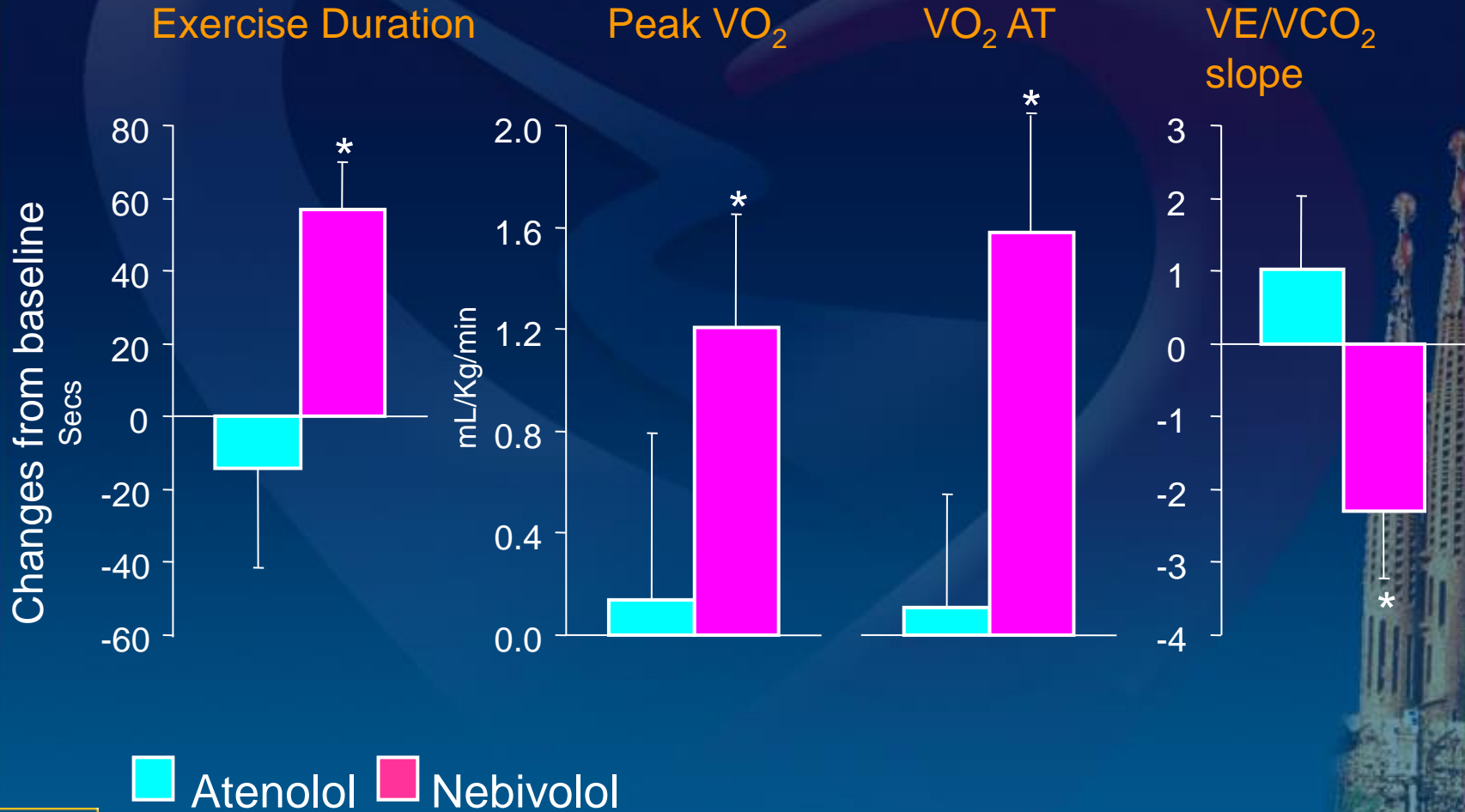


■ Baseline ■ 6 months

Effects of Beta-blocker therapy on the Relation Between LV Filling Pressure and Stroke Volume in Patients with Diastolic Heart Failure



Secondary End-points: Effects on the Maximal Functional Capacity



Treatment of Diastolic Heart Failure (ESC Guidelines)

- **Diuretics**
 - Necessary with episodes of fluid overload
 - Use cautiously not to lower preload excessively and thereby reduce stroke volume and cardiac output
- **ACE Inhibitors & AT₁ Receptor antagonists**
 - May improve relaxation and cardiac distensibility directly
 - May have a long-term effect through regression of hypertrophy
 - Reduce hypertension
- **Beta-blockers**
 - To lower heart rate and increase the diastolic period
- **Verapamil-type calcium antagonists**
 - For the same reasons as the beta-blockers

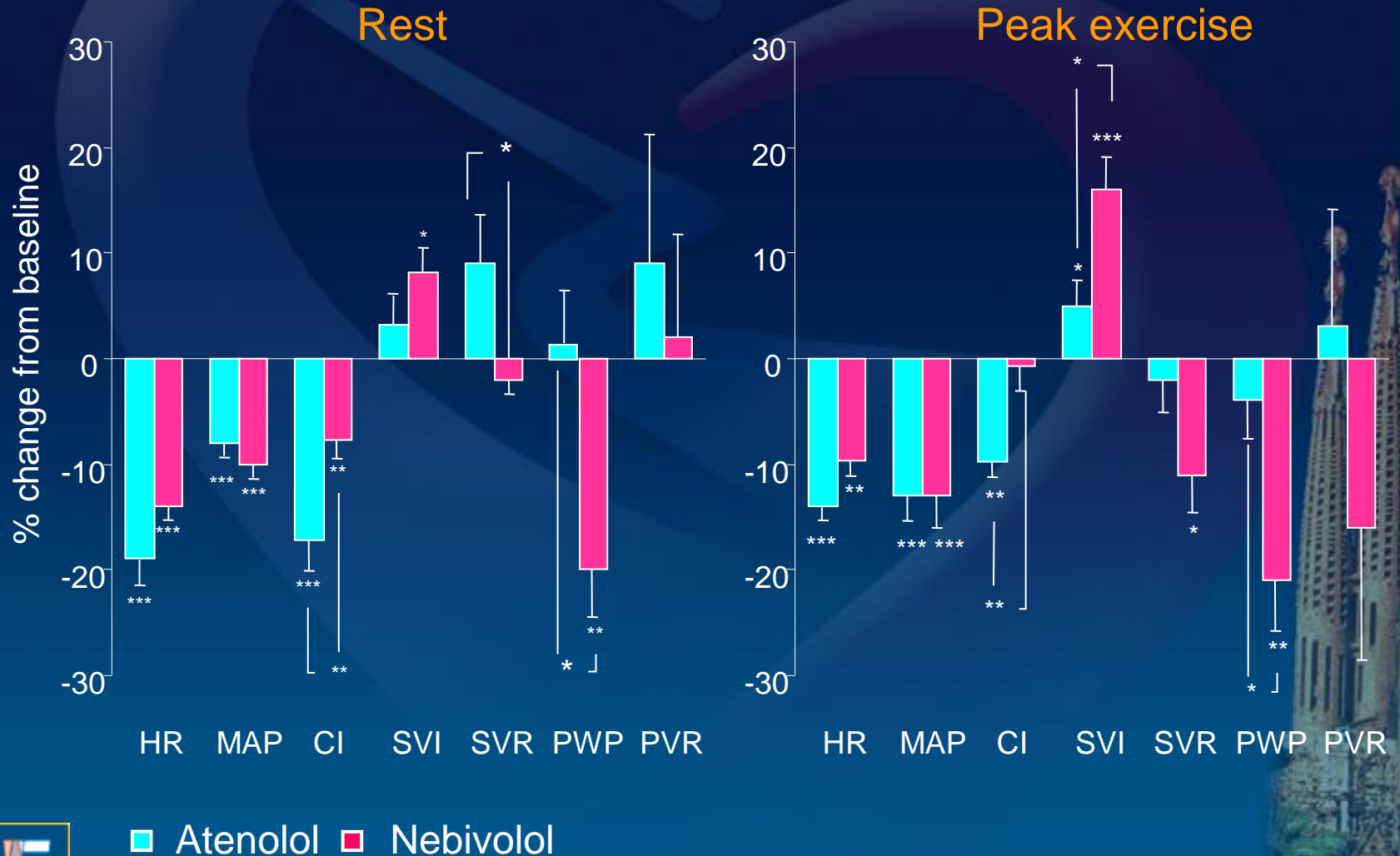
Treatment of Diastolic Heart Failure (ESC Guidelines)

- *The recommendations provided below are largely speculative, as limited data exist in patients with diastolic dysfunction, patients being excluded from nearly all large controlled trials in heart failure.*
- *... pure diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction.*
- *... conditions under which diastolic dysfunction occurs vary between patients ...*
- *In general, the treatment of this condition remains unsatisfactory.*

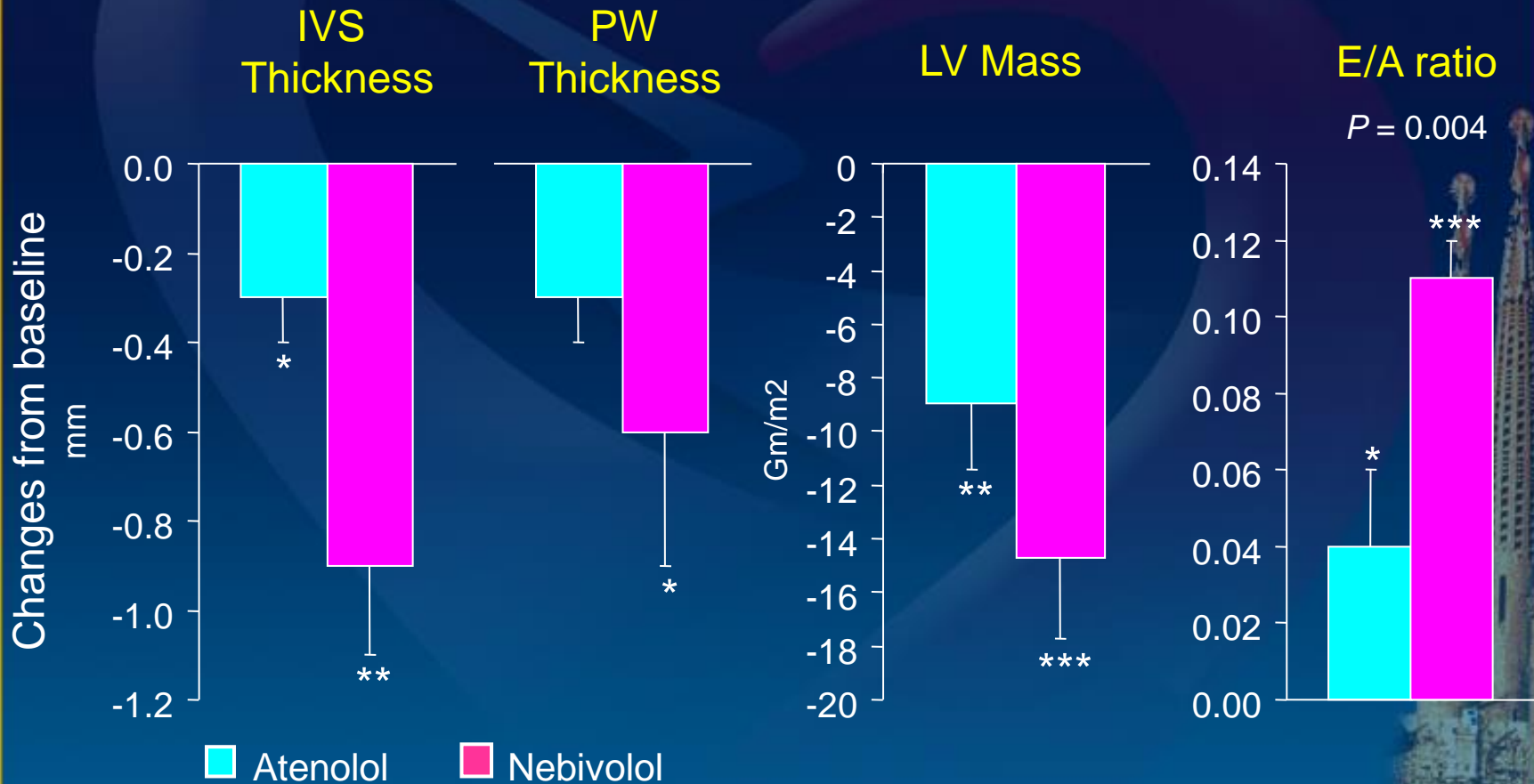
Baseline characteristics of the studied patients

	Atenolol (n=13)	Nebivolol (n=13)
Age (years)	65±9	62±13
Sex (M/F)	8/5	7/6
NYHA class, II/III (n)	7/6	6/7
Systolic arterial pressure (mm Hg)	151±19	147±23
Diastolic arterial pressure (mm Hg)	91±7	92±6
LV ejection fraction (%)	57±6	57±7
LV End diastolic diameter (mm/m ²)	28±2	28±2
Transmitral flow, E/A ratio	0.84±0.12	0.79±0.13
Cardiac index at rest (L/min/m ²)	3.62±0.51	3.46±0.45
Pulmonary wedge pressure at rest (mm Hg)	14±5	15±4
Peak VO ₂ (ml/kg/min)	18.4±4.5	17.6±5.4

Hemodynamic Effects of Atenolol or Nebivolol Administration in Diastolic Heart Failure



Secondary End-points: Effects on the Echo-Doppler Parameters



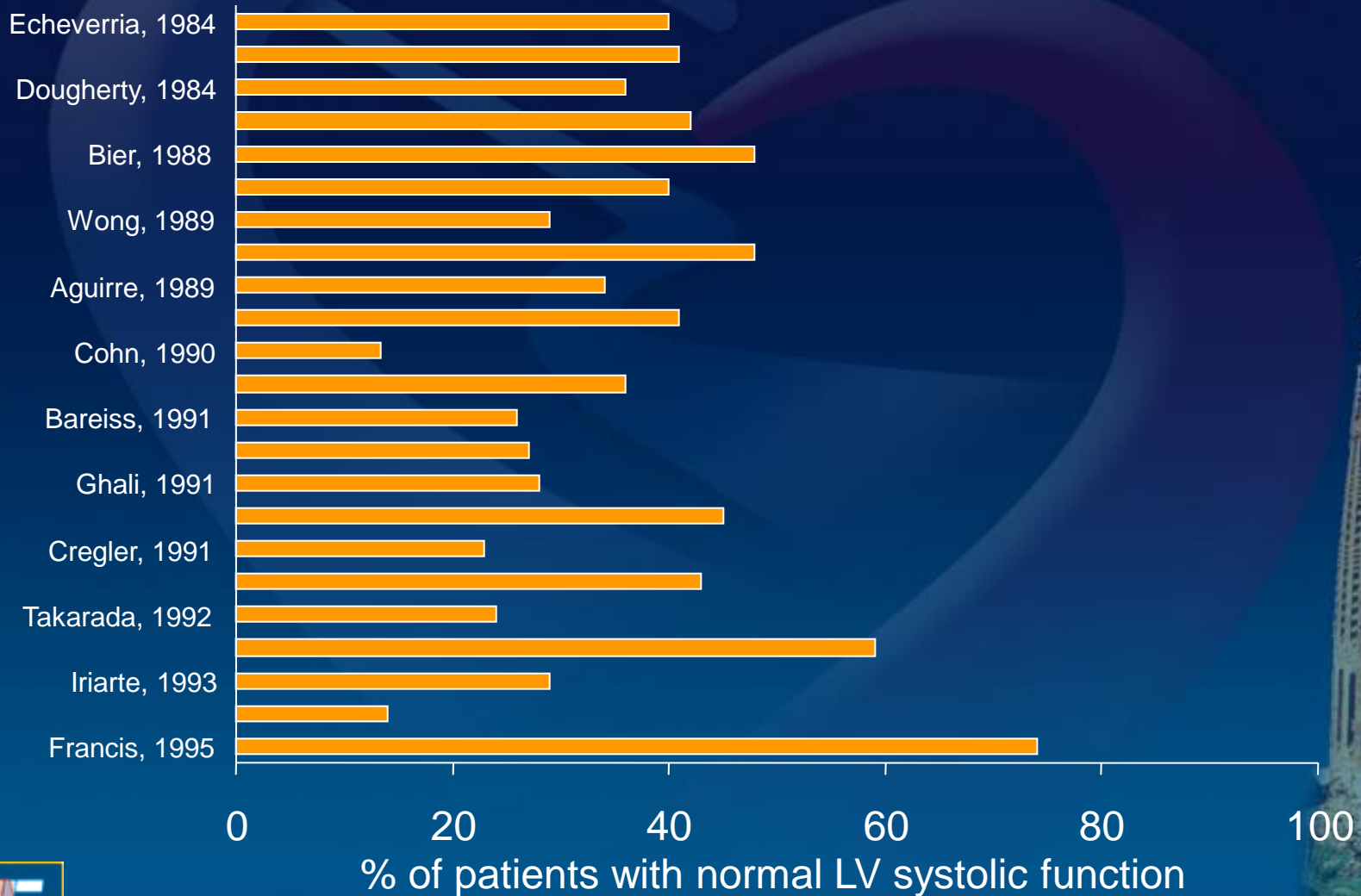
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Treatment of Diastolic Heart Failure (ESC Guidelines)

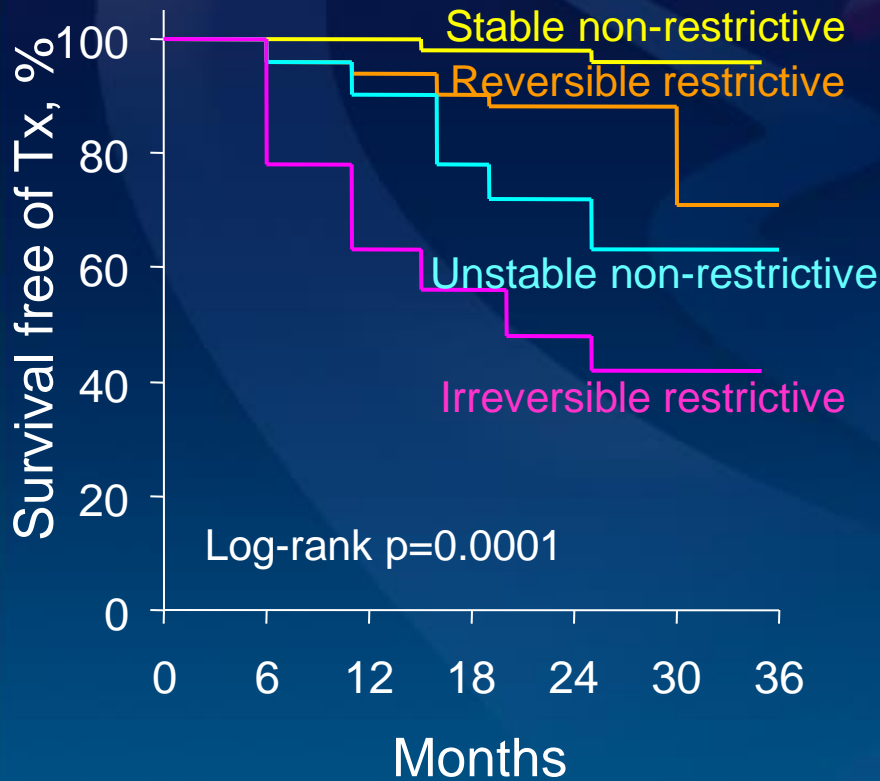
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Prevalence of Normal LV Systolic Function in Clinical Studies of Patients with CHF

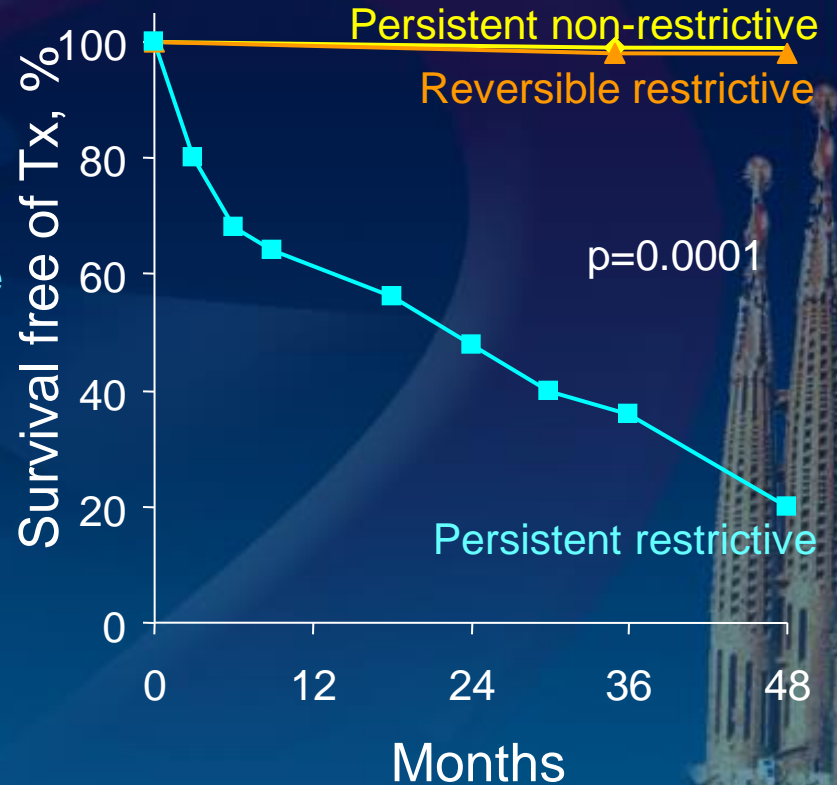


Prognostic Value of Persistent Restrictive LV Filling in Chronic Heart Failure

Acute loading manipulations



Reassessment after 3 months



Pozzoli et al., *Circulation* 1997; 95:1222

Pinamonti et al., *JACC* 1997; 29:604



46

Do Patients Suffer From Diastolic Heart Failure or From Misdiagnosis ?

159 consecutive pts. with suspected CHF

LV Systolic dysfunction, 34 (21%)
Valve disease, 2 (1%)
Atrial Fibrillation, 10 (6%)

109 pts. with suspected diastolic HF

Mean age, 71 (11) years, 74 (69%) women, E/A ratio < 1, 67%

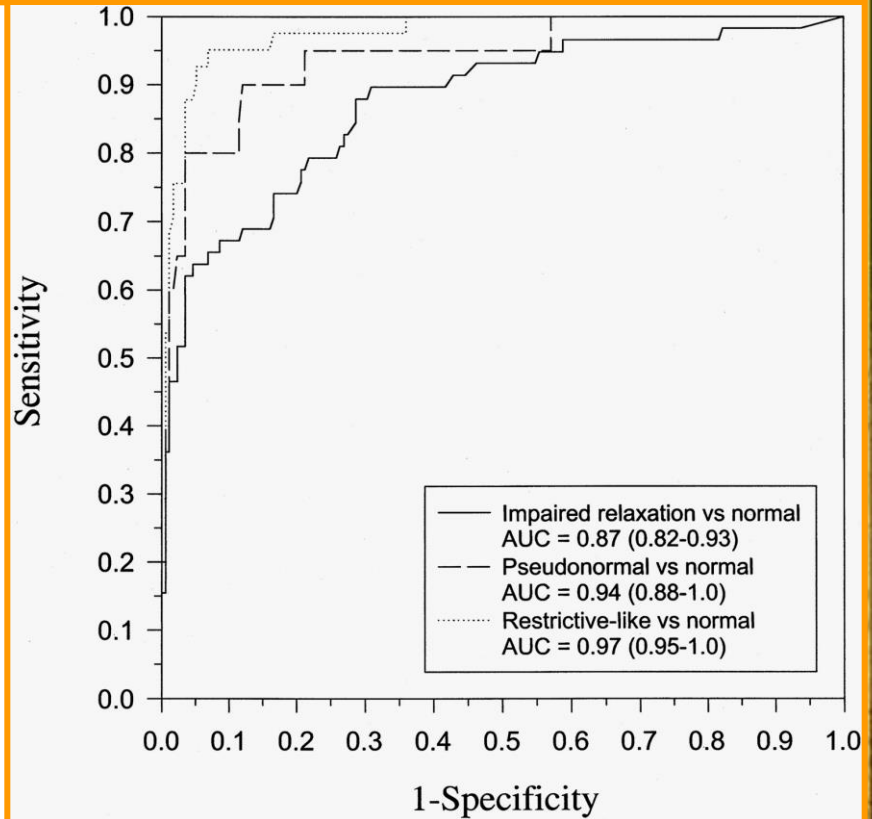
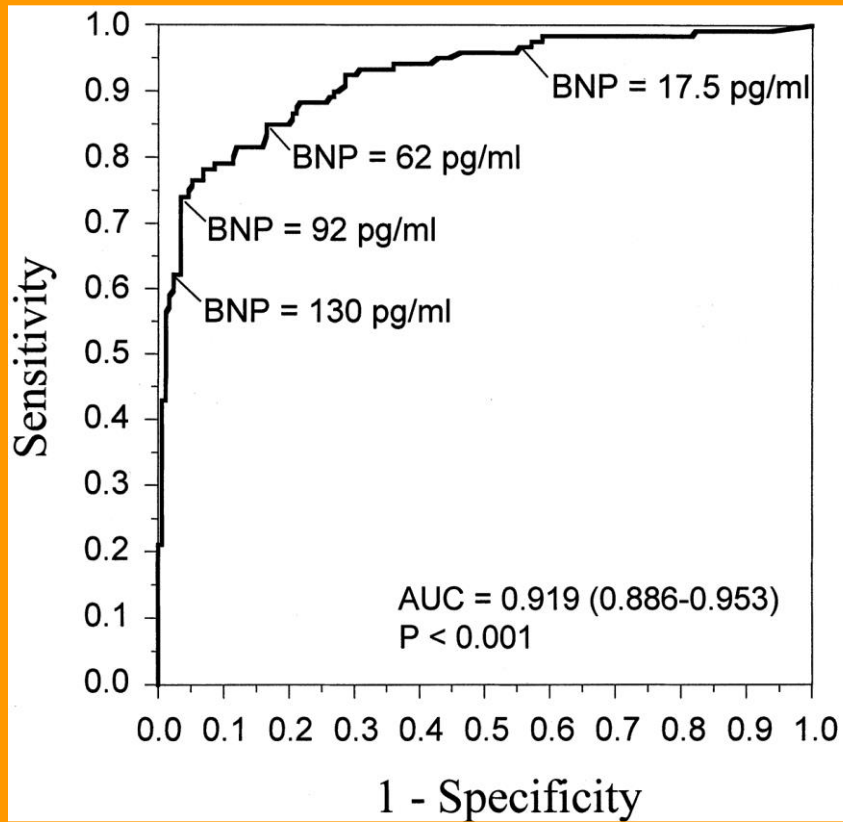
Obesity, 35 (32%)
FEV1 < 70%, 54 (50%)
CAD, 41 (38%)

No evidence of obesity,
respiratory disease or CAD
7 patients (6%)



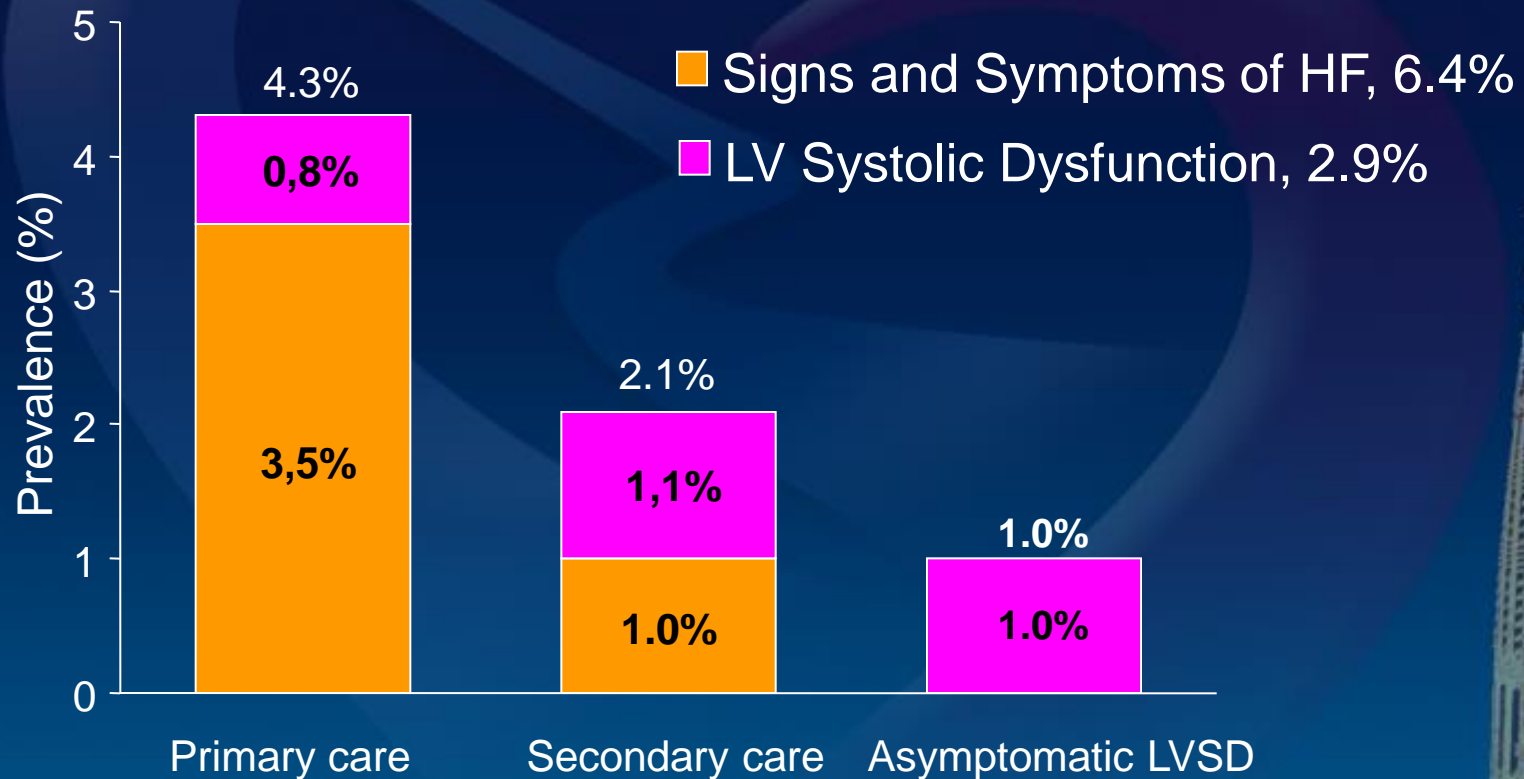
Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction.

Comparison with Doppler Velocity Recordings in 294 patients



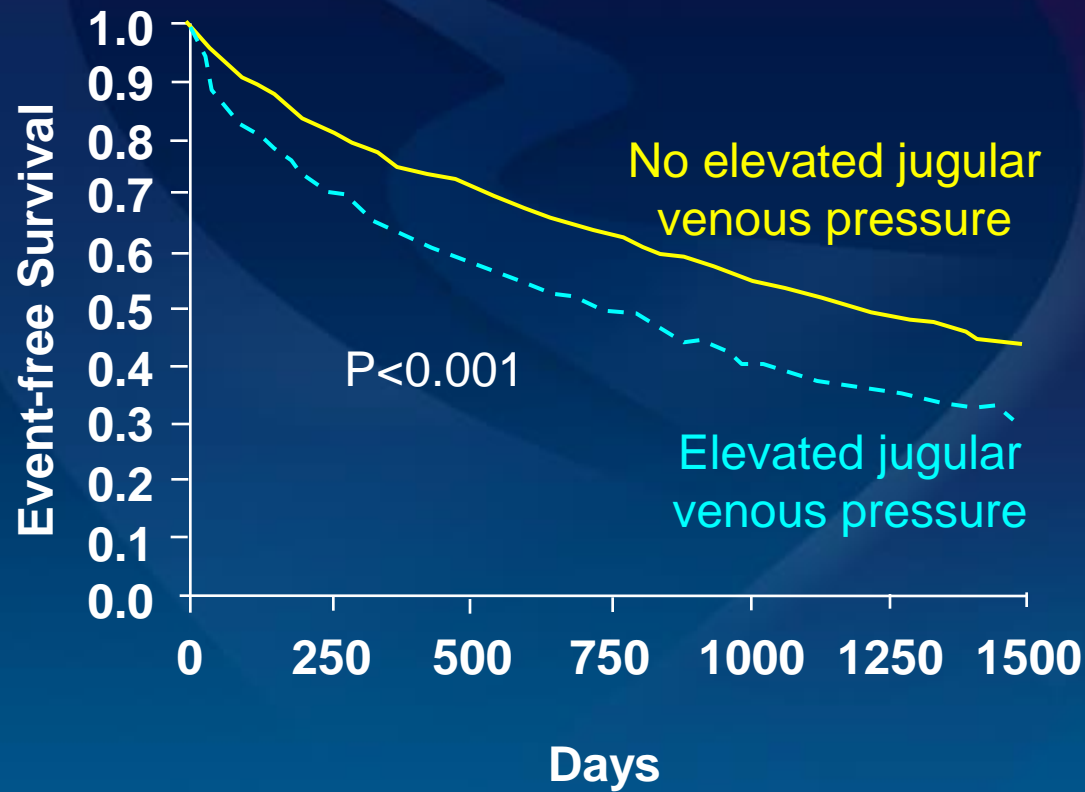
Prevalence of Heart Failure and LV Systolic Dysfunction in Community Patients ≥ 50 Years of Age

(National Health Insurance Registry in the Copenhagen Municipality)

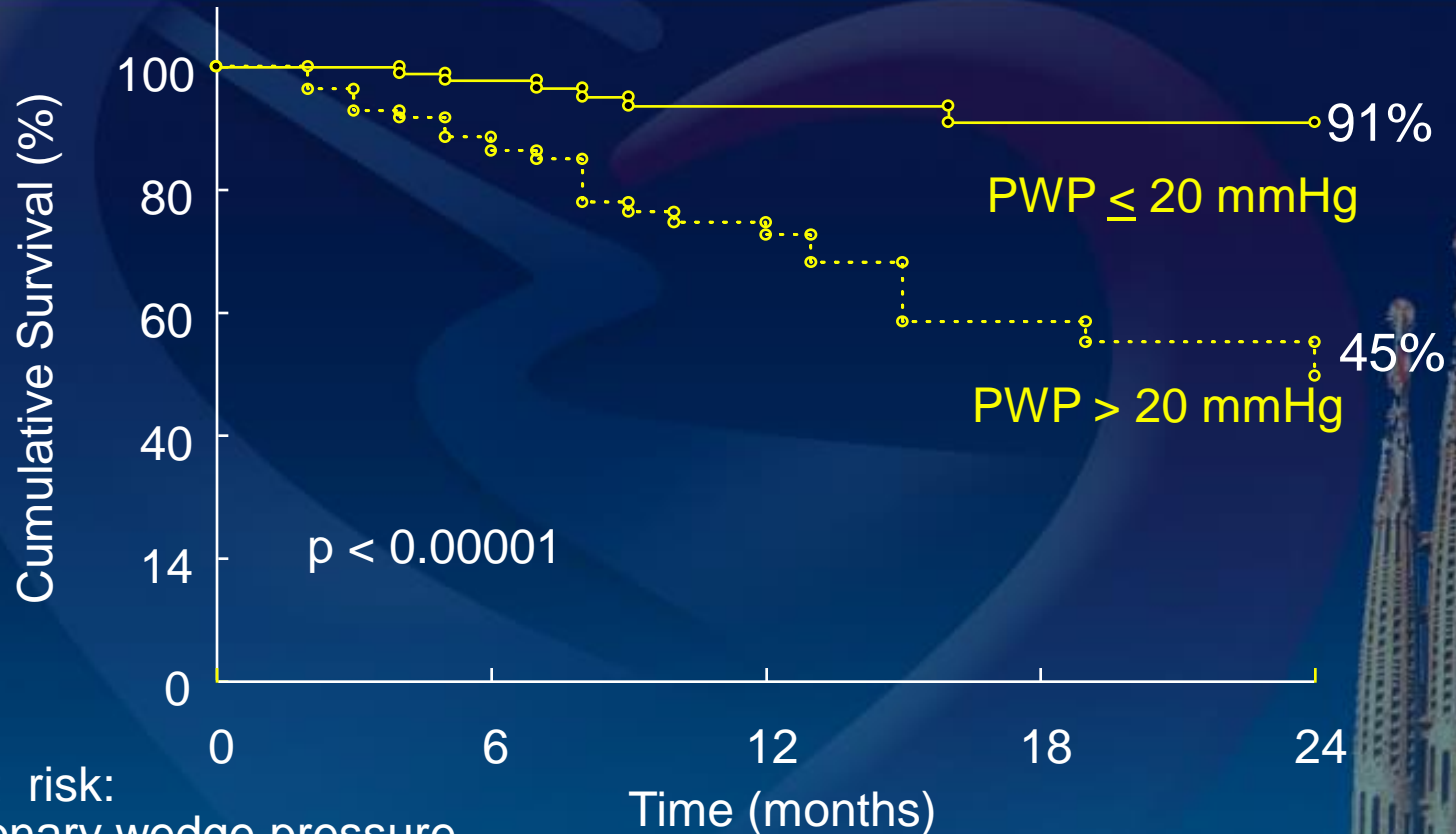


⇒ 7.4 % of the total population ≥ 50 years with signs and symptoms of HF and/or LV systolic dysfunction

SOLVD: Presence or Absence of Elevated Jugular Venous Pressure at Entry



Prognostic Value of Pulmonary Wedge Pressure in CHF



No. at risk:	0	6	12	18	24
Pulmonary wedge pressure					
> 20 mmHg	111	77	36	19	8
≤ 20 mmHg	107	80	46	32	30

Independent Prognostic Value of Echo-Doppler Derived Parameters of LV Diastolic Function

79 patients with dilated cardiomyopathy;
mean age, 39±15 years

145 patients with ischemic or idiopathic
cardiomyopathy; mean age, 70 years

	P value	RR		P value	RR
E Dec. time	< 0.001	6.42	NYHA class	0.002	2.02
Age	0.012	1.69	Age > 70 years	0.009	3.33
NYHA class	< 0.001		LVEF<25%	0.025	2.38
Mean AorticP	0.008	2.83	Pulmonary venous AR - mitral A difference ≥30 ms	0.026	2.96
Mean PWP	0.059	2.17			

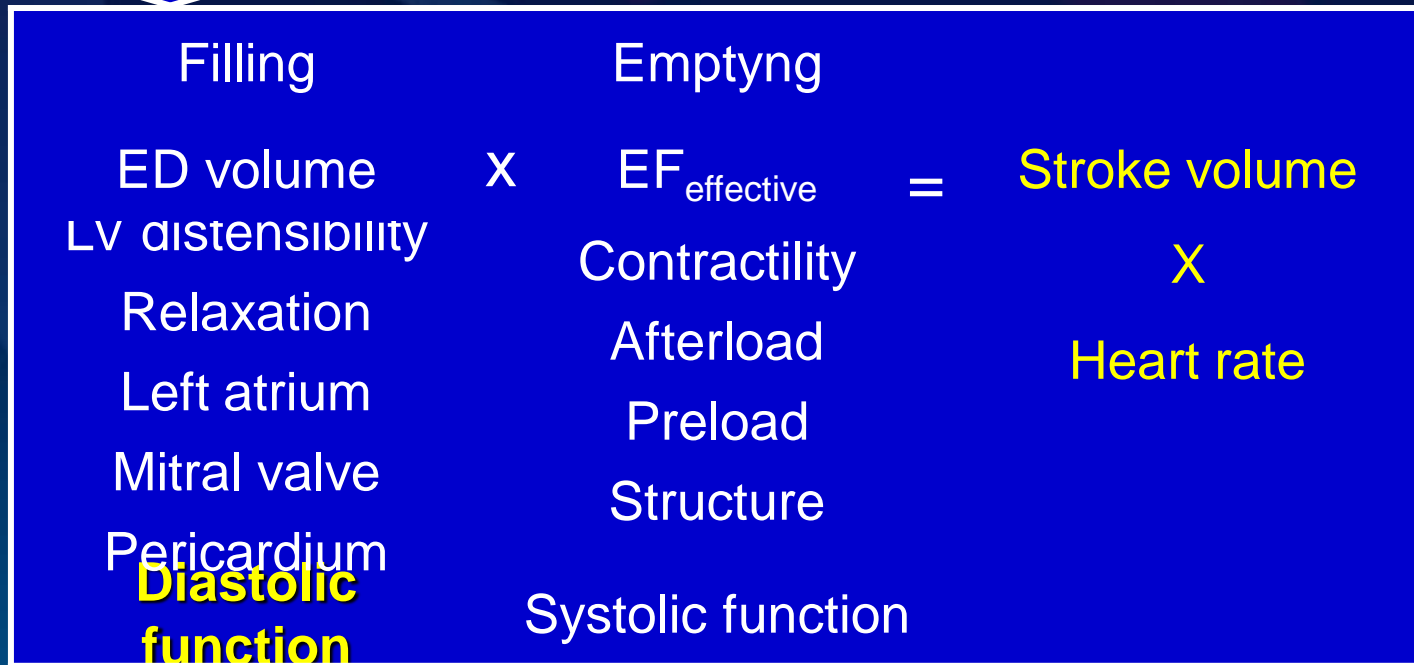
(Pinamonti et al., JACC 1993; 22:808)

(Dini et al., JACC 2000; 36:1295)

Left Ventricular Performance as Pump Performance

Pulmonary venous pressure

Input



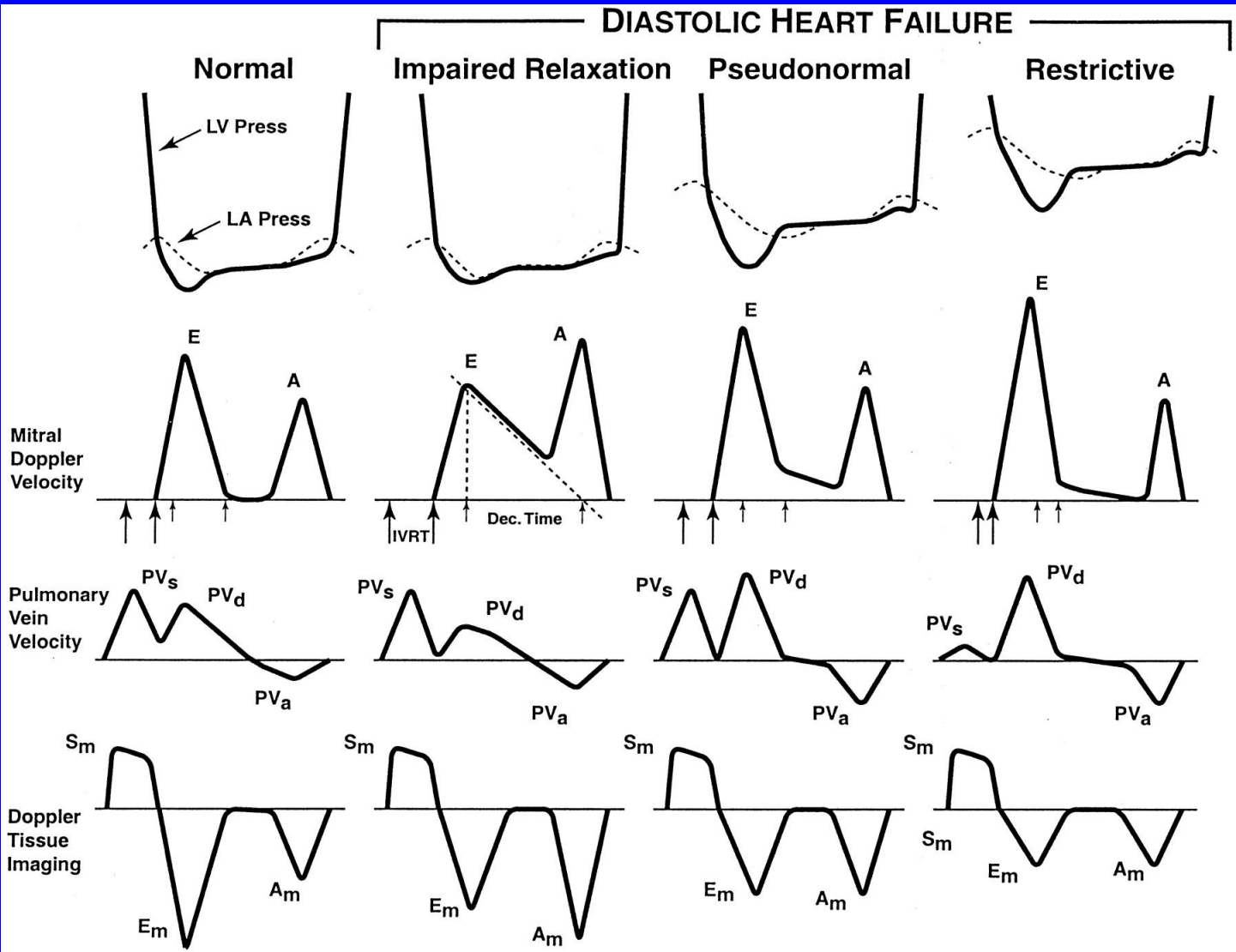
Output

Cardiac output

Potentially Useful Effects of the ACE Inhibitors and AT₁ Receptor Blockers in the Treatment of Diastolic Heart Failure

- Positive lusitropic effect
- Regression of myocardial hypertrophy
- Reduction of myocardial fibrosis
- Control of hypertension
- Prevention of myocardial ischemia

Abnormalities of Diastolic Function



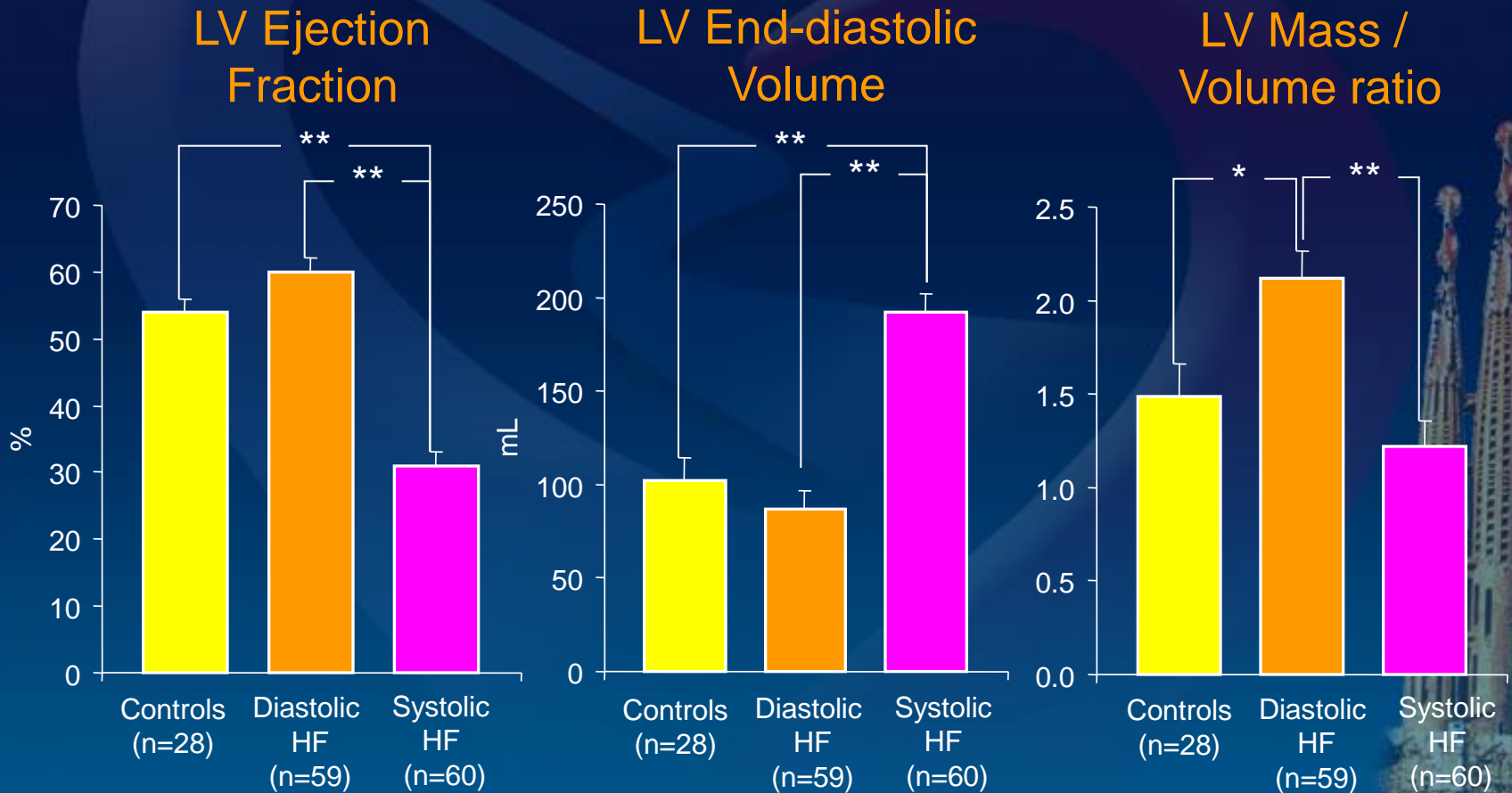
Clinical Predictors for Presence of Normal LV Systolic Function in Patients with CHF

Study, year	Clinical predictors
Warnowicz, 1983; Kinney, 1989; Stone, Cocchi, Taffet, 1991	None
Dougherty, 1984; Bier, 1988	Hypertension
Wong, 1989	Old age, female gender, AF, echo LVH
Aguirre, 1989	Old age, echo LVH, absence of CAD
Aronow, 1990	Age > 80 ys, absence of S ₃
Bareiss, 1991	Age, acute onset, female gender, HTN, absence of cardiac enlargement
Ghali, 1991	Female gender, obesity, absence of JV distension, DBP > 105
Takarada, 1992	Age > 65 ys

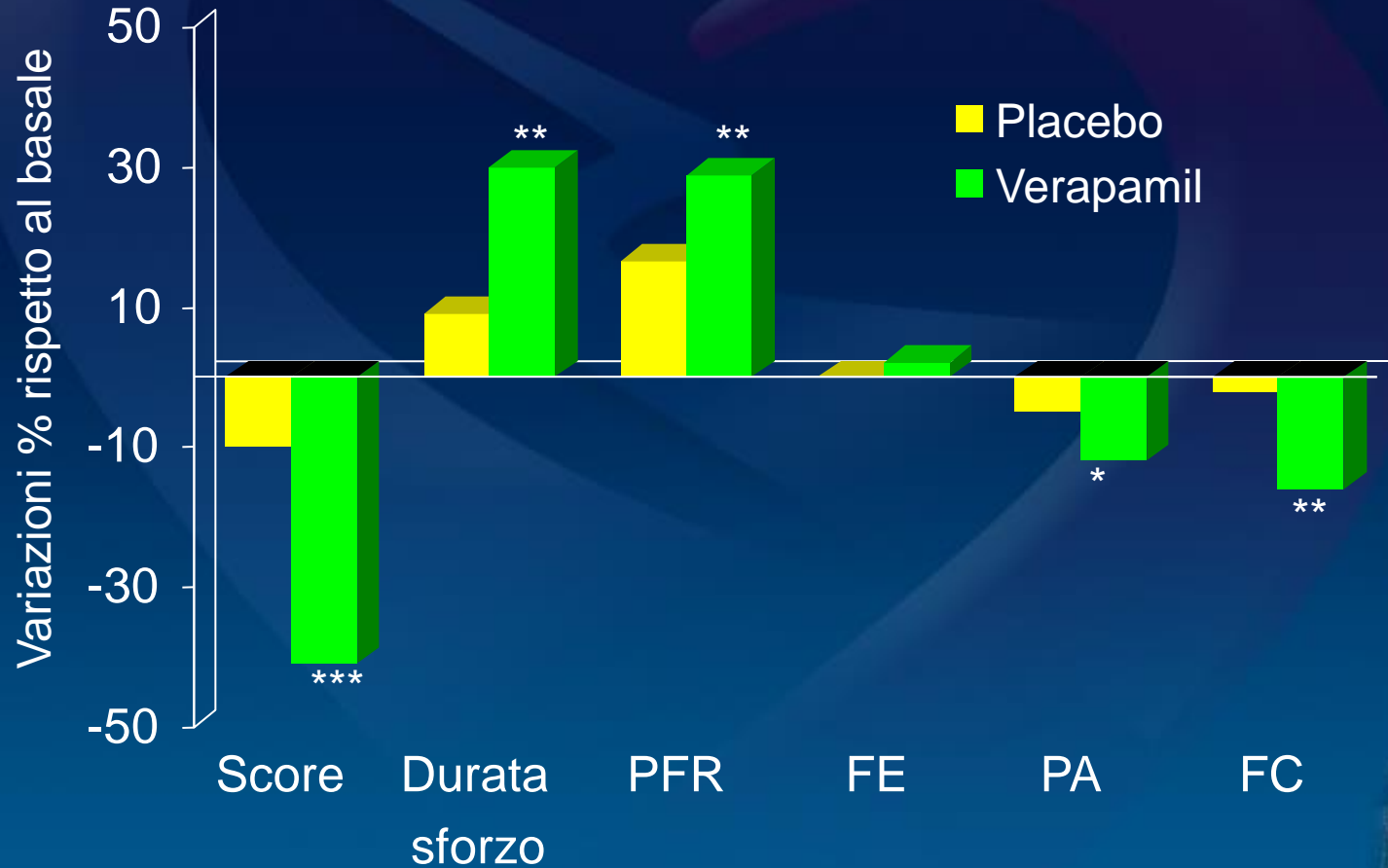
Conditions Involving Diastolic Heart Failure

Condition	Mechanism
Constrictive pericarditis	↓ ventricular diastolic capacity
Restrictive cardiomyopathy Idiopathic Amyloidosis	↑ LV stiffness
Hypertrophic cardiomyopathy	Diastolic calcium overload ↑ LV stiffness
Mitral or tricuspid stenosis	↑ resistance to atrial emptying
LV pressure overload (hypertension, aortic stenosis...)	LV concentric hypertrophy and fibrosis ↑ LV stiffness
LV volume overload (aortic or mitral regurgitation...)	↑ LV diastolic volume relative to ventricular capacity (pericardial restraint); hypertrophy and fibrosis
Ischemic heart disease Acute ischemia Postinfarction LV remodeling	↓ LV relaxation rate; calcium overload Pericardial restraint; (↑ LV stiffness)
Dilated cardiomyopathy	↓ LV relaxation rate; calcium overload ↑ LV stiffness; pericardial restraint

Characterization of Isolated Diastolic Heart Failure in Comparison to Systolic Heart Failure



Effetti della Terapia Calcioantagonista nei Pazienti con Disfunzione Vsinx. Prevalentemente Diastolica



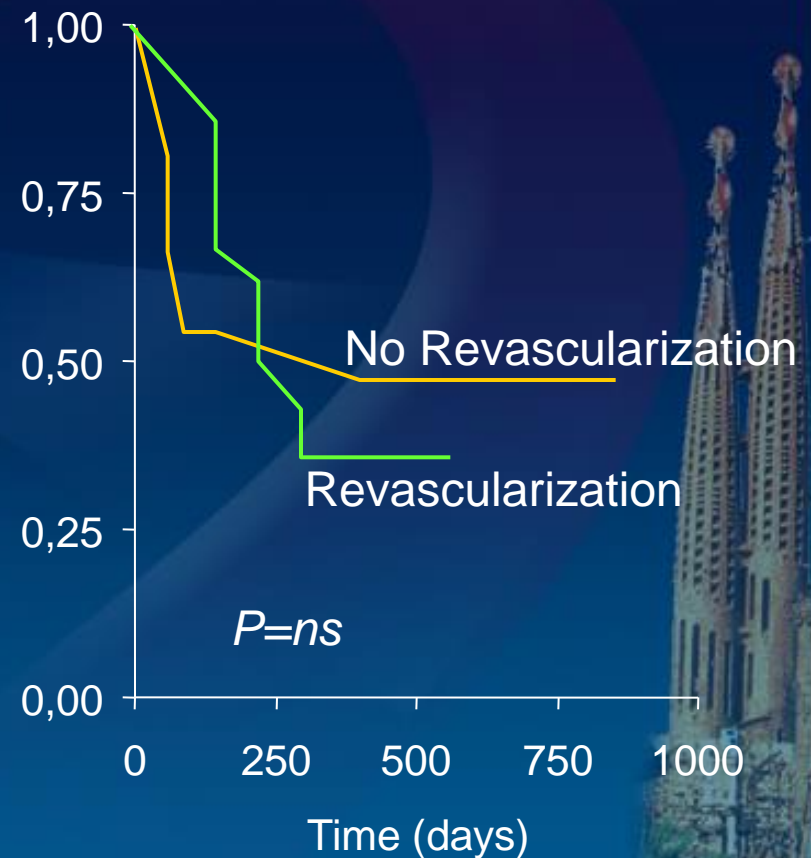
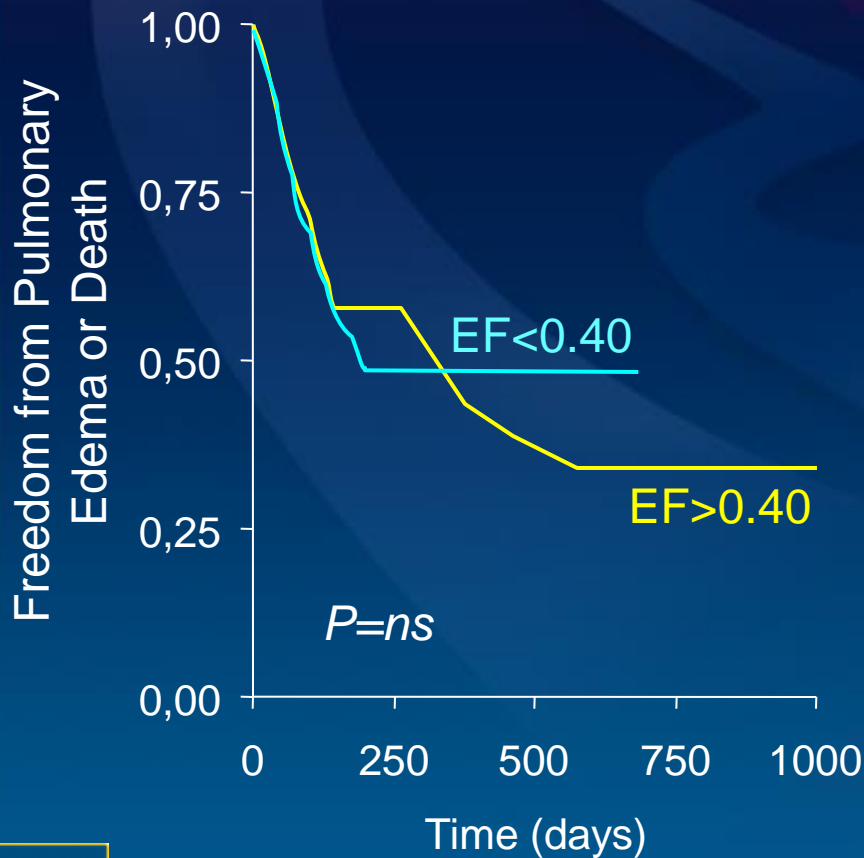
Diagnostic Criteria for Diastolic Heart Failure

ESC Guidelines on Diastolic Heart Failure

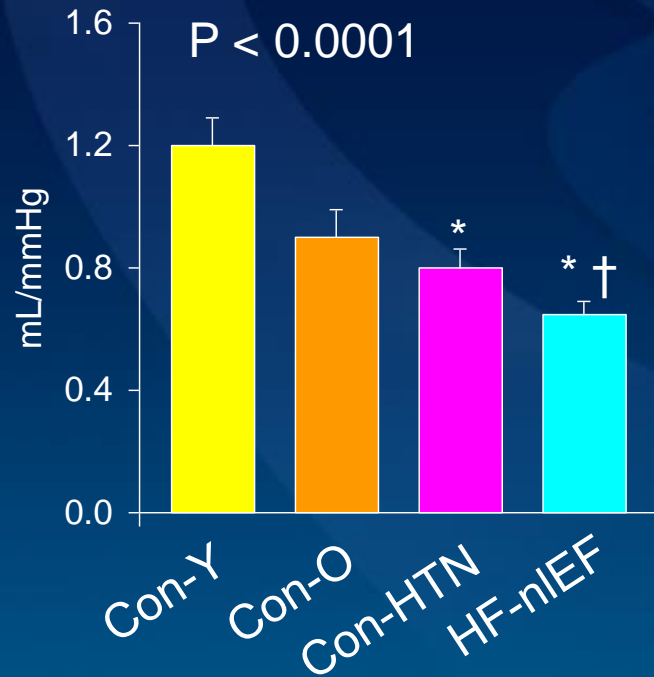
- **Signs and symptoms of congestive heart failure**
 - Exertional dyspnea, peak $\text{VO}_2 < 25 \text{ ml/kg/min}$, orthopnea, gallop sounds, lung crepitation, pulmonary edema
- **Normal or mildly reduced left ventricular systolic function**
 - $\text{LVEF} \geq 45\%$
 - $\text{LVEDD} < 3.2 \text{ cm/m}^2$ or $\text{LVEDVI} < 102 \text{ ml/m}^2$
- **Evidence of abnormal left ventricular diastolic function**
 - Relaxation
 - Filling
 - Diastolic distensibility
 - Diastolic stiffness

Flash Pulmonary Edema with Hypertension:

Frequent Association with a Normal LV Systolic Function and High Incidence of Reoccurrences Despite Coronary Revascularization



Total Arterial Compliance



Mean Blood Pressure

