ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ ΜΕ ΔΙΑΤΗΡΗΜΕΝΟ ΚΛΑΣΜΑ ΕΞΩΘΗΣΗΣ – ΝΕΟΤΕΡΕΣ ΑΠΟΨΕΙΣ

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Professor of Cardiology

Previous definition

- ~~Diastolic heart failure~~

New definition = heart failure with preserved ejection fraction

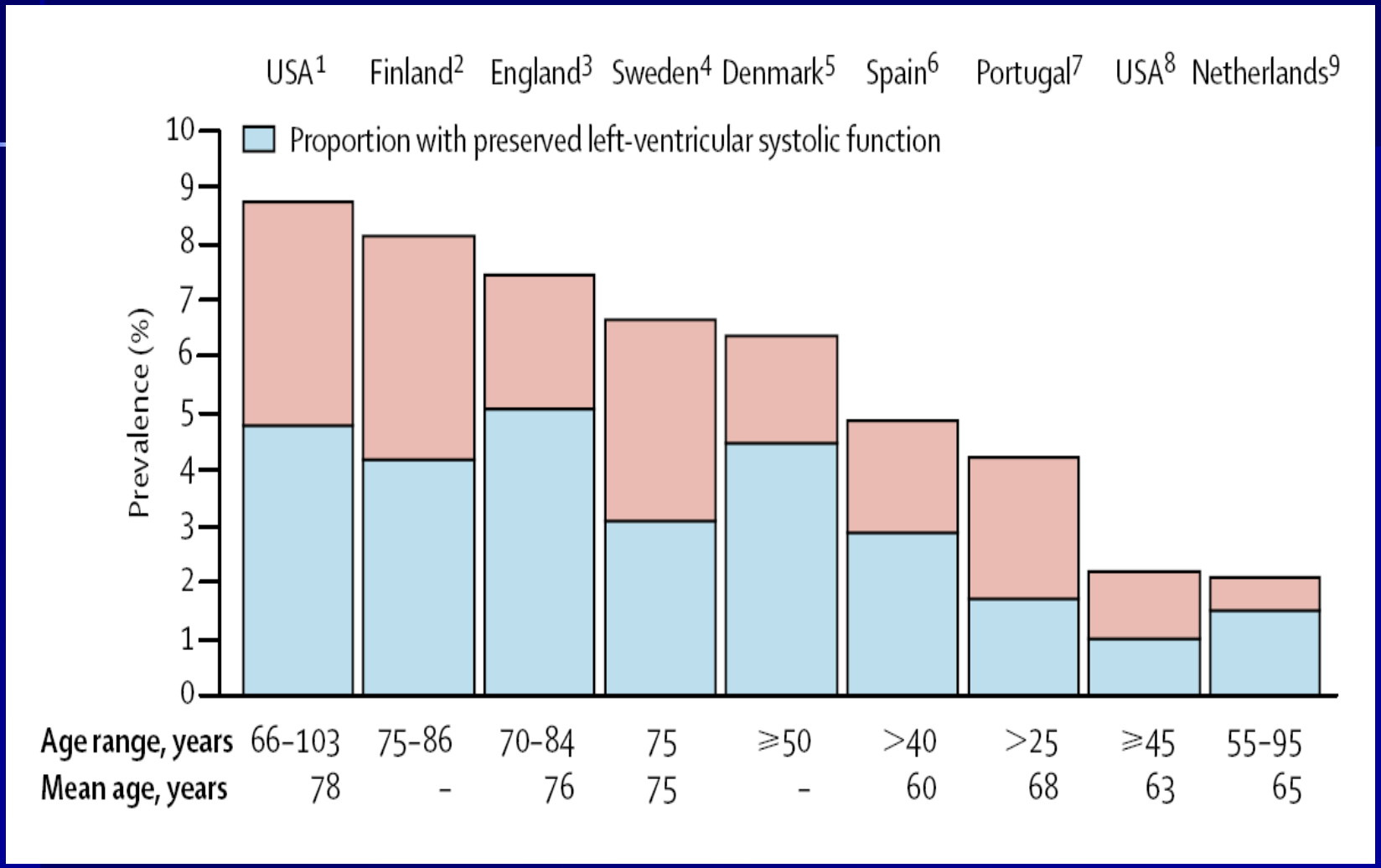
- symptoms and signs of HF
- normal or near normal left ventricular systolic function
- evidence of diastolic dysfunction (eg, abnormal left ventricular filling and elevated filling pressures)

Definition

Table 1 Overview of Diagnostic Guidelines for HFNEF

	HFNEF Guidelines Year Published (Ref. #)			
	ESC 1998 (10)	**NHLBI 2000 (15)**	**LAHEY 2005 (16)**	**ESC 2007 (5)**
HF signs and symptoms (other criteria)	Present	Present	Present	Present
Normal LV systolic function	LVEF >45% LVEDVI <102 ml/m^2	LVEF >50% within 72h HF episode	LVEF >50% LVEDVI <97 ml/m^2	LVEF >50% LVEDVI <97 ml/m^2
LV diastolic dysfunction	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms PVV >0.35 m/s Ard-Ad >20 ms	LVEDP >16 mm Hg PCW >12 mm Hg	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms LAE LVH	LVEDP >16 mm Hg PCW >12 mm Hg E/E′ >15 E/E′ >8 + NT-proBNP >220 pg/ml

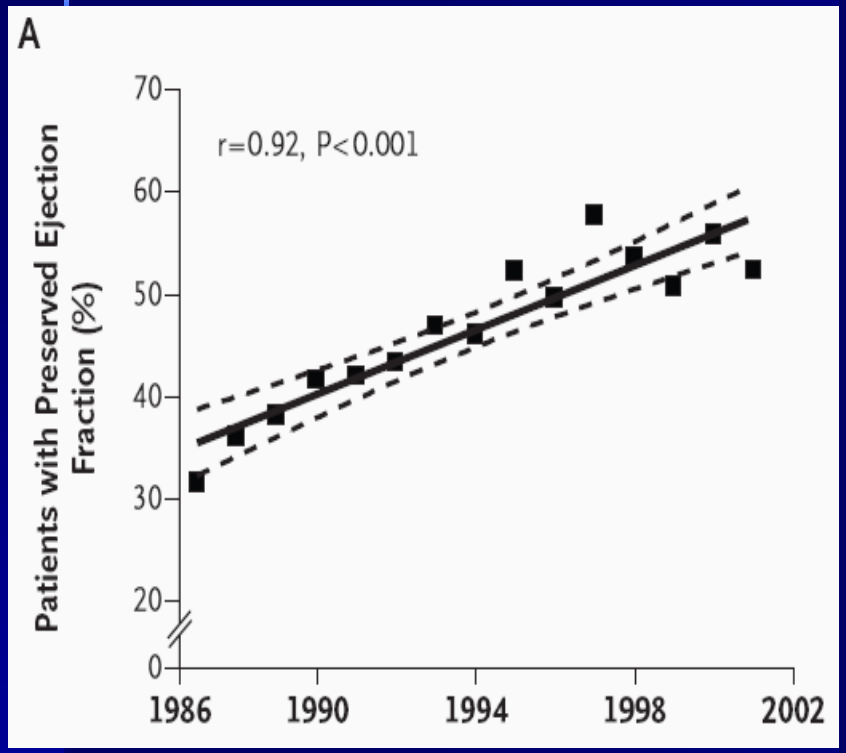
Prevalence of HF in Cross-sectional Population Echo-studies and Proportion of Pts with Preserved LVEF

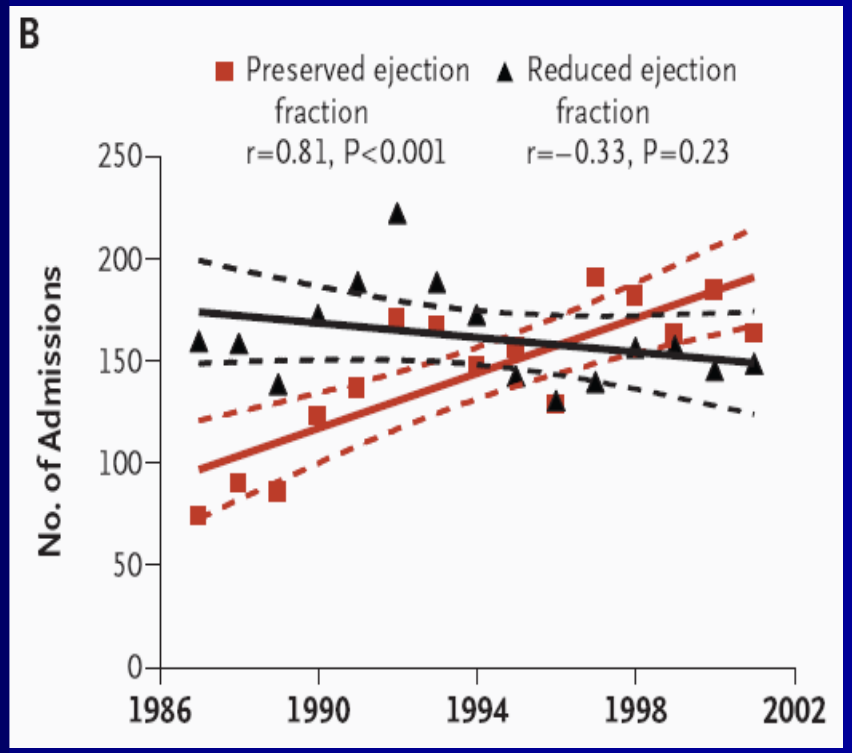


McMurray and Pfeffer.
Lancet 2005; 365:1877-89

Prevalence of HF with Preserved LVEF

All consecutive patients hospitalized with decompensated HF at Mayo Clinic Hospitals, from 1987 through 2001 were studied. A total of 6076 patients with HF were discharged over the 15-year period; data on LVEF were available for 4596 of these patients (76 percent). Of these, 53 % had a reduced LVEF and 47 %t had a preserved LVEF. Secular trends in type of HF, associated CV disease, and survival were defined.





Owan, et al. N Engl J Med 2006;355:251-9

PATHOPHYSIOLOGY

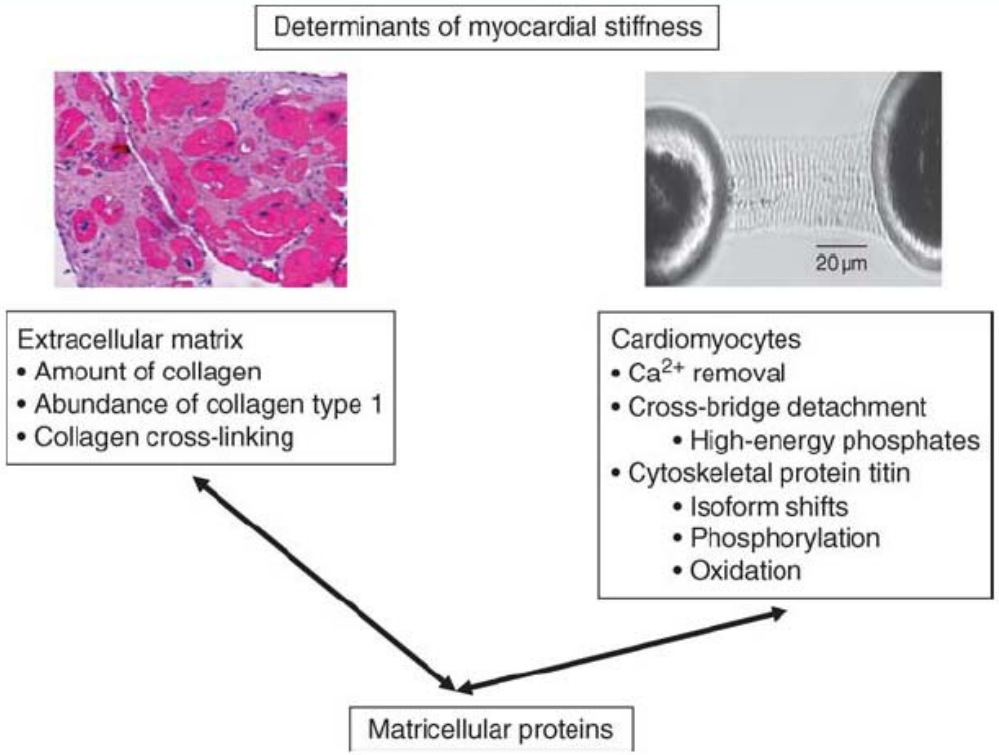


Figure 1 Extracellular matrix and cardiomyocytes determine myocardial stiffness and interact via matricellular proteins.

PATHOPHYSIOLOGY

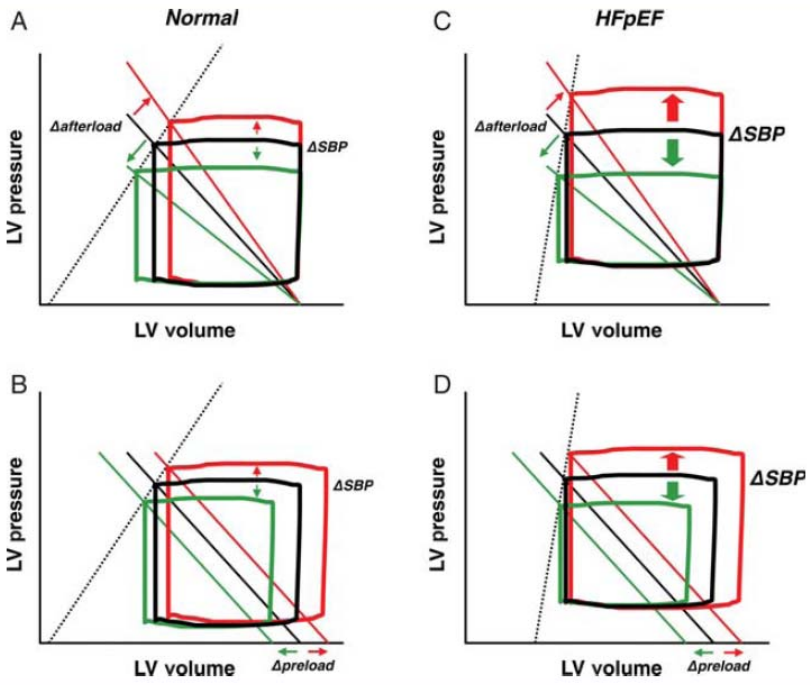


Figure 3 Compared with normal controls (*A* and *B*), the slope of the end-systolic pressure–volume relationship (end-systolic elastance; Ees, dotted lines) is increased in heart failure with preserved ejection fraction (HFpEF) (*C* and *D*). This leads to exaggerated increases and decreases in blood pressure for the same change in afterload (A and C) or preload (B and D) in HFpEF, accounting for the greater predilection for hypertensive crisis and/or hypotension and azotemia with over-diuresis or overly vigorous vasodilation.

PATHOPHYSIOLOGY

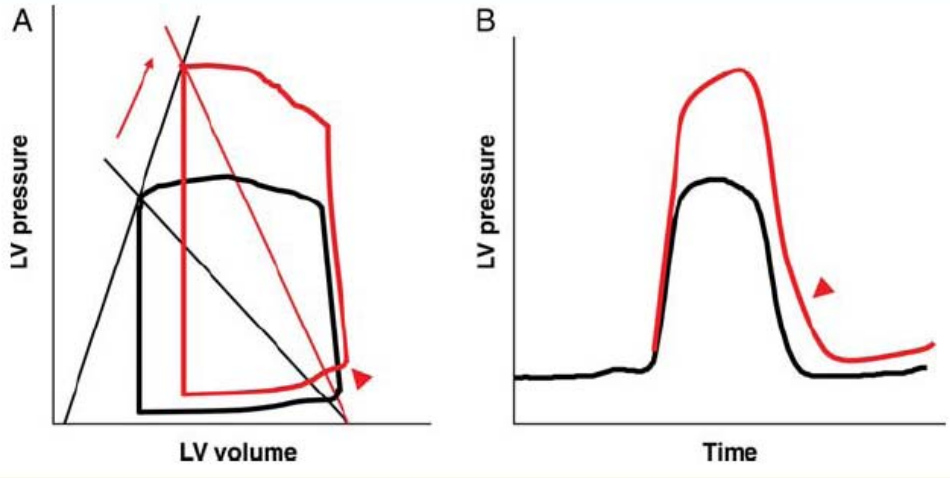


Figure 4 (*A*) Combined ventricular–arterial stiffening in heart failure with preserved ejection fraction may lead to dramatic elevations in blood pressure with afterload increase (red arrow). This feeds back to increase LV end-diastolic pressures (arrowhead), by altering the slope or position of the diastolic pressure–volume relation, and/or (*B*) by prolonging LV pressure decay during isovolumic relaxation (arrowhead).

PATHOPHYSIOLOGY

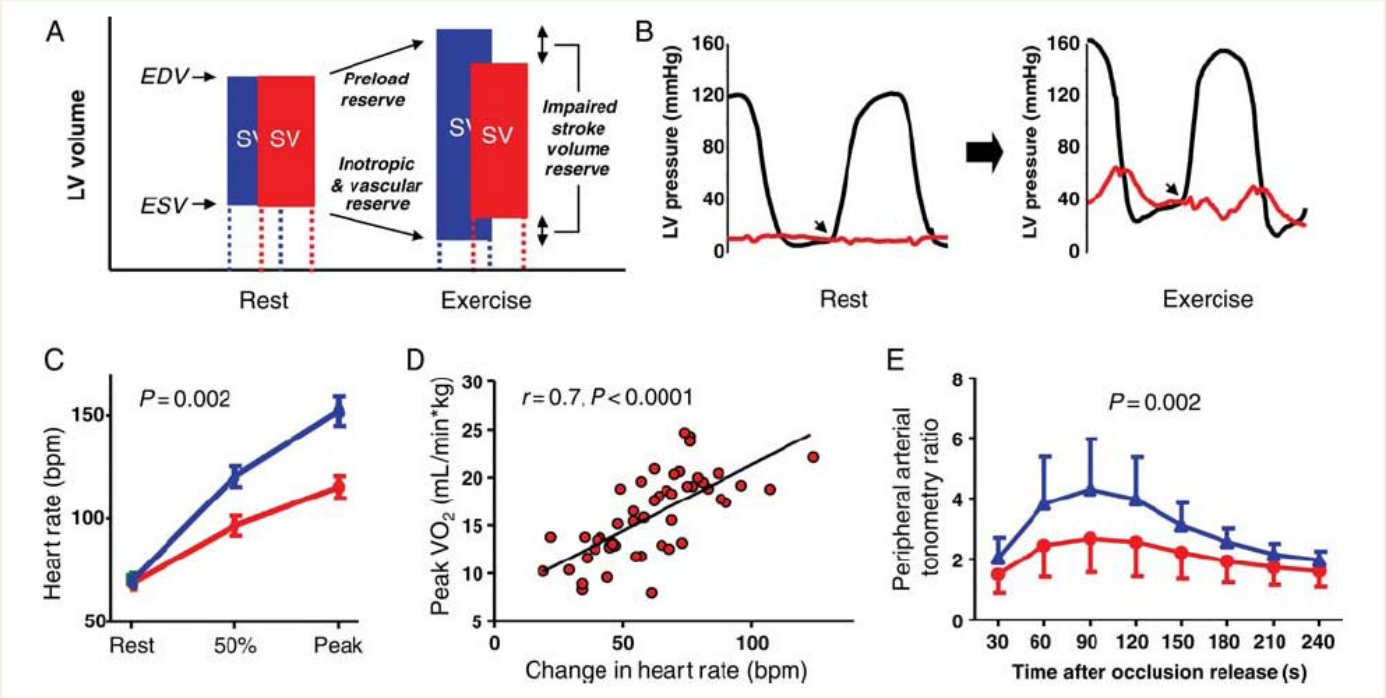


Figure 5 (*A*) Chamber volumes and EF are similar at rest in heart failure (HF) with preserved ejection fraction (HFpEF) (red) and controls (blue), but HFpEF patients are less able to enhance preload volume (end-diastolic volume, EDV) and also contract to as low an end-systolic volume (ESV) during exercise stress. These impairments are related to diastolic, systolic, and vasodilator reserve dysfunction, which contribute to impaired stroke volume (SV) responses with exercise in HFpEF. (*B*) Despite less enhancement of EDV with exercise, there is a much larger increase in LV filling pressures, measured as LV end-diastolic pressure (arrow) or pulmonary wedge pressure (red). (*C*) Chronotropic response during submaximal and peak workload is impaired in HFpEF (red) compared with controls (blue) and the extent of chronotropic impairment is associated with more severely depressed aerobic capacity (*D*). Peripheral vascular function is also impaired in HFpEF, which may be related to impaired endothelium-dependent vasodilation, measured as the increase in peripheral arterial blood flow after upper arm cuff occlusion (*E*). These figures were created based upon previously published data in Borlaug *et al.*[28,33]

Differential diagnosis

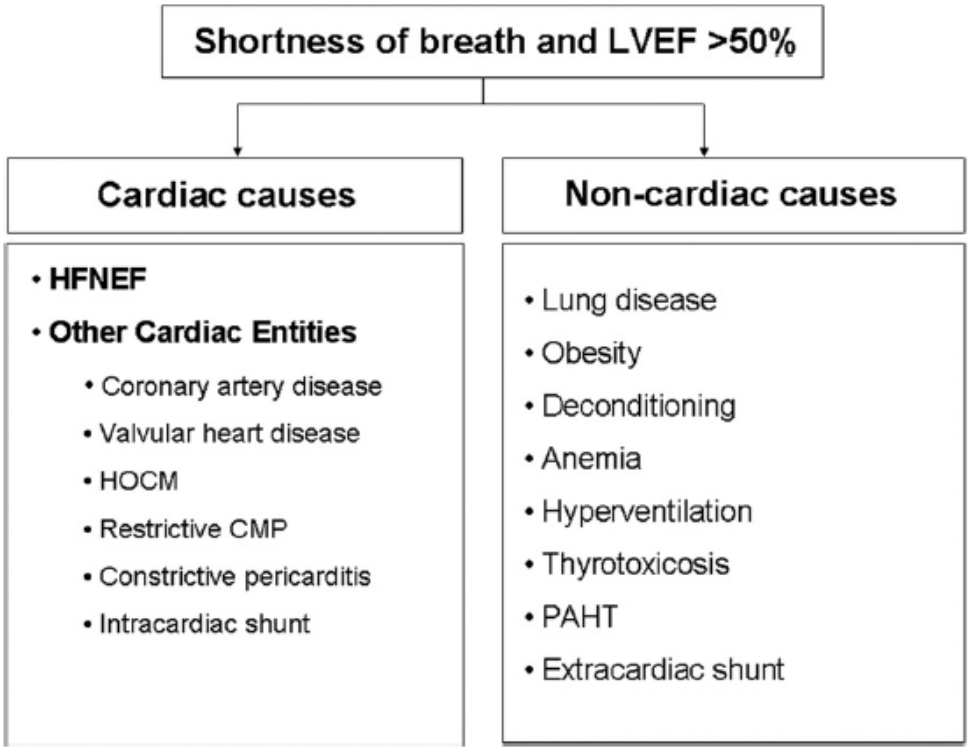


Figure 1 **Scheme Illustrating the Differential Diagnoses to the Syndrome of HFNEF**

It is suggested that a certain proportion of patients given the clinical diagnosis of heart failure in the presence of a left ventricular ejection fraction (LVEF) >50% likely do not have symptoms arising from primary ventricular dysfunction. Within the group of patients with heart failure and LVEF >50%, only a subgroup has heart failure with normal left ventricular ejection fraction (HFNEF) in the sense that the term has been defined by pathophysiology studies (Tables 1 and 2) and the recently proposed diagnostic criteria (Fig. 3) (10). CMP = cardiomyopathy; HOCM = hypertrophic obstructive cardiomyopathy; PAHT = pulmonary arterial hypertension.

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Are Systolic and Diastolic Heart Failure Overlapping or Distinct Phenotypes Within the Heart Failure Spectrum?

- all forms of HF are hybrids, showing both systolic and diastolic abnormalities in varying proportions

De Keulenaer, et al. Circulation 2011

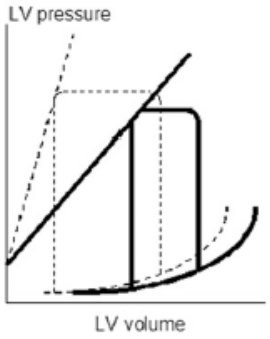
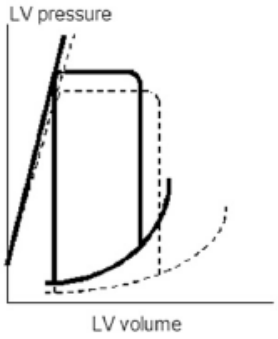
The Problem of the Intermediate Group (EF 40% to 50%)

Is it part of the HF with reduced ejection fraction subgroup?

Or

closes the gap in a continuous disease spectrum of overlapping phenotypes

Comparison of HFpEF with HF with impaired EF

	HF with impaired LVEF	HFNEF
LV morphology		
Pressure-volume loop		
LVEDV	↑	normal
LV mass	eccentric LV hypertrophy	concentric LV hypertrophy or concentric LV remodeling
Left atrium	dilated	dilated
LVEF	↓	normal
dp/dt	↓	normal
LVEDP	↑	↑
β	normal	↑
E/E´	↑	↑
BNP/NT-proBNP	↑	↑

Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study **N Engl J Med 2006; 355:260-269**

Characteristic	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
Mean LVEF — %	25.9	62.4	<0.001
Age — yr	71.8 ± 12	75.4 ± 11.51	<0.001
Male sex — no. (%)	983 (62.6)	302 (34.3)	<0.001
Coronary artery disease or ischemia — no. (%)	764 (48.7)	312 (35.5)	<0.001
Hypertension — no. (%)	772 (49.2)	485 (55.1)	0.005
Hyperlipidemia — no. (%)	350 (22.3)	136 (15.5)	<0.001
Diabetes — no. (%)	611 (38.9)	279 (31.7)	<0.001
Cerebrovascular accident or transient ischemic attack — no. (%)	229 (14.6)	133 (15.1)	0.72
Angina — no. (%)	440 (28.0)	201 (22.8)	0.005
Ever smoked — no. (%)	754 (48.0)	322 (36.6)	<0.001
Currently smoking — no. (%)	271 (17.3)	106 (12.0)	<0.001
Peripheral vascular disease — no. (%)	236 (15.0)	92 (10.5)	<0.001
Atrial fibrillation — no. (%)	370 (23.6)	280 (31.8)	<0.001
Cancer — no. (%)	182 (11.6)	105 (11.9)	0.80
COPD — no. (%)	207 (13.2)	156 (17.7)	0.002
Prior myocardial infarction — no. (%)	612 (39.0)	146 (16.6)	<0.001
Prior CABG — no. (%)	203 (12.9)	51 (5.8)	<0.001
Prior PCI — no. (%)	48 (3.1)	16 (1.8)	0.07
Peptic ulcer disease — no. (%)	94 (6.0)	74 (8.4)	0.02
Hepatitis or cirrhosis — no. (%)	20 (1.3)	16 (1.8)	0.28
Dementia — no. (%)	76 (4.8)	49 (5.6)	0.43
Hemoglobin <10 g/dl — no. (%)	155 (9.9)	186 (21.1)	<0.001
Mean systolic blood pressure — mm Hg	146	156	<0.001
Mean respiratory rate — breaths/min	26	26	0.17
Serum sodium <136 mmol/liter — no. (%)	362 (23.1)	209 (23.8)	0.70
Serum creatinine >150 mmol/liter — no. (%)	296 (18.9)	195 (22.2)	0.95
Dialysis — no. (%)	18 (1.1)	9 (1.0)	0.78

Diagnostic algorithm

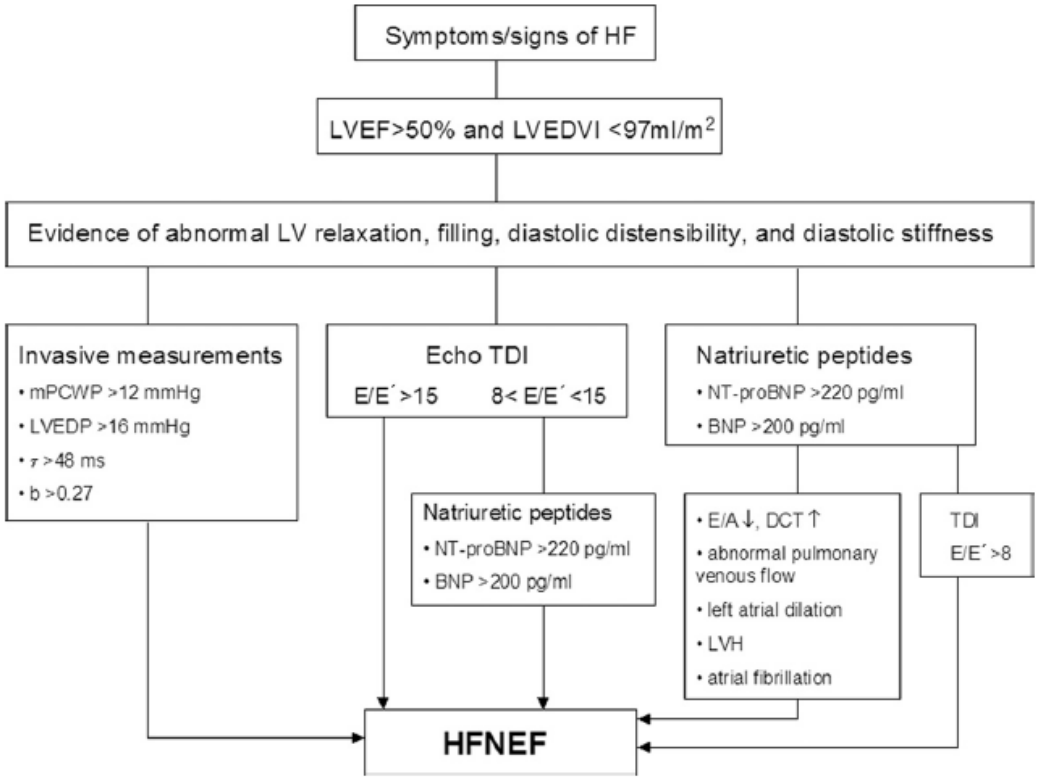
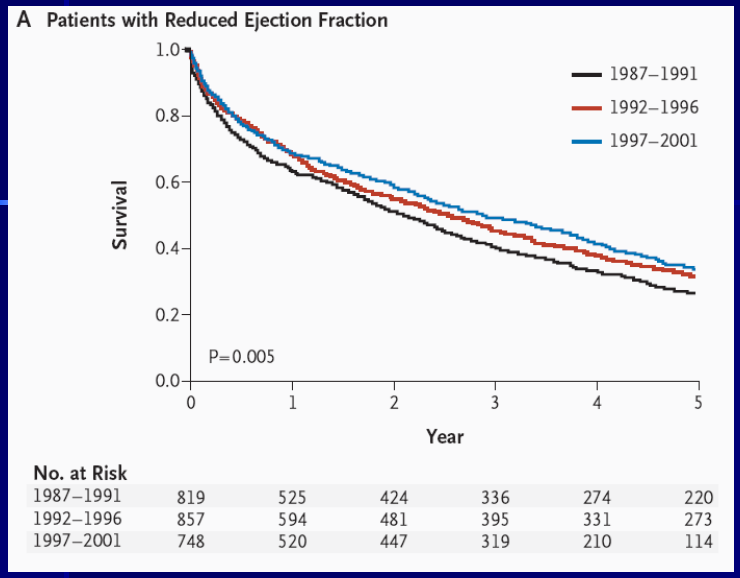


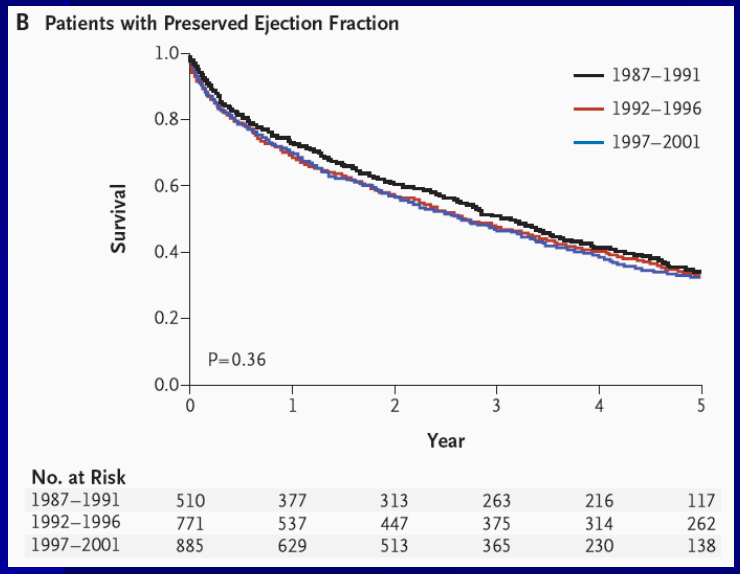
Figure 3 **Principles of the Algorithm Proposed for the Diagnosis of HFNEF by the Working Group of the European Society of Cardiology**

b = left ventricular passive stiffness; DCT = deceleration time; E/A = ratio of early to late diastolic peak mitral inflow velocities; LVEDVI = left ventricular end-diastolic volume index; LVH = left ventricular hypertrophy; mPCWP = mean pulmonary capillary wedge pressure; τ = time constant of the isovolemic pressure decline; TDI = tissue Doppler imaging; other abbreviations as in Figures 1 and 2. Adapted from Paulus et al. (10), with permission from Oxford press.

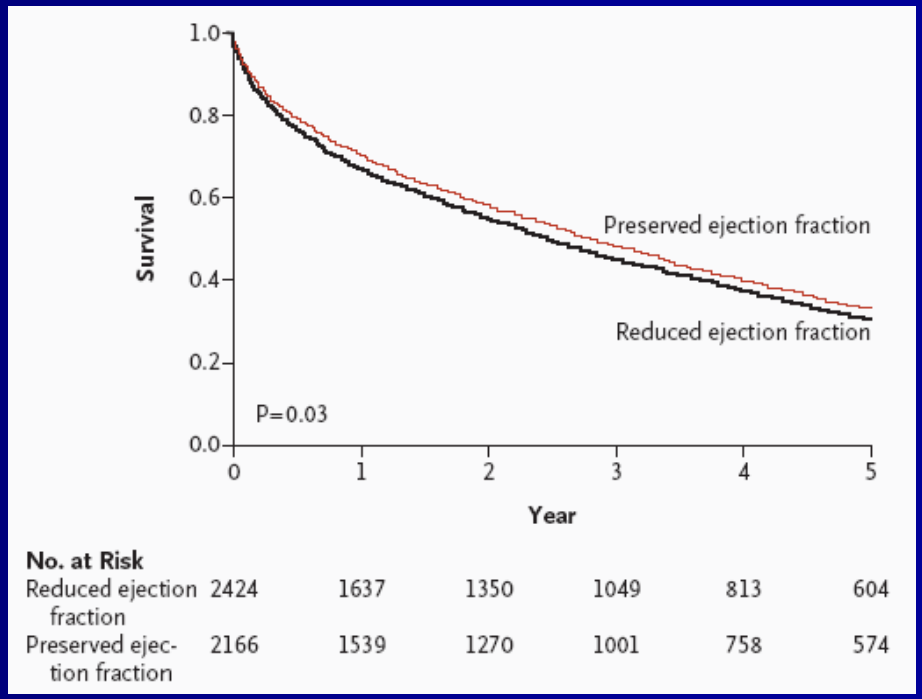
Secular Trends in Survival among Patients with HF and Preserved or Reduced LVEF



No. at Risk						
1987–1991	819	525	424	336	274	220
1992–1996	857	594	481	395	331	273
1997–2001	748	520	447	319	210	114



No. at Risk						
1987–1991	510	377	313	263	216	117
1992–1996	771	537	447	375	314	262
1997–2001	885	629	513	365	230	138



No. at Risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Owan, et al. N Engl J Med 2006;355:251-9

Enrollment criteria

Table 2 Enrollment Criteria of Large HFNEF Outcome Trials

	Trial Compound Duration (Ref. #)					
	V-HeFTII Enalapril 2 years (27)	DIG Digoxin 37 months (31)	CHARM-P Candesartan 3 years (33)	SENIORS Nebivolol 12 months (37)	PEP-CHF Perindopril 2.1 years (38)	I-PRESERVE Irbesartan 49.5 months (2)
HF signs and symptoms (other criteria)	Present (VO_2 ↓)	Present	Present	Present	Present (3/9 criteria including prior MI)	Present
Normal LV systolic function	LVEF >35% CTR >0.55 LVEDDI >2.7 cm/m^2	LVEF >45%	LVEF >40%	LVEF >35%	LVEF >40% WMI >1.4	LVEF >45%
LV diastolic dysfunction	—	—	—	—	WT >13 mm IVRT >105 ms E/A <0.5 DT >280 ms LA diameter >25 mm/m^2	LAE LVH
Positive outcomes	Mortality −40%	Hospitalizations	Hospitalizations	Mortality+hospitalizations −14%	Hospitalizations and symptoms at 1 yr follow-up	—

CTR = cardiothoracic ratio; DT = deceleration time; LVEDDI = left ventricular end-diastolic dimension index; MI = myocardial infarction; V_{O_2} = maximal oxygen consumption during exercise; WMI = wall motion index; WT = wall thickness; other abbreviations as in Table 1.

Table 3 Enrollment Criteria of HFNEF Registries

	Trial Compound Duration (Ref. #)			
	Dobre et al. Beta-Blockers 25 months (39)	COHERE Carvedilol 1 year (41)	OPT-HF ACEI, ARB, Beta-Blockers 60–90 days* (29)	Tribouilloy ACEIs 5 years (40)
HF signs and symptoms (other criteria)	Present	Present	Present	Present
Normal LV systolic function	LVEF >40%	LVEF >40%	LVEF >50%	LVEF >50%
LV diastolic dysfunction	—	—	—	—
Positive outcomes	Mortality −43%	Mortality −6%; hospitalizations	—	Mortality −30%

*Use of beta-blockers also had no effect on 1-year mortality or hospitalization rates (42).
Abbreviations as in Table 1.

Mode of Death Distribution in I-Preserve Compared With Previous RCTs

Zile, M. R. et al. Circulation 2010;121:1393-1405

	HFPEF, n (%)				HFREF, mean % (range)	
	I-Preserve	CHARM-Preserved	PEP-CHF	DIG-Preserved	Drugs*	Devices†
Total	881	481	109	231		
Sudden death	231 (26)	134 (28)	NR	NR	42 (23–58)	28 (21–34)
Heart failure	125 (14)	102 (21)	NR	64 (28)	36 (27–56)	45 (34–63)
MI	44 (5)	13 (3)	NR	NR	7 (2–15)	6 (3–15)
Stroke	76 (9)	33 (7)	NR	NR	5 (3–6)	5 (3–6)
CV procedure	13 (1)	13 (3)	NR	NR	2 (1–3)	2 (1–3)
Other cardiac	10 (1)	35 (7)	NR	NR	7 (2–11)	6 (3–10)
Other vascular	32 (4)	NR	NR	NR	NR	NR
Noncardiovascular	268 (30)	141 (29)	31 (28)	69 (30)	14 (4–20)	15 (5–17)
Unknown	81 (9)	NR	NR	NR	NR	NR

PEP-CHF indicates Perindopril in Elderly People With Chronic Heart Failure; CV, cardiovascular; and NR, not reported.

*Data obtained from studies described in References [13 through 28].

†Data obtained from studies described in references [29–39].

Treatment

To date, results from existing clinical trials of HF-PEF have been largely inconclusive, and treatments that have been shown to reduce morbidity and mortality in patients with HF-REF showed either no or only marginal benefits in patients with HF-PEF

- What should we do in the light of the uncertainty?

General principles — Guidelines for treatment of patients with DHF were published in 2005 by the ACC/AHA task force on chronic HF

- Control of systolic and diastolic hypertension
- Control of ventricular rate in patients with atrial fibrillation
- Control of pulmonary congestion and peripheral edema with diuretics
- Coronary revascularization in patients with CHD in whom ischemia is judged to have an adverse effect on diastolic function
- Pneumococcal vaccination and annual influenza vaccination are recommended for all patients with heart failure

Choice of medications

The choice of medications in patients with diastolic dysfunction is determined by two factors:

Treatment of specific underlying processes such as hypertension or symptomatic CHD

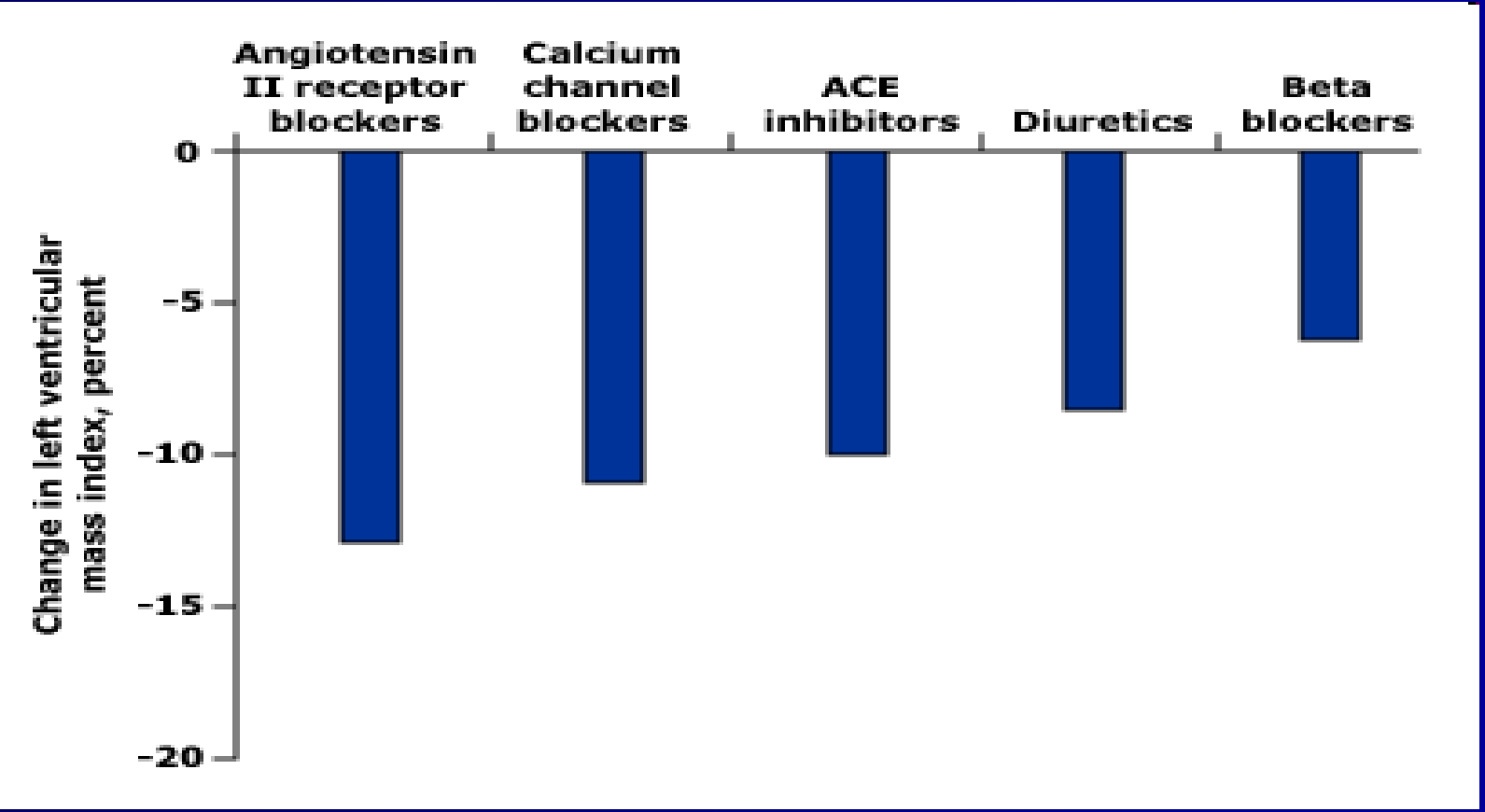
The possibly beneficial effect of the drug on the pathophysiology of DHF

Caution: excessive preload reduction

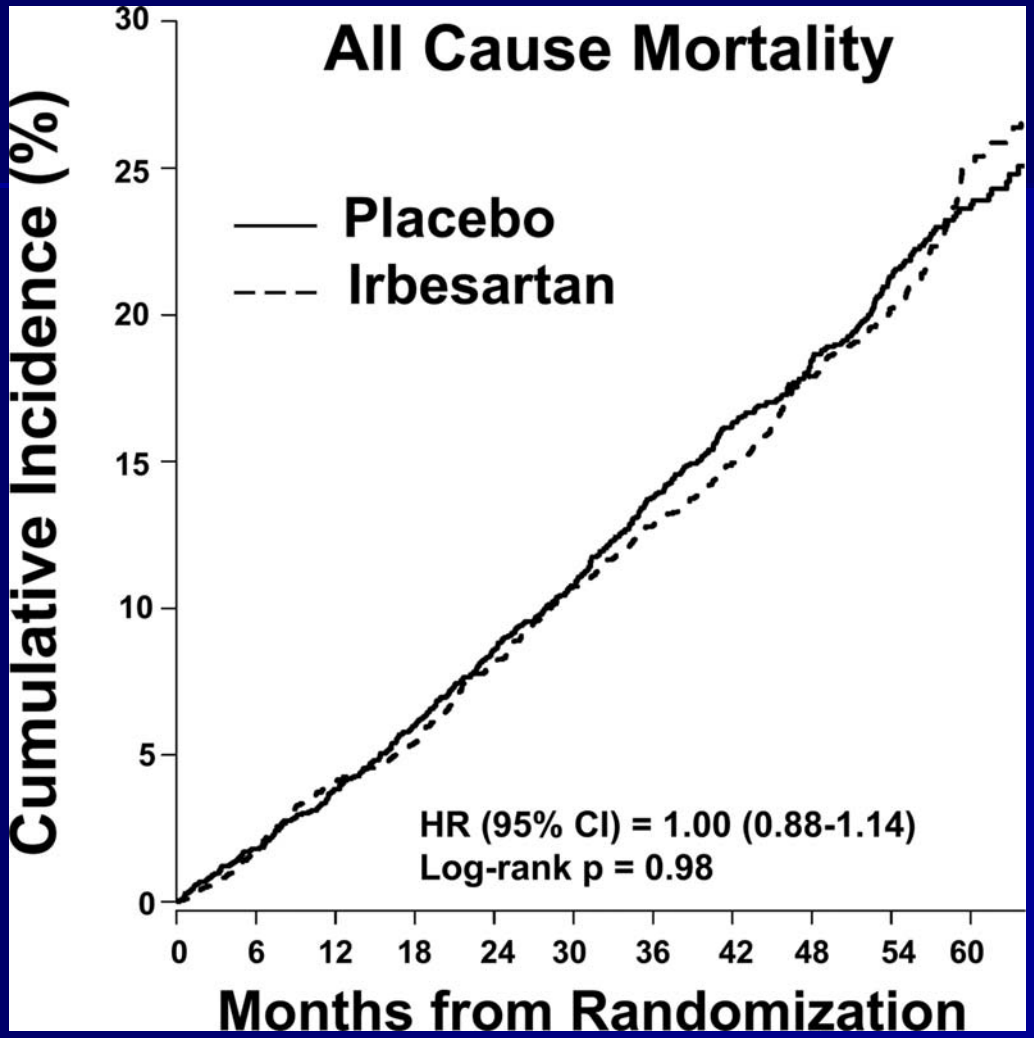
Antihypertensive therapy

Regression of left ventricular hypertrophy

(Am J Med 2003; 115:41)



Cumulative incidence of all cause mortality rate in I-Preserve patients treated with placebo vs irbesartan



Zile, M. R. et al. Circulation 2010;121:1393-1405

Circulation

Chronic Atrial Fibrillation

- loss of atrial contraction
- shortening the time of diastole

restoration and maintenance of sinus rhythm

rate control (Beta blockers, calcium channel blockers)

anticoagulation

Antiischemic therapy

- Ischemia can result from CHD and/or LVH (beta blockers, calcium channel blockers, nitrates)
- Revascularization

Treatment

Table 3 Substances Evaluated for the Treatment of Patients With HFNEF in Completed but Unpublished or Ongoing Clinical Studies (According to NIH Clinical Trials Registry*)

Substance	Drug Class	Postulated Targets
Valsartan	Angiotensin-receptor blocker	RAAS, blood pressure, LVH, LV relaxation
Aliskiren	Selective renin inhibitor	RAAS, blood pressure, LVH, LV relaxation
Spironolactone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness
Eplerenone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness, endothelial dysfunction
Sitaxsentan	Endothelin receptor A antagonist	Blood pressure, LVH
Alagebrium	Advanced glycation end products cross-links breaker	Advanced glycation end products, LV relaxation and stiffness
Atorvastatin	Statin	Collagen turnover, LV relaxation and stiffness, vascular function
Sildenafil	Phosphodiesterase-5 inhibitor	LVH, LV stiffness, vascular stiffness
Exenatide	Glucagon-like peptide-1 receptor antagonist	Aortic stiffness, LV stiffness
Ranolazine	Inhibitor of the slowly inactivating component of the cardiac Sodium current (late I_{Na} channel)	Intracellular calcium, LV relaxation
Ivabradine	Inhibitor of the "funny" channel (I_f channel)	Heart rate, duration of diastole

*National Institutes of Health (NIH) Clinical Trials Registry (78).
RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Table 1.

PDE-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure: the RELAX trial

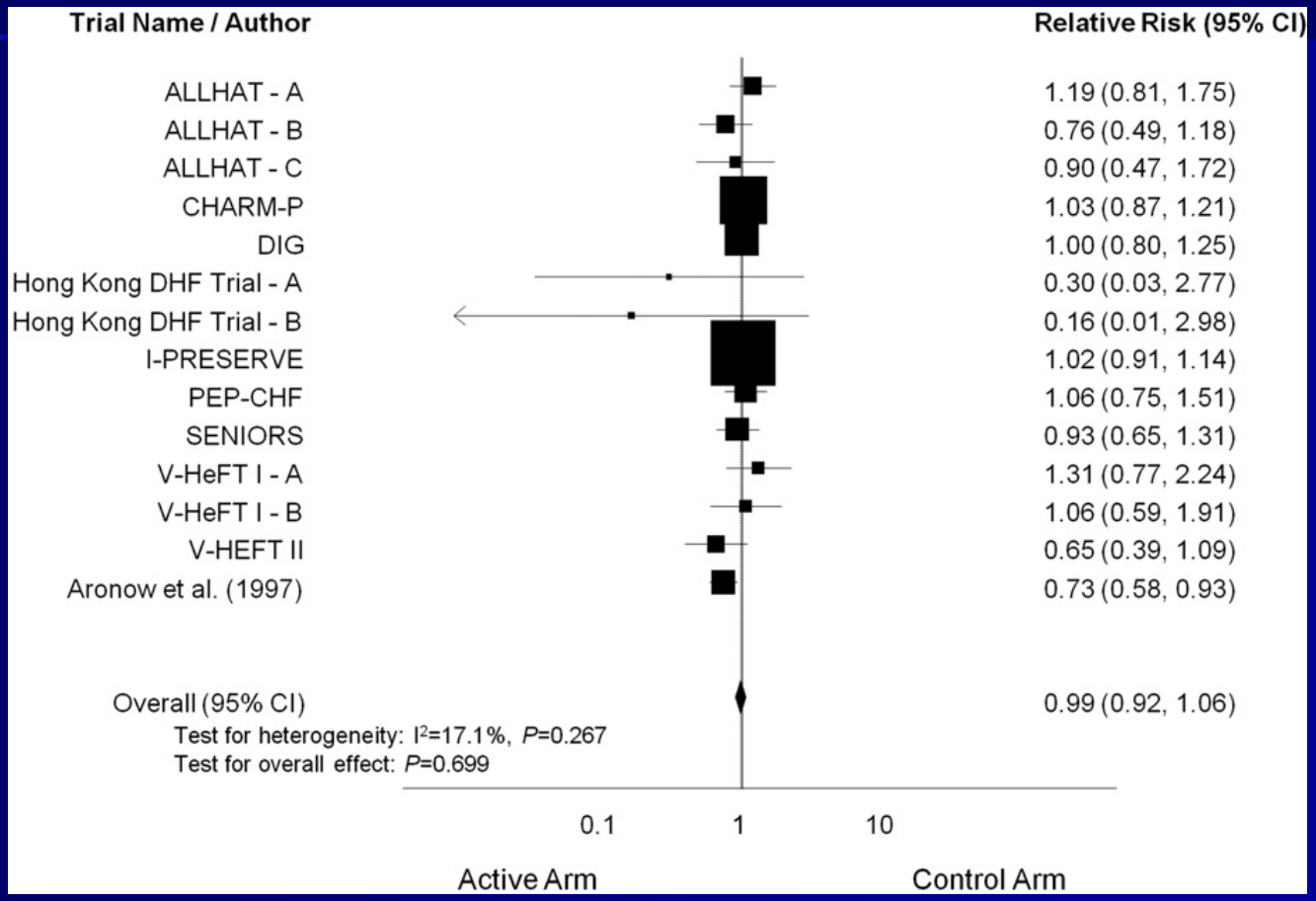
A large NIH-funded, randomized, placebo-controlled trial that is currently ongoing in patients with HF and preserved LV function.

Preliminary results show:

- Increase in exercise capacity
- Improvement in arterial stiffness

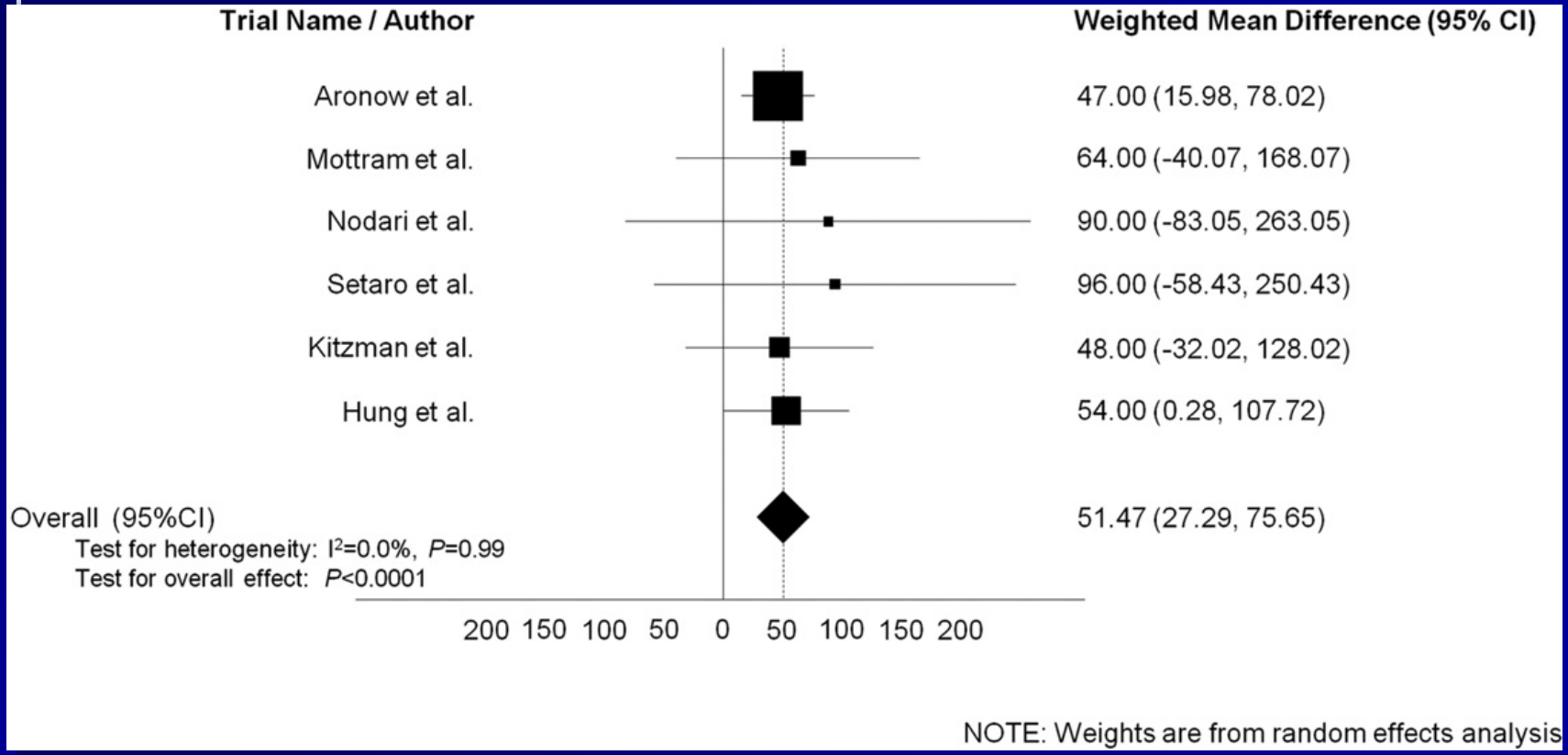
in the sildenafil group

Effect on mortality



Holland et al. JACC 2011

Effect on exercise capacity



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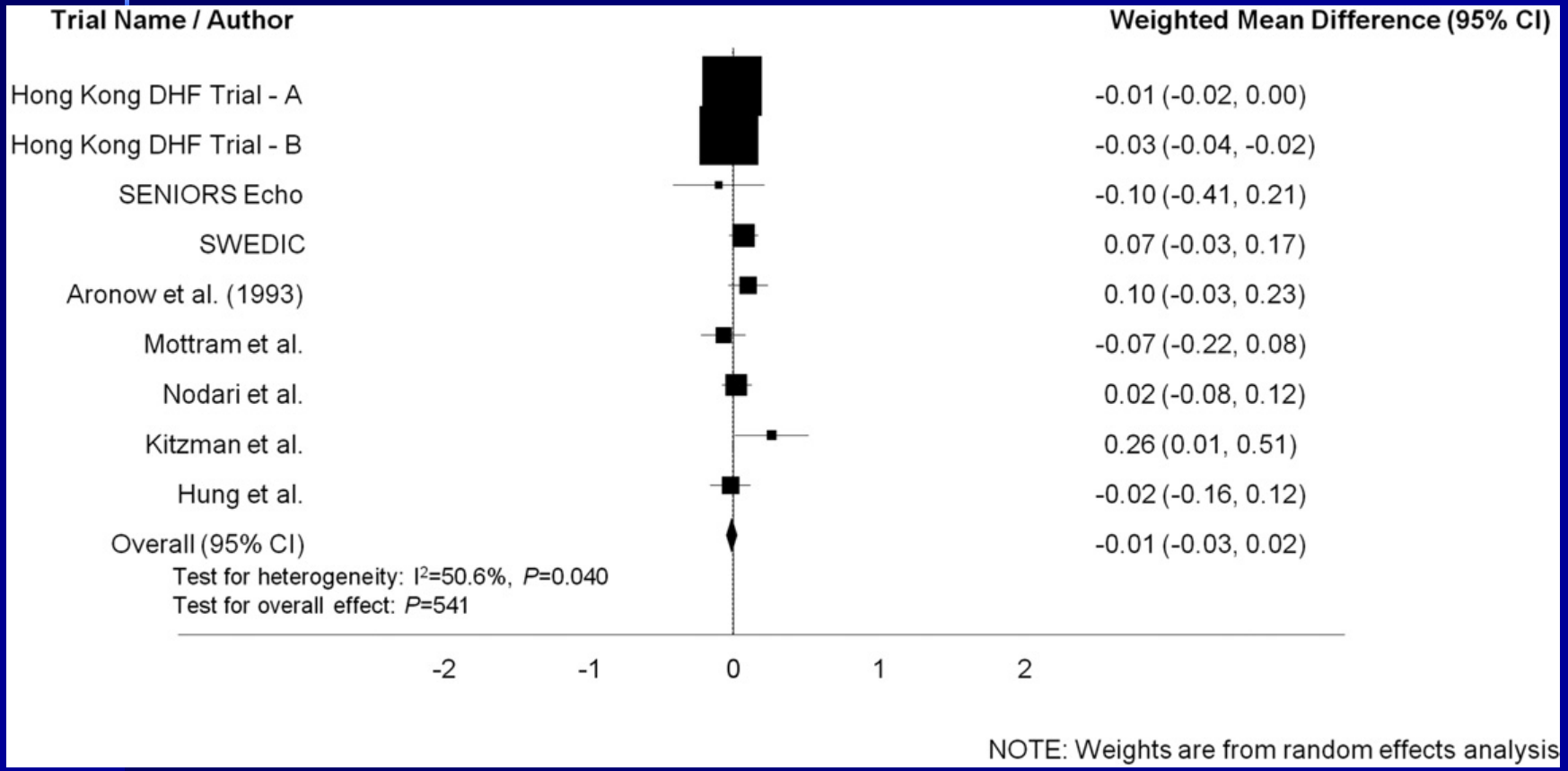
Effect on diastolic function



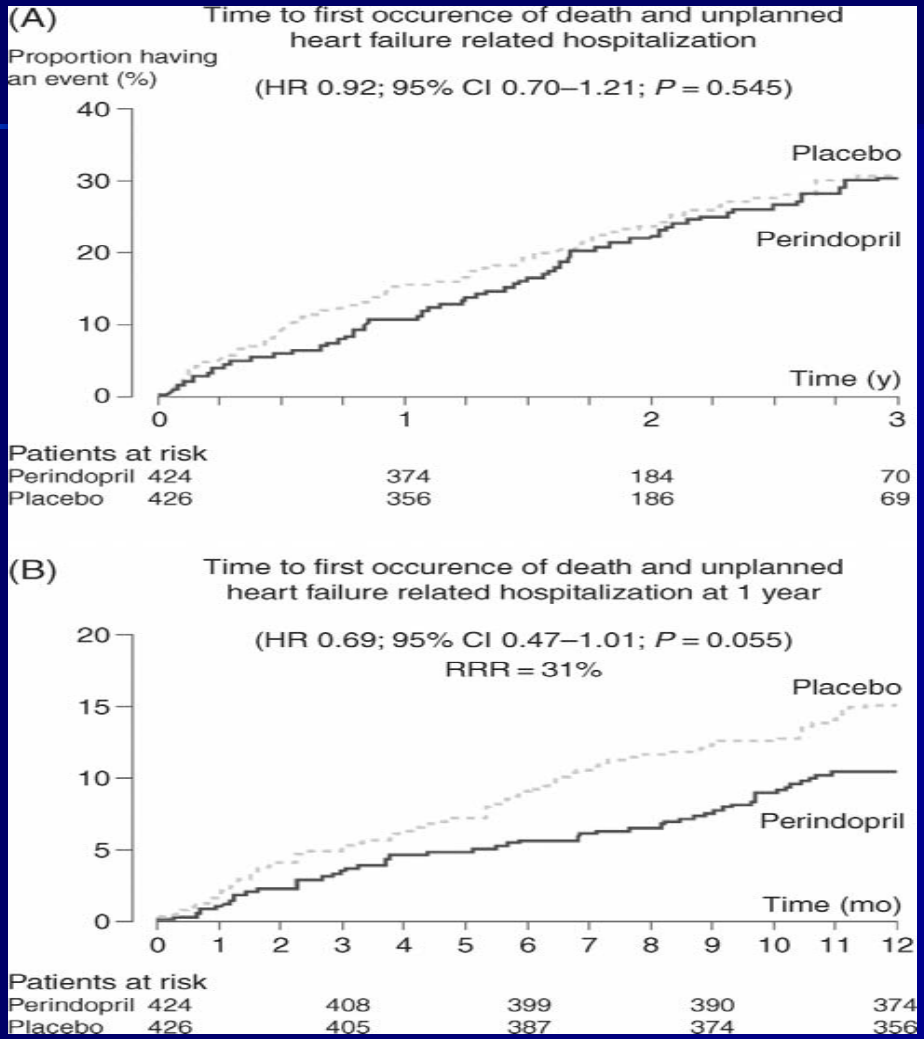
Holland et al. JACC 2011

Conclusions

- HFpEF is a frequent clinical entity and should not be overlooked especially in specific populations
- Pure diastolic heart failure does not exist, systolic and diastolic abnormalities coexist
- Treatment should target the underlying disease
- In contrast to HFREF, the prognosis of HFNEF failed to improve over the last 3 decades, despite similar use of ACEIs, ARBs, and beta-blockers in both conditions
- Meta-analysis of drug trials in HFpEF reveals significant improvement in symptomatic status measured by exercise capacity in the absence of changes in diastolic function or mortality benefits
- Further research is needed in order to find new compounds based on the pathophysiology of the disease

- **Randomised controlled trials of HF-PEF**

(A) Kaplan–Meier curves showing time to first occurrence of the primary endpoint, all-cause mortality or unplanned heart failure related hospitalization, for the entire duration of the study.



Cleland J G et al. Eur Heart J 2006;27:2338-2345

European Heart Journal

Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet2003;362:777-81

candesartan in HF-PEF and an ejection fraction of >40%

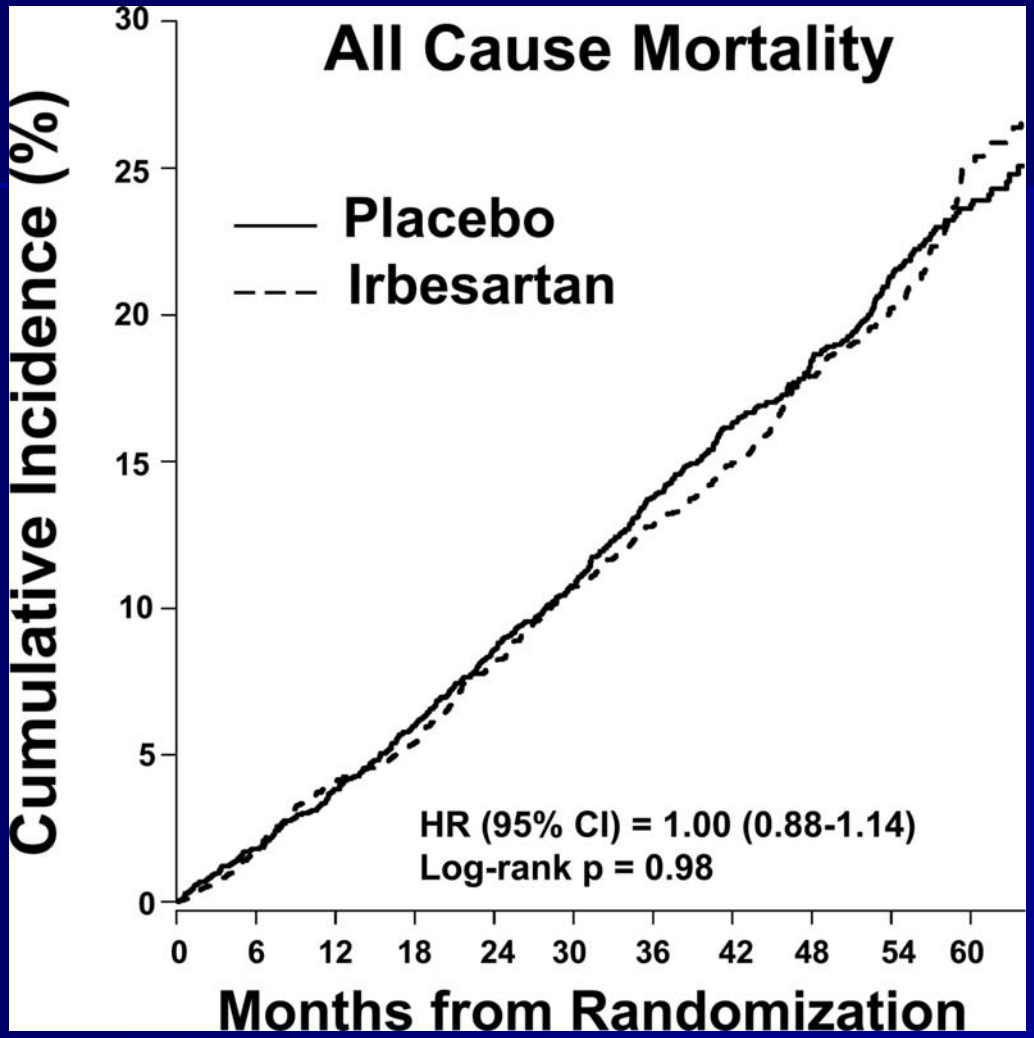
- compared with placebo did not reduce the composite outcome of cardiovascular death or admission to hospital for heart failure (0.89; 0.77 to 1.03)
- less worsening of symptoms of heart failure

Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med2008;359:2456-67.

irbesartan in HF-PEF and an ejection fraction of ≥45%

- compared with placebo did not reduce the composite outcome of all cause death or admission to hospital for cardiovascular causes (hazard ratio 0.95; 0.86 to 1.05)

Cumulative incidence of all cause mortality rate in I-Preserve patients treated with placebo vs irbesartan



Zile, M. R. et al. Circulation 2010;121:1393-1405

Circulation

Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial.

Circulation2006;114:397-403.

Digitalis in HF-PEF and an ejection fraction of >45%

- compared with placebo did not reduce the composite outcome of death from heart failure and admission to hospital (0.82; 0.63 to 1.07) or admission to hospital alone for worsening heart failure (0.79; 0.59 to 1.04

Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J2005;26:215-25.

nebivolol in elderly patients with an ejection fraction of >35%

- compared to placebo did not reduce the composite outcome of all cause death or admission to hospital for cardiovascular causes (hazard ratio 0.82; 0.63 to 1.05)

OTHER DRUGS IN HFPEF

- No large trial has yet evaluated the role of aldosterone antagonists, direct vasodilators, calcium channel blockers, antiarrhythmics, antiplatelets, anticoagulants, cardiac resynchronization treatments, or implantable cardioverter defibrillators in patients with HF-PEF.
- A multicentre, international, randomised, double blind placebo controlled trial of aldosterone antagonist treatment (the TOPCAT trial, www.topcatstudy.com/) is under way