Optimal treatment of heart failure with preserved LV systolic function (HF-PSF)

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What is HF-PSF?

- Definition of HF-PSF:

  HF with EF > 45 -50%

- But, still controversial in both pathology & terminology

Is LV systolic function really preserved in HF-PSF?

EF is imperfect to assess LV systolic function

- Outcome data of volume reduction
- Load dependent

  preload: high EF ≠ good contractility in severe MR

  afterload: low EF ≠ poor contractility in severe AS
- Not reflect intrinsic muscle function

Technical Pitfalls of EF

- Identification of endocardial border
- Rhythm

  beat to beat variation in AF or VPC
- Load dependent
- Geometry of LV

  reduced midwall shortening in LVH

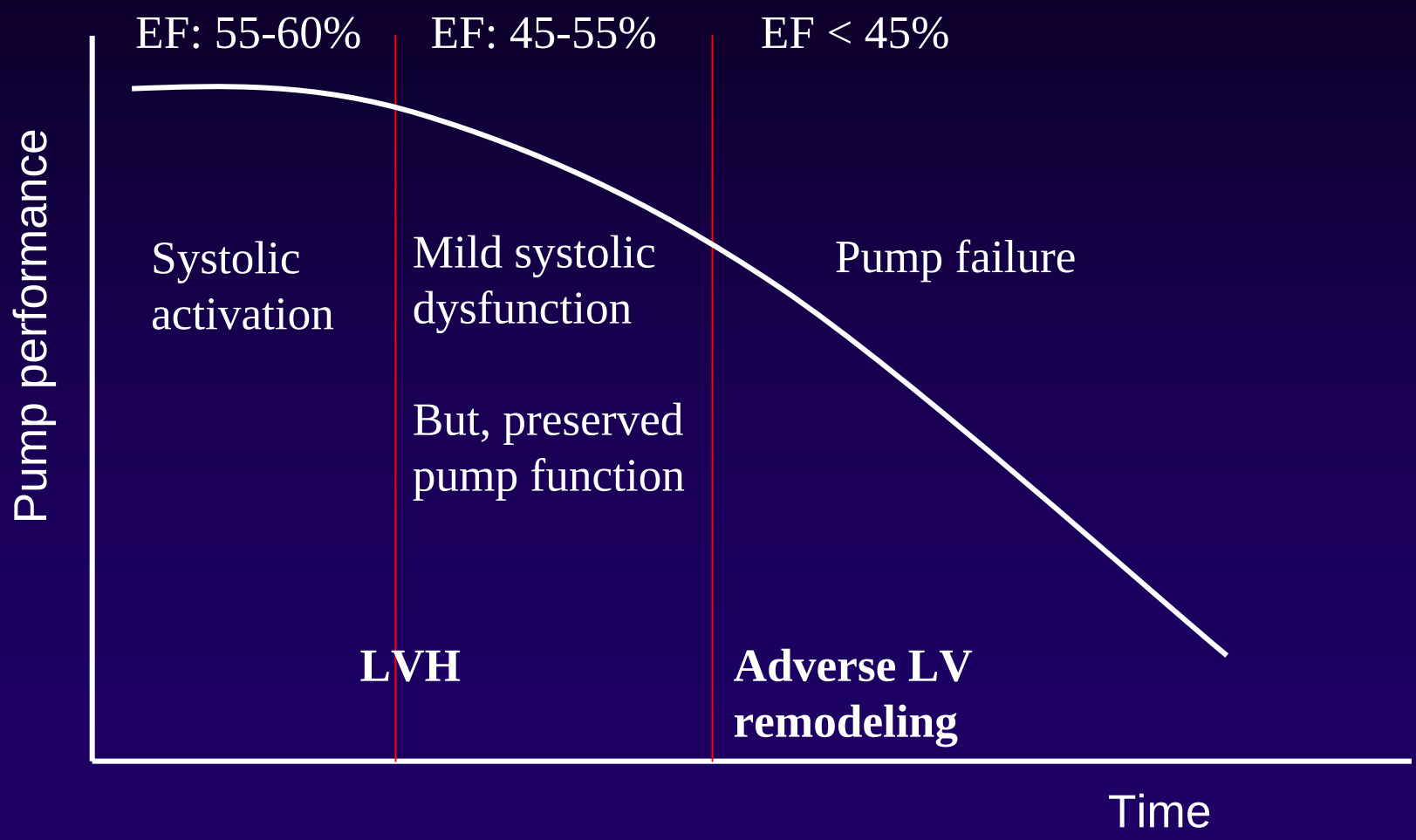
If LV systolic function is preserved, HF-PSF = Diastolic HF ?

Causes of HF-PSF

- Diastolic HF: pure DHF + DHF with subtle SHF
- Valvular HD
- Pericardial disease
- HF due to circulatory cause
- Cor pulmonale

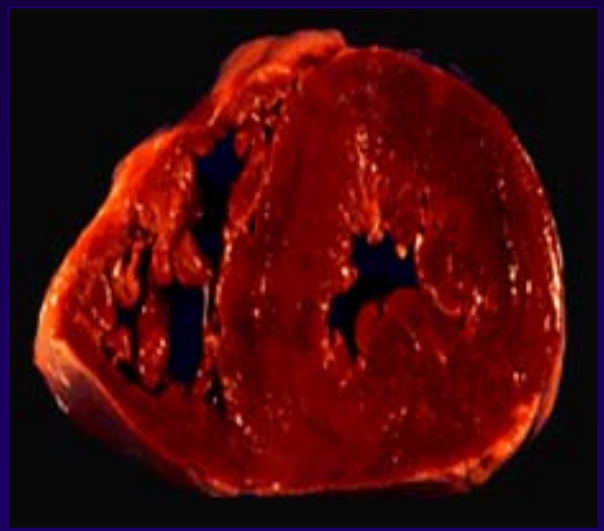
HF-PSF as a hybrid within the spectrum of HF phenotype

General course of HF

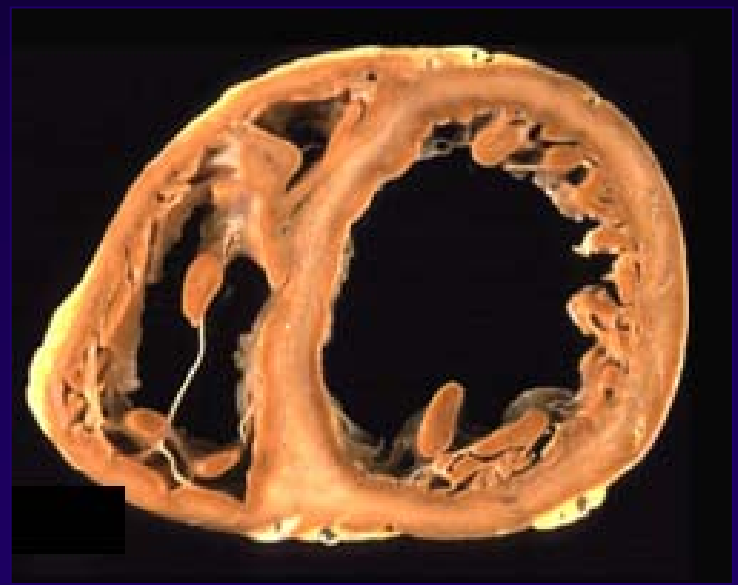


Brutsaert DL ACC 2005

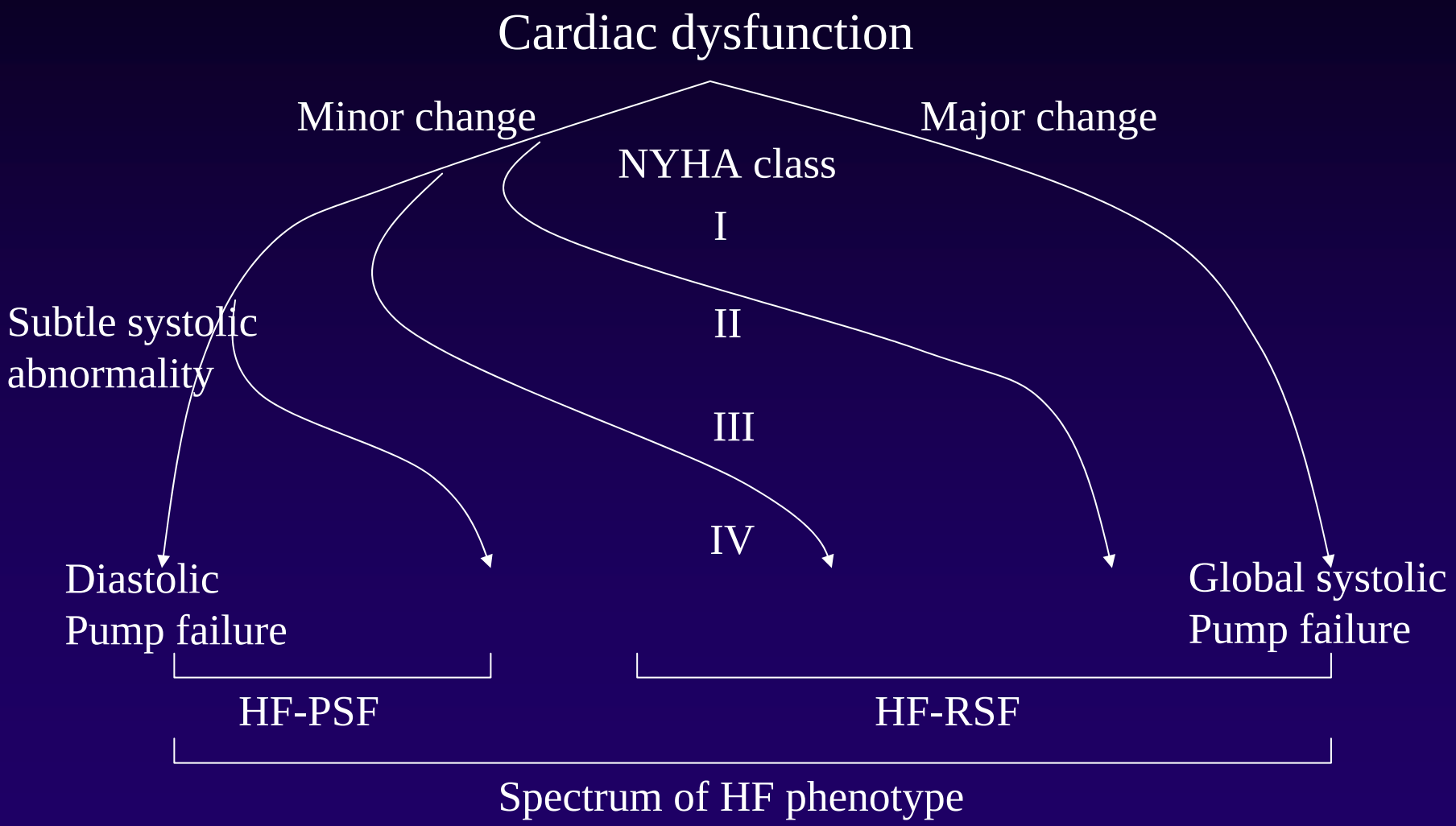
Preserved left ventricular systolic function



Reduced left ventricular systolic function



Spectrum of HF phenotype



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Stages of HF from ACC/AHA Guideline

Stage A: identifies the patient who is at high risk for developing HF

Stage B: refers to a patient with structural disorder of the heart but who has never developed symptoms of HF

Stage C: denotes the patient with past or current symptoms of HF

Stage D: designates the patient with end stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

- Pure DHF or advanced SHF is the extreme of either side of HF
- HF-PSF is one of the hybrids within the spectrum of HF phenotype

Clinical significance of HF-PSF

- Not a minor clinical SD any more

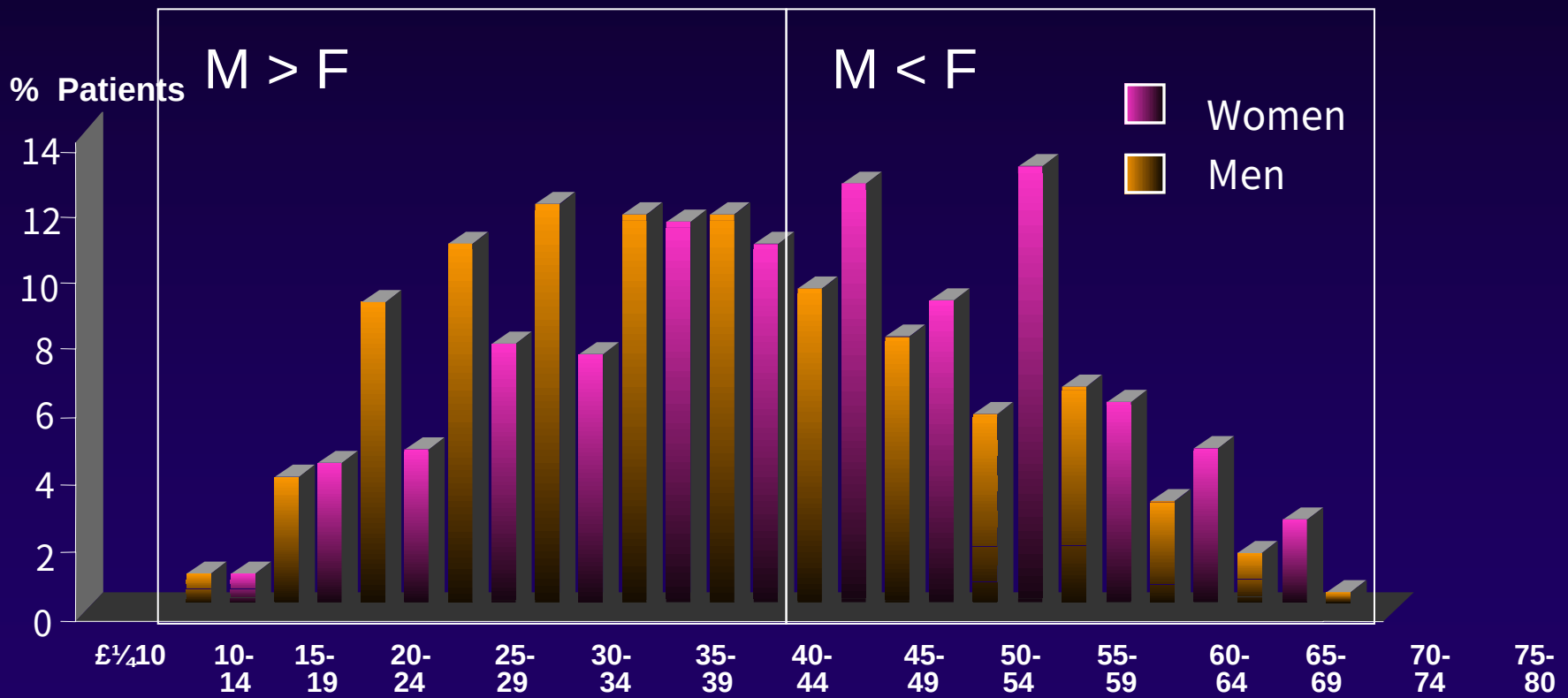
  30-60% of HF

- Lower mortality than HF-RSF, but still 30-45% mortality during 4-5 year

- Comparable degree of morbidity

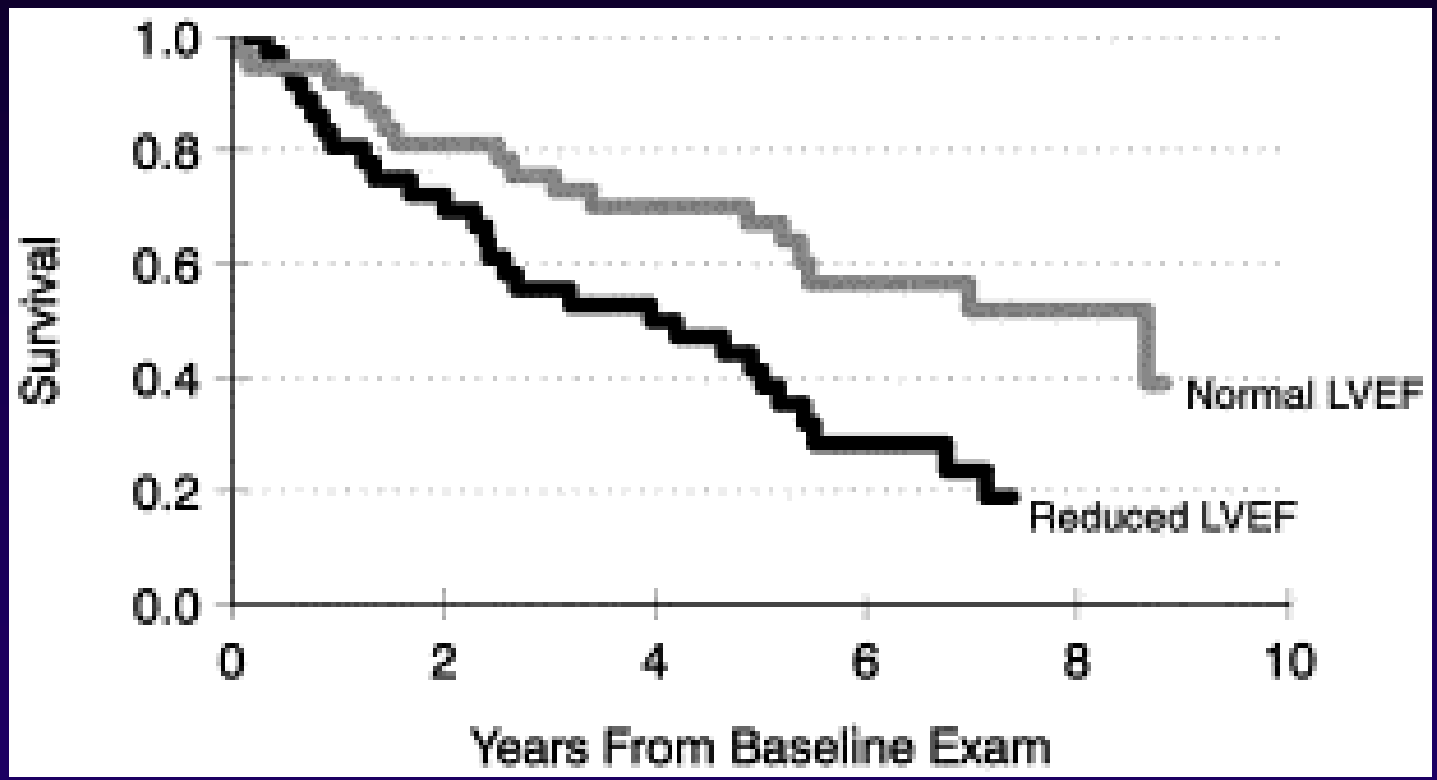
Euroheart Failure: Distribution of left ventricular ejection

11,322 patients from 115 hospitals in 24 countries



Cleland et al, EHJ 2003

Kaplan-Meier survival plots of CHF patients with normal and reduced LVEF



Vasan et al. JACC 1999

Study–Year of Publication	No. of Patients (% DHF)	Mean Age (yrs)	CHF Diagnosis	Mortality–SHF	Mortality–DHF	p Value SHF vs. DHF Mortality
Studies where mean age <65 yrs						
Warnowicz–1983 (22)	39 (41%)	DHF 63 ± 9 SHF 66 ± 11	Acute pulmonary edema	30% (9 mo)	25% (9 *mo*)	NS
Kinney–1989 (11)	91 (48%)	All 64 ± 10	2 major or 1 major + 1 minor§	Median SURVIVAL = 11 mo	Median SURVIVAL = 26 mo	0.01
Cohn–1990 (12)	623 (13%)	DHF 60 ± 7 SHF 58 ± 8	VO_2max <25/ml/kg/min	19% (annualized)	8% (*annualized*)	0.0001
Ghali–1992 (13)	78 (28%)	DHF 60 ± 11	2 major or 1 major + 2 minor§	24% (1 yr)	22% (1 *yr*)	0.04
		SHF 59 ± 14		46% (2 yr)	26% (2 *yr*)	
Studies where mean age >65 yrs						
Aronow–1990 (14)	166 (40%)	DHF 84 ± 6	Rales + CXR vascular congestion	47% (1 yr)	22% (1 *yr*)	0.001
		SHF 81 ± 8		71% (2 yr)	38% (2 *yr*)	
Taffet–1992 (15)	94 (43%)	DHF 82 ± na	Framingham	≈24% (1 yr)	≈ 24% (1 *yr*)	NS
		SHF 83 ± na		≈42% (2 yr)	≈ 30% (2 *yr*)	NS
McDermott–1997 (16)	192 (46%)	DHF 73 ± na SHF 72 ± na	Framingham	35% (27 mo)	35% (27 *mo*)	NS (0.78)
Kupari–1997 (17)	41 (51%)	ALL ≈ 80	Other†	54% (4 yr)	43% (4 *yr*)	NS
Permenkil–1997 (19)	501 (34%)	DHF 81 ± 6	Other‡	38% (1 yr)	28% (1 *yr*)	p = 0.045
		SHF 78 ± 6		19% (3–12 mo)	17% (3–12 *mo*)	p = NS
Senni–1998 (5)	137 (43%)	DHF 78 ± 12 SHF 74 ± 13	Framingham	24% (1 yr) 42% (3 yr)	24% (1 *yr*) 42% (3 *yr*)	NS (0.369)
McAlister–1999 (18)	566 (21%)	DHF 69 ± 14 SHF 65 ± 14	Framingham	17% (1 yr) 38% (3 yr)	12% (1 *yr*) 42% (3 *yr*)	NS (0.25)
Vasan–1999 (4)	73 (51%)	DHF 72 ± 9 SHF 74 ± 7	Framingham	64% (5 yr)	32% (5 *yr*)	p = 0.023 Adj*p = 0.13
Ansari–2001(abstr) (23)	376 (27%)	ALL 72 ± na	Framingham	20% (20 mo)	20% (20 *mo*)	NS

Treatment of “HF-PSF”

The theory — Hundreds of papers

The evidence — Virtually none!!

Theoretical treatment of HF-PSF

- Sx targeted Tx

  Consider pathophysiology

- Disease targeted Tx
- Mechanism targeted Tx

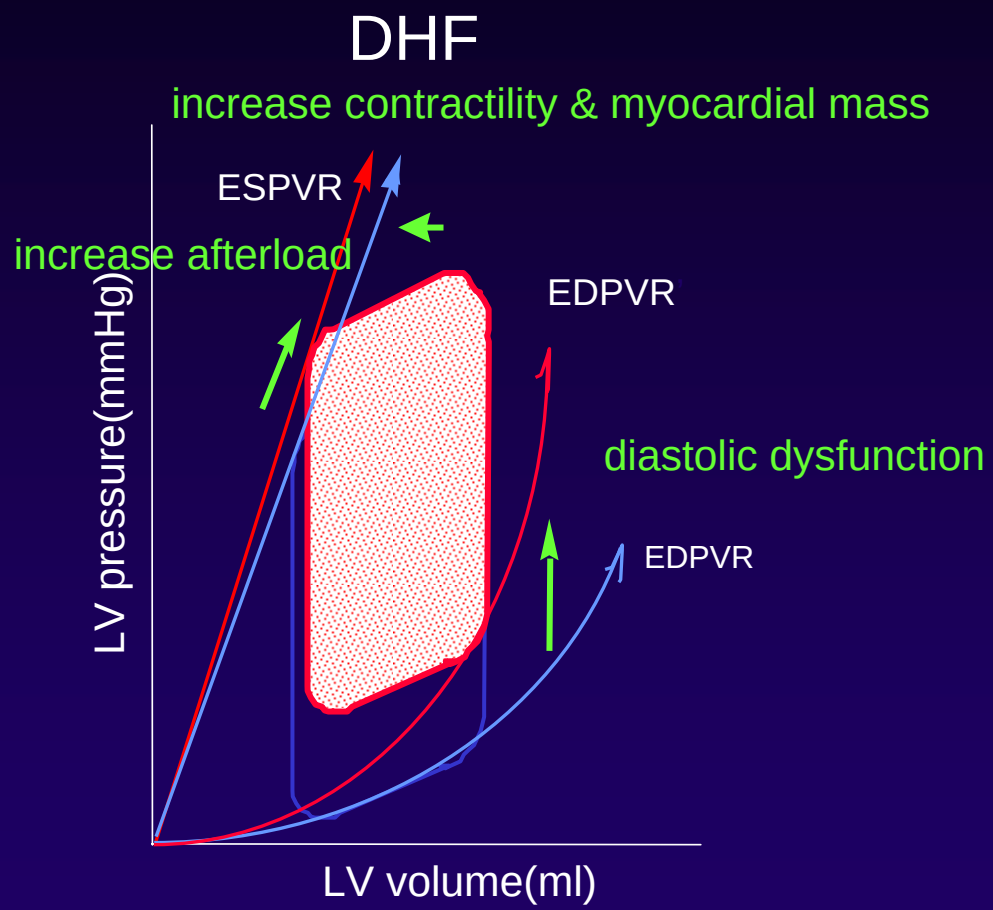
Sx targeted Tx

Decrease diastolic pressure

- Reduce LV volume with diuretics or nitrate
- Enhance LV relaxation
- Maintain atrial contraction: keep sinus rhythm
- Prevent tachycardia or rate control in A fib. with HR limiting Ca antagonist or beta blocker:
- Use inotropic agents with caution (prevent excess contractility)

Consider Pathophysiology

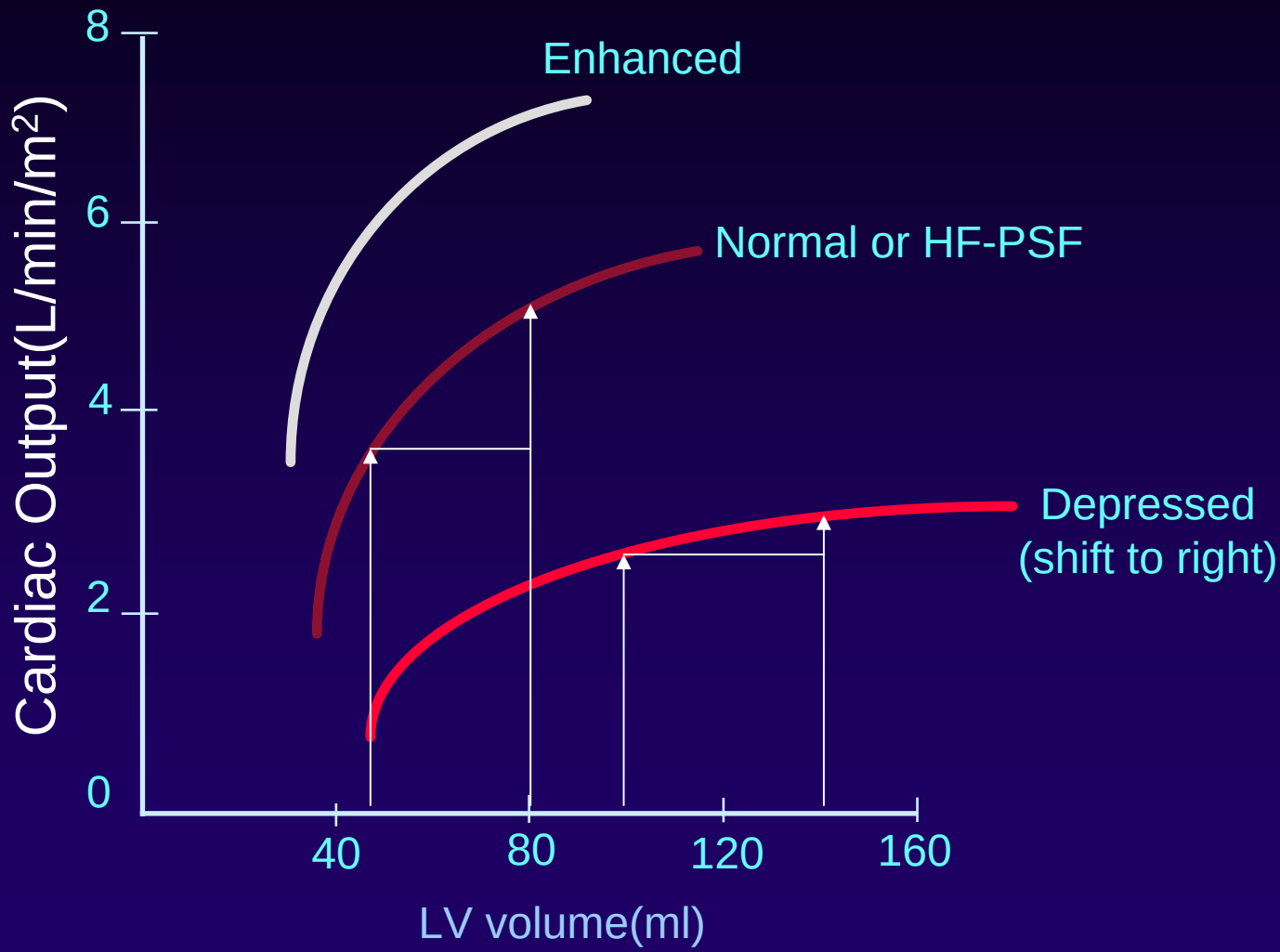
(Pressure-Volume Loop in HF-PSF)



Even small volume reduction may be quite effective for Sx improvement

Consider Pathophysiology

(Frank-Starling LV Function Curve)



Even small volume reduction may result in significant BP decrease

Disease targeted Tx

Resolve causative and aggravating factor

- HiBP: JNC targeted BP control with ACE I or ARB
- AS or LVOT obstruction: Surgical resolution

  prevent or regress LVH

  reduce mortality and morbidity
- CAOD: prevent / treat myocardial ischemia

Mechanism Targeted Treatement

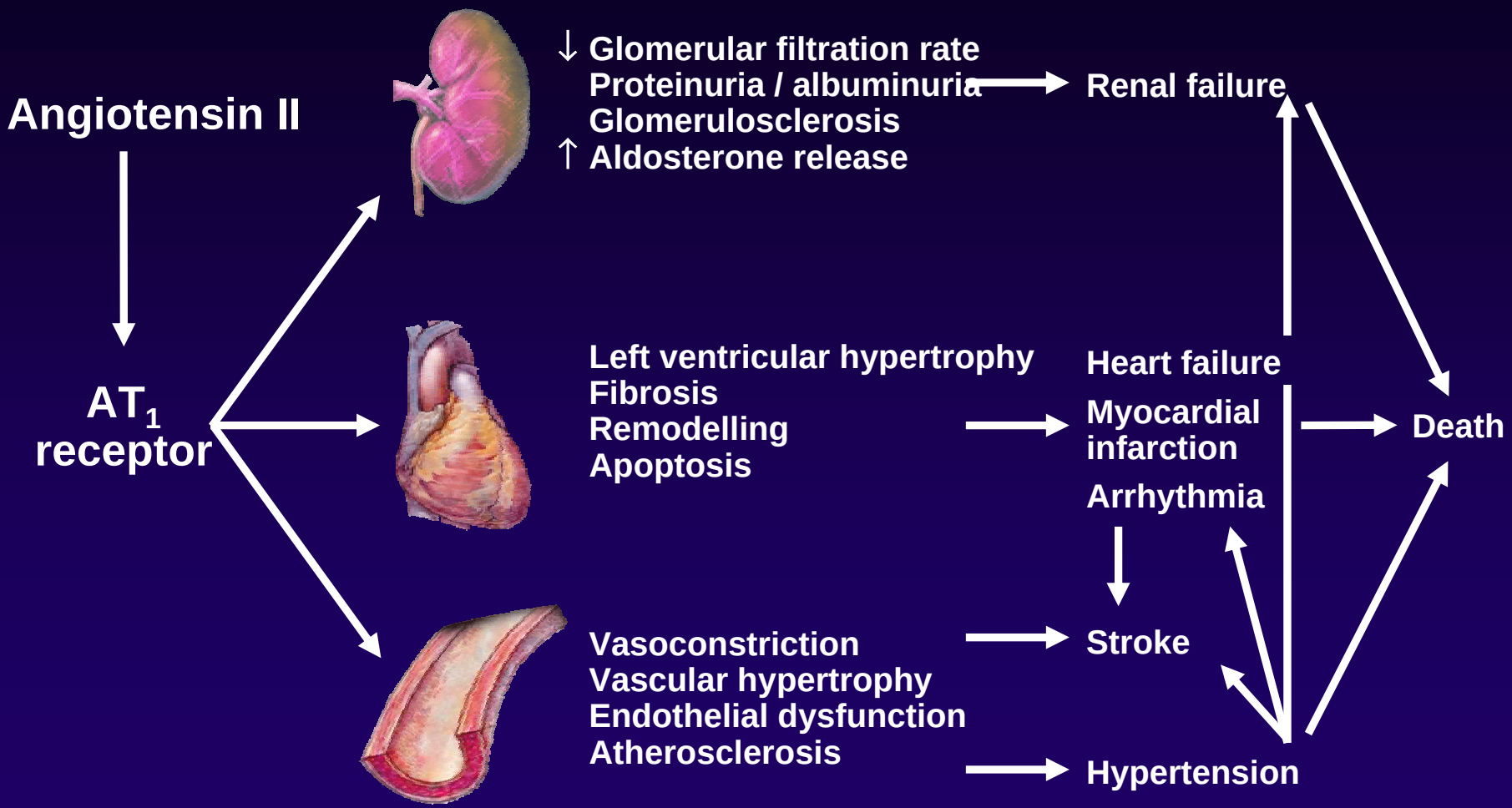
- Modify myocardial and extramyocardial mechanism
- Modify intracellular and extracellular mechanism

Blunt neurohormonal activation

Prevent / regress LVH

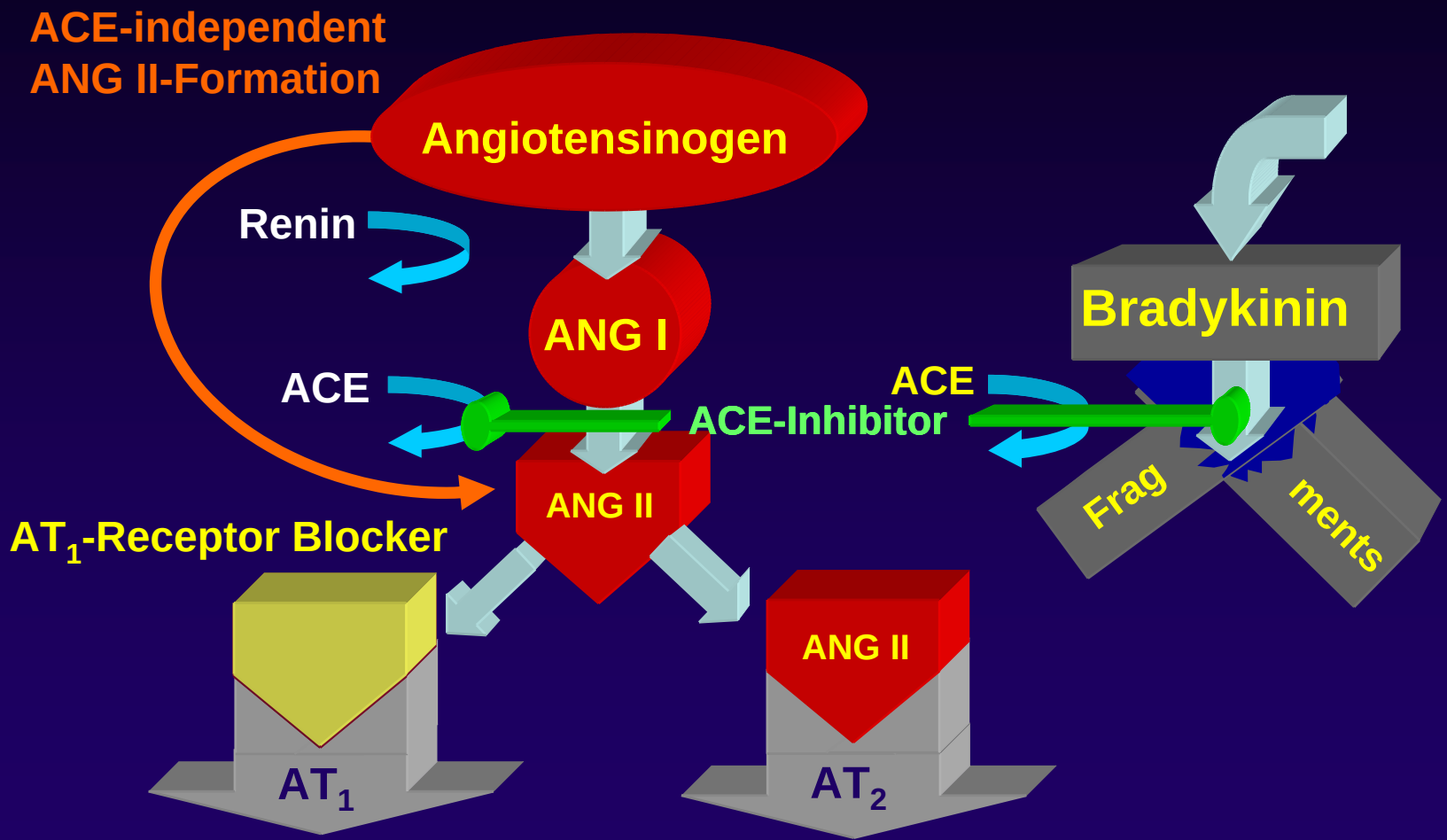
Angiotensin II

Direct and indirect effects in organ damage



Chung, Unger. Am J Hypertens 1999;12:150S–156S

Inhibition of the Renin Angiotensin System



Differences between pharmacological treatment of HF-RSF and HF-PSF

	HF-RSF	HF-PSF
Diuretics	high dose	smaller dose
ACE, ARB	increase CO prevent LV dilatation need titration	BP control prevent, regress LVH yes or no titration
B blocker	B receptor ↑ need titration	slow HR, LV filling ↑ no titration
Ca antagonist	contra-Ix	slow HR, improve relaxation

Treatment of “HF-PSF”

The theory — Hundreds of papers

The evidence — Virtually none!!

Lack of Clinical Evidence

All evidence based therapy is for patients with *low* LVEF CHF

How should CHF with “preserved LV systolic function” (or “diastolic dysfunction”) be treated?

Randomised trials in HF-PSF

Symptoms/functional capacity as endpoints

Published randomised trials of treatment of “diastolic heart failure”

- Calcium channel blocker

  2 placebo-controlled trials with Verapamil (n ~20)

  Improve Sx, exercise tolerance

  Serato et al. Am J Cardiol 1990
  Hung et al. Int J Clin Pract 2002

- ACE inhibitor

  Philbin et al. Am Heart J 1997

  350 pts of EF≥ 40% but non-randomised

  Aronow et al. Am J Cardiol 1993 (Enalapril)

  21 pts of >80 yrs, EF≥ 50%

  improve CT ratio, EF, NYHA class and exercise tol.

  too small No, uncontrolled, not double-blind

Randomised trials in HF-PSF

Morbidity/mortality outcomes as endpoints

Randomised trials of treatment of HF-PSF

Completed

- Beta-blocker (propranolol)
- Digitalis glycoside (digoxin)
- ARB (candesartan)

Ongoing

- ACE inhibitor (perindopril)
- Beta-blocker (nebivolol)
- ARB (irbesartan)

Proposed

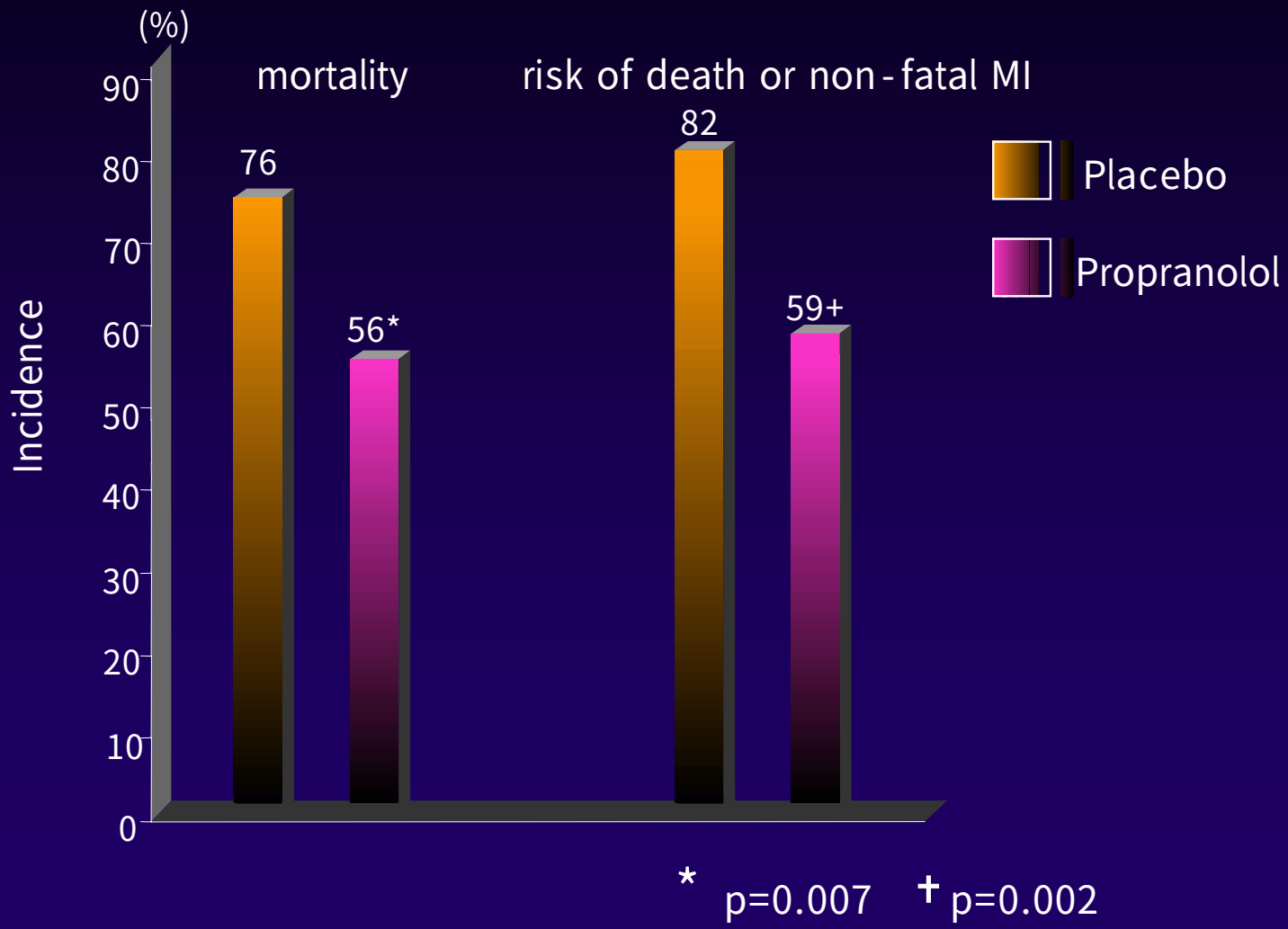
- Aldosterone-blocker (spironolactone/eplerenone?)

Beta-blocker - propranolol

- Randomised trial: *lack of placebo (control) group*
- 158 patients ≥62 (mean 81 yrs) with NYHA II/III CHF, >2 months diuretic therapy, prior Q-wave (>6months) MI and LVEF >0.40
- Excluded valve disease, COPD
- Propranolol 30mg tid or no propranolol for 32 months

Aronow et al, Am J Cardiol 1997;2:207-9

Effects of propranolol in HF-PSF



Digoxin in HF-PSF

GOOD?

Reduces HR and favorable autonomic actions

- sympatho-inhibitory
- pro-parasympathetic
- suppress RAAS

BAD?

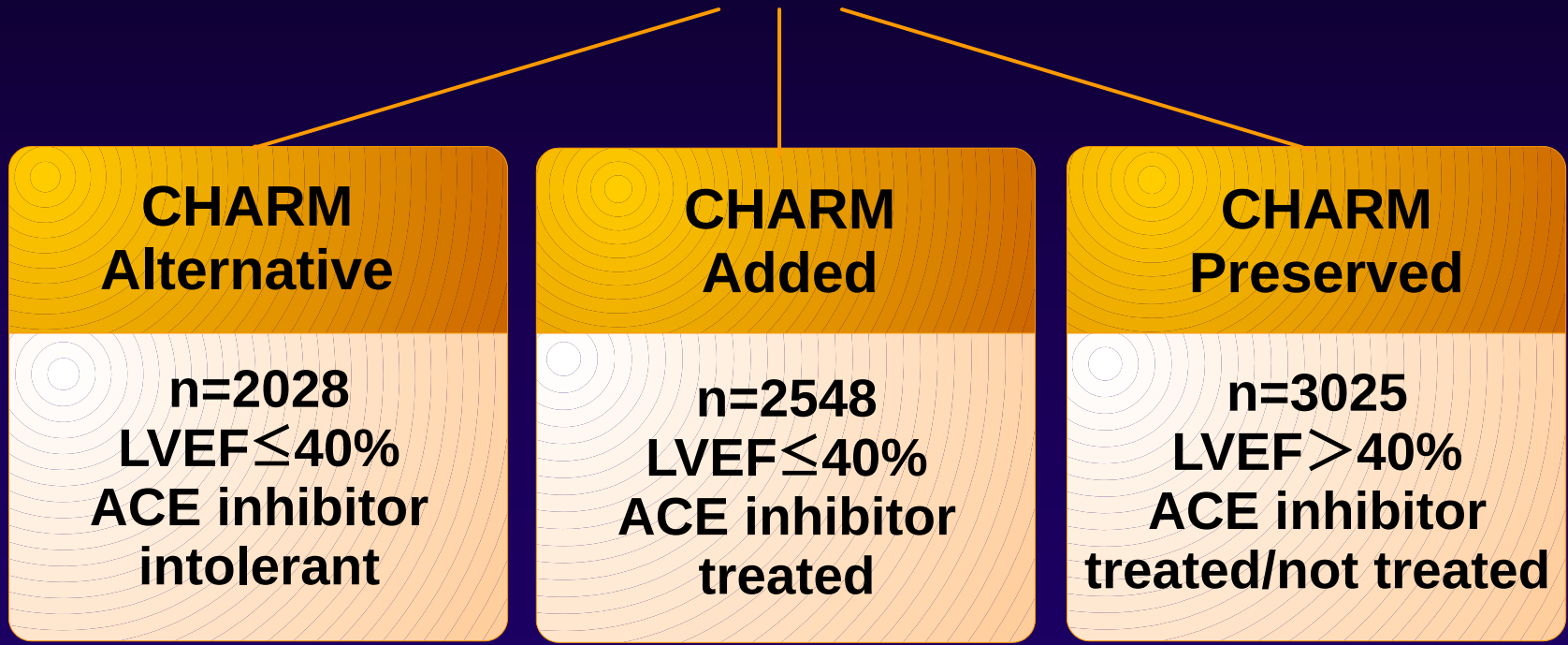
Increases intracellular calcium and impairs myocardial relaxation?

Digitalis investigation group

- 7,788 patients with CFH
- NYHA Class I-IV
- Sinus rhythm
- LVEF ≤0.45 main trial (n=6800)
  LVEF ＞0.45 ancillary trial (n=988)
- *Qualitatively similar effects on mortality/morbidity in the LVEF＞0.45 subgroup*
  No further information

CHARM Program

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

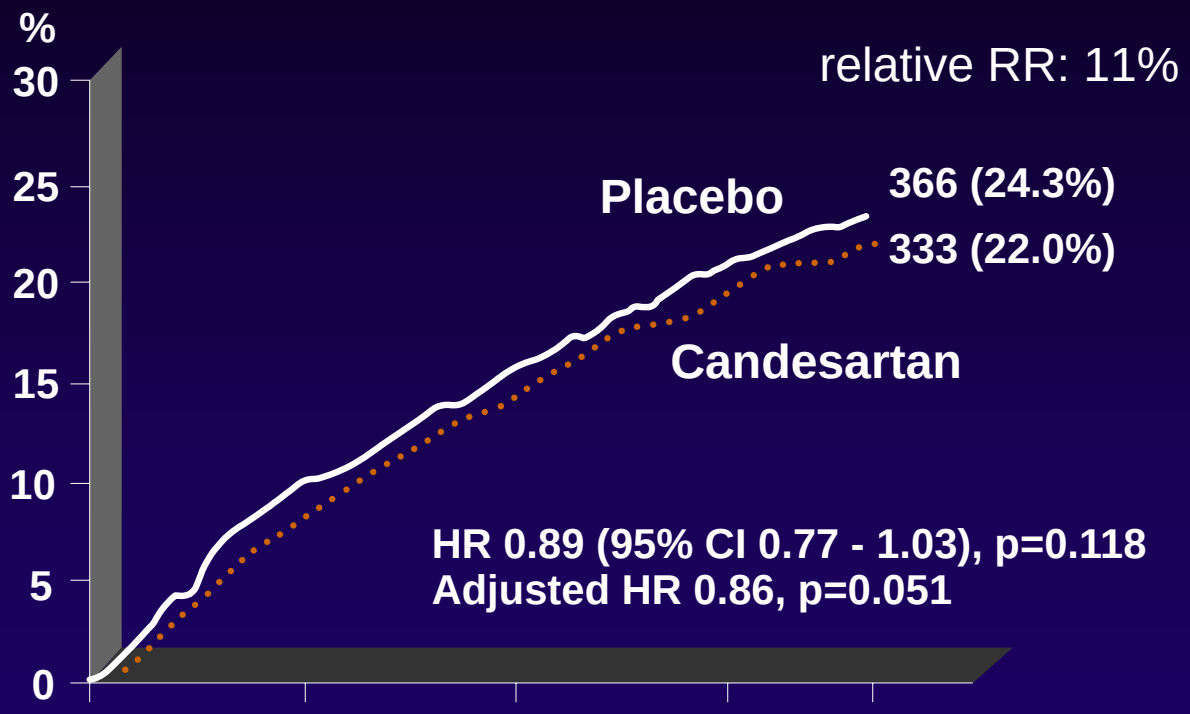


Primary outcome for each trial: CV death or CHF hospitalisation

The first major outcome study in this type of CHF to complete

CHARM-Preserved: Primary outcome

CV death or CHF hospitalisation

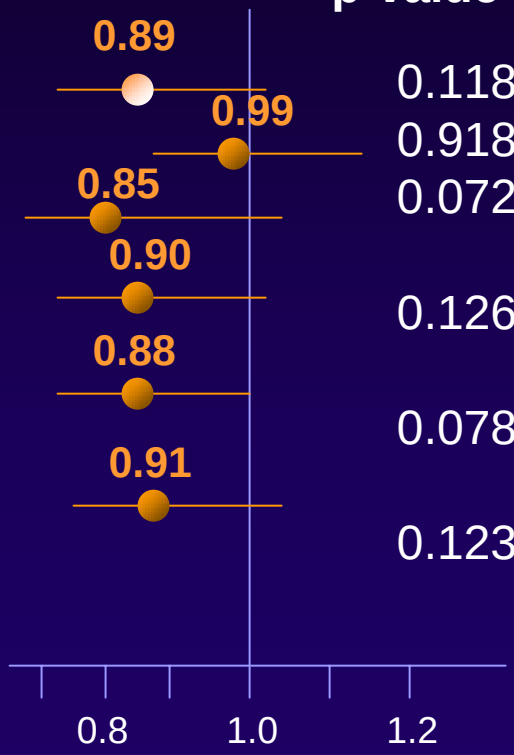


Number at risk	0	1	2	3	3.5
Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

CHARM-Preserved:

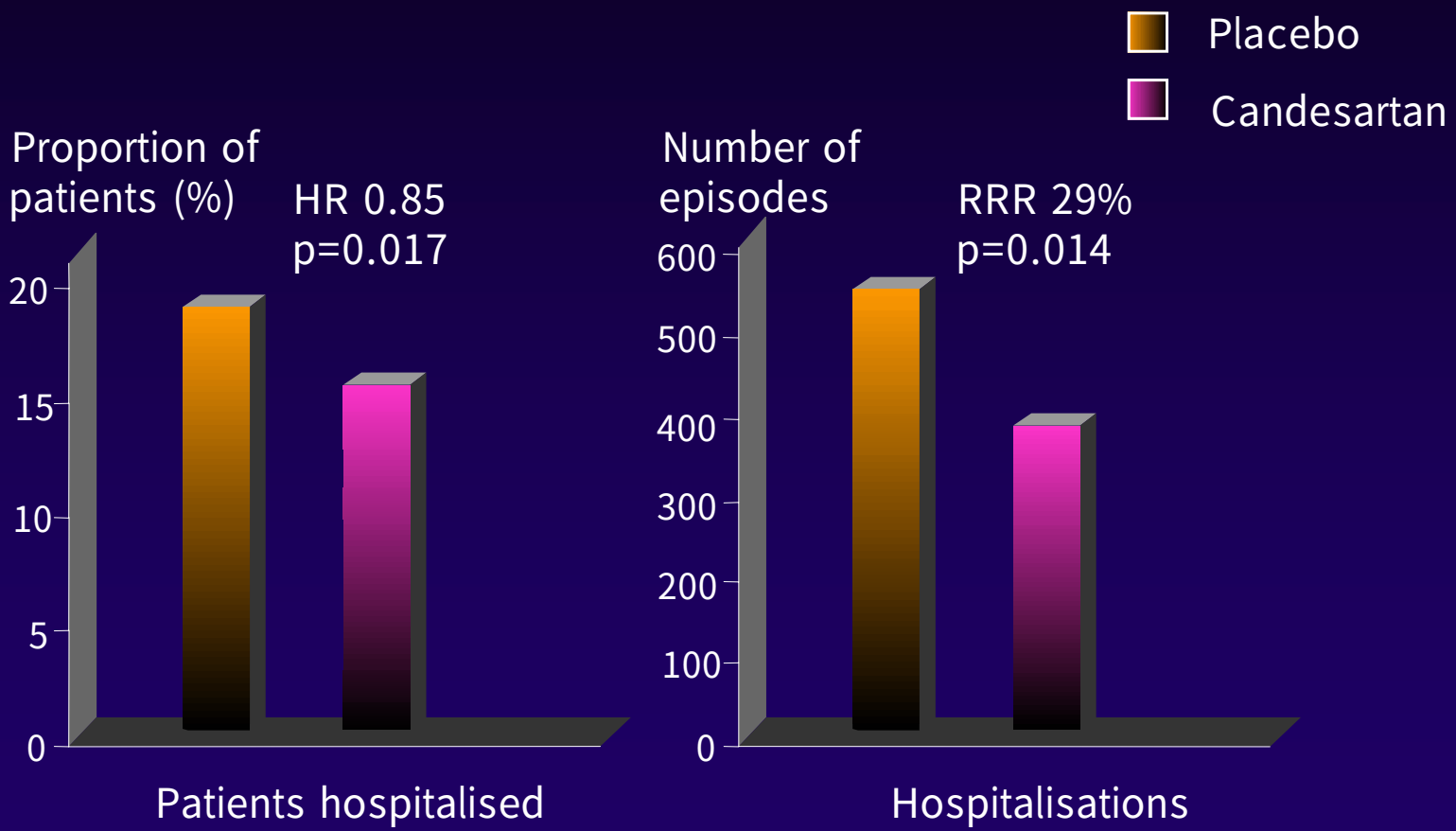
Primary and secondary outcomes

	Candesartan	Placebo	Covariate adjusted p-value	p-value
CV death CHF hosp.	333	366	0.118	0.051
- CV death	170	170	0.918	0.635
- CHF hosp.	241	276	0.072	0.047
CV death, CHF hosp, MI	365	399	0.126	0.051
CV death, CHF hosp, MI, stroke	388	429	0.078	0.037
CV death, CHF hosp, MI, stroke, revasc	460	497	0.123	0.130



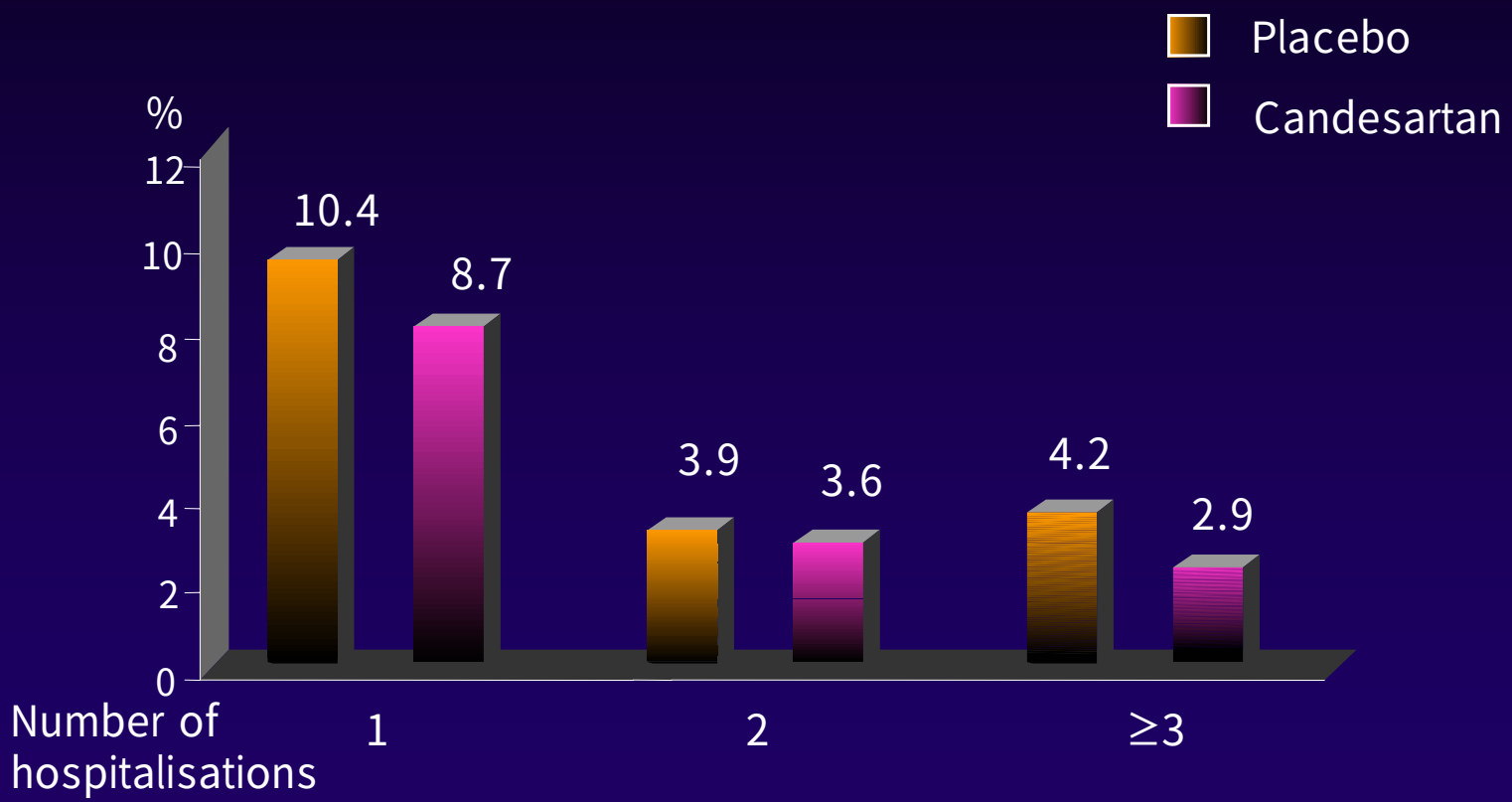
CHARM-Preserved:

Investigator reported CHF hospitalisations



CHARM-Preserved:

Patients with single or multiple CHF hosps.



p=0.014 test for difference in distribution

- CHARM-Preserved, the largest trial of HF-PSF, provided a direct information on Tx of HF-PSF, despite a moderate benefit, that candesartan reduces the number of hospital admission for CHF

ARBs in HF-PSF: why should they work?

- Angiotensin II seems to play a causal role in LVH
- Angiotensin II reduces LV relaxation/increases LV stiffness
- ARBs regress LVH, fibrosis and improve diastolic function

More to Evaluate

- In comparison with ACE-I ?
- Same target dose as HF-RSF ?

  Not need to reduce afterload as much as HF-RSF to increase CO & prevent LV remodeling

  Not need to suppress N-H as much as HF-RSF

  More prominent BP lowering effect in HF-PSF with no association with clinical improvement (CHARM)
- More effective in combination with ACE-I ?

Randomised trials of treatment of HF-PSF

Completed

- **Beta-blocker (propranolol)**
- **Digitalis glycoside (digoxin)**
- **ARB (candesartan)**

Ongoing

- **ACE inhibitor**
  PEP-CHF (perindopril)
  1000 pts of >70yrs, EF ≥ 40%
- **Beta-blocker**
  SENIORS (nebivolol)
  2000/3 pts of >70yrs, EF ≥ 40%
- **ARB**
  I-PRESERVE (irbesartan)
  pts of >60yrs, EF ≥ 45%

Proposed

- **Aldosterone-blocker (spironolactone/eplerenone?)**

Conclusion

- Current recommendations for treatment of *HF-PSF* are based not only on the pathophysiological theory but also sparse data or extrapolations from trials involving related disorders (HF-RSF).
- For evidence based therapy for *HF-PSF*, further large randomized clinical trials, including several ongoing trials, should be initiated and completed in the future.