

Heart failure randomized clinical trials: how we changed standard of care.

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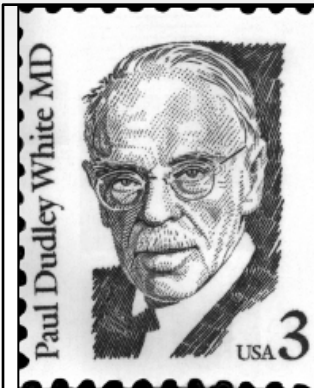
Disclosures:

**Honoraria/Consultancy: Amgen, Astrazeneca, Novartis,
Pfizer, Servier, Vifor**

Research grants: Amgen, Servier

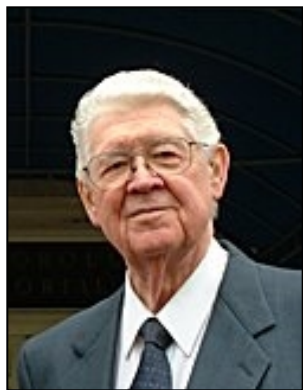
Treatment of heart failure

From two textbooks 1929 and 1974



"...and for all this there is only digitalis and rest..."

Paul Dudley White: Textbook in Cardiology, 1929



J Willis Hurst
1920-2011

Moderately severe heart failure
Decrease physical activity
Institute digitalis
Give thiazide every day plus potassium
If not enough use furosemide and
if insufficient, combine them

J W Hurst: The Heart 3rd edition, 1974



Diuretics to relieve symptoms/signs of congestion^a

GUIDELINES

ESC G
of acut

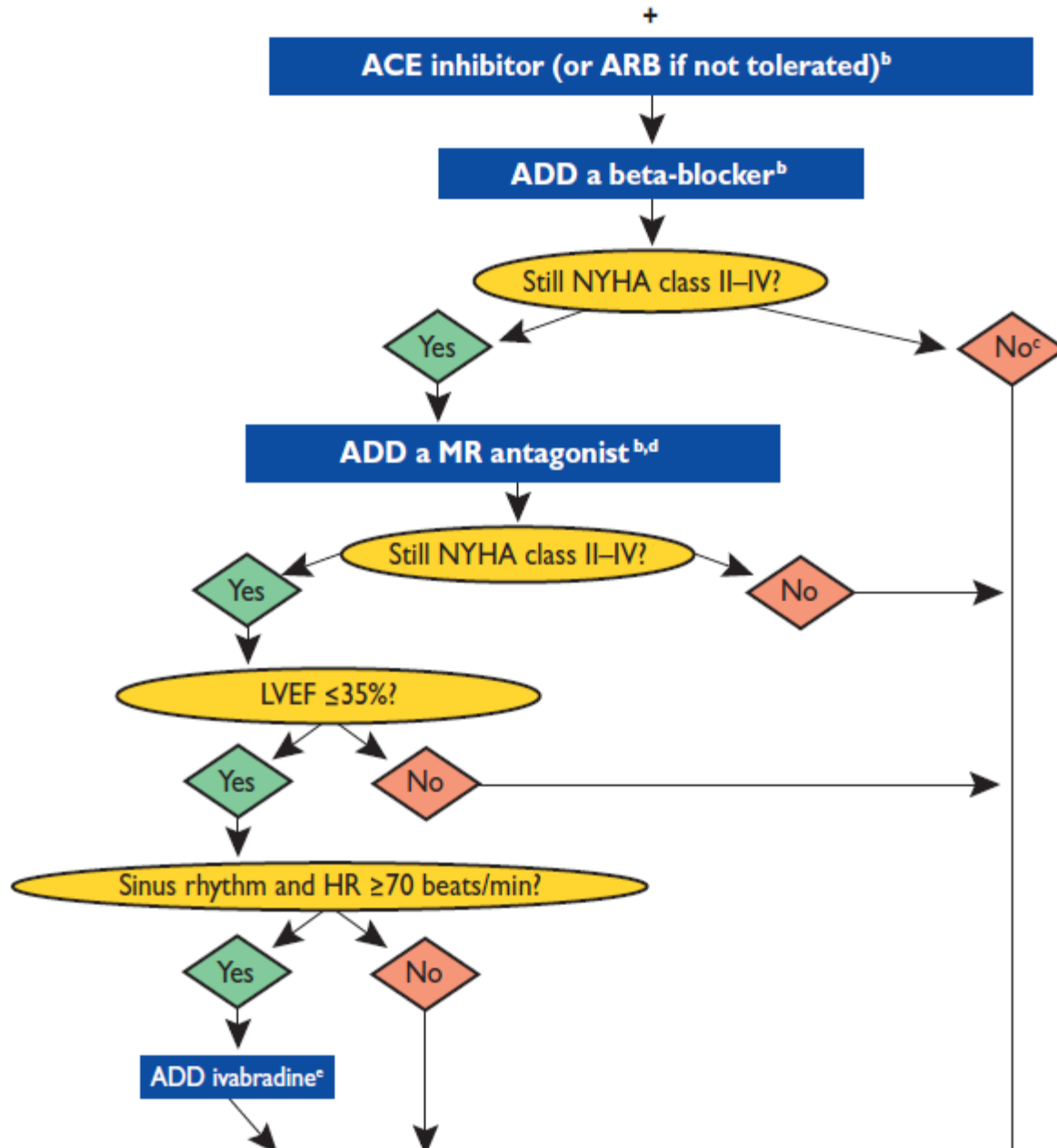
The Task
Chronic I
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Beta-blockade in heart failure

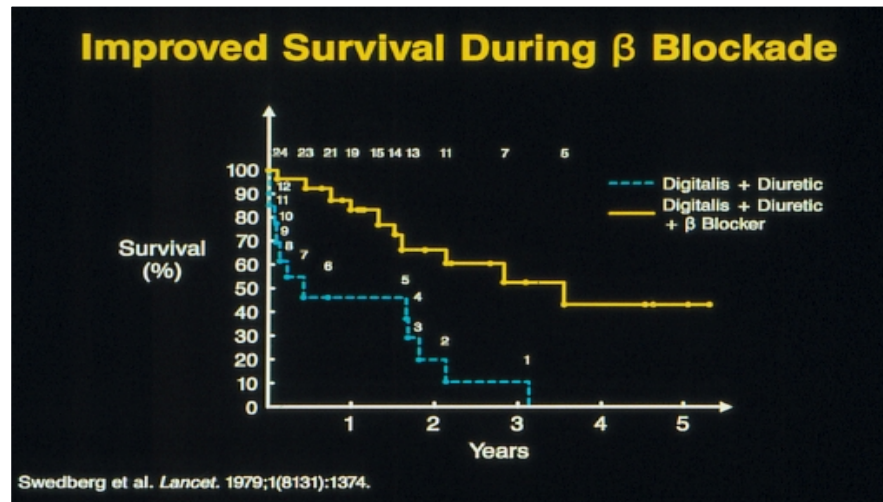
Slow introduction of efficient therapy

- 1975
- 1979

- First report
- Indication improved survival

(Waagstein et al)

(Swedberg et al)

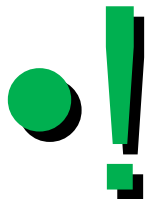


- 1993

•to

- Confirmed in large clinical trials
- carvedilol, bisoprolol and metoprolol

- 1999



ACC/AHA Guidelines for the management of CHF 1995

1376

JACC Vol. 26, No. 5
November 1, 1995:1376-98

ACC/AHA TASK FORCE REPORT

Guidelines for the Evaluation and Management of Heart Failure

Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure)

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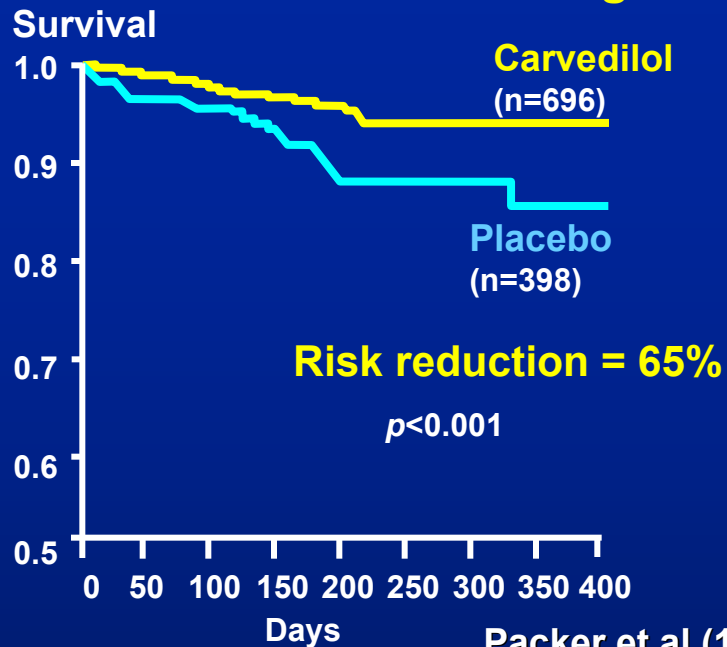
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ACC/AHA Guidelines 1995

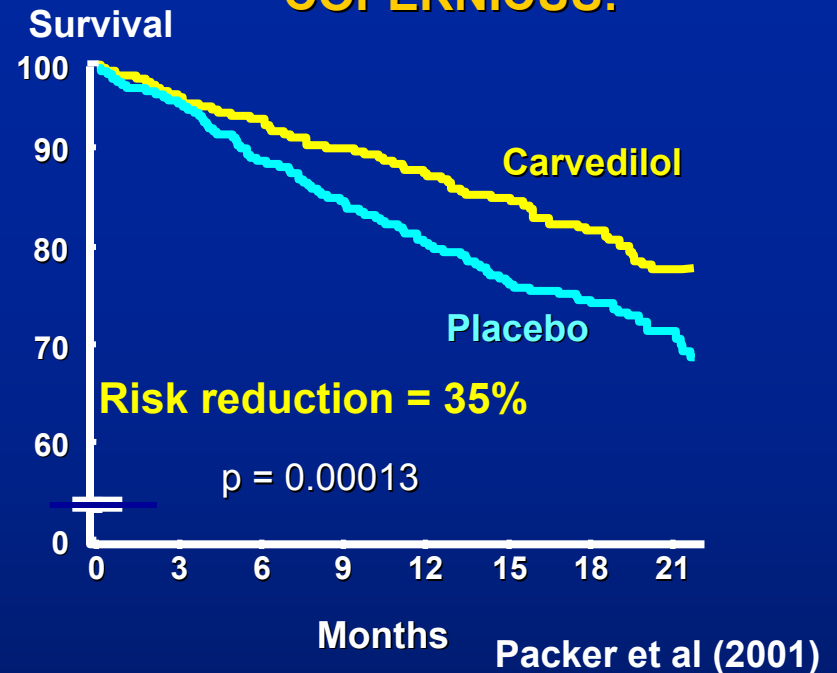
- " use of beta-blockers for the treatment of chronic heart failure remains investigational, but the official status of beta-blockers may change as recent data are reviewed. Hence, physicians might consider the use of a beta-blocker in selected patients with chronic heart failure."

US Carvedilol Programme

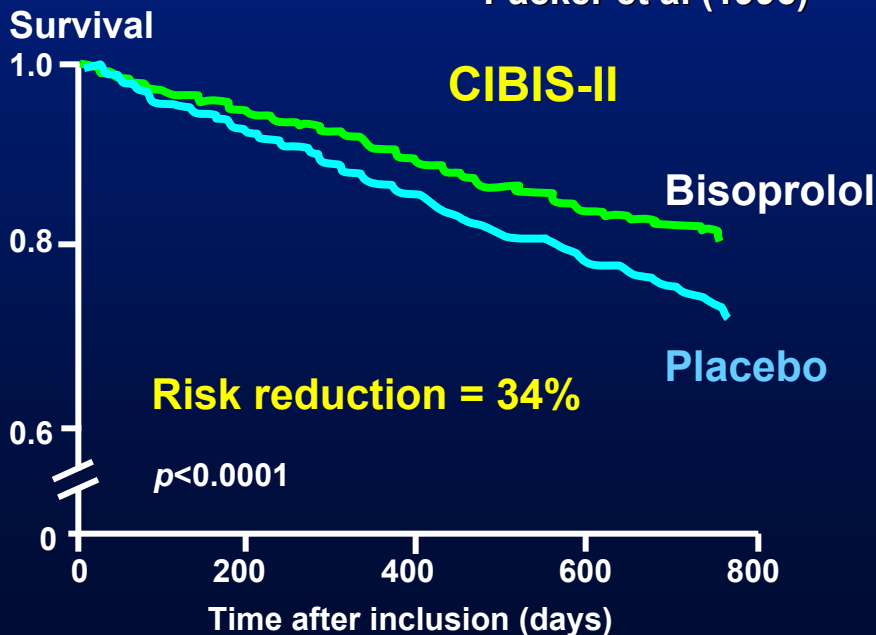


Packer et al (1996)

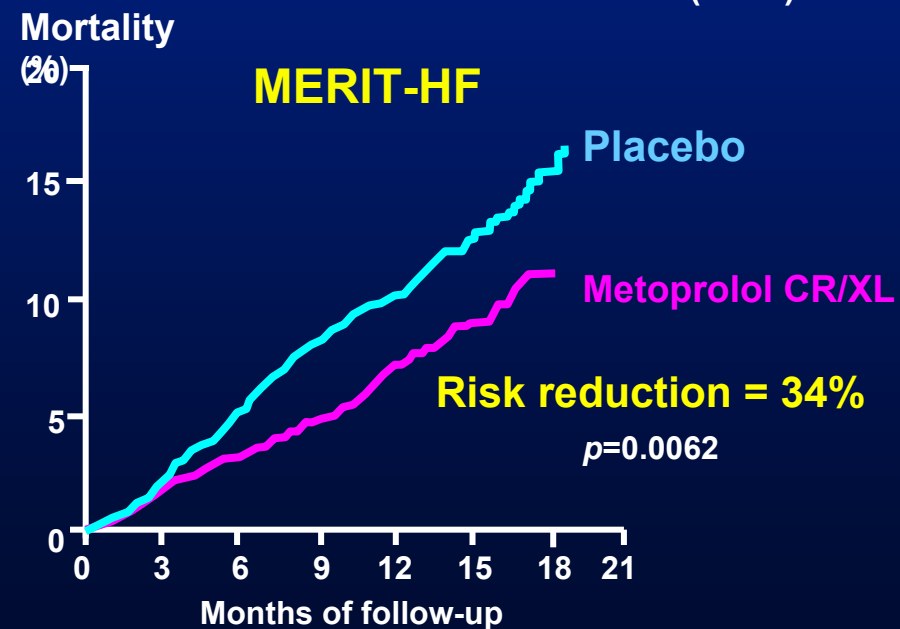
COPERNICUS:



Packer et al (2001)

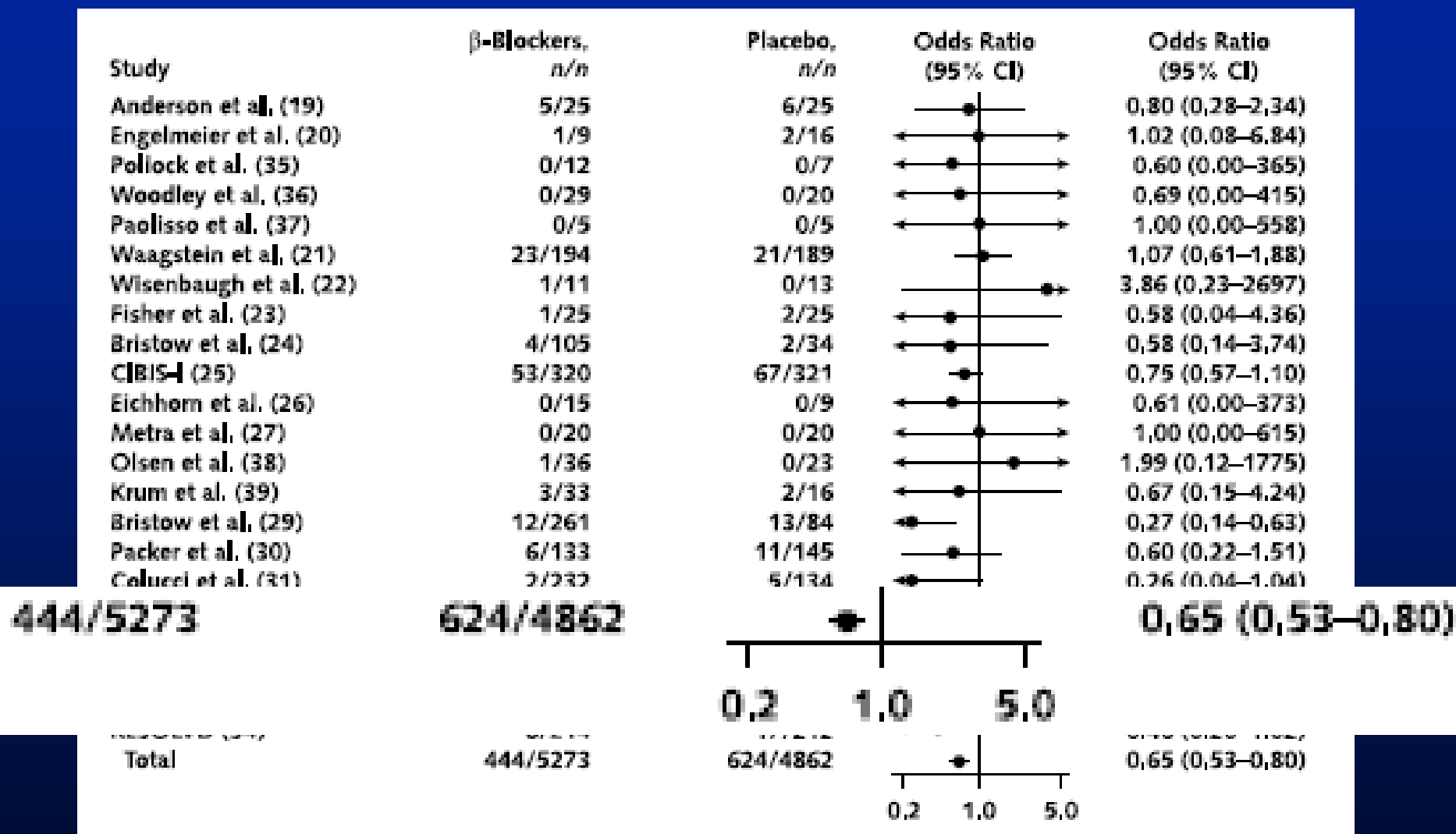


CIBIS-II Investigators (1999)

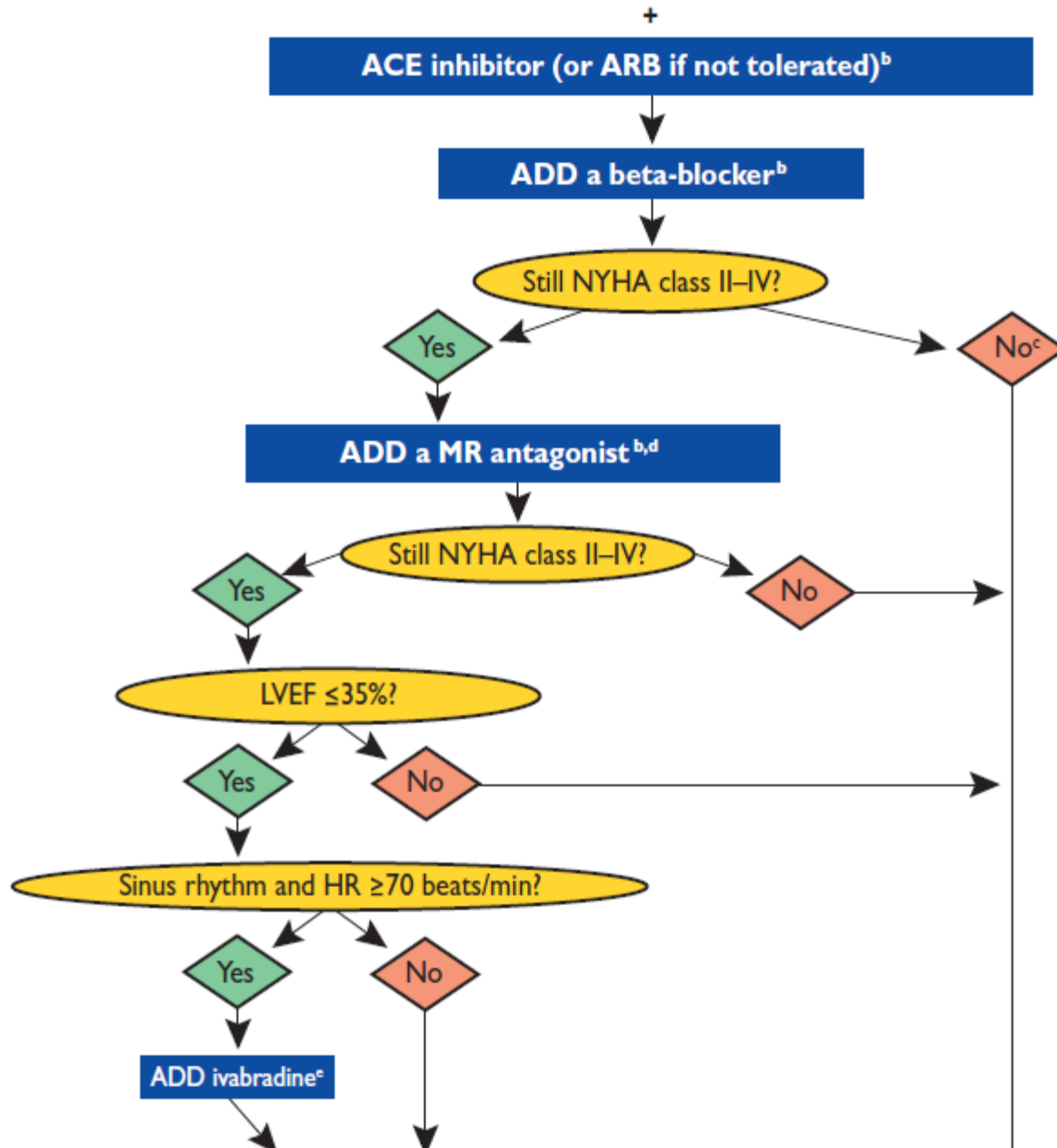


The MERIT-HF Study Group (1999)

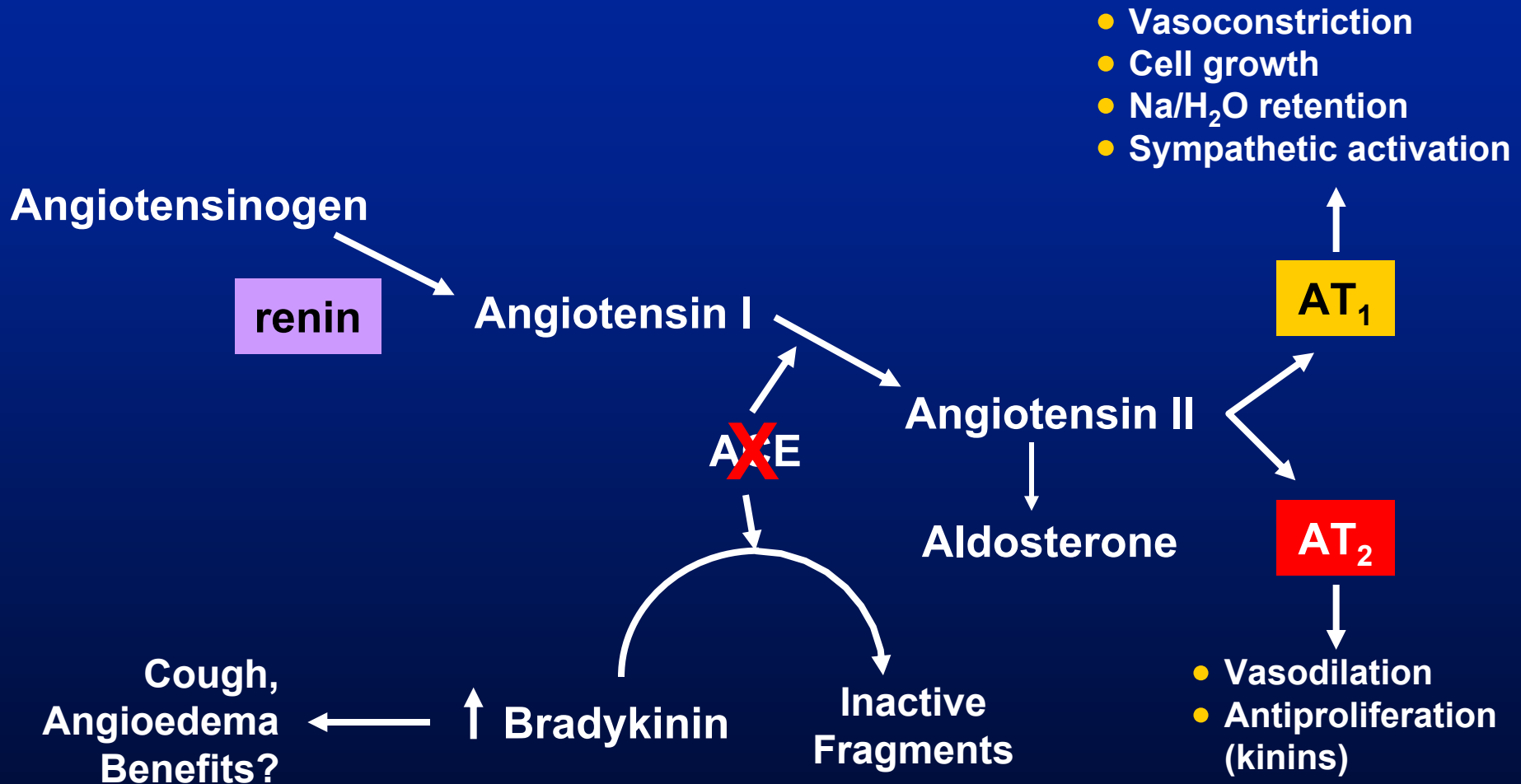
Meta-analysis of 22 beta-blocker studies in CHF



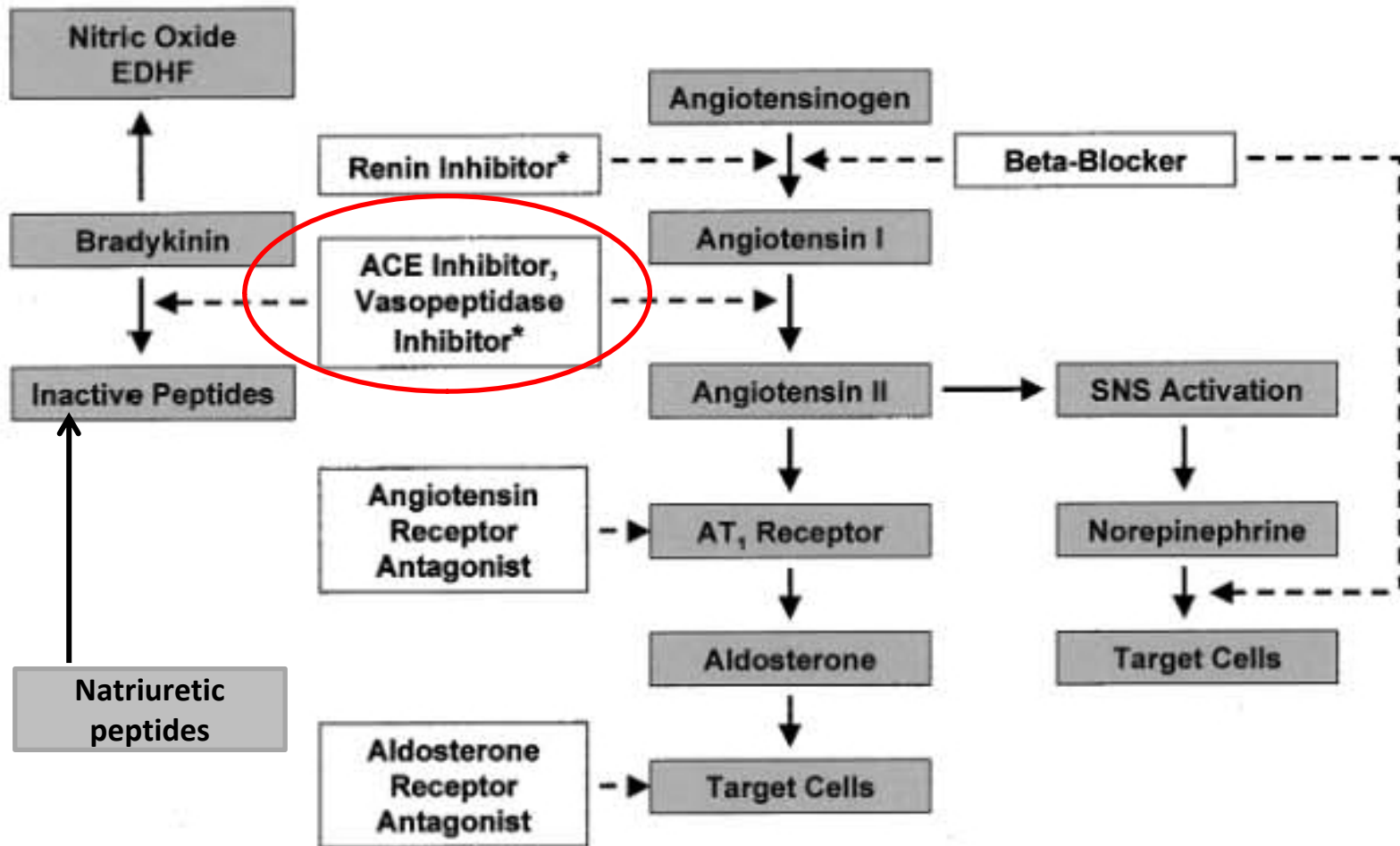
Diuretics to relieve symptoms/signs of congestion^a



Renin-angiotensin in aldosterone system

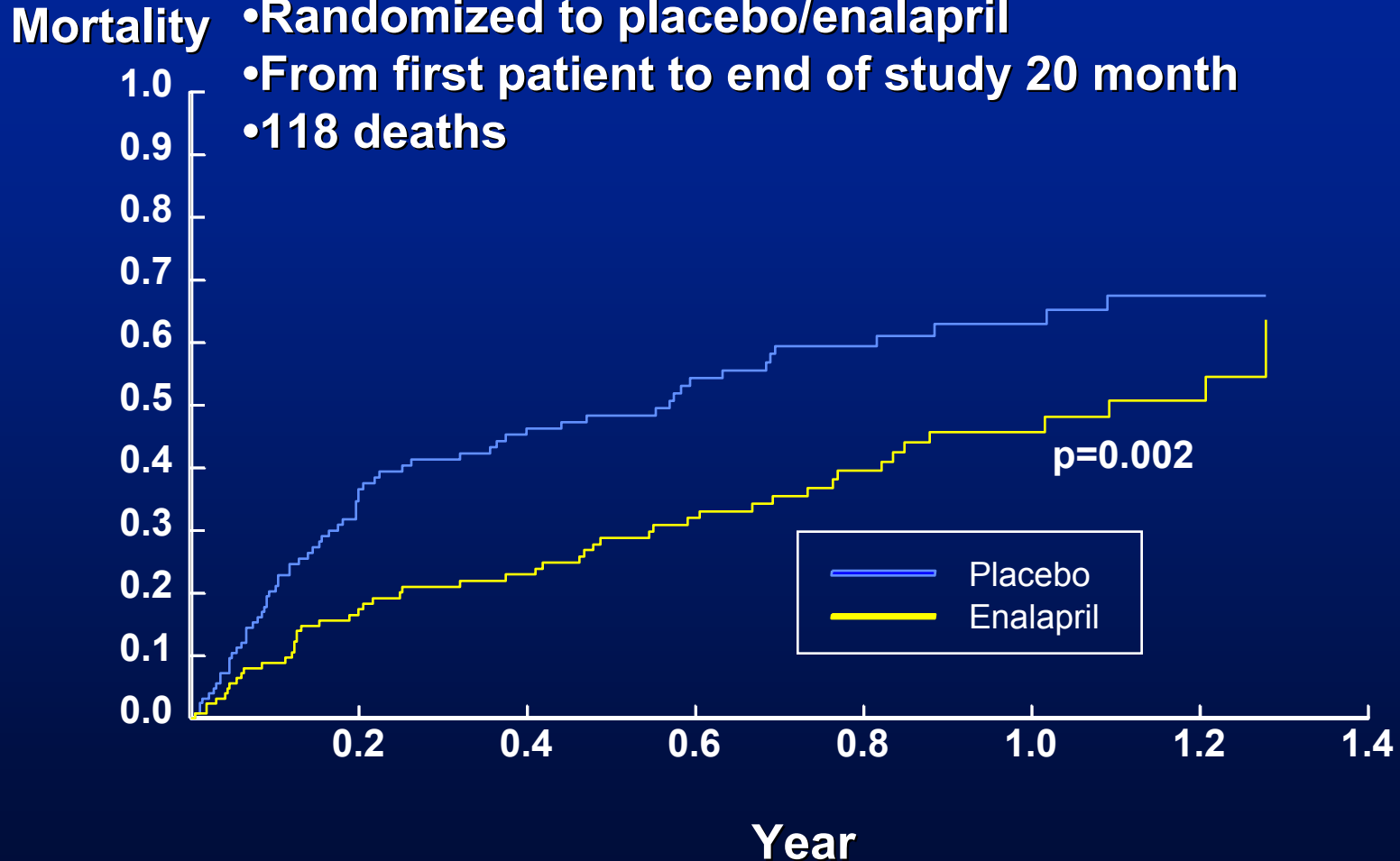


Classes of RAAS-inhibitors



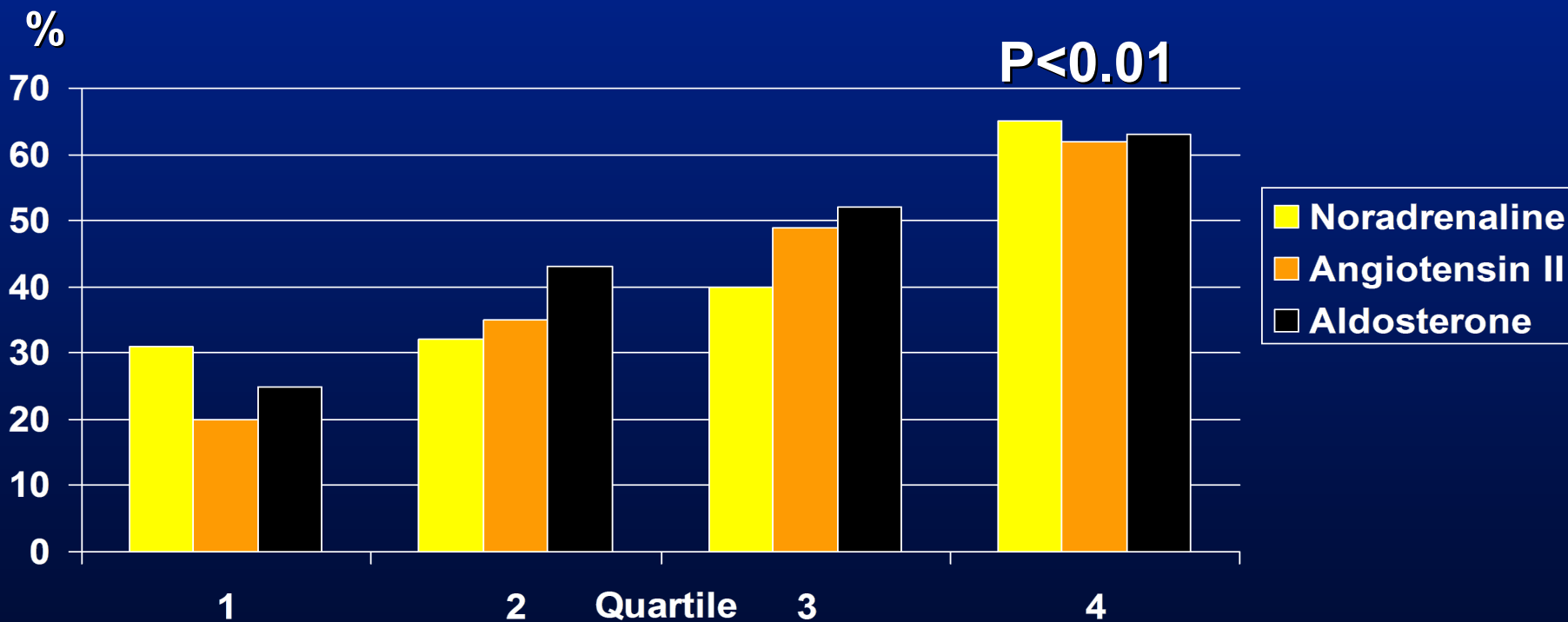
CONSENSUS

- 253 patients in NYHA class IV
- Randomized to placebo/enalapril
- From first patient to end of study 20 month
- 118 deaths



Neuroendocrine Activation and Mortality

**Six Month Mortality (%) by Plasma Levels of Hormones
From CONSENSUS I Placebo Group N=120**



Modified from Swedberg et al 1990

The New England Journal of Medicine

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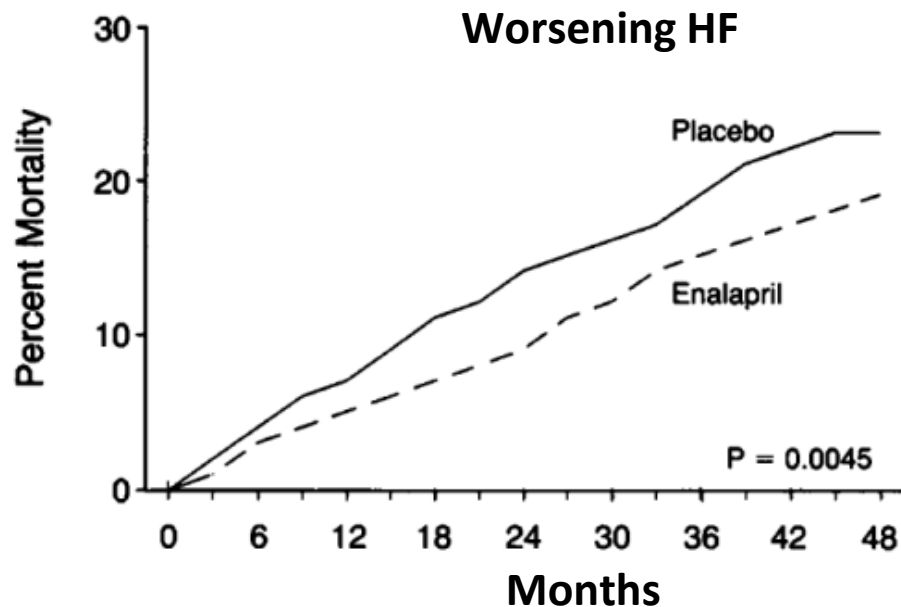
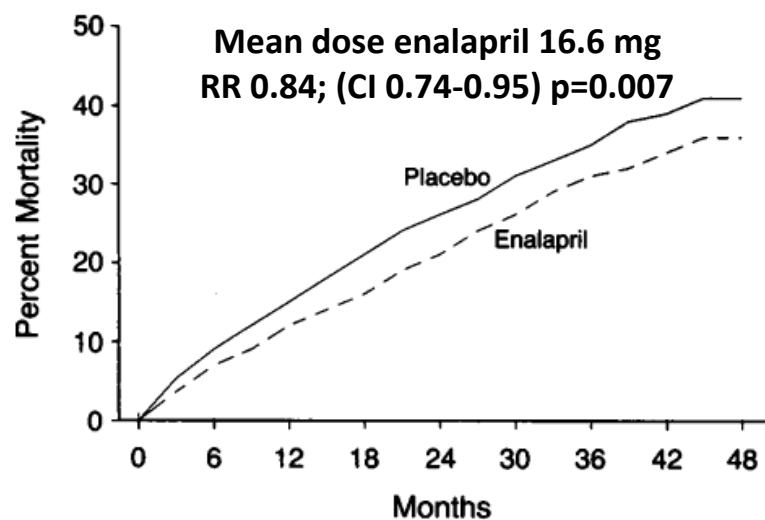
Volume 325

AUGUST 1, 1991

Number 5

EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

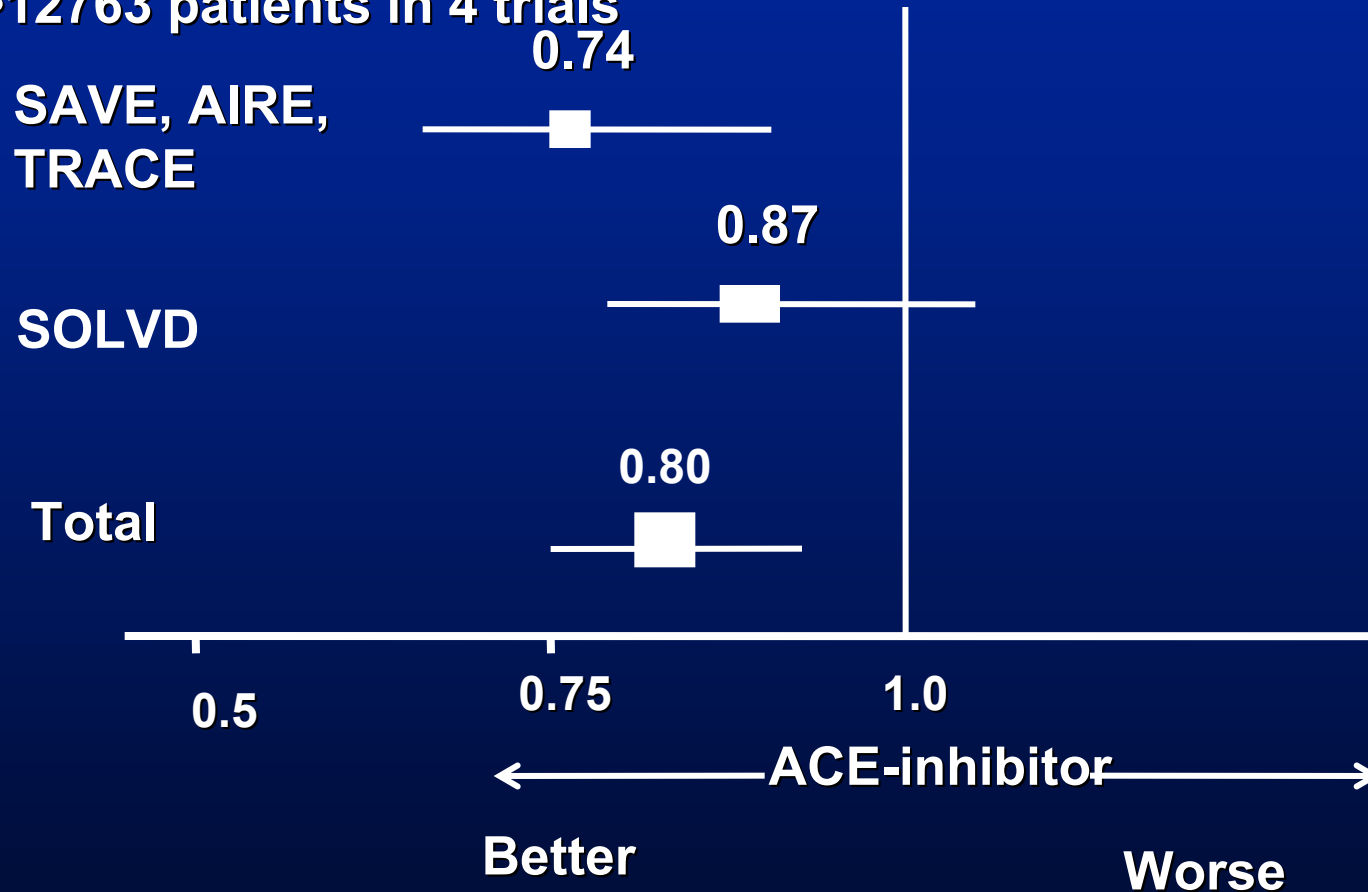
THE SOLVD INVESTIGATORS*



Placebo	1284	1159	1085	1005	939	819	669	487	299
Enalapril	1285	1195	1127	1069	1010	891	697	526	333

ACE-inhibitor Trials in Heart Failure/LV-dysfunction Mortality

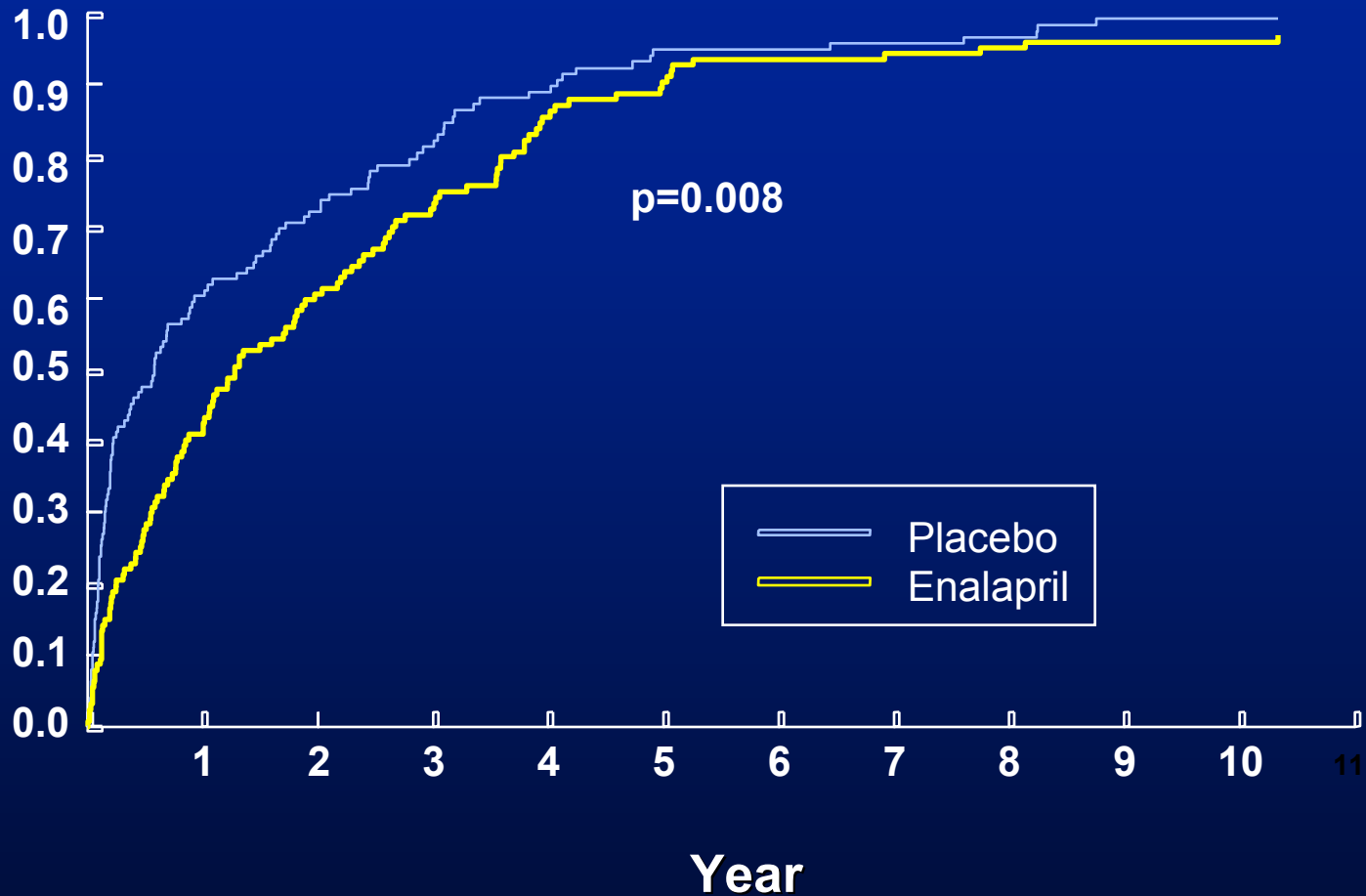
- Randomized large (>1000 patients), long-term (1 year) trials
- ACEI vs. placebo
- 12763 patients in 4 trials



CONSENSUS 10-Year Follow-Up

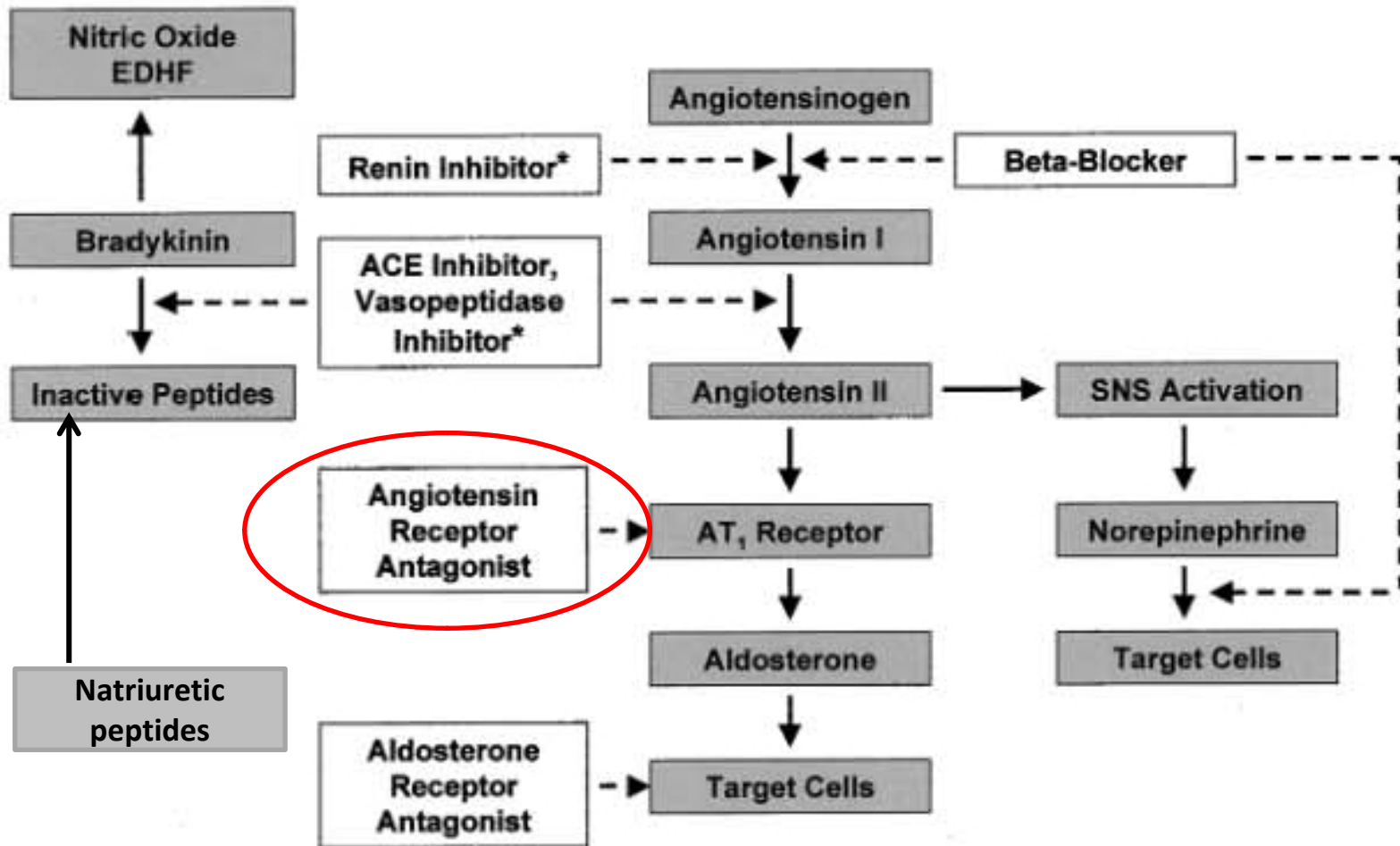
All Randomized Patients, Original and Follow-Up

Mortality



Swedberg et al EHJ 1999

Classes of RAAS-inhibitors

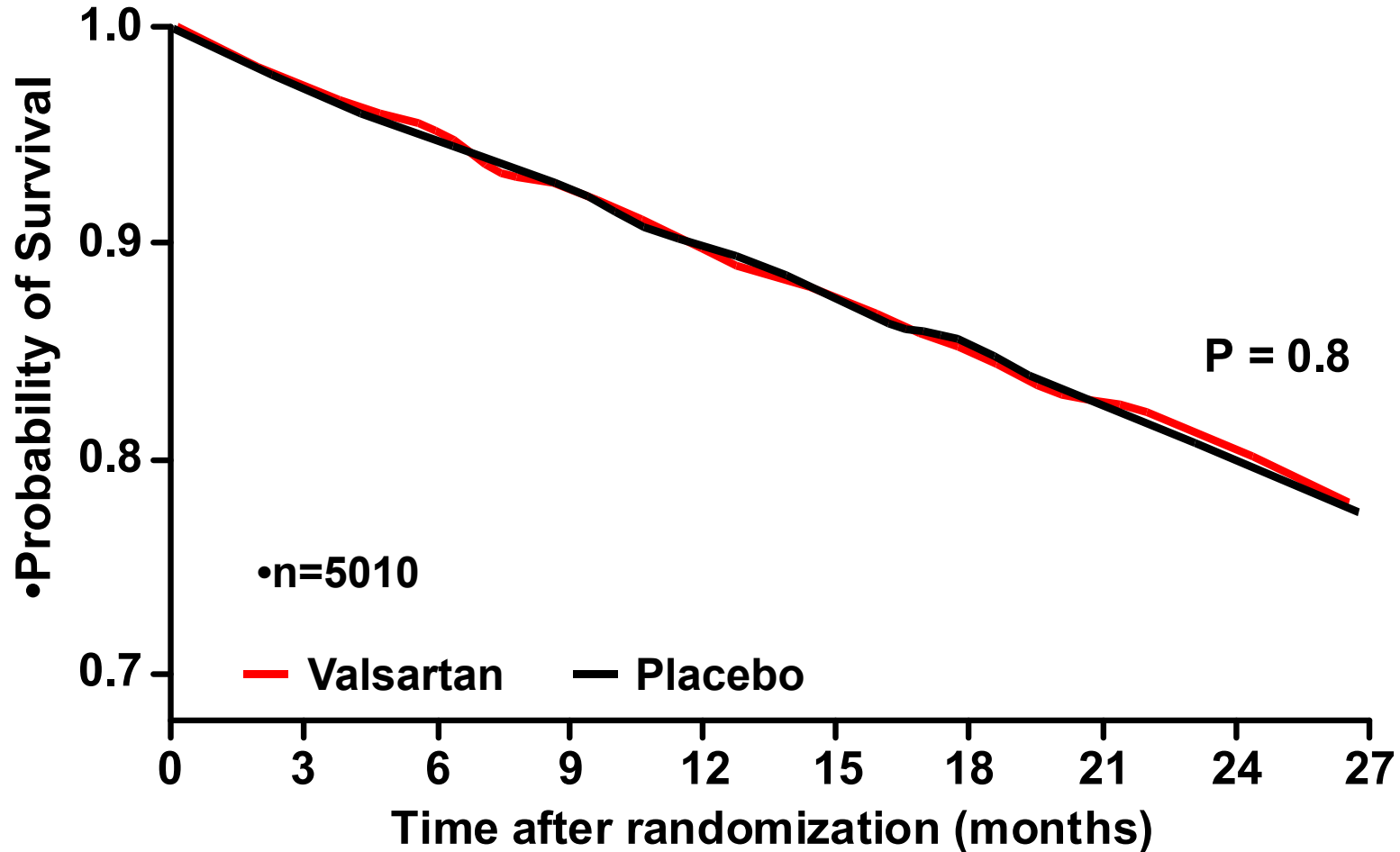


VAL-Heft

5010 pts in NYHA class II (61.7%), III (36.2%) or IV (3.1%).
Mean EF 27% and mean age 62 years
Background: ACEI 92.3%, Beta-blocker 35.5%

	Placebo	Valsartan	RR (C.I.)	P
<i>Primary endpoints</i>	N=2511	N=2499		
All cause mortality	484 (19.4%) (0.9-1.15)	(495(19.7%)	1.02	0.8
Mortality and all cause hosp.	801 (32.1%) (0.79-0.96)	723(28.8%)	0.87	0.009

•All Cause Mortality in the Val-HeFT Trial

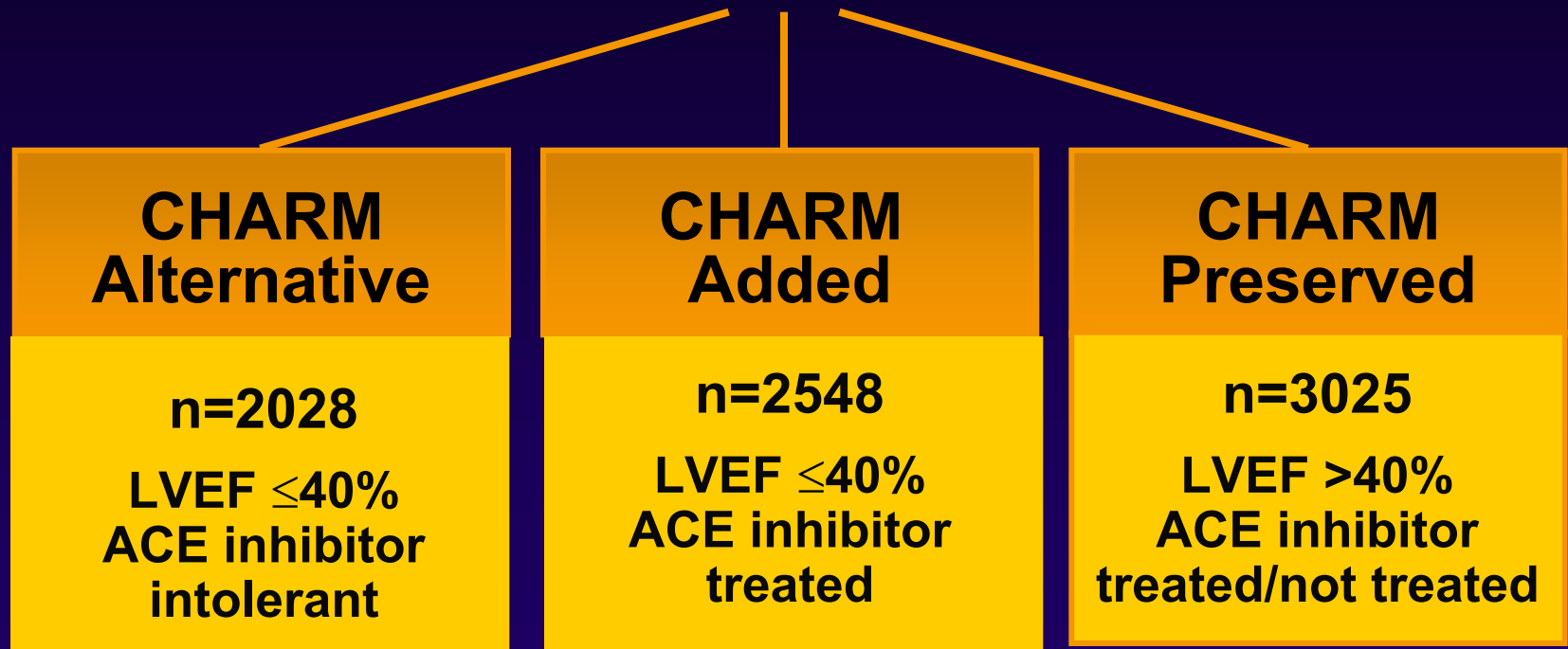




CHARM

CHARM Programme

3 component trials (N=7601) comparing candesartan to placebo in patients with symptomatic heart failure



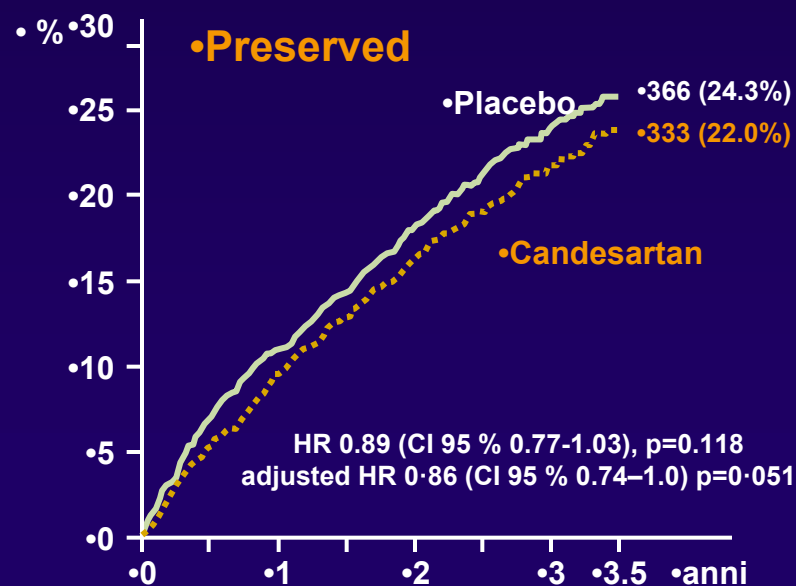
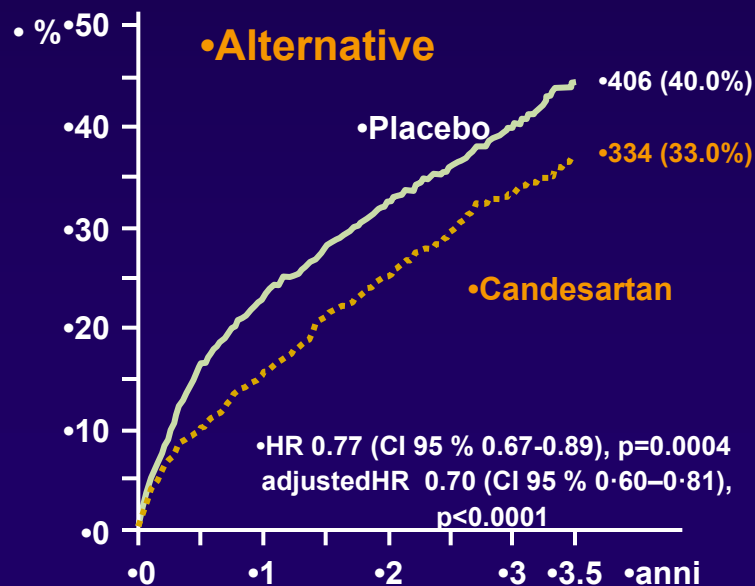
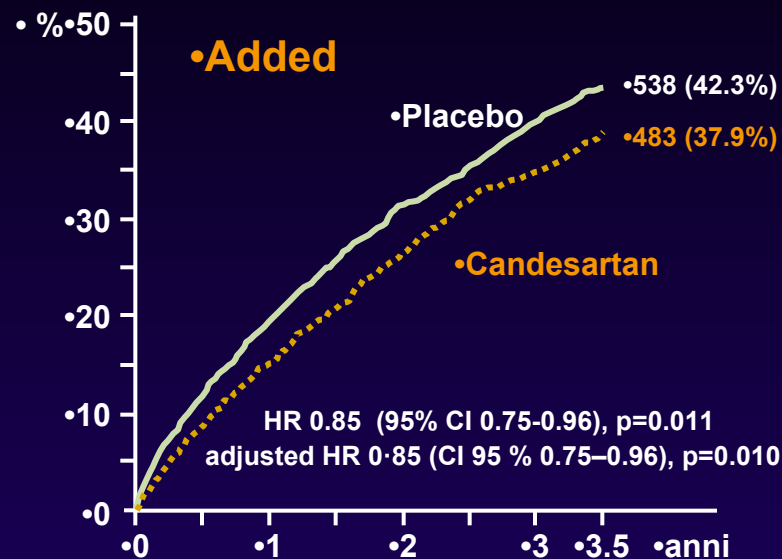
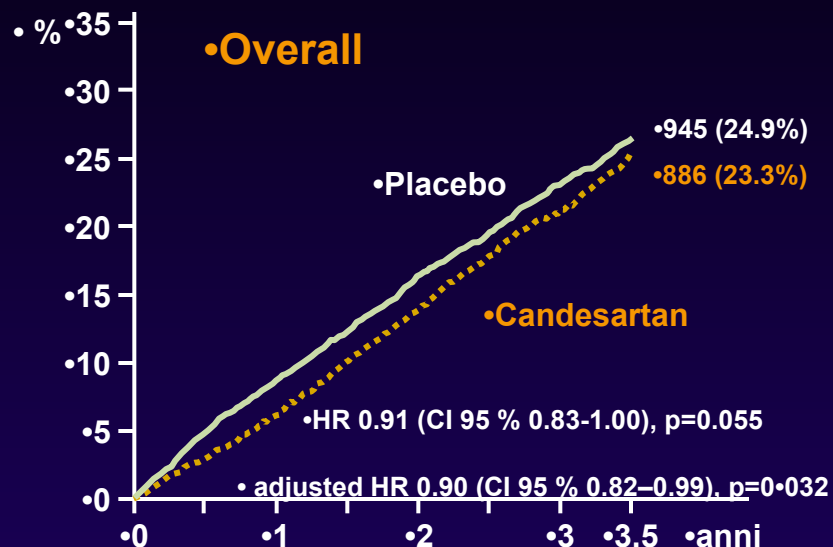
Primary outcome for each trial: CV death or CHF hospitalization

Primary outcome for Overall Programme: All-cause death



CHARM

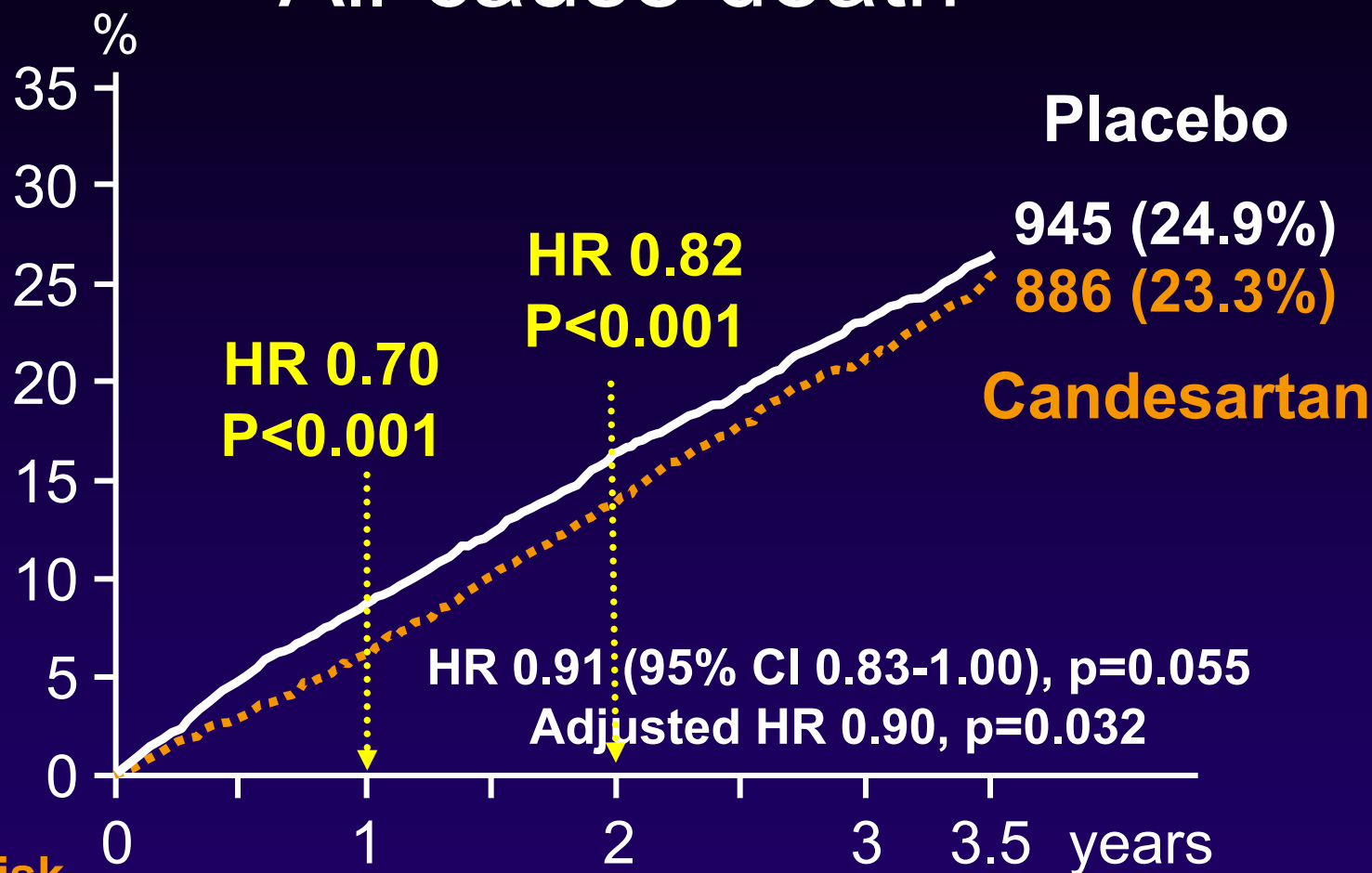
CHARM: Primary endpoint





CHARM

CHARM-Overall: All-cause death



Number at risk

Candesartan	3803	3563	3271	2215	761
Placebo	3796	3464	3170	2157	743

Pfeffer et al Lancet 2003

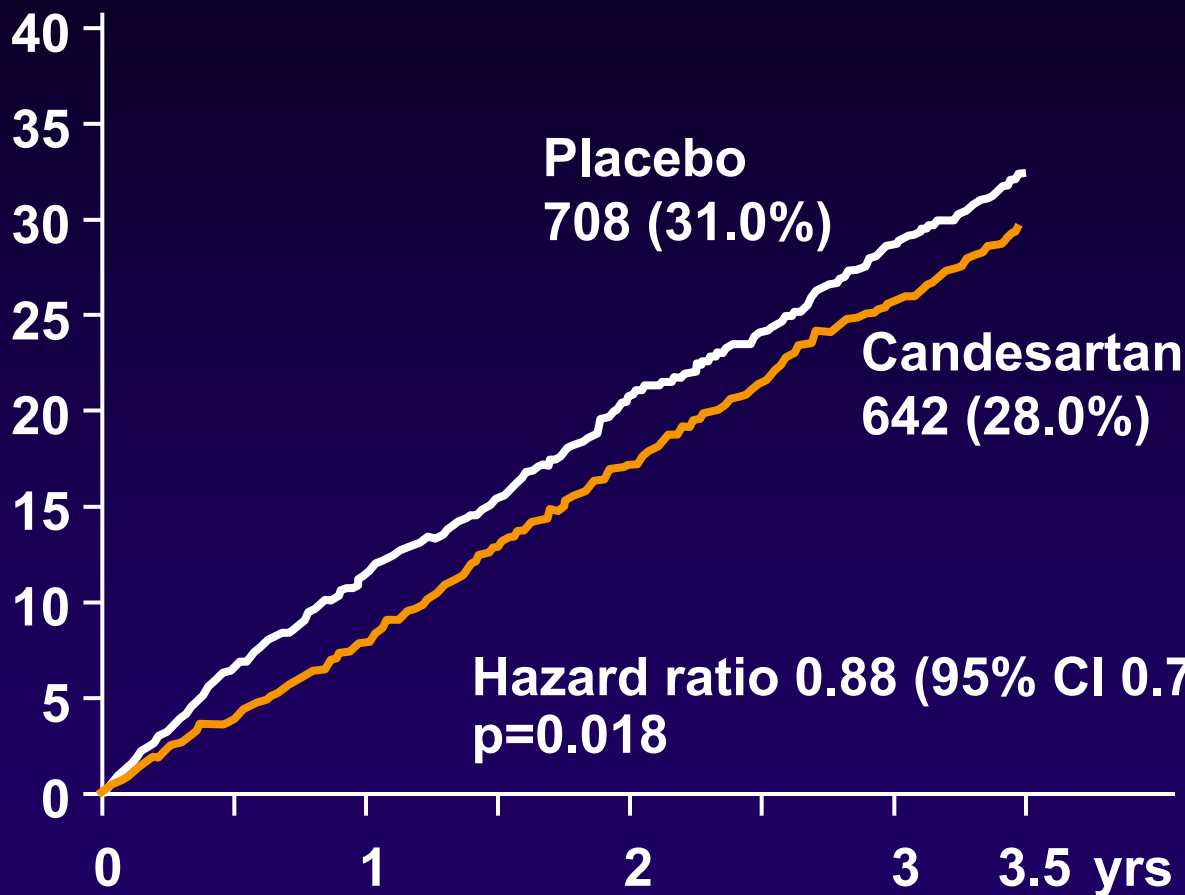


CHARM

CHARM - Low EF trials

All-cause death

All cause death (%)



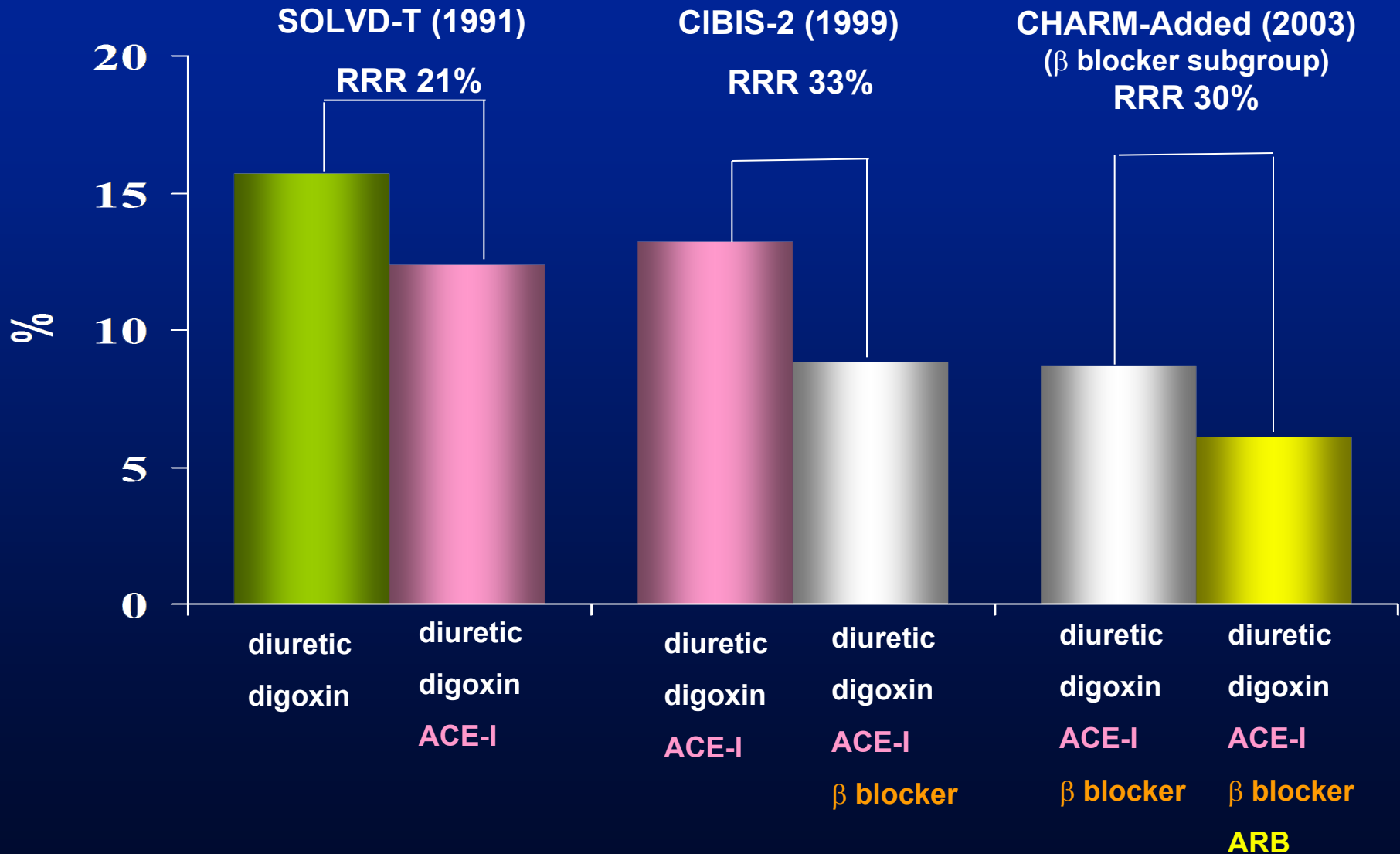
Number at risk

Candesartan	2289	2105	1894	1382	580
Placebo	2287	2023	1811	1333	548

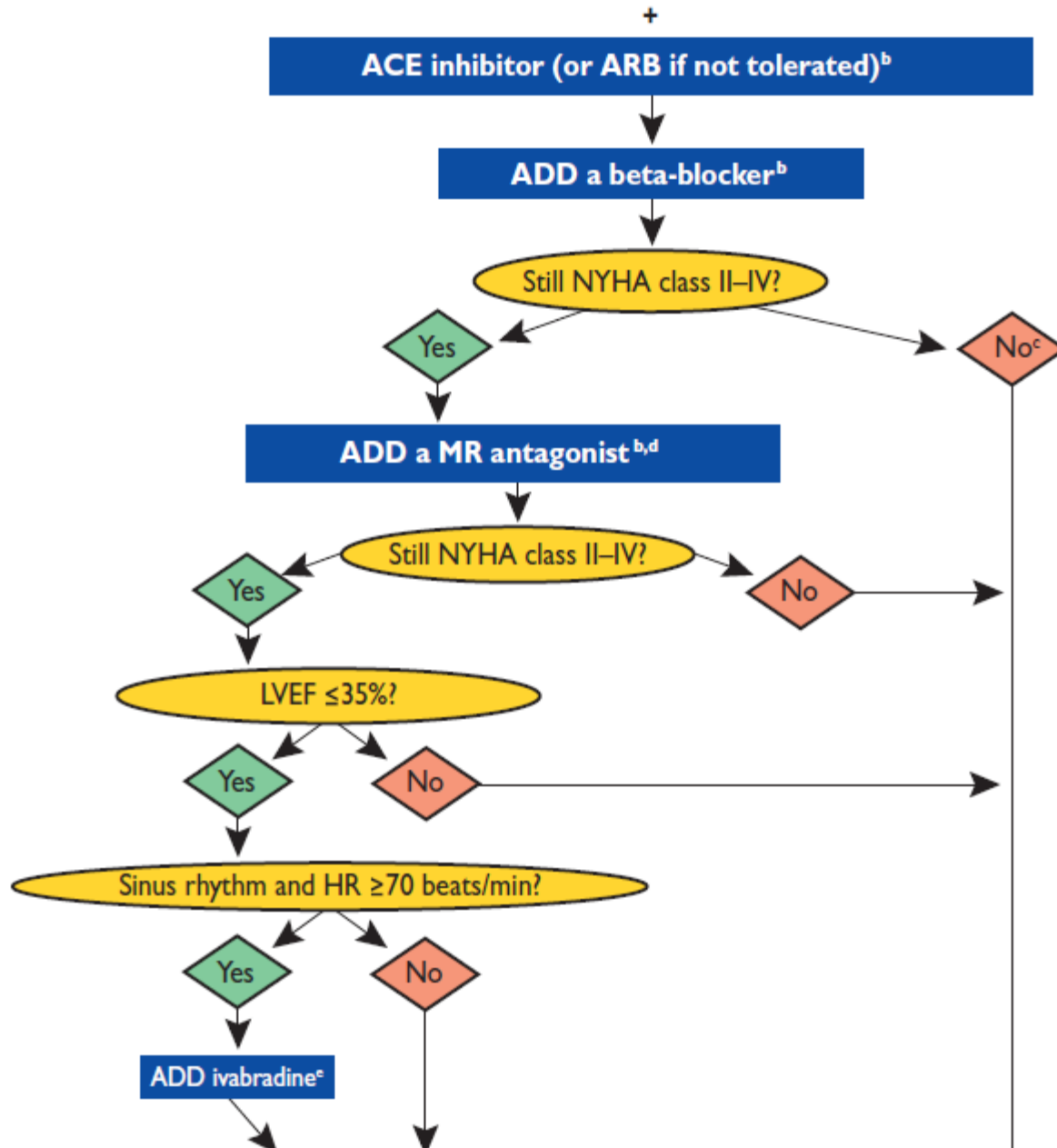
Young et al Circ 2004

Improving survival in CHF

1 year mortality



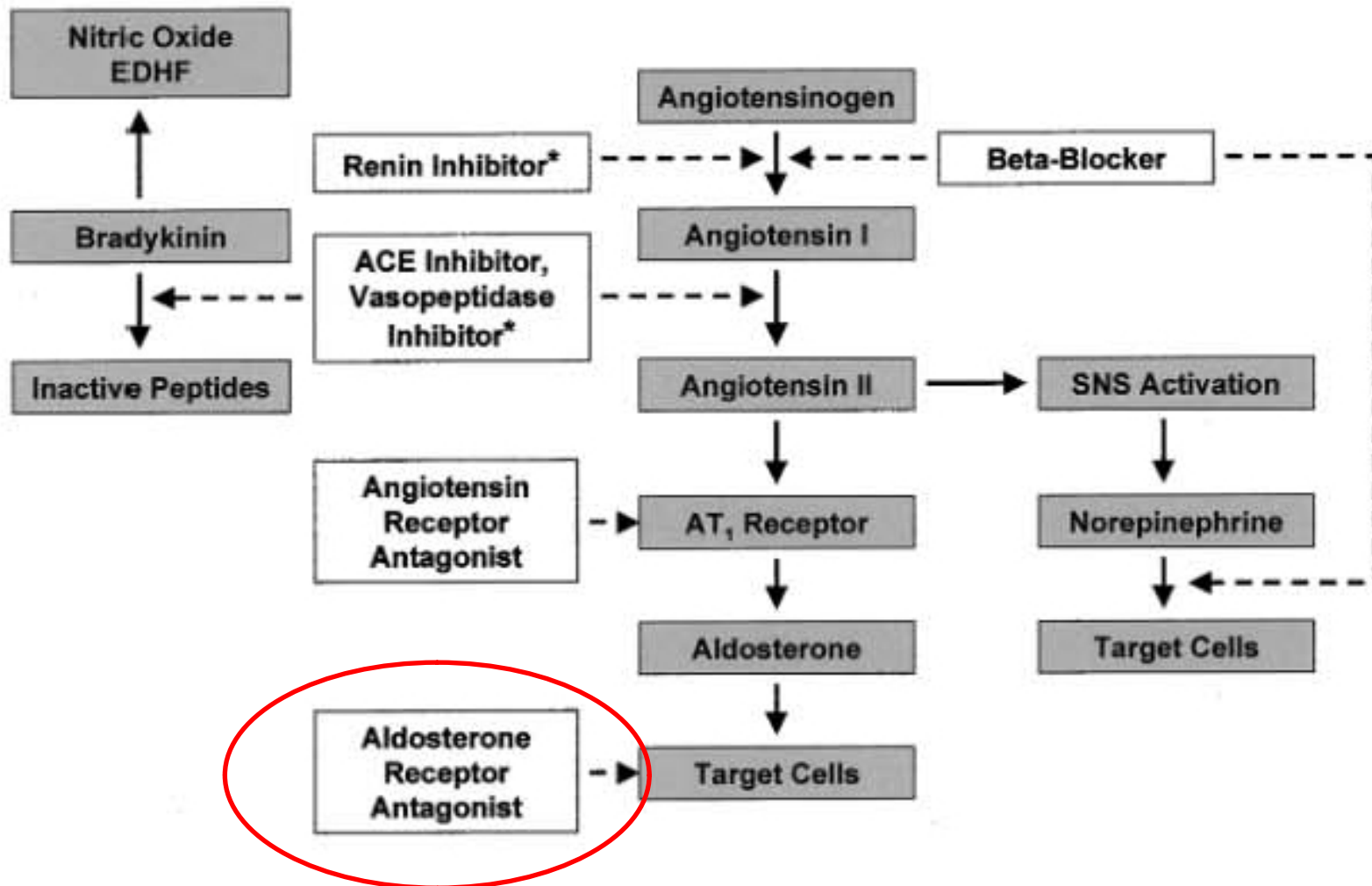
Diuretics to relieve symptoms/signs of congestion^a



ACC/AHA Guidelines 1995

- " trials support the use of ACE inhibitors in all patients with symptomatic heart failure, unless the inhibitors are contraindicated or not tolerated."

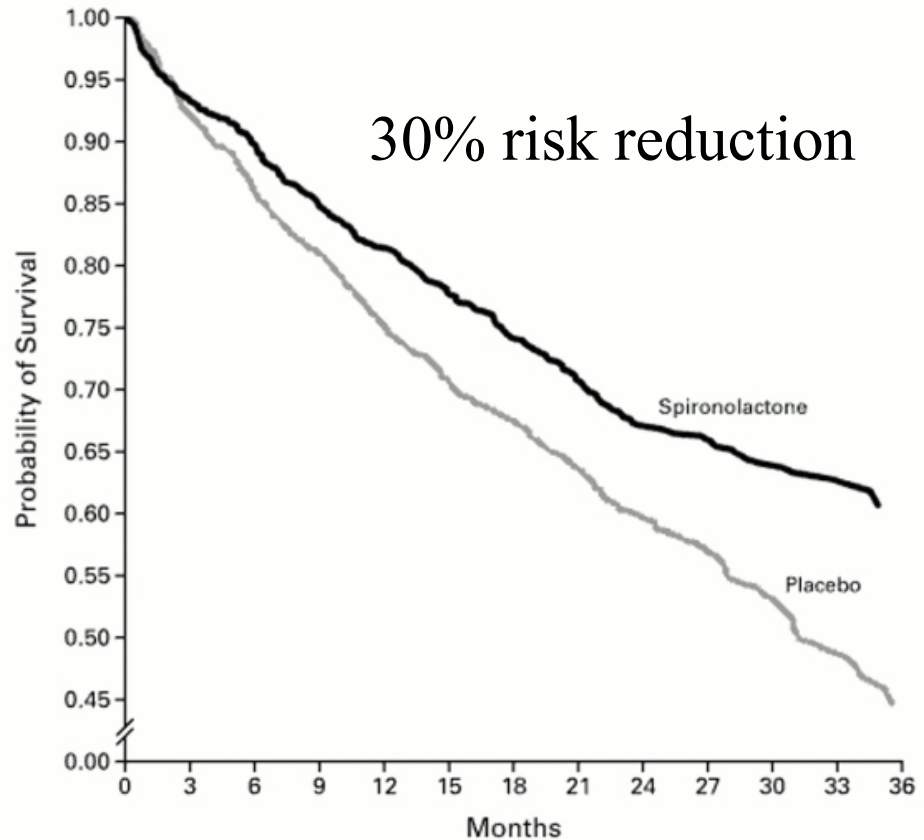
Classes of RAAS-inhibitors



RALES

Randomized ALdactone Evaluation Study

- 1663 pts HF (NYHA III or IV, EF <35%)
- spironolactone vs. placebo
- Endpoint:
 - Total mortality



No. AT RISK

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Pitt et al NEJM 1999

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JANUARY 6, 2011

VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D.,
Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D.,
and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

Inclusion Criteria

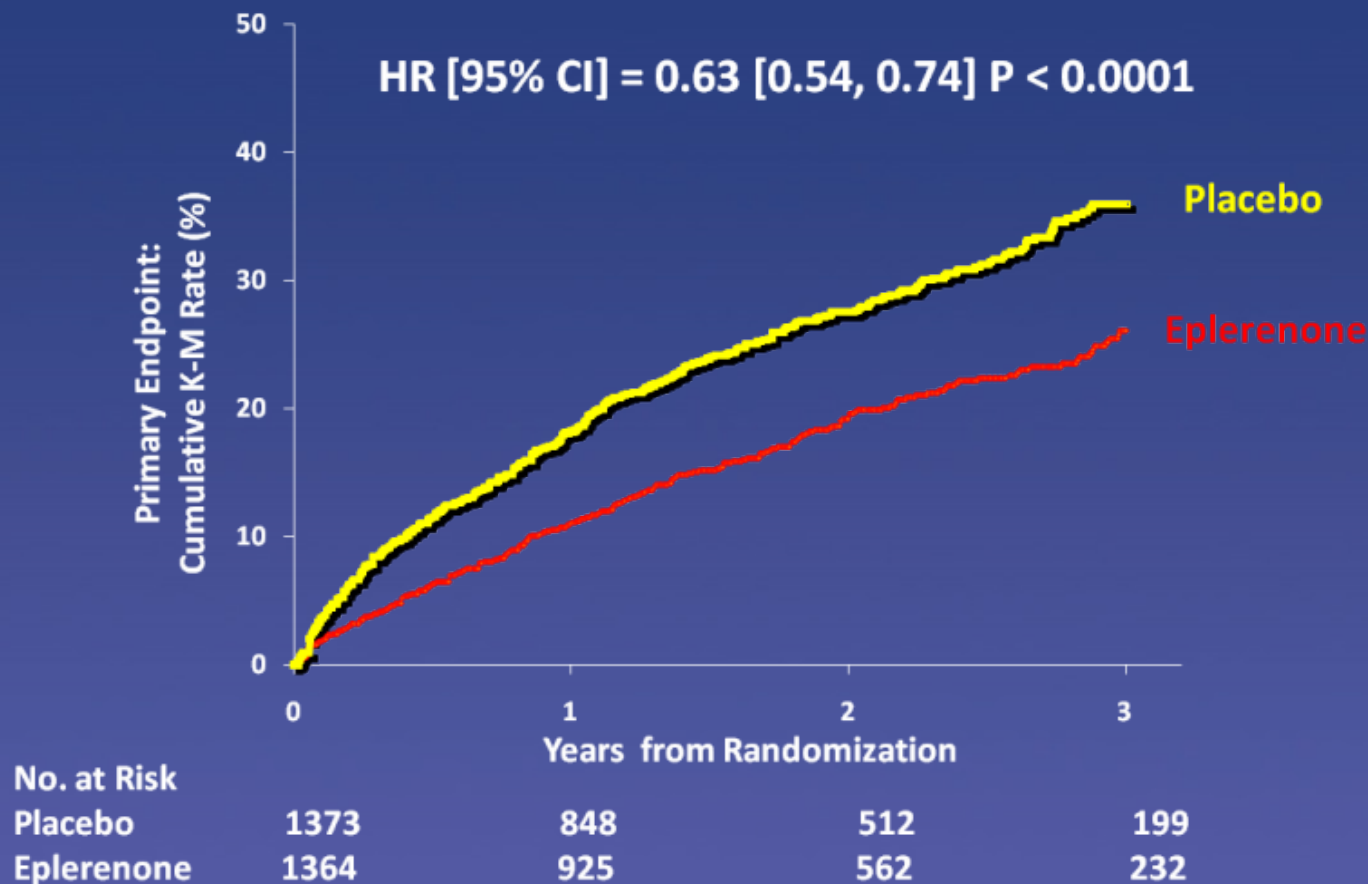
- Inclusion

- > 55 years of age
- **NYHA functional class II**
- **Ejection fraction < 30% (or, if between 30% and 35%, QRS >130 msec)**
- Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
- within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP > 250 pg/ml or Nt-pro-BNP >500 pg/ml (males) or 750 pg/ml (females).]

- Exclusion

- Serum potassium > 5.0 mmol/L
- eGFR < 30 ml/min/1.73 m²
- Need for a potassium-sparing diuretic
- Any other significant comorbid condition.

Primary Endpoint Cardiovascular Death or Hospitalization for HF -37%



Safety

(Investigator reported events)

**Patients with an adverse event
— no. (%)**

Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	979 (72)	1007 (73.6)	0.37
Hyperkalemia – n (%)	109 (8)	50 (3.7)	<0.001
Hypokalemia – n (%)	16 (1.2)	30 (2.2)	0.05
Renal failure – n (%)	39 (2.9)	42 (3.1)	0.82
Hypotension – n (%)	46 (3.4)	37 (2.7)	0.32
Gynecomastia and other breast disorders – n (%)	10 (0.7)	14 (1.0)	0.54

ESC HF Guidelines 2012

Diuretics to relieve symptoms/signs of congestion^a

+

ACE inhibitor (or ARB if not tolerated)^b

ADD a beta-blocker^b

Still NYHA class II–IV?

Yes

No^c

ADD a MR antagonist^{b,d}

Relative risk of primary composite endpoint in the placebo group divided by quintiles of heart rate

Böhm et al Lancet 2010

Heart rate at
baseline (bpm)

70 - <72

72 - <75

75 - <80

80 - <87

≥ 87

HR

1.00

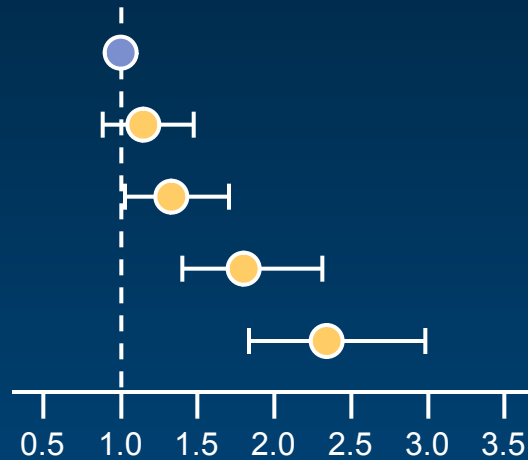
1.15

1.33

1.80

2.34

Primary composite endpoint



HR

1.00

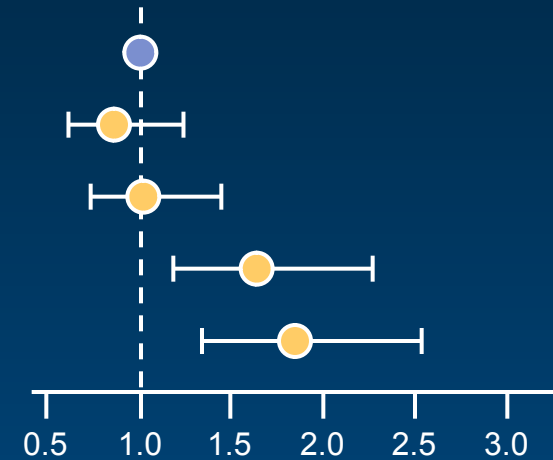
0.87

1.03

1.64

1.85

CV death



Heart rate at
baseline (bpm)

70 - <72

72 - <75

75 - <80

80 - <87

≥ 87

HR

1.00

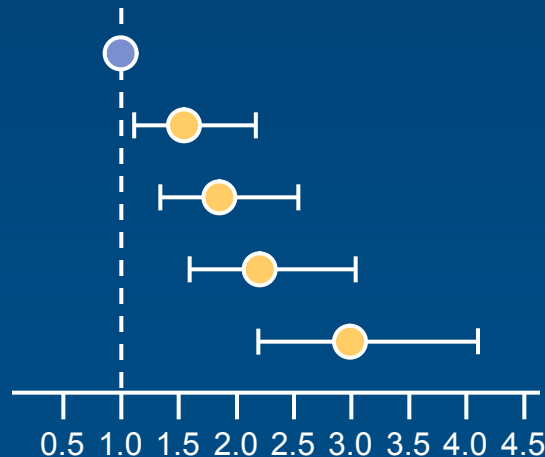
1.55

1.85

2.20

2.99

HF hospitalisation



HR

1.00

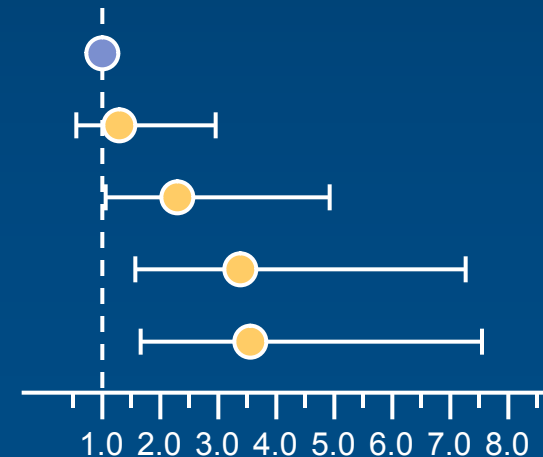
1.29

2.29

3.40

3.56

Death from HF



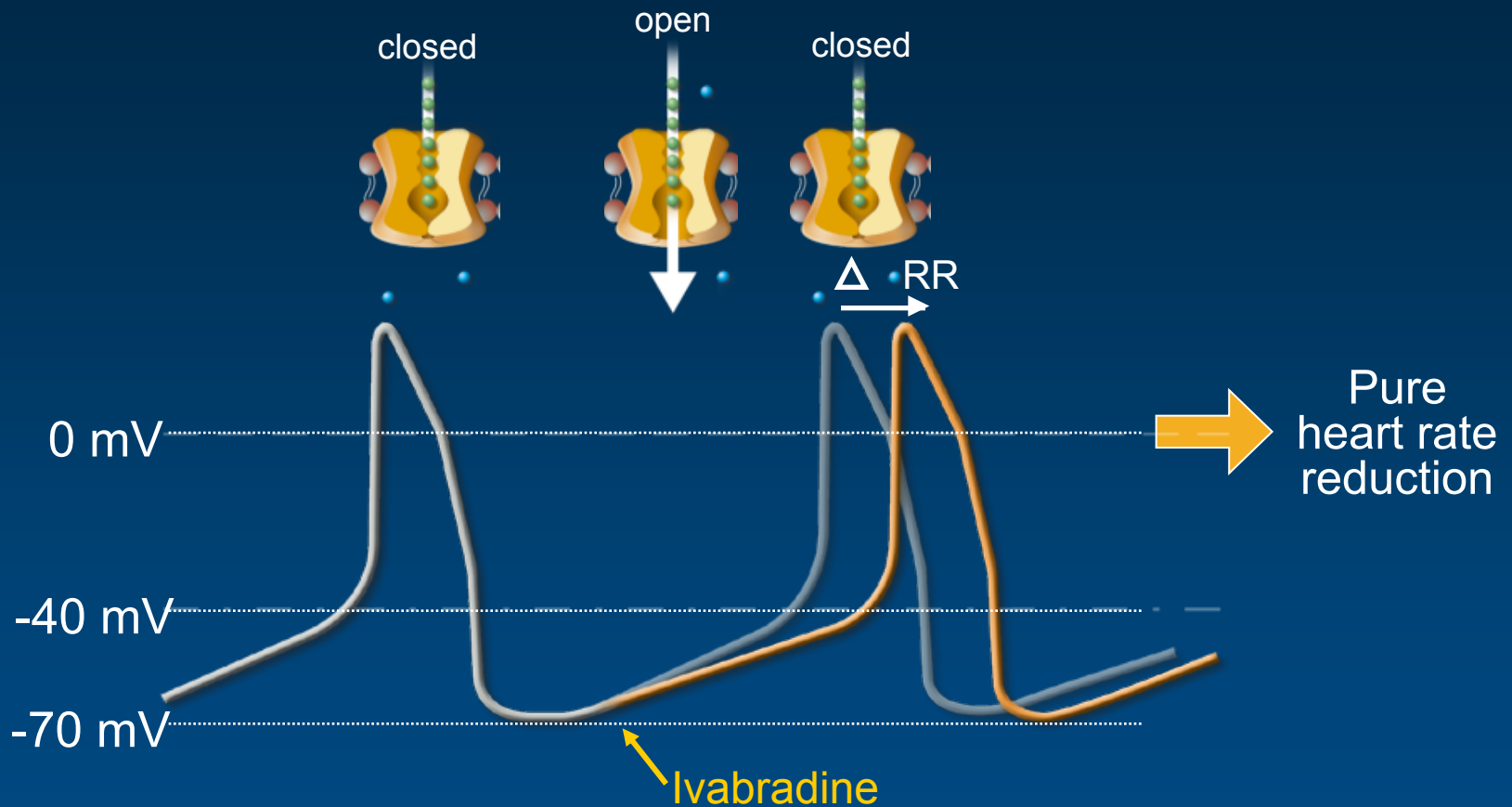
Beta-blocker dose and heart rate reduction in chronic HF patients

23 trials in 19 209 HF patients with beta-blocker (mean EF=17%-36%)

Results of 13 univariable meta-regressions evaluating the effect of individual covariates on mortality benefits of beta-blockers in heart failure

Potential Modifier	Trials, <i>n</i>	Patients, <i>n</i>	Ratio of Relative Risks (95% CI)	<i>P</i> Value
Percentage of men	21	18 773	0.93 (0.79–1.10) per 10% increment	0.38
Mean age	21	18 773	1.04 (0.86–1.24) per decade	0.69
Percentage with an ischemic cause	21	18 773	0.99 (0.86–1.14) per 20% increment	0.88
Mean baseline LVEF	20	18 392	1.04 (0.92–1.18) per 5% increment	0.54
Percentage with NYHA class III or IV symptoms	21	18 773	1.00 (0.96–1.05) per 10% increment	0.84
Percentage with atrial fibrillation	8	8915	1.00 (0.91–1.09) per 5% increment	0.95
Percentage of digoxin use	19	18 336	1.01 (0.96–1.06) per 10% increment	0.64
Baseline heart rate	19	17 981	1.07 (0.88–1.32) per 5 beats/min	0.47
Heart rate reduction*	17	17 831	0.82 (0.71–0.94) per 5 beats/min	0.006
β-Blocker dose	17	17 660	1.02 (0.93–1.10) per increment	0.69
Mean baseline SBP	17	17 516	1.00 (0.73–1.35) per 20 mm Hg	0.99
Mean SBP reduction	10	5462	1.02 (0.87–1.20) per 2 mm Hg	0.78
Agent	21	18 773	–	–
Carvedilol	–	–	Reference	–
Bisoprolol	–	–	1.05 (0.82–1.35)	0.68
Metoprolol	–	–	1.03 (0.77–1.38)	0.85
Atenolol	–	–	0.89 (0.29–2.76)	0.83
Bucindolol	–	–	1.36 (1.09–1.69)	0.009
Nebivolol	–	–	1.30 (0.99–1.71)	0.056

Ivabradine: pure heart rate reduction

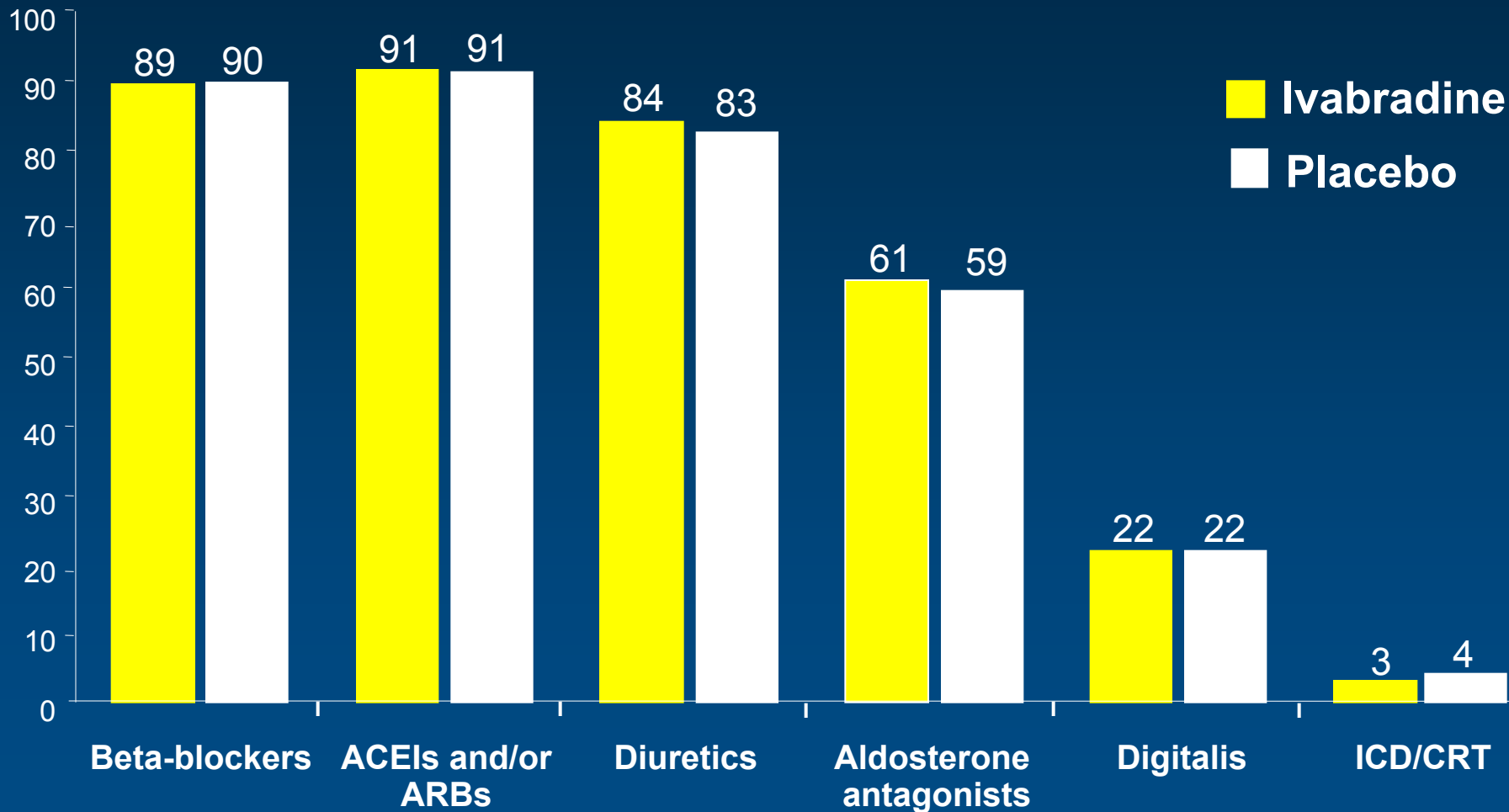


I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

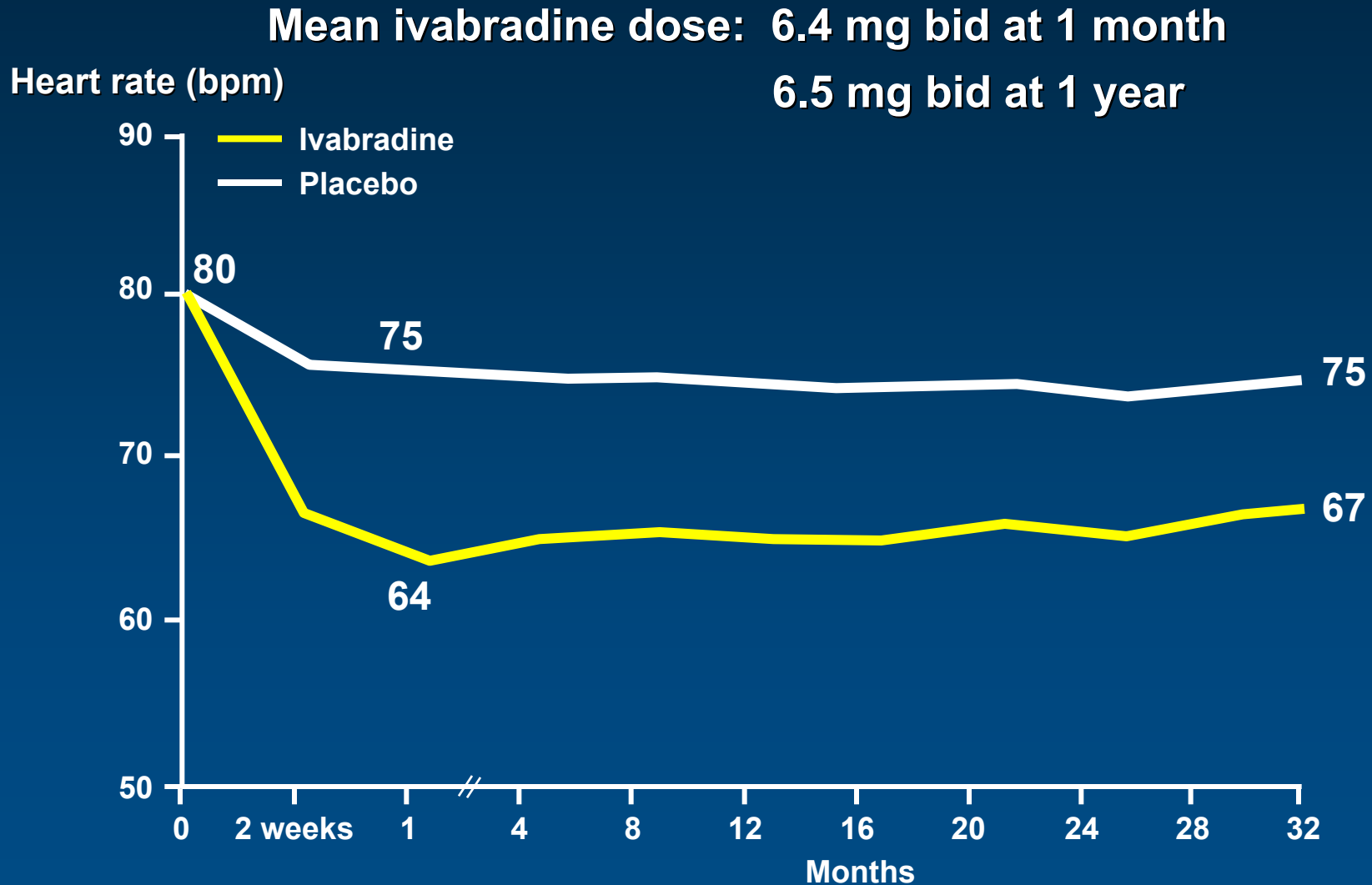
- ≥ 18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction ($EF \leq 35\%$)
- Heart rate ≥ 70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤ 12 months

Chronic HF background treatment

Patients (%)



Mean heart rate reduction

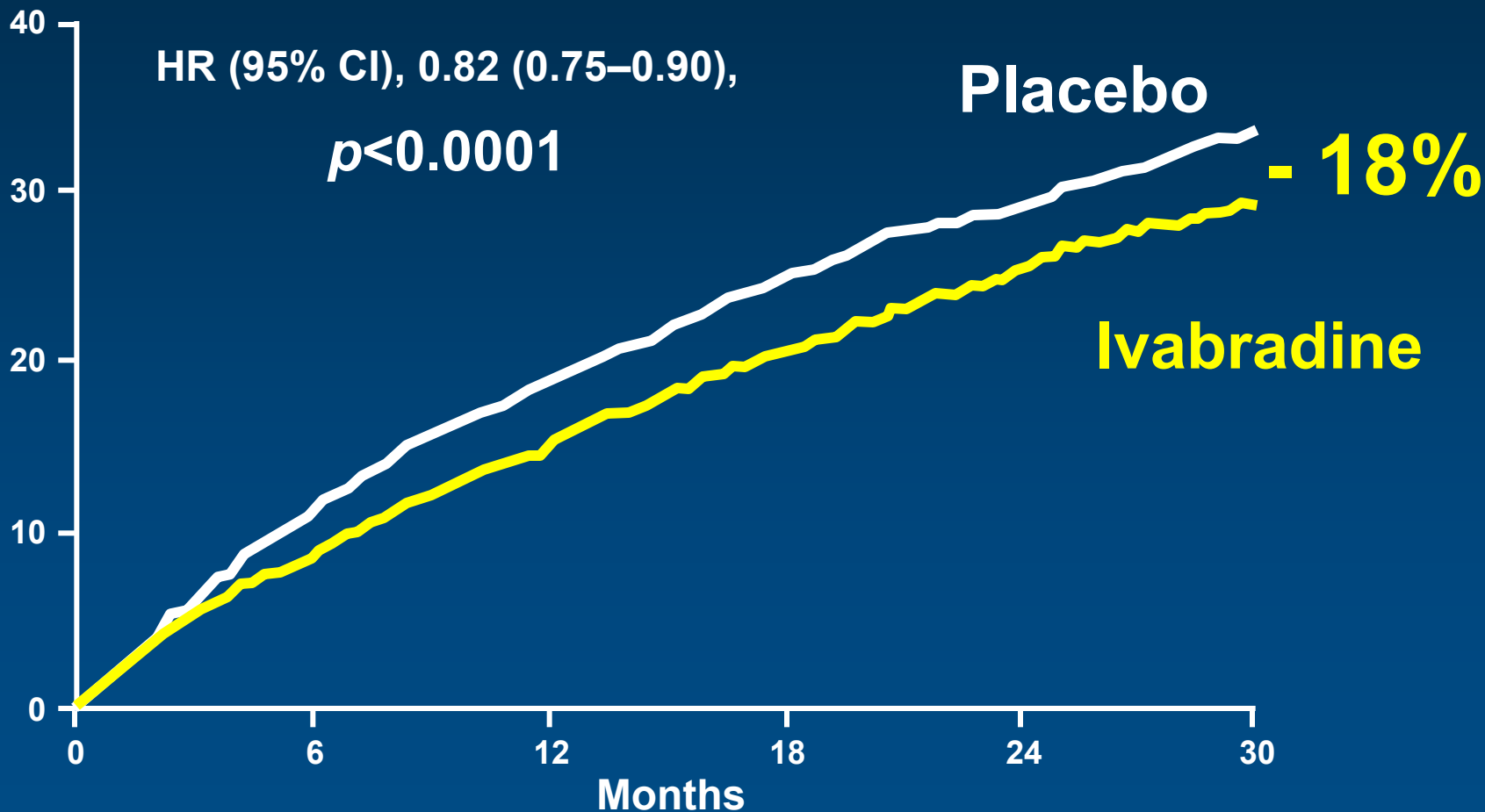


Swedberg K, et al. *Lancet*. 2010.



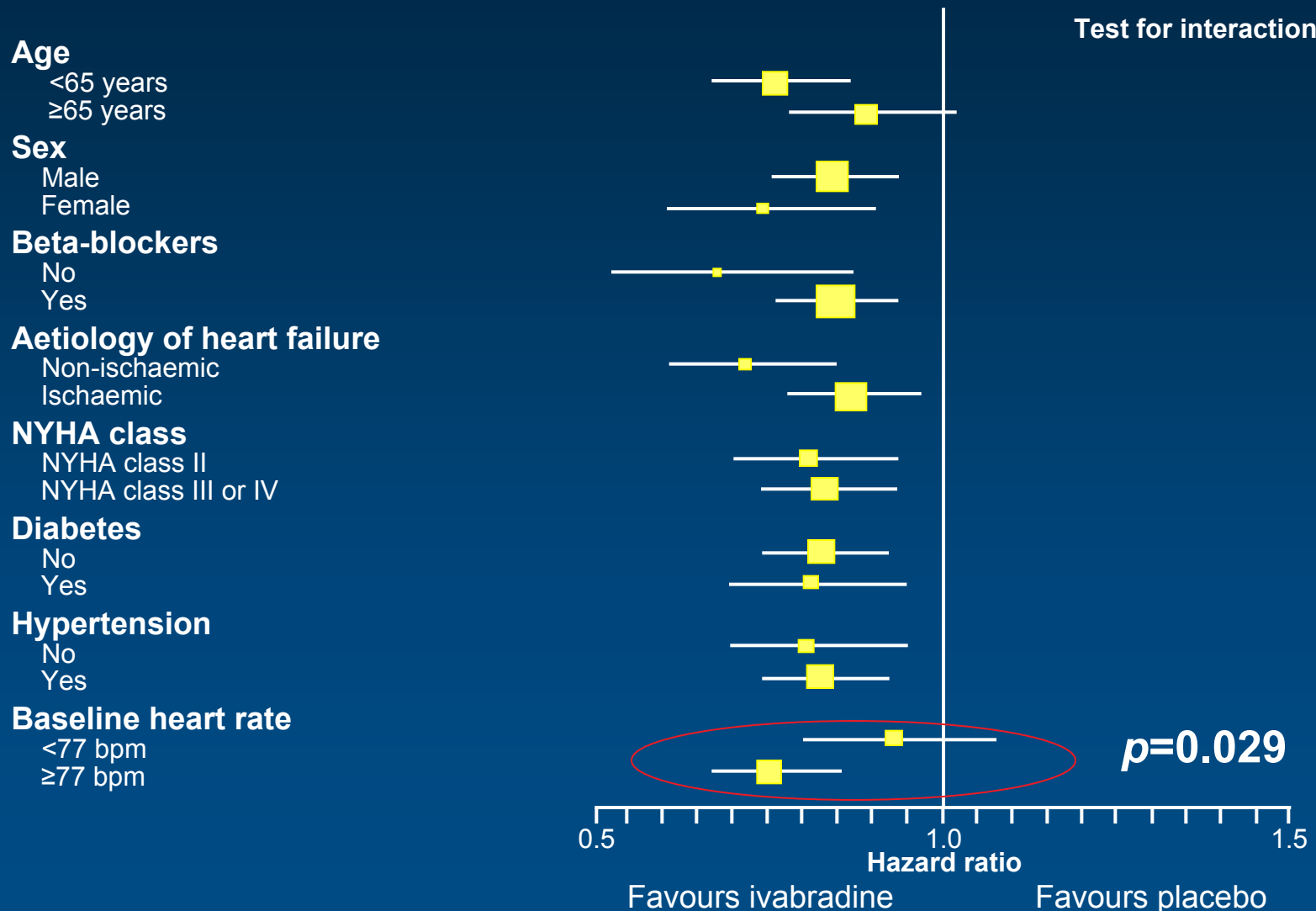
Primary composite endpoint (CV death or hospital admission for worsening HF)

Cumulative frequency (%)



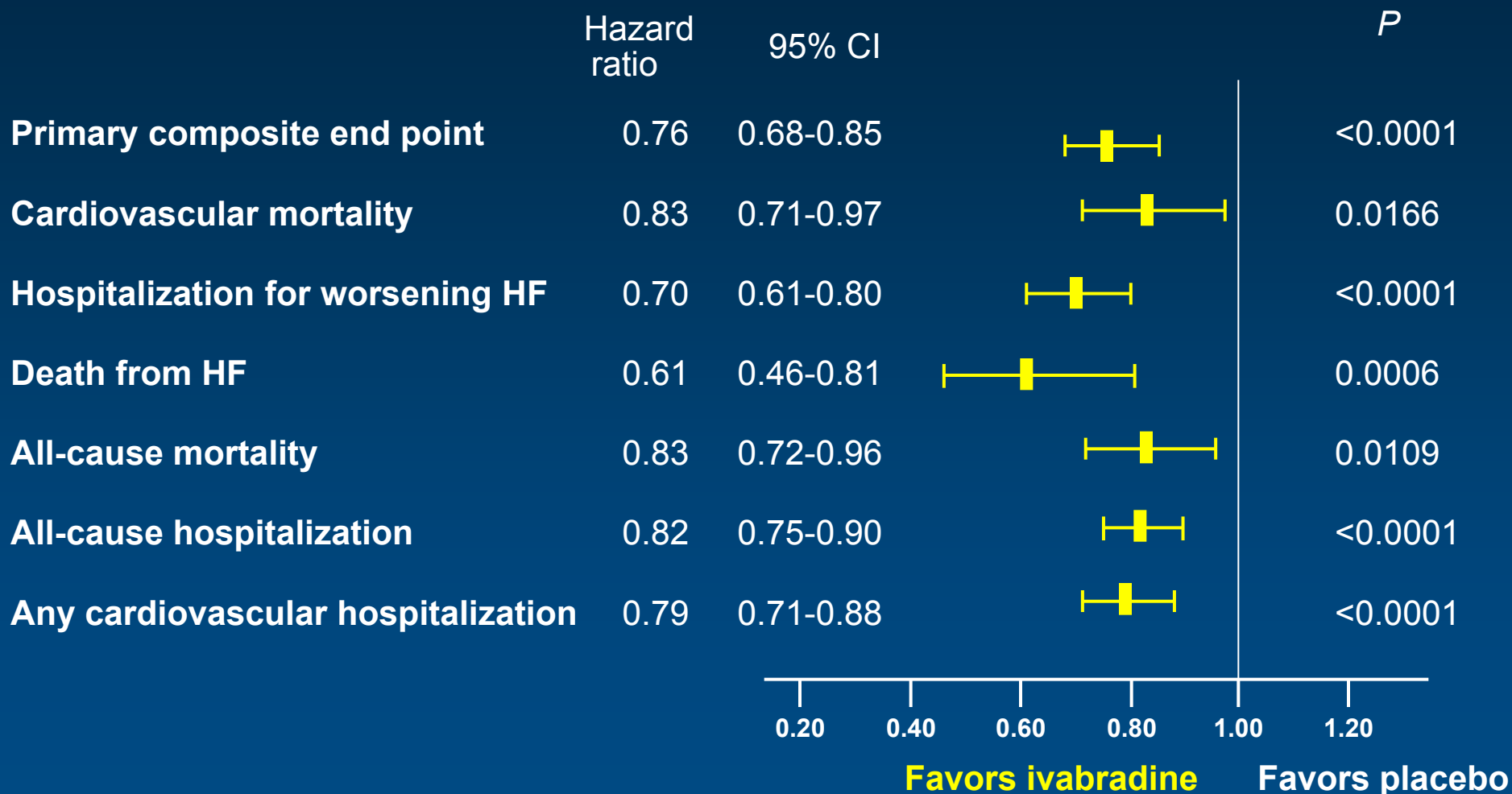
Swedberg K, et al. *Lancet*. 2010.

Effect of ivabradine in prespecified subgroups



- A cut-off of ≥ 75 bpm was chosen by the EMA for the approval of ivabradine in chronic heart failure
- 64% of the patients enrolled in SHIFT had a heart rate ≥ 75 bpm

Effect of ivabradine on major outcomes in patients with HR ≥ 75 bpm



Diuretics to relieve symptoms/signs of congestion^a

GUIDELINES

ESC G
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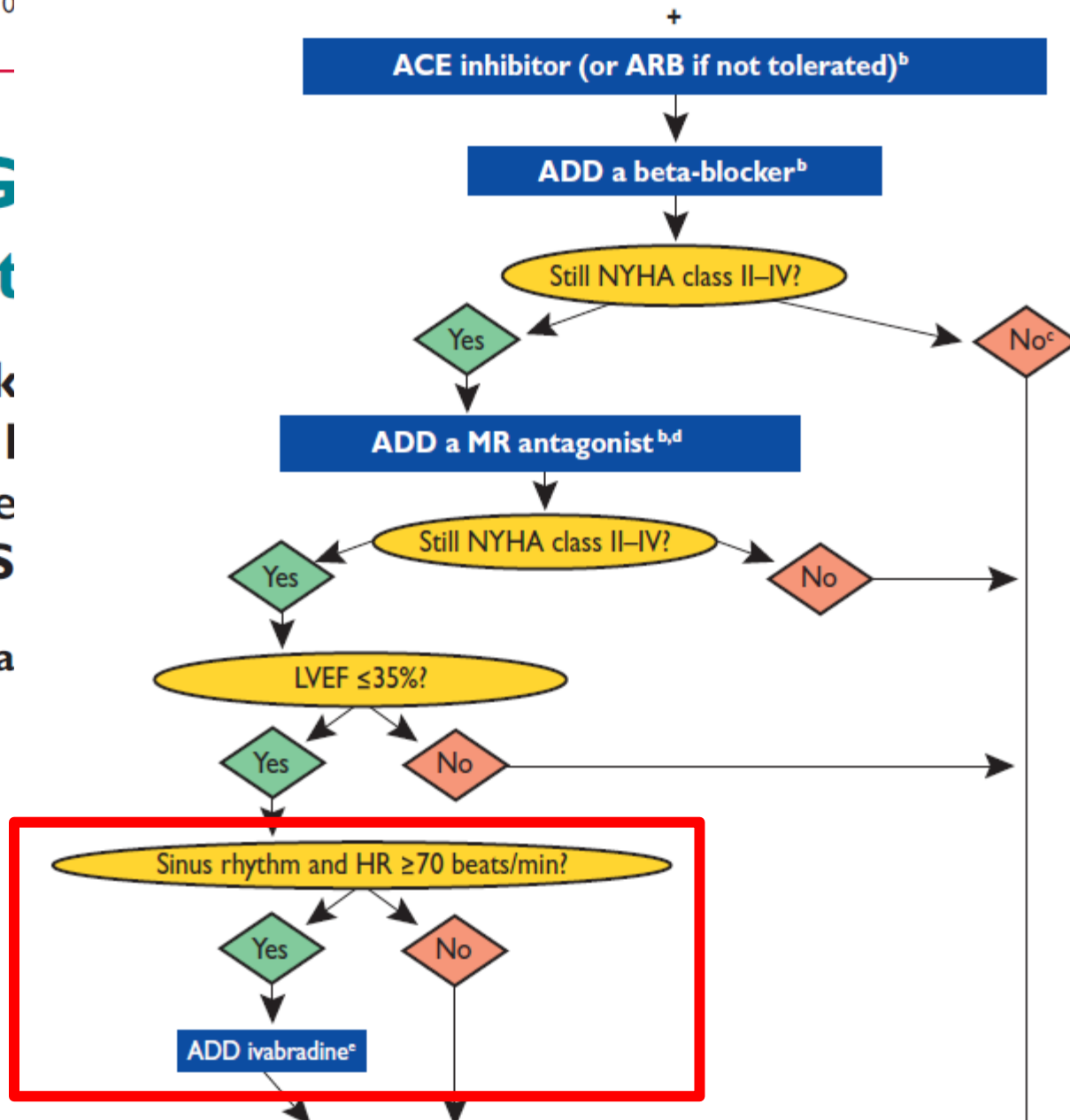
The Task
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 ion (HFA)

)*,



Summary

- **Over the last 40 years, treatment of chronic heart failure has improved dramatically**
- **A series of randomized, controlled trials have led to a change in standard of care**
- **Further improvements should hopefully replace old by new therapies more than adding them.**