Beta-blockers in heart failure: evidence put into practice

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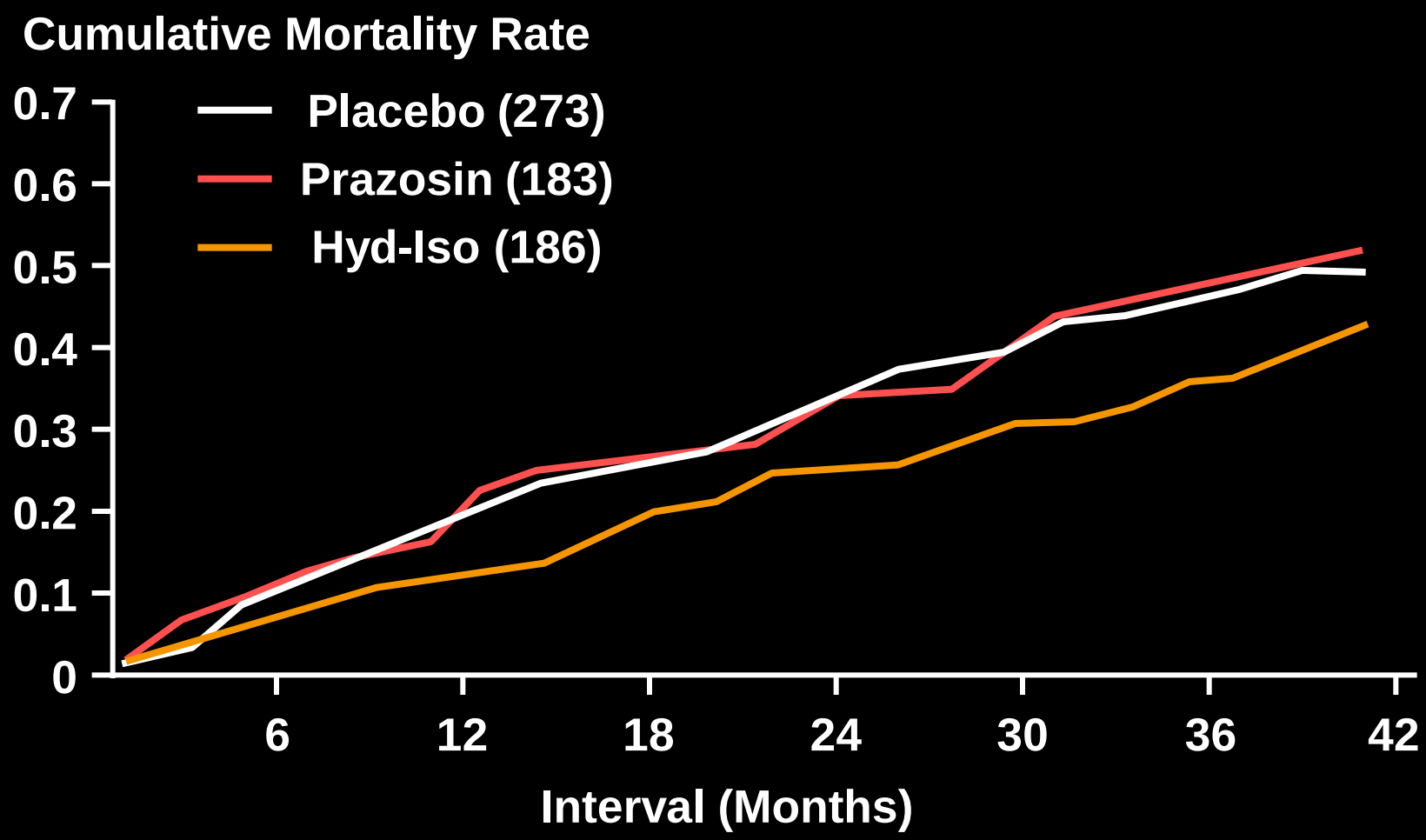
V-HEFT I



Cohn et al. NEJM 1986.

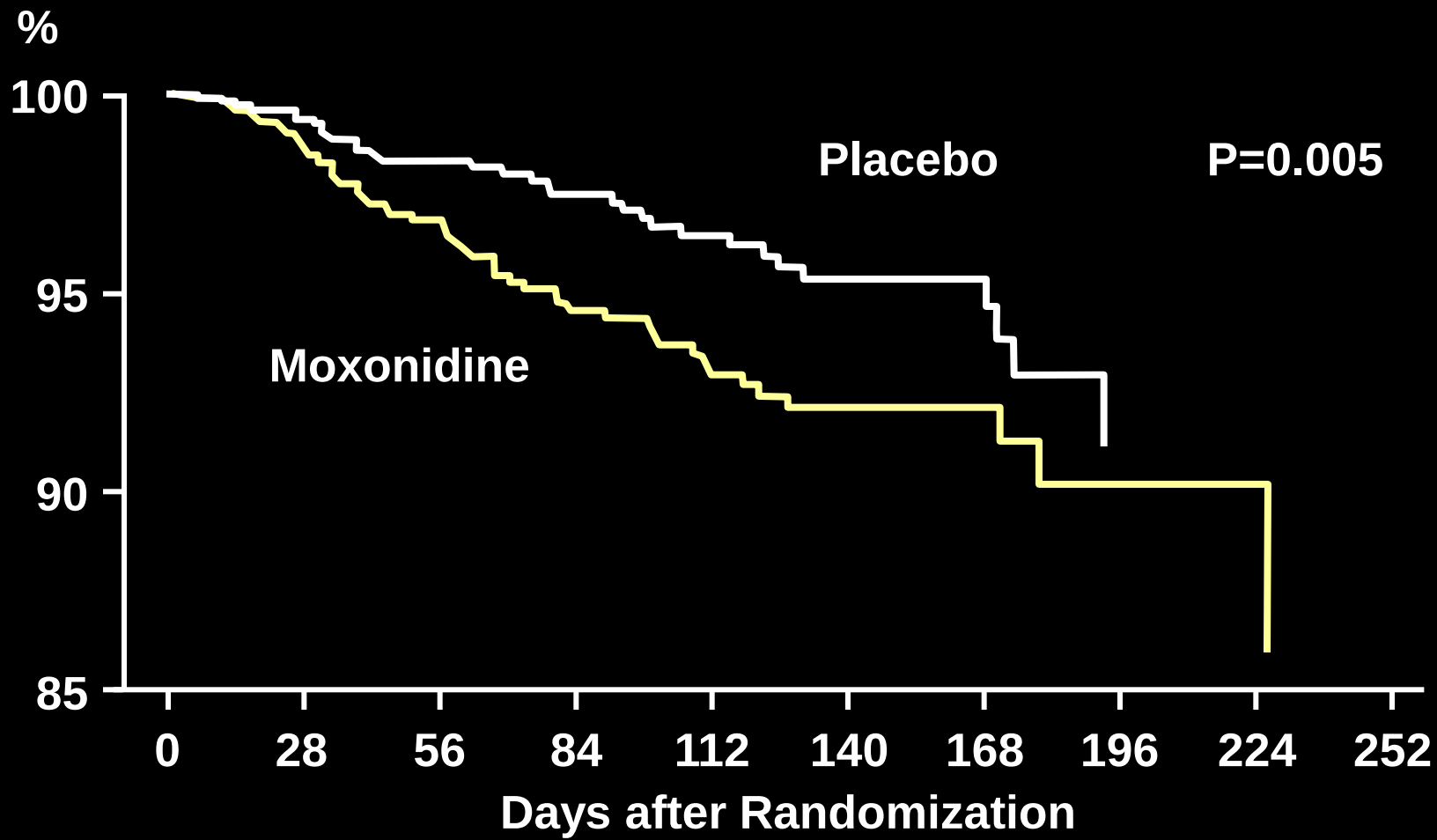
V-HEFT I
Δ Systolic Blood Pressure

	Placebo	H/N	Prazosin
Baseline	118.9	119.6	119.2
8 weeks	+0.2	0	-4.2
1 year	-0.3	+0.6	-4.6

Lives saved not related to Δ in BP

Cohn et al. NEJM 1986

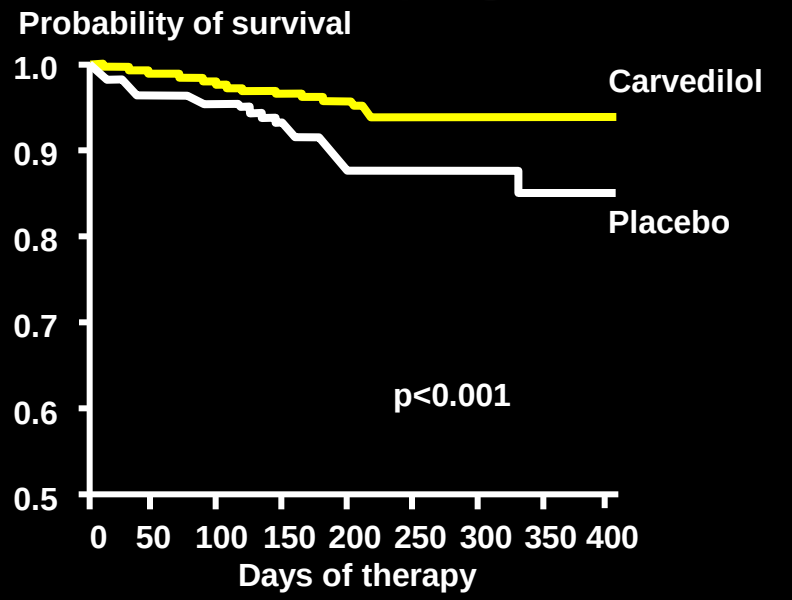
MOXCON
moxonidine CHF trial



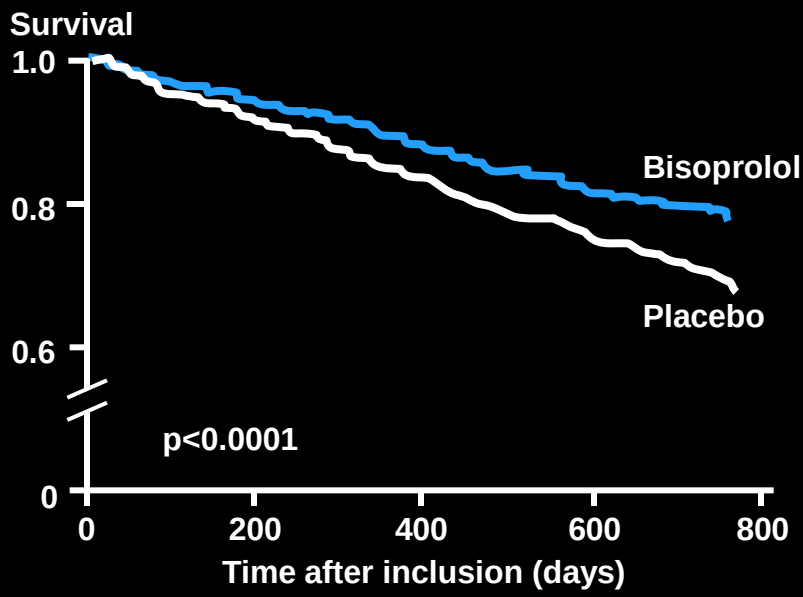

SUCCESS
FAILURE

Beta-blocker HF trials

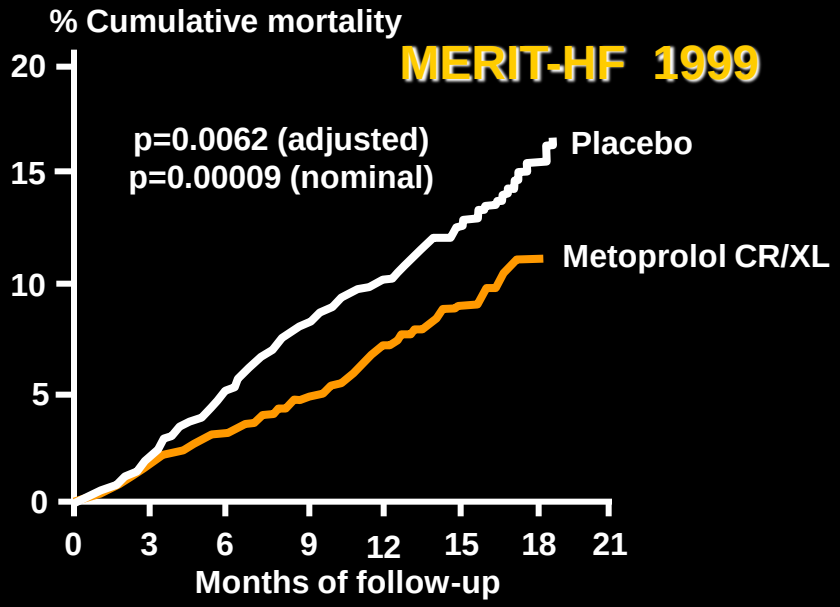
US carvedilol programme 1996



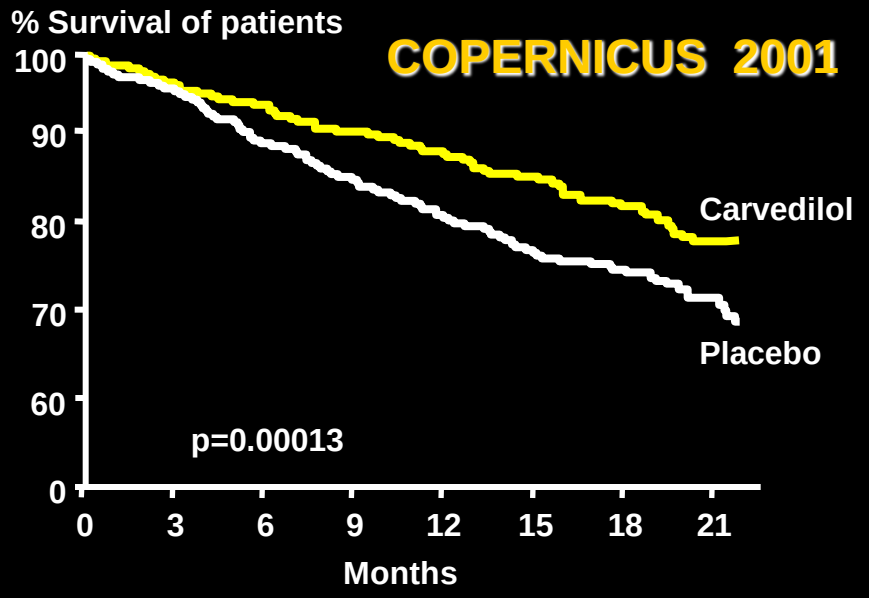
CIBIS-2 1998



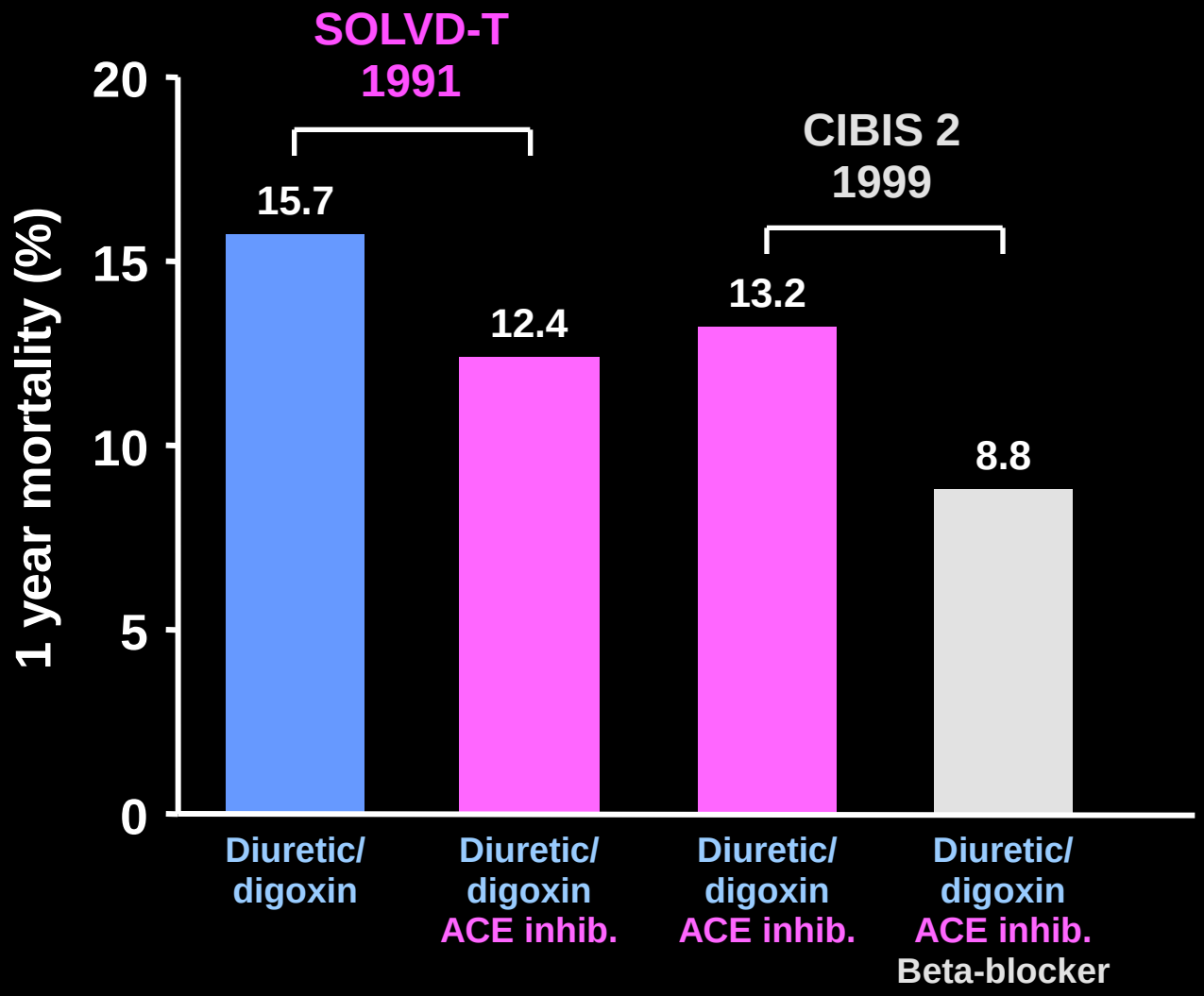
MERIT-HF 1999



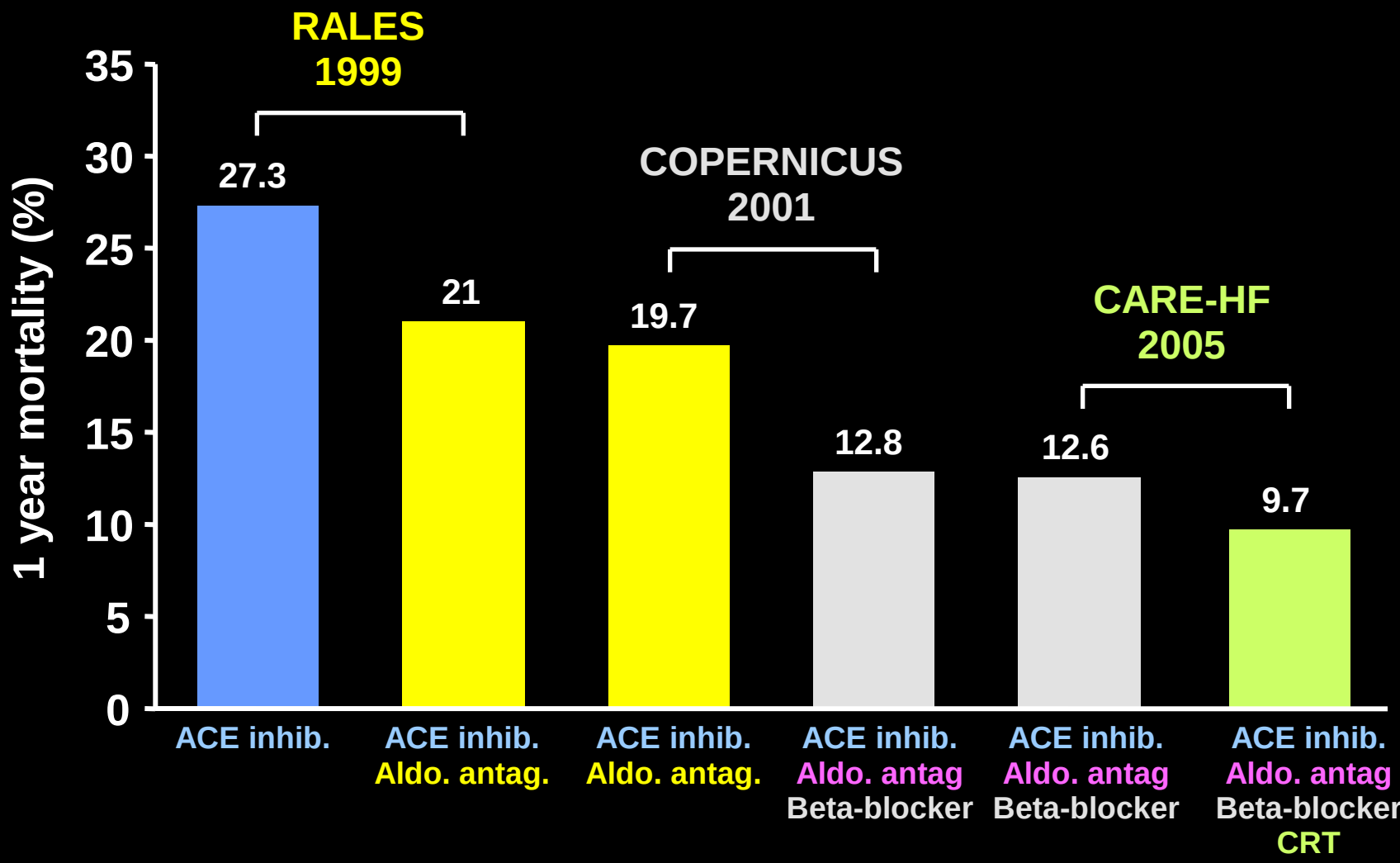
COPERNICUS 2001



Cumulative benefit of poly-pharmacy in mild-moderate HF



Cumulative benefit of poly-pharmacy (and CRT) in severe HF



Beta-blocker trials in HF - what do the results mean?

- for every 1000 “COPERNICUS like” patients treated with a beta-blocker for 1 year - approximately 70 premature deaths avoided
- compares with 40 premature deaths avoided in milder (“MERIT-HF/CIBIS-2 type”) patients
- compares with 57 premature deaths avoided per 1000 patient years with spironolactone in “ RALES type” patients

Question: which subgroup of patients has most benefit from beta-blockers?

- A. Men (versus women)?
- B. Younger (versus elderly)?
- C. Mild symptoms (versus severe)?
- D. Higher BP (versus lower)?
- E. None (no subgroup found to benefit more than another)

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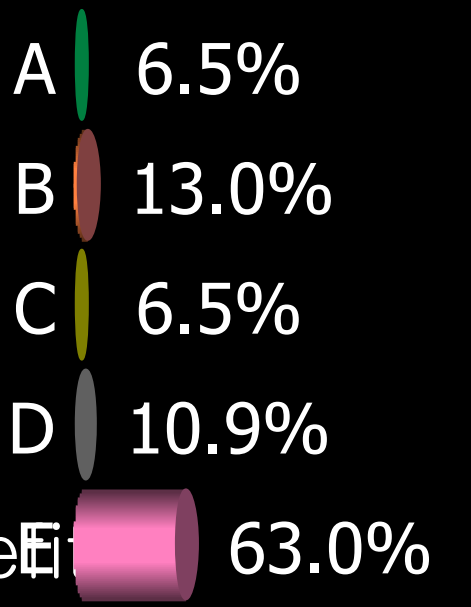
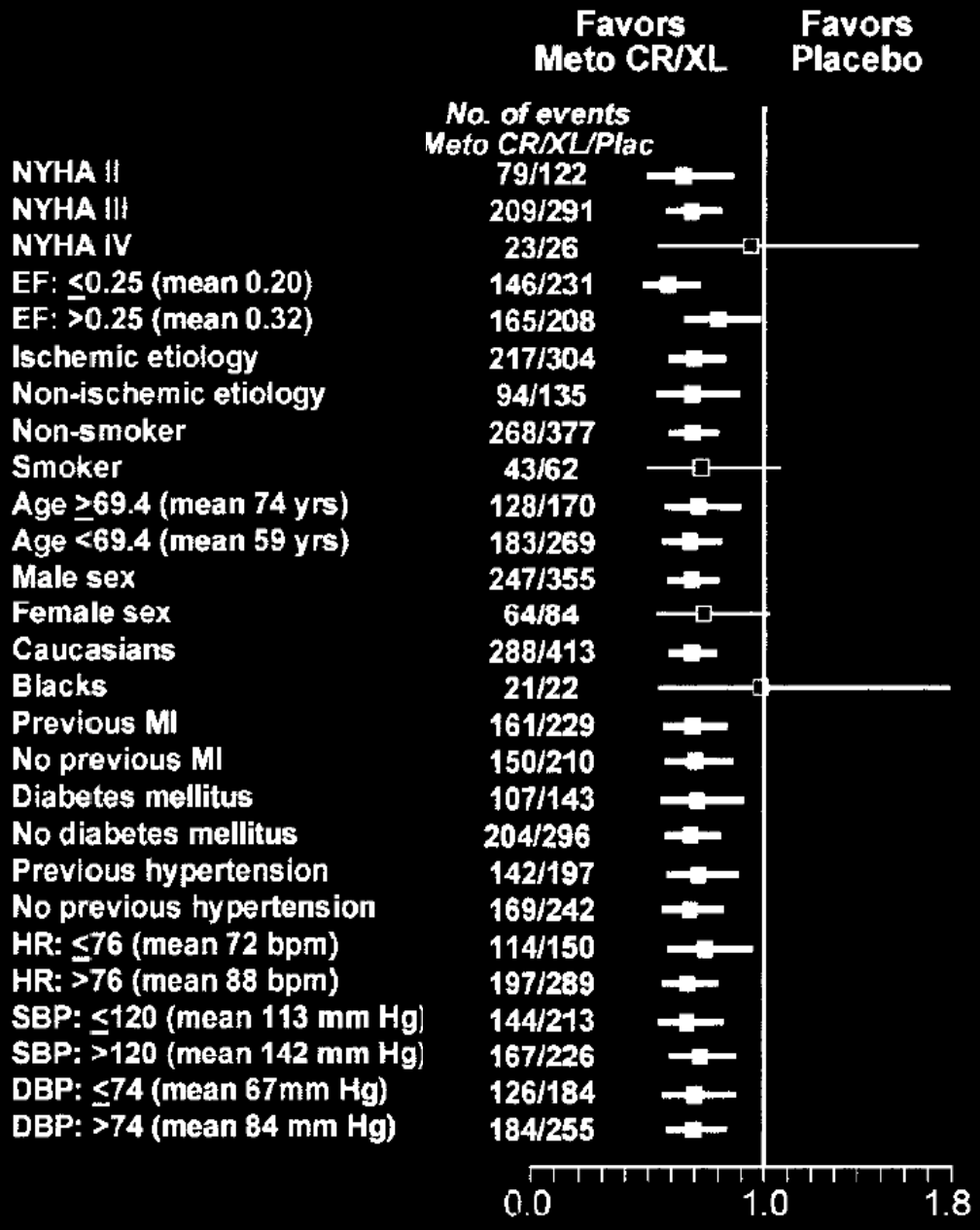
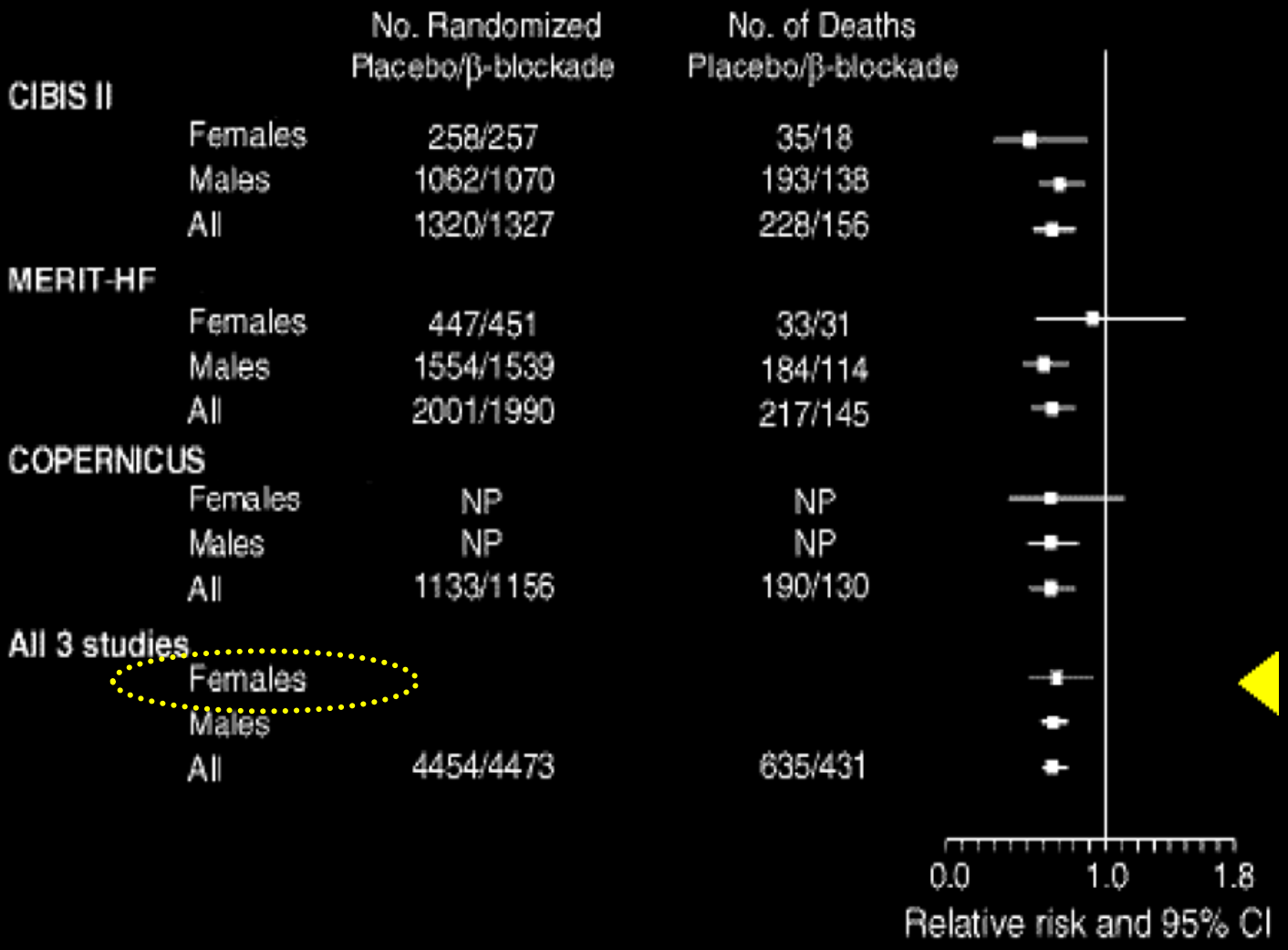


MERIT-HF subgroups: Death or HF hospitalisation



Women

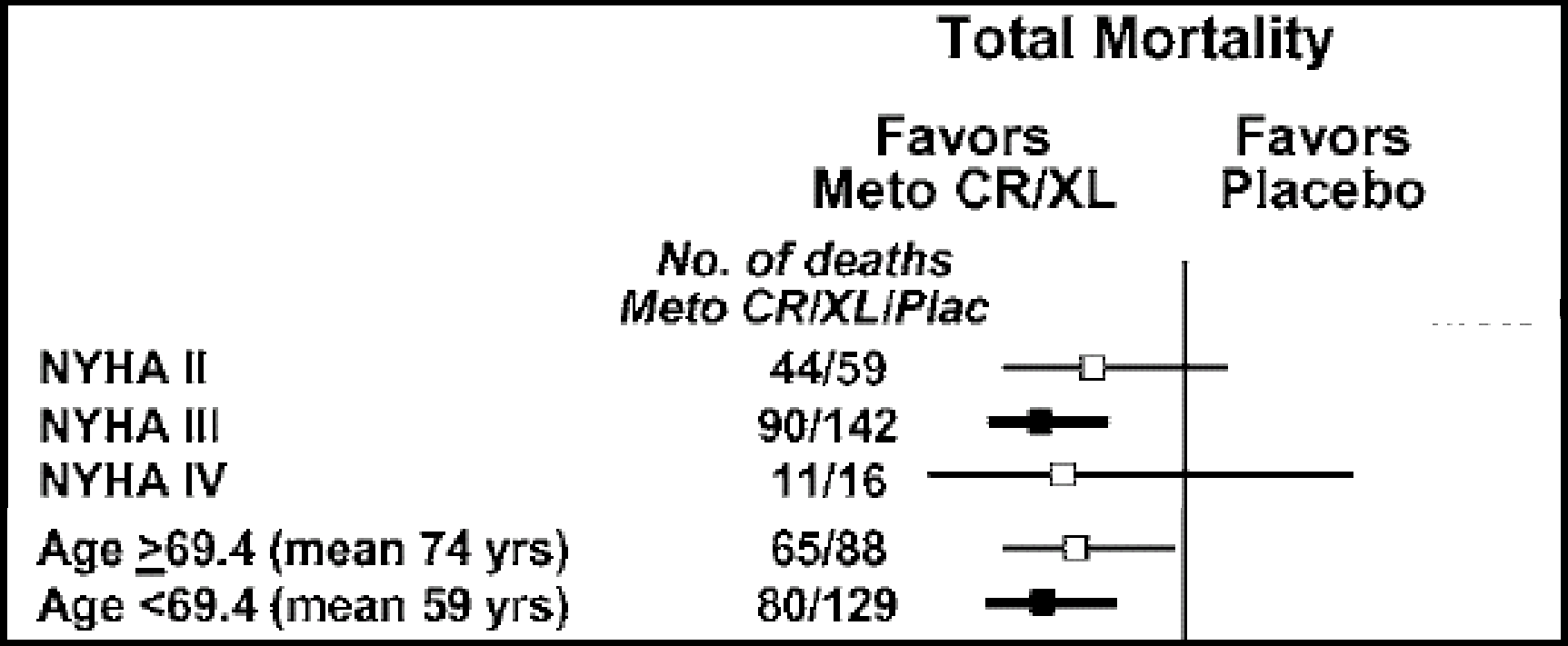
Meta-analysis of CIBIS 2, MERIT-HF and COPERNICUS



The elderly


OVER
THE
HILL

MERIT-HF: subgroups



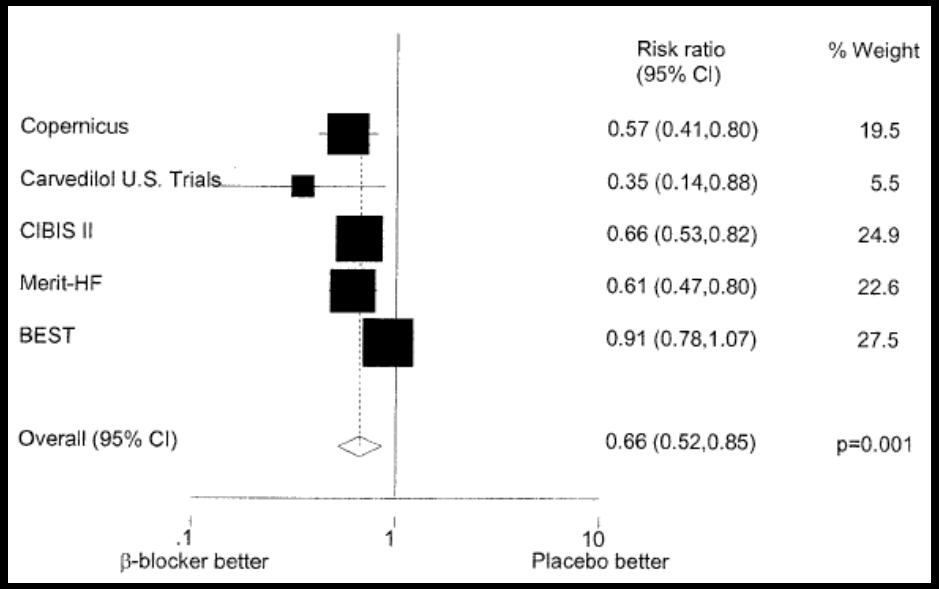
Do Elderly Systolic Heart Failure Patients Benefit from Beta Blockers to the Same Extent as the Non-Elderly? Meta-Analysis of >12,000 Patients in Large-Scale Clinical Trials

Brian R. Dulin, MD, Steven J. Haas, BPharm, BPharmSci(Hons), William T. Abraham, MD, and Henry Krum, MBBS, PhD

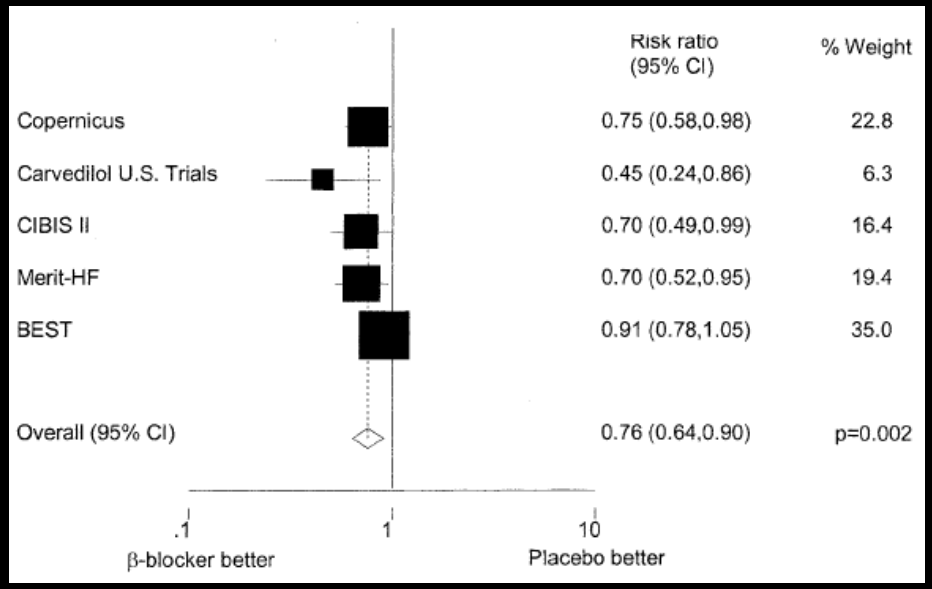
Am J Cardiol 2005;95:896–898

Beta-blocker trials meta-analysis

Non-elderly



Elderly



SENIORS

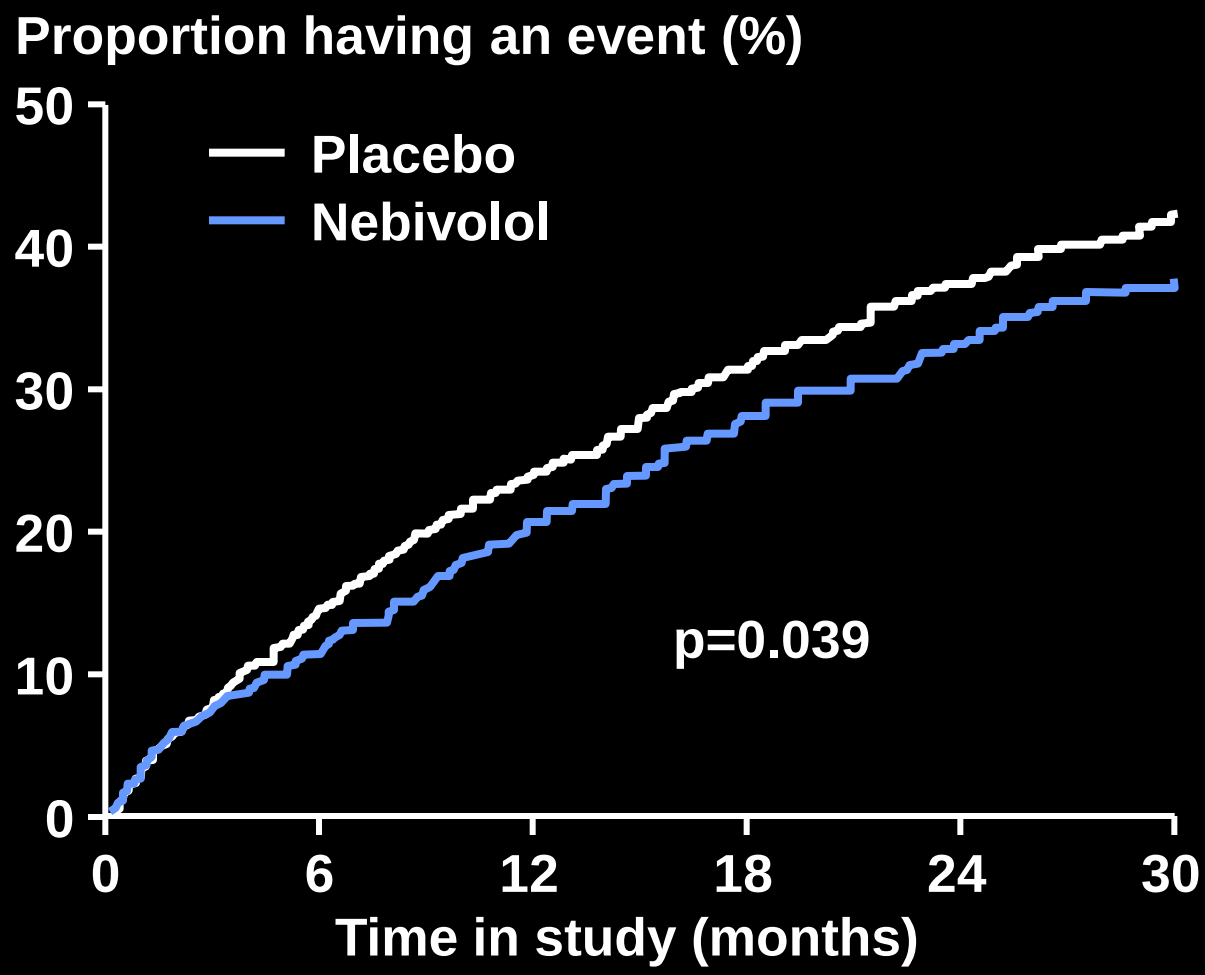
Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

2128 patients ≥ 70 years (median age 75 years)

SENIORS: nebivolol vs placebo

2128 patients ≥70 yrs with prior HF hospitalization or LVEF ≤0.35
Followed for a mean of 21 months

Primary endpoint: Death or CV hospitalization



Flather et al. Eur Heart J 2005;26:215-25

Question: Are all beta-blockers the same in heart failure: Which beta-blocker is not of proven benefit in heart failure

- A. Bisoprolol?
- B. Bucindolol?
- C. Carvedilol?
- D. Metoprolol succinate?
- E. Nebivolol?

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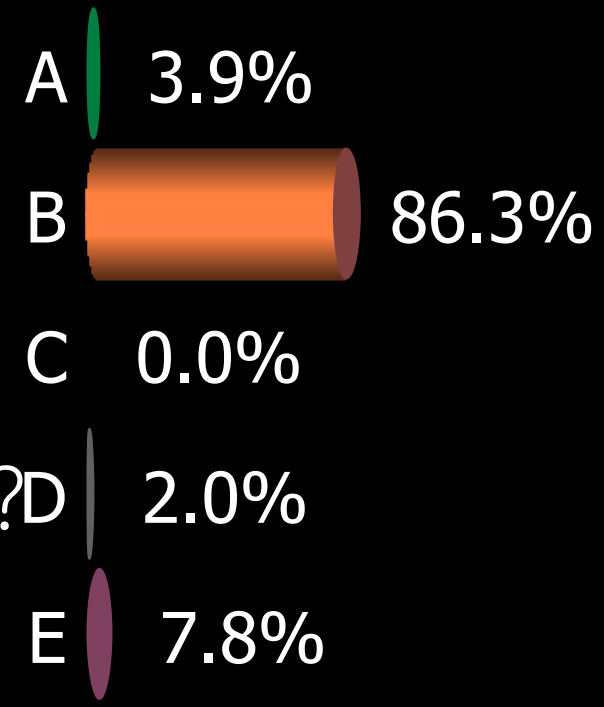
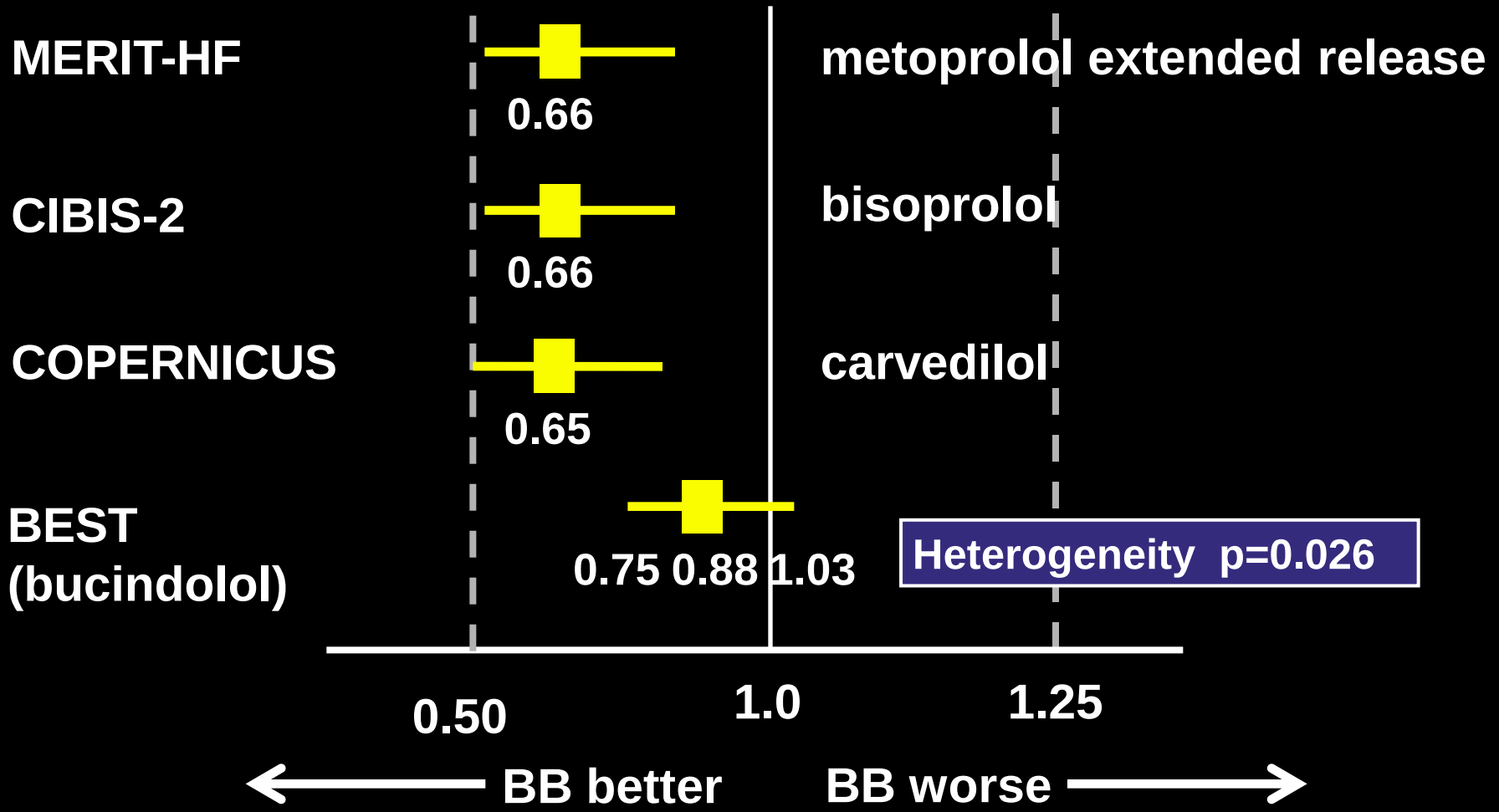


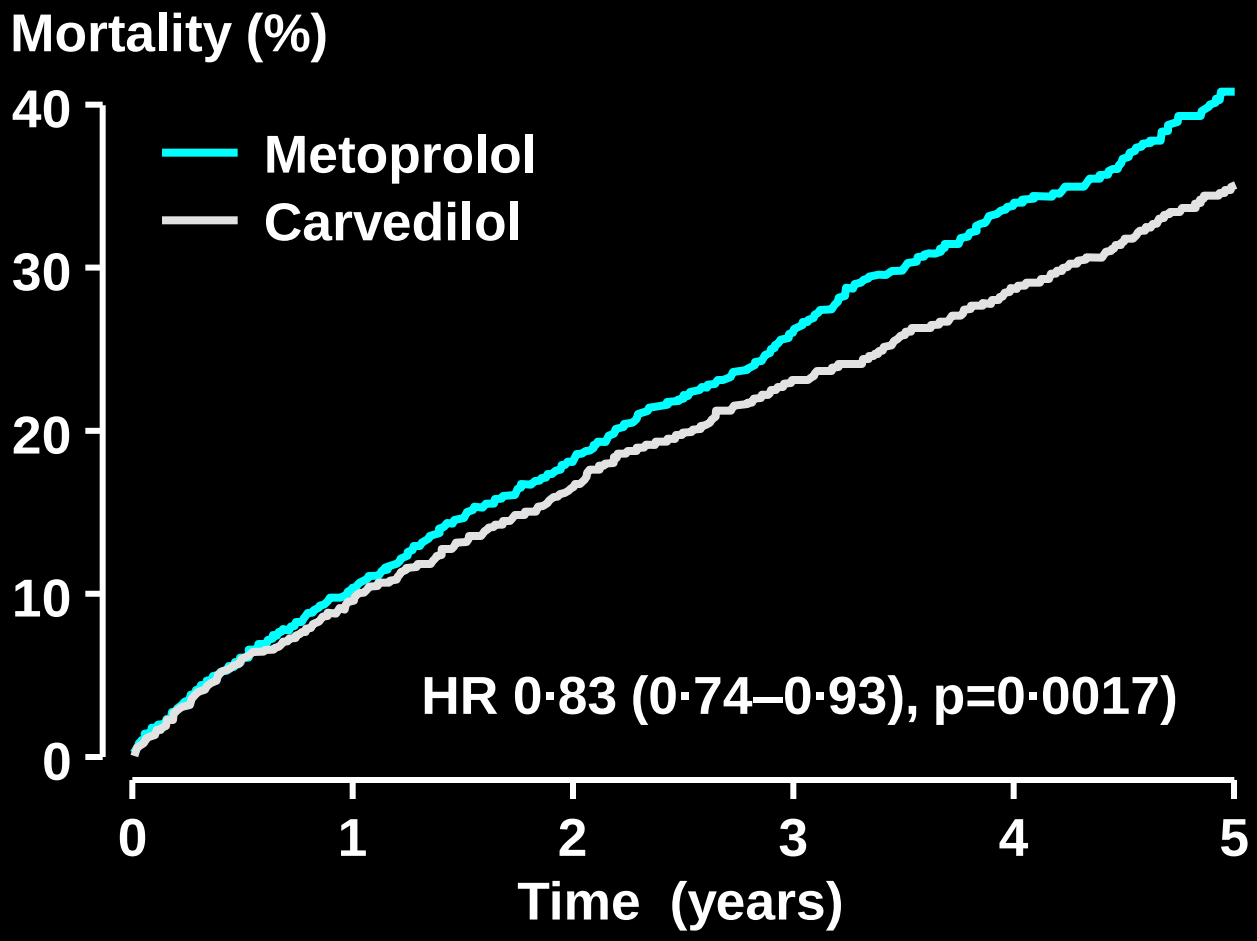
Beta-blockers in HF: Is it a class effect?

Mortality



COMET: carvedilol vs. metoprolol tartrate

3029 patients with NYHA class II-IV HF and a LVEF ≤0.35
Followed for a mean of 58 months



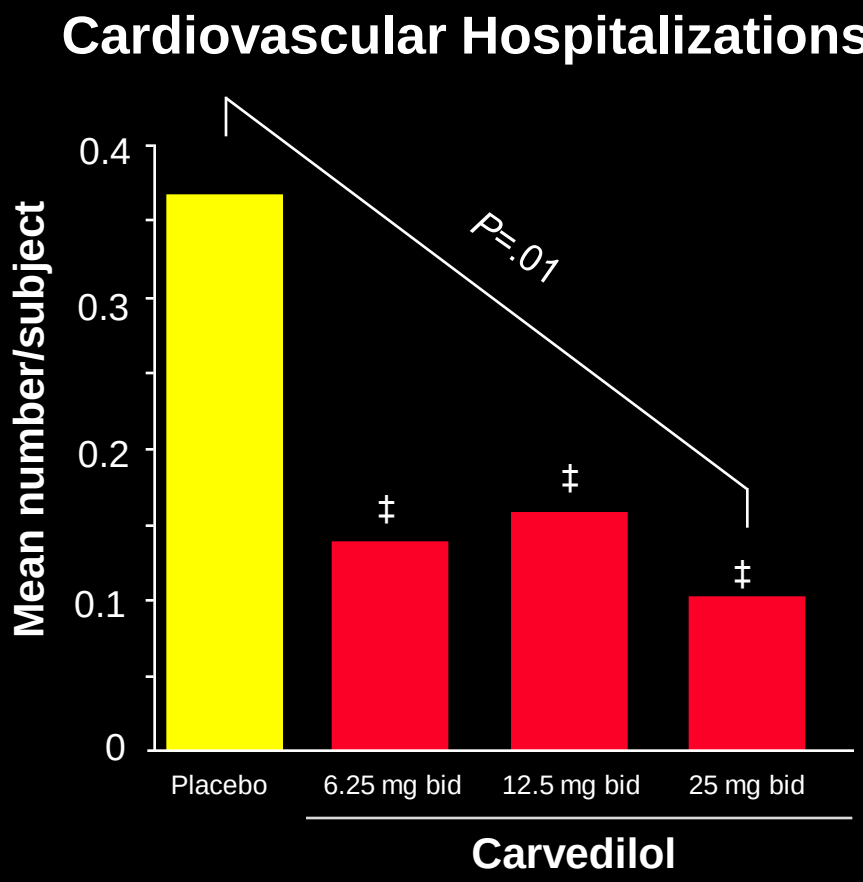
Poole-Wilson et al. Lancet 2003;362:7–13

COMET: a fair comparison?

- Compared an unproven dose of short acting metoprolol tartrate to a proven dose of carvedilol (which has a much longer $t_{1/2}$)
- Only prior trial experience with short acting metoprolol was in MDC – dosing bd/tds; average dose 108 mg/day; average in COMET 85 mg/day
- In a comparator study HR was higher in metoprolol tartrate 50mg tds group than in CR/XL 200mg/d group
- Reduction in HR with metoprolol in MERIT-HF 14.0 beats/min; in COMET -11.7 beats/min (c.f. carvedilol 14.0 beats/min)
- But, can a 17% mortality reduction really be explained by underdosing?

Does dose matter?

Carvedilol Dose-Response Trial (MOCHA*): Effect on Mortality and Morbidity



§ *P*=.07 vs placebo
‡ *P*=.05 vs placebo

Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n=261).
*Multicenter Oral Carvedilol Heart Failure Assessment.
Adapted from Bristow MR et al. *Circulation*. 1996;94:2807–2816.

Question: Which is the most evidence-based drug-treatment in heart failure?

- A. ACE inhibitors?
- B. Aldosterone antagonists?
- C. Beta blockers?
- D. Diuretics?
- E. Digoxin?

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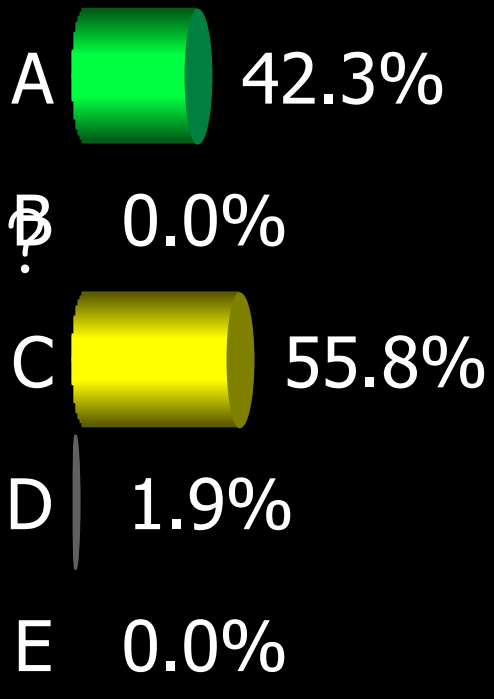


CHF trials: beta-blockers and ACE inhibitors

Trial	No. of patients
USCP	1094
CIBIS II	2647
MERIT - HF	3991
COPERNICUS	2289
BEST	2708
SENIORS	2128
COMET	3029
CONSENSUS I	253
SOLVD-T	2569
VHeFT II	804
ATLAS	3164

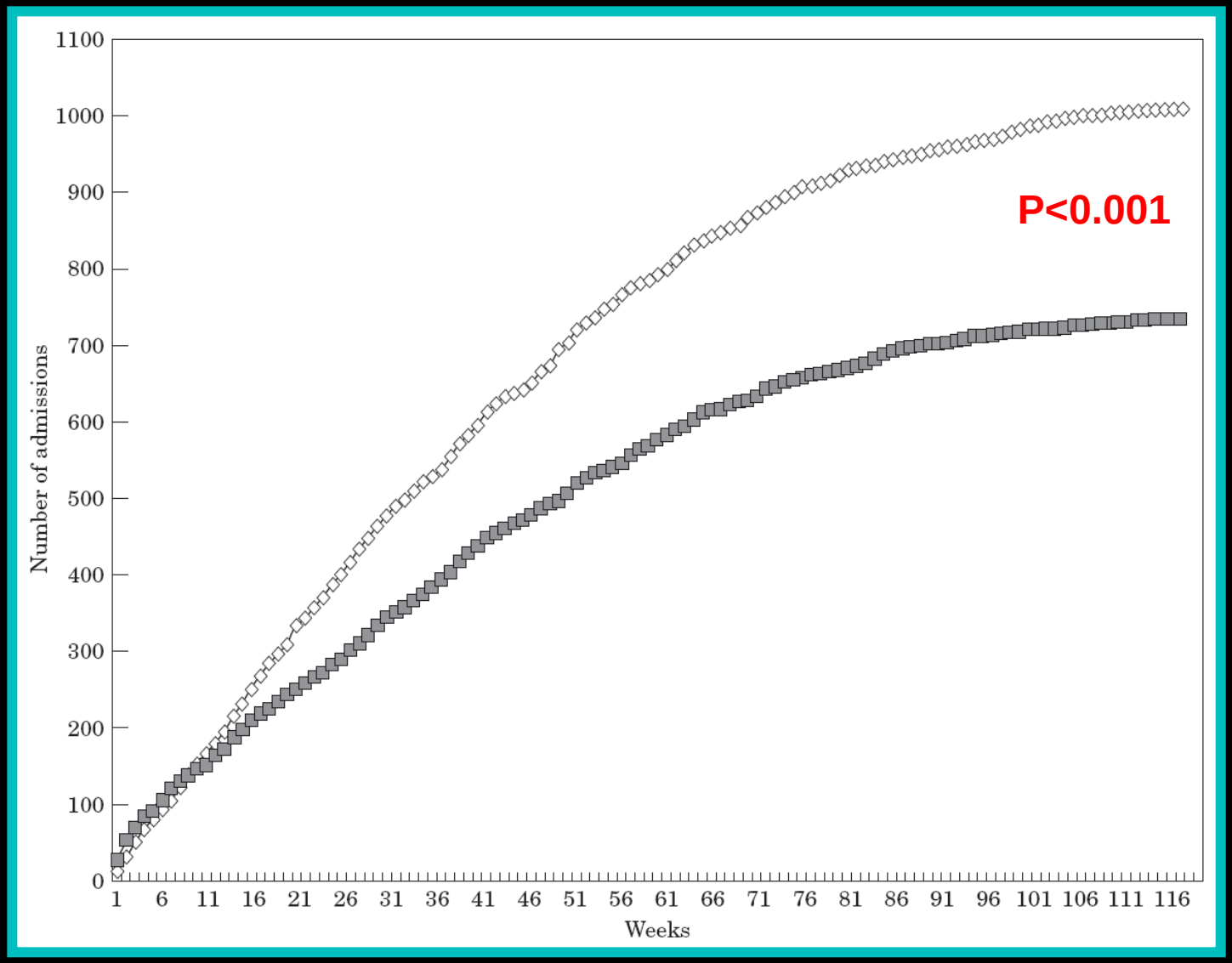
BETA-BLOCKERS IN CHF

- 3 mega-trials (and USCP) all stopped prematurely because of highly statistically significant reductions in mortality
- Also improvement in symptoms, decreased number of hospital admissions and improved QoL
- Beta-blockers now mandatory first line treatments, along with an ACE inhibitor in CHF

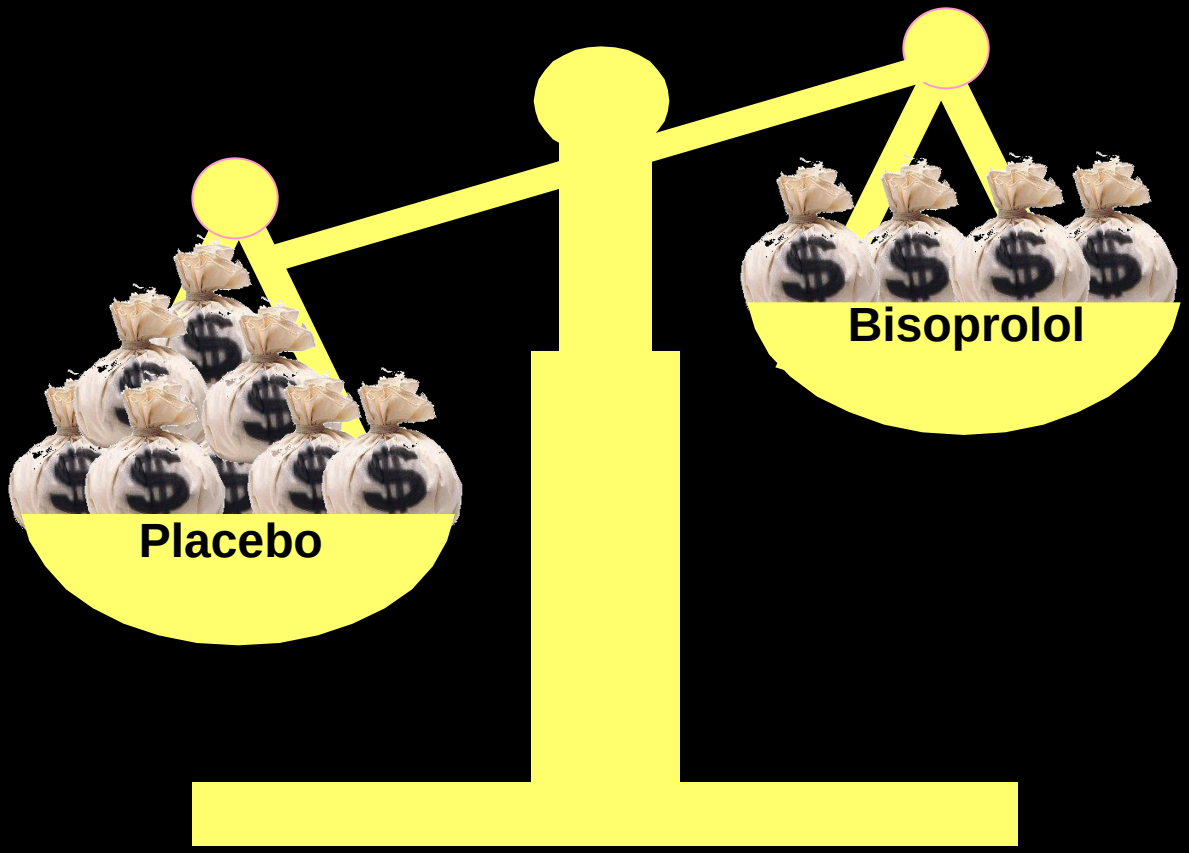
Improving outcomes cost-effectively

CIBIS II

Hospital admissions (all causes)



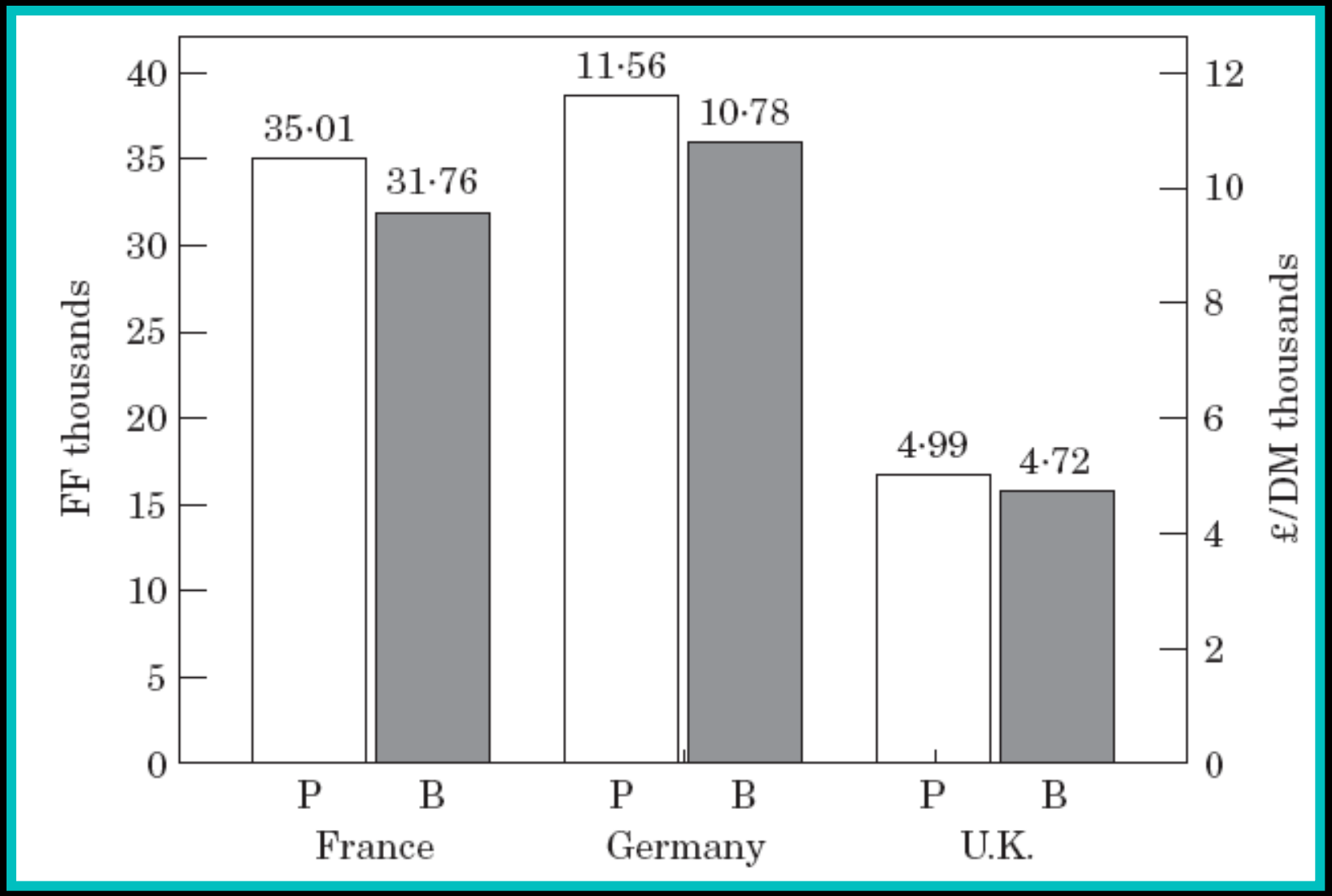
The Bottom Line



- More hospital admissions

- Cost of beta-blocker
- Cost of monitoring
- Cost of adverse effects

CIBIS II – Economic analysis



Eur Heart J 2001

Question: Which of the following is true about beta-blockers in heart failure?

- A. They are worse tolerated than placebo?
- B. They cause erectile dysfunction?
- C. They cannot be given to patients with COPD?
- D. All of the above?
- E. None of the above?

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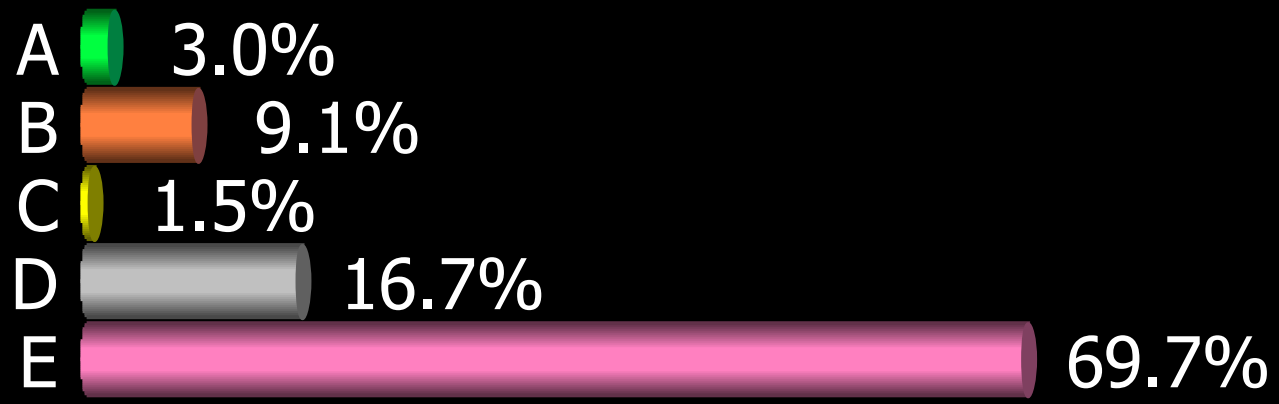
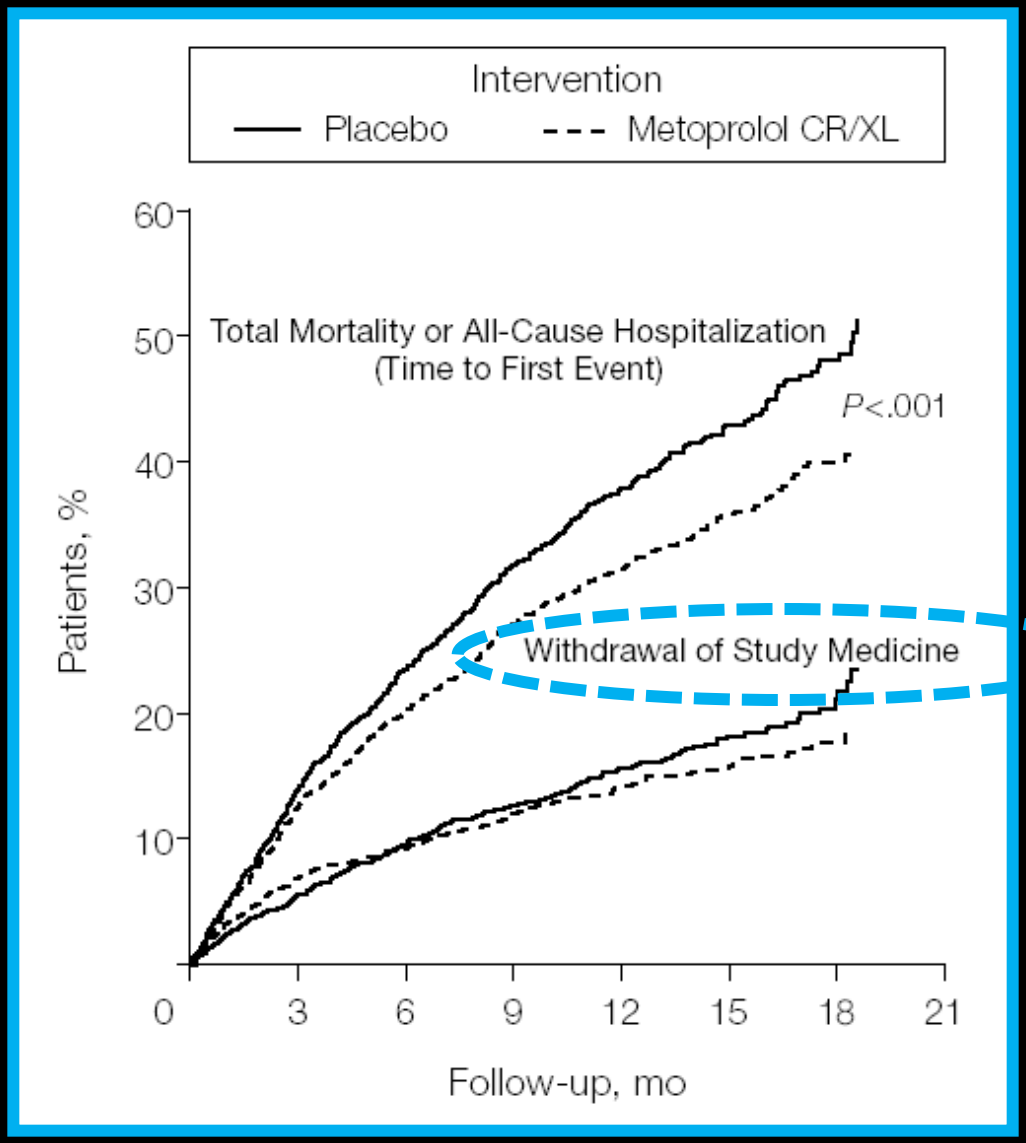


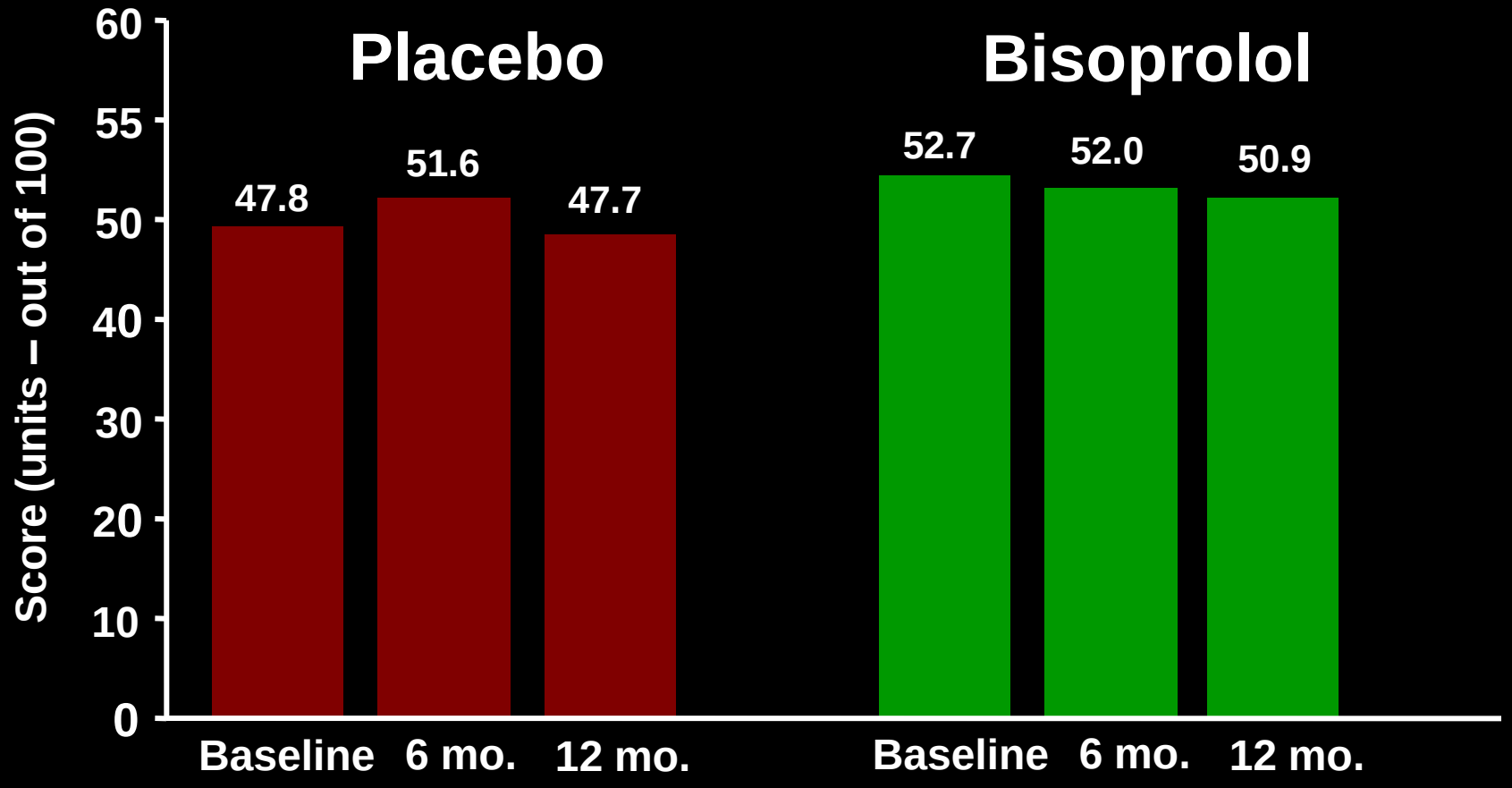
Myths about beta-blockers

MERIT-HF: Efficacy and tolerability



CIBIS-2: Sexual relationships (n=353)

FSQ: score out of 100; higher score better

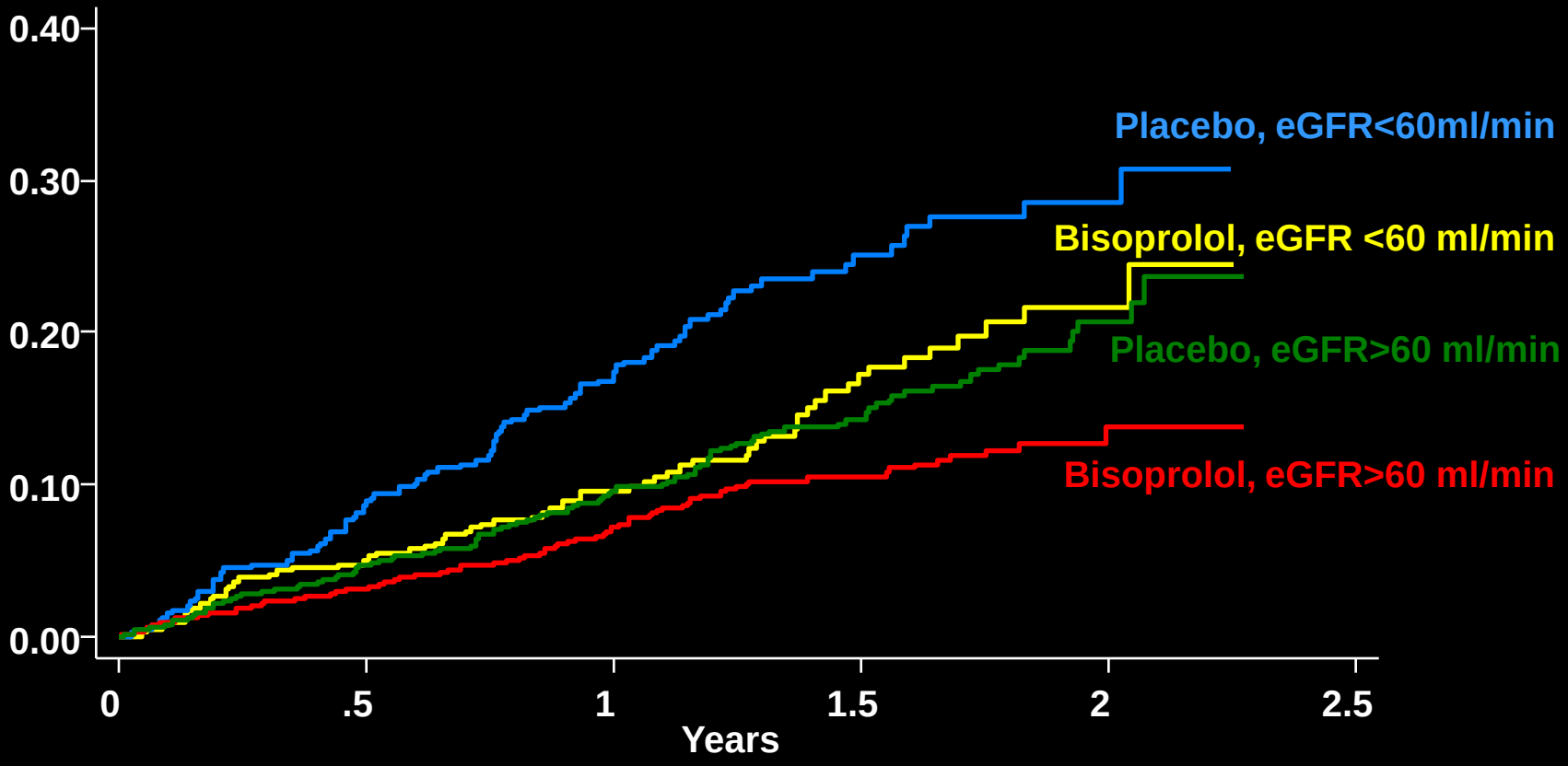


New data

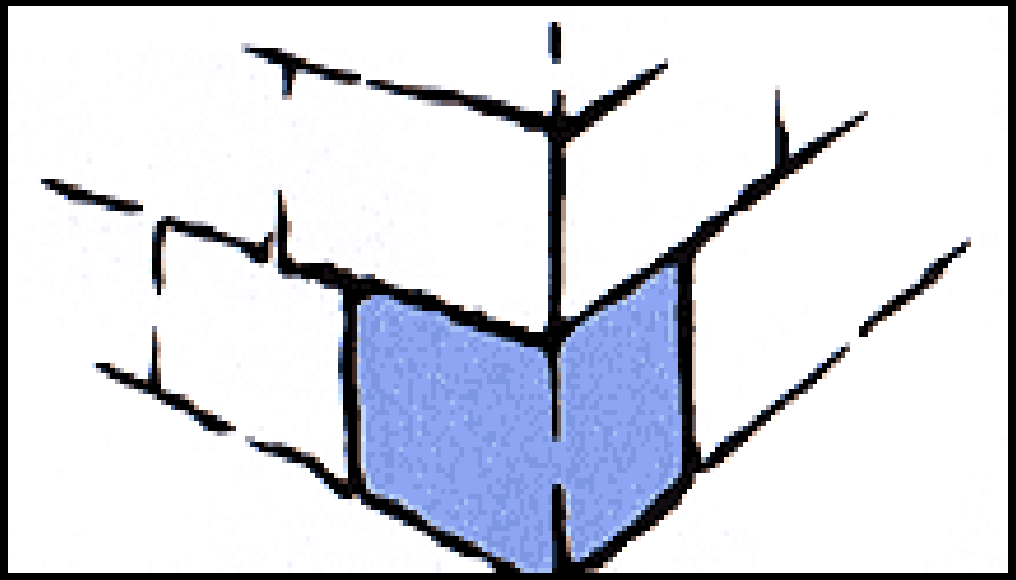
CIBIS-ELD

- Double-blind RCT comparing bisoprolol and carvedilol in 883 elderly patients with heart failure (aged ≥65 yrs/mean 73yrs)
- Greater reduction in HR with bisoprolol: 8.4 vs. 6.0 beats/min (and more bradycardia-relates AEs)
- Greater reduction in FEV1 with carvedilol: -42 vs. +3 ml (and more pulmonary AEs)
- Fall in Hb/anaemia with carvedilol

CIBIS-2: all cause mortality according to baseline eGFR

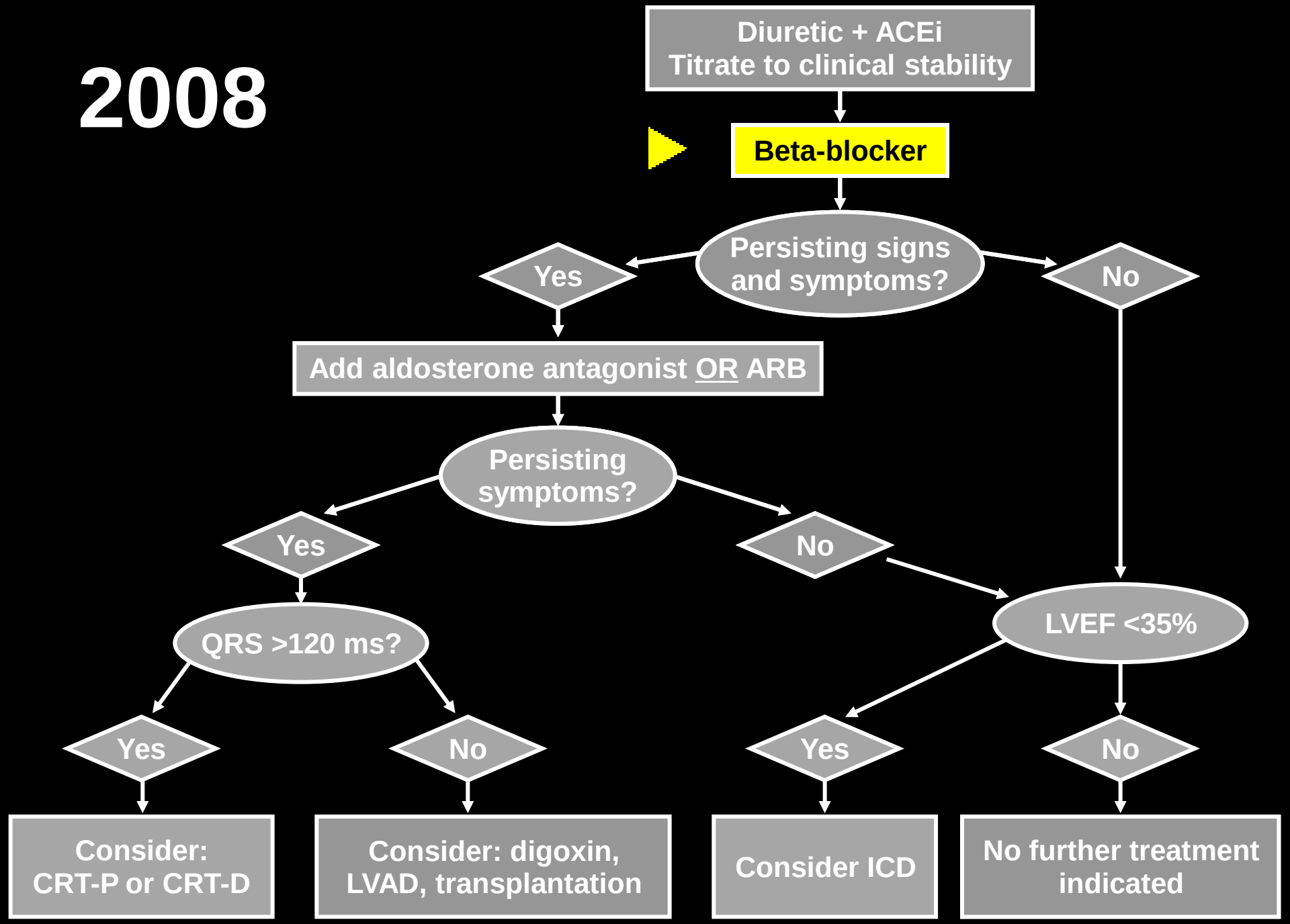


The cornerstone of therapy



ACE inhibitor (or ARB)
Beta-blocker

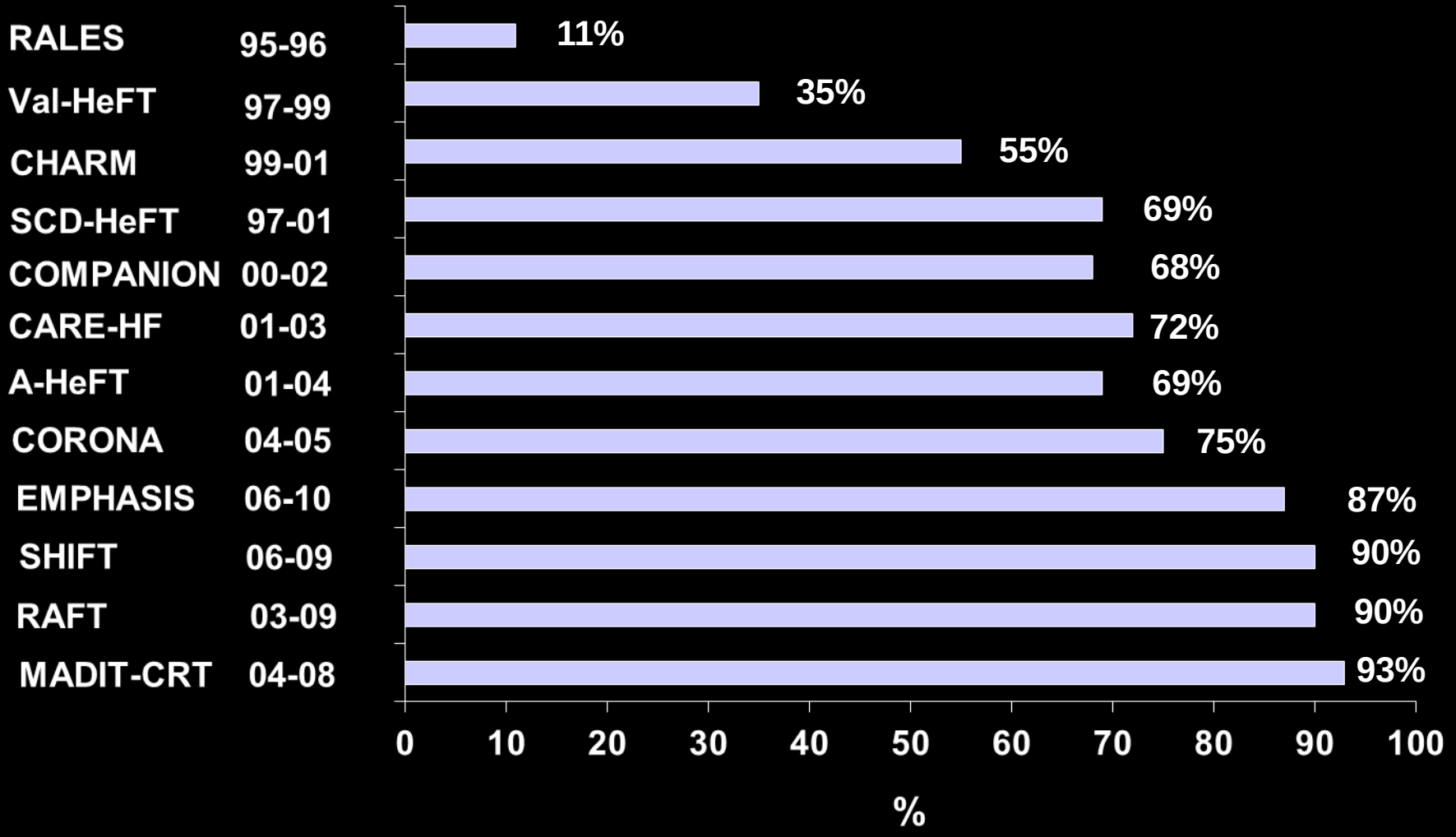
2008


Diuretic + ACEi
Titrate to clinical stability
Beta-blocker
Persisting signs and symptoms?
Yes
No
Add aldosterone antagonist OR ARB
Persisting symptoms?
Yes
No
QRS >120 ms?
LVEF <35%
Yes
No
Yes
No
Consider: CRT-P or CRT-D
Consider: digoxin, LVAD, transplantation
Consider ICD
No further treatment indicated

Guidelines: Beta-blockers

ESC		ACC/AHA		CCS		HFSA		Aust/NZ	
Level	Class	Level	Class	Level	Class	Level	Class	Level	Class
A	I	A	I	A	I	A	I	A	I

Beta-blocker use in recent CHF trials



Practical *guidance*: beta-blockers

BETA-BLOCKERS

Practical guidance on the use of beta-blockers in patients with HF due to left ventricular systolic dysfunction

Why?

Several major randomised controlled trials (i.e., USCP, CIBIS II, MERIT-HF, COPERNICUS) have shown, conclusively, that certain beta-blockers increase survival, reduce hospital admissions and improve NYHA Class and quality of life when added to standard therapy (diuretics, digoxin and ACE inhibitors) in patients with stable mild and moderate HF and in some patients with severe HF. In the SENIORS trial which differed substantially in design from the aforementioned studies (older patients, some patients with preserved left ventricular systolic function, longer follow-up), nebivolol appeared to have a smaller treatment effect, though direct comparison is difficult. One other trial (BEST) did not show a reduction in all cause mortality but did report a reduction in cardiovascular mortality and is otherwise broadly consistent with the aforementioned studies. The COMET trial showed that carvedilol was substantially more effective than short-acting metoprolol tartrate* (long acting metoprolol succinate was used in MERIT-HF).

In whom and when?

Indications:

- Potentially all patients with stable mild and moderate HF; patients with severe HF should be referred for specialist advice
- 1st line treatment (along with ACE inhibitors) in patients with stable NYHA Class II–III HF; start as early as possible in course of disease

Contraindications:

- Asthma

Cautions/seek specialist advice:

- Severe (NYHA Class IV) HF
- Current or recent (<4 weeks) exacerbation of HF e.g., hospital admission with worsening HF
- Heart block or heart rate <60/min
- Persisting signs of congestion, hypotension/low blood pressure (systolic <90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema

Drug interactions to look out for:

- Verapamil/diltiazem (should be discontinued)**
- Digoxin, amiodarone

Where?

- In the community in stable patients (NYHA Class IV/severe HF patients should be referred for specialist advice)
- Not in unstable patients hospitalised with worsening HF
- Other exceptions – see Cautions/seek specialist advice

Which beta-blocker and what dose?

	Starting dose	Target dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25–50 mg twice dail
Metoprolol CR/XL	12.5–25 mg once daily	200 mg once daily*
Nebivolol	1.25 mg once daily	10 mg once daily

McMurray et al Eur J HF 2005; 7:710-21

Summary and conclusions

Beta-blockers in patients with low LVEF heart failure:

- Feel better
- Stay out of hospital
- Live longer
- Cut costs