Ποιά η Θέση των Αποκλειστών AT1 στη Θεραπεία της Καρδιακής Ανεπάρκειας

Αθανάσιος Ι. Μανώλης

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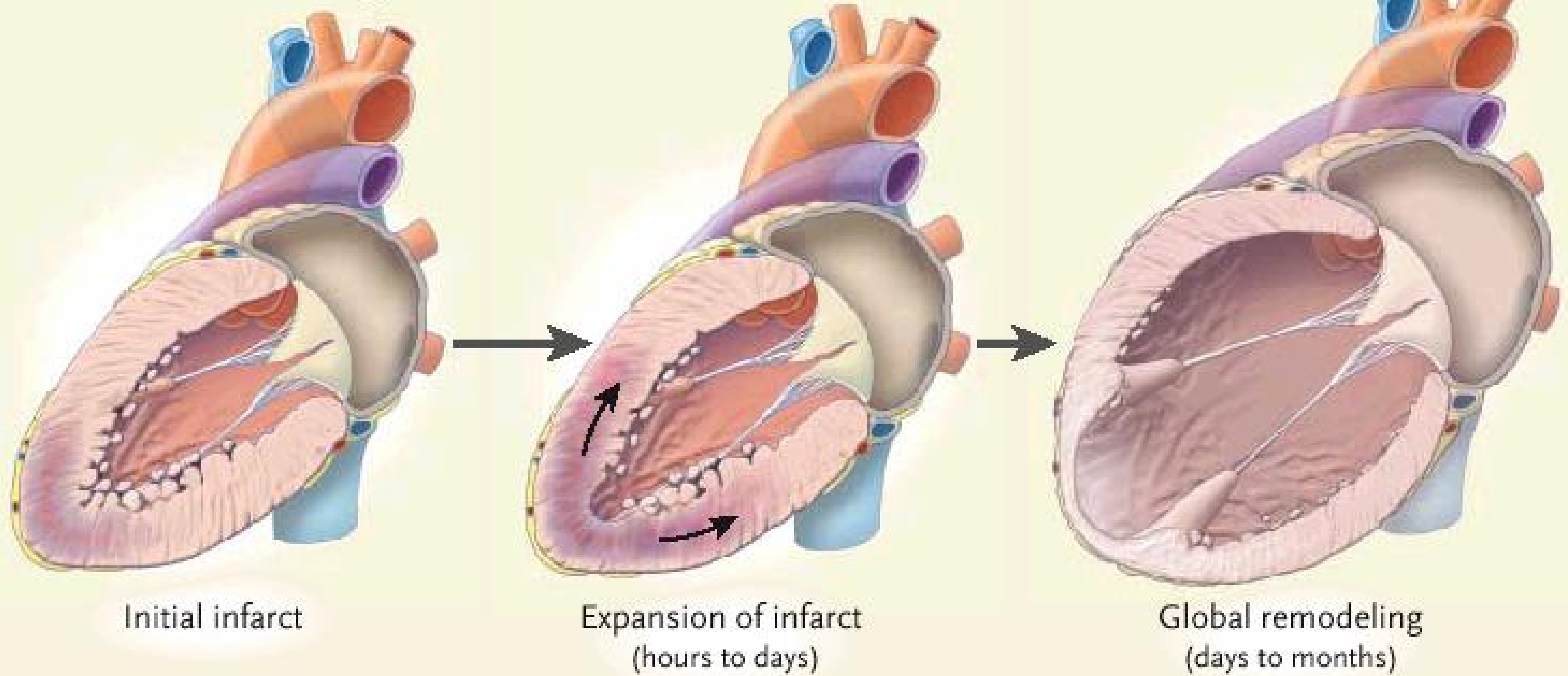
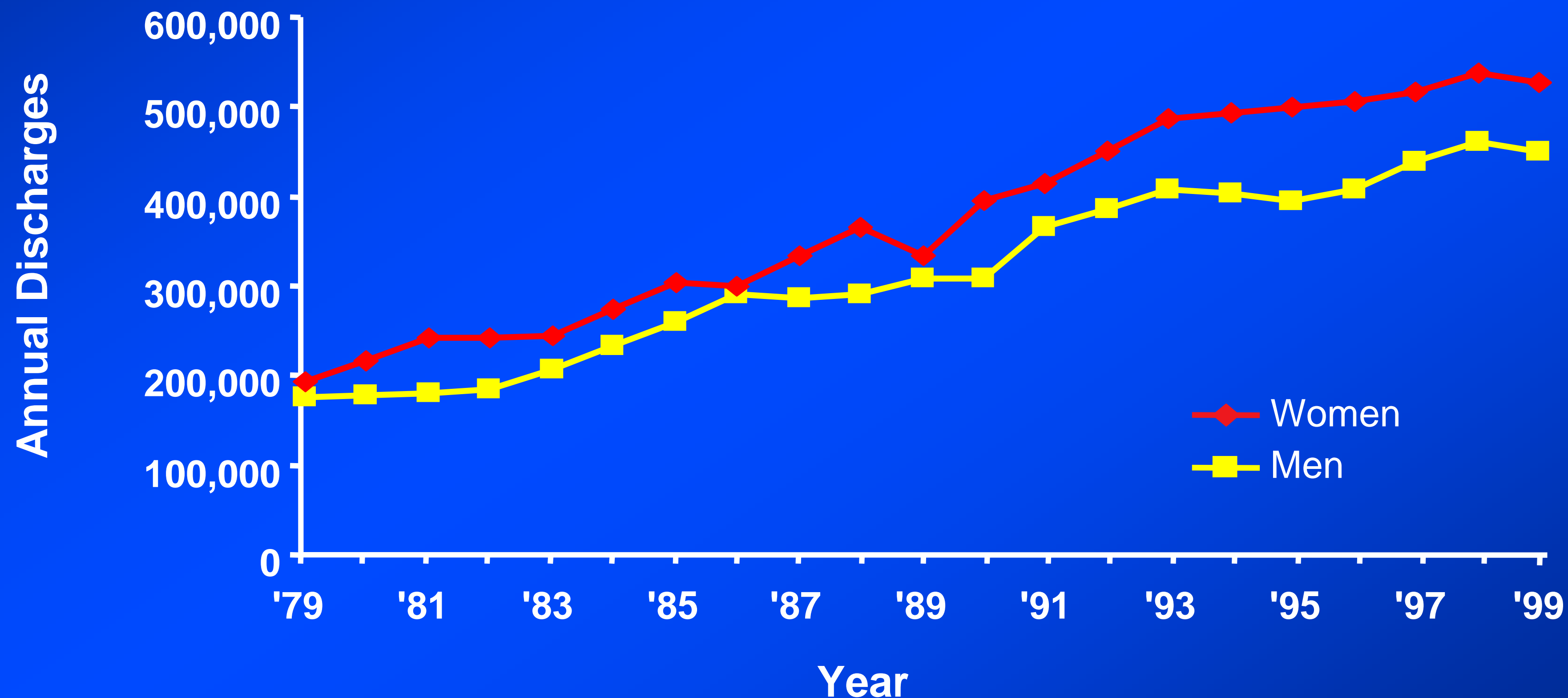
Επίκουρος Καθηγητής Υπέρτασης, Ιατρικής Σχολής Πανεπιστημίου Βοστώνης, ΗΠΑ

Καθηγητής Καρδιολογίας, Πανεπιστημίου** Emory, **Ατλάντας, ΗΠΑ


Ventricular remodeling after acute infarction
Initial infarct
Expansion of infarct
(hours to days)
Global remodeling
(days to months)

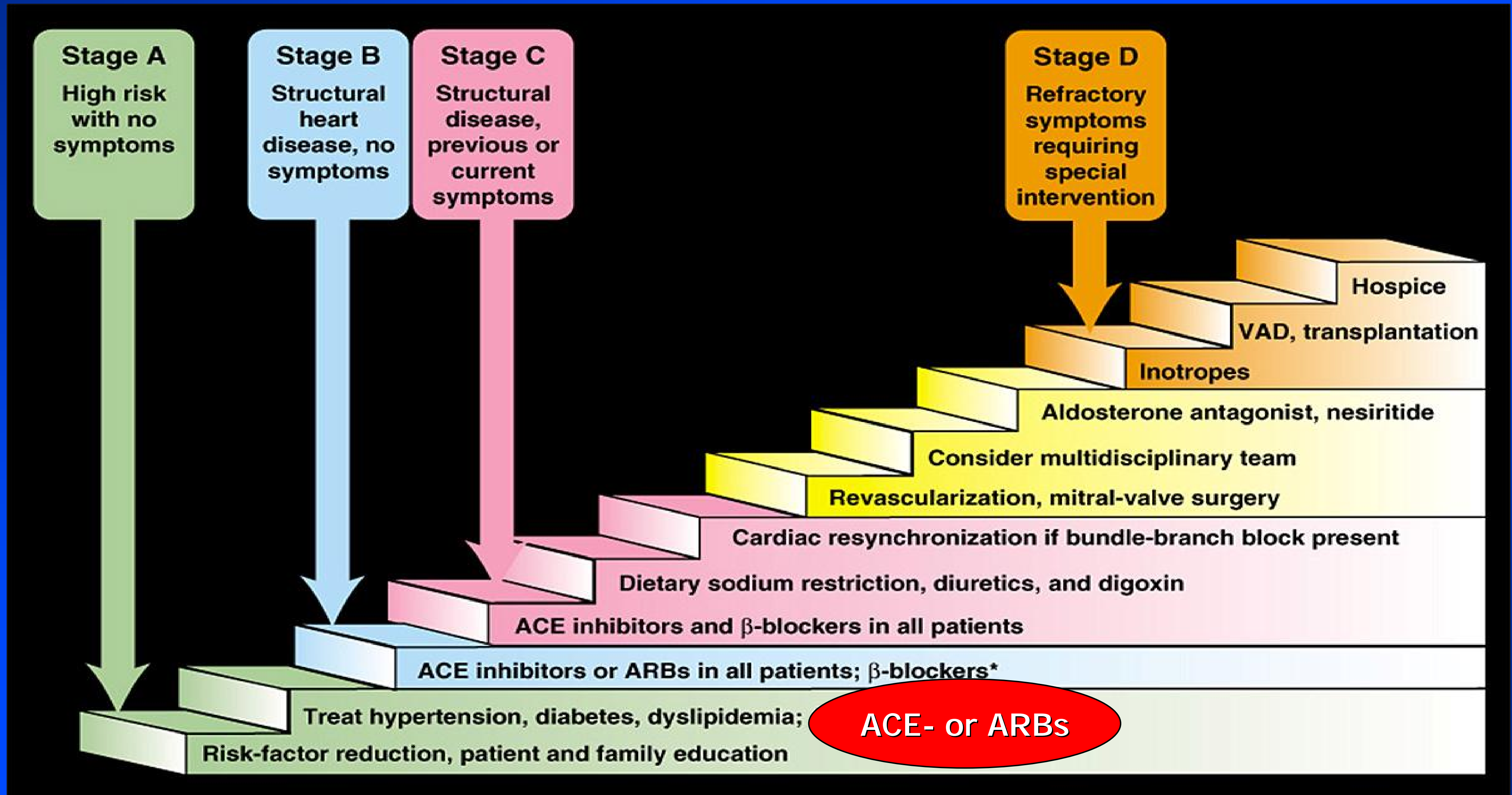
Heart Failure Hospitalizations

The Number of Heart Failure Hospitalizations Is Increasing in Both Men and Women



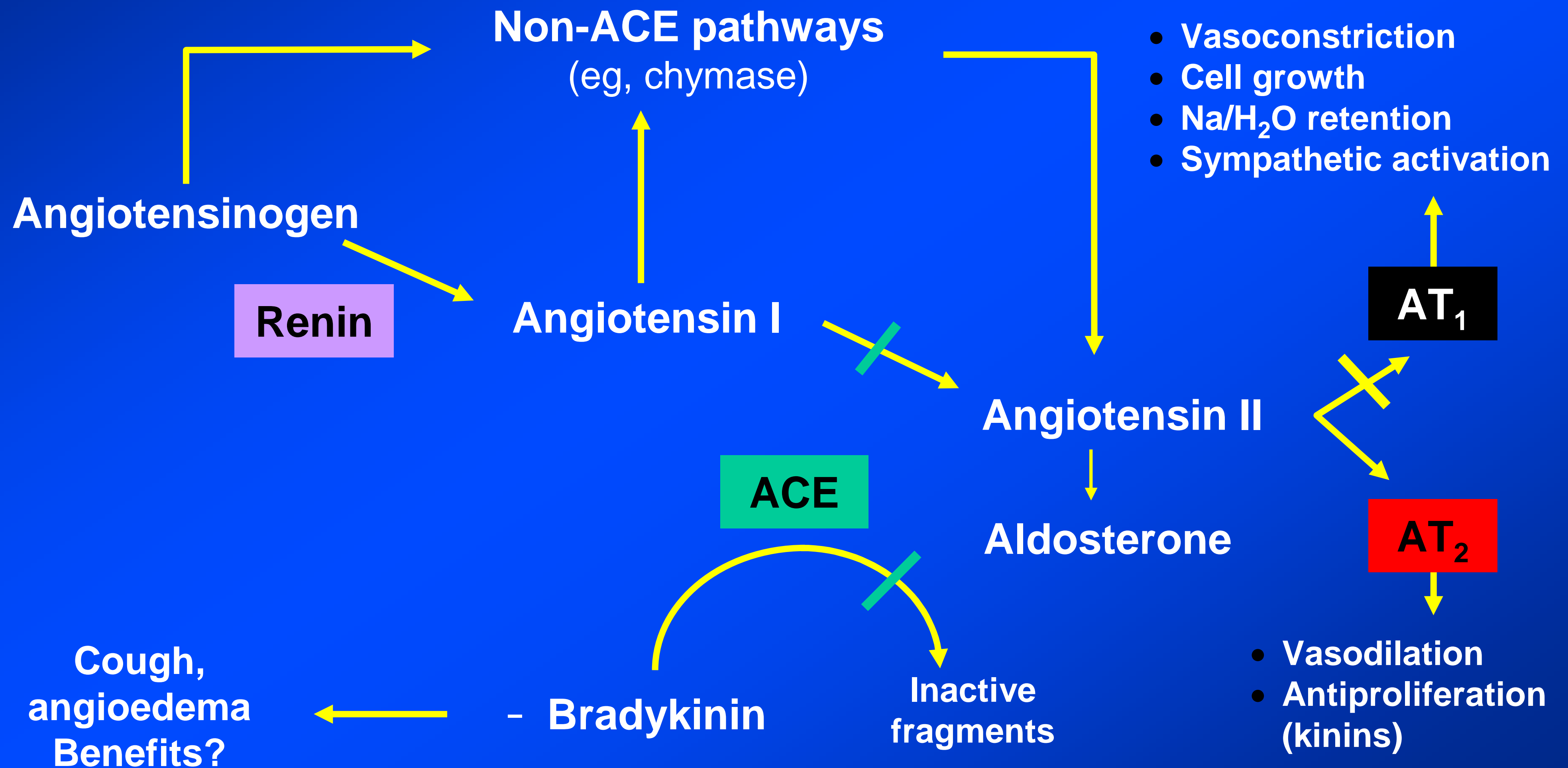
AHA. 2002 Heart and Stroke Statistical Update. 2001.

ACC/AHA Stages of Systolic HF and Treatment Options

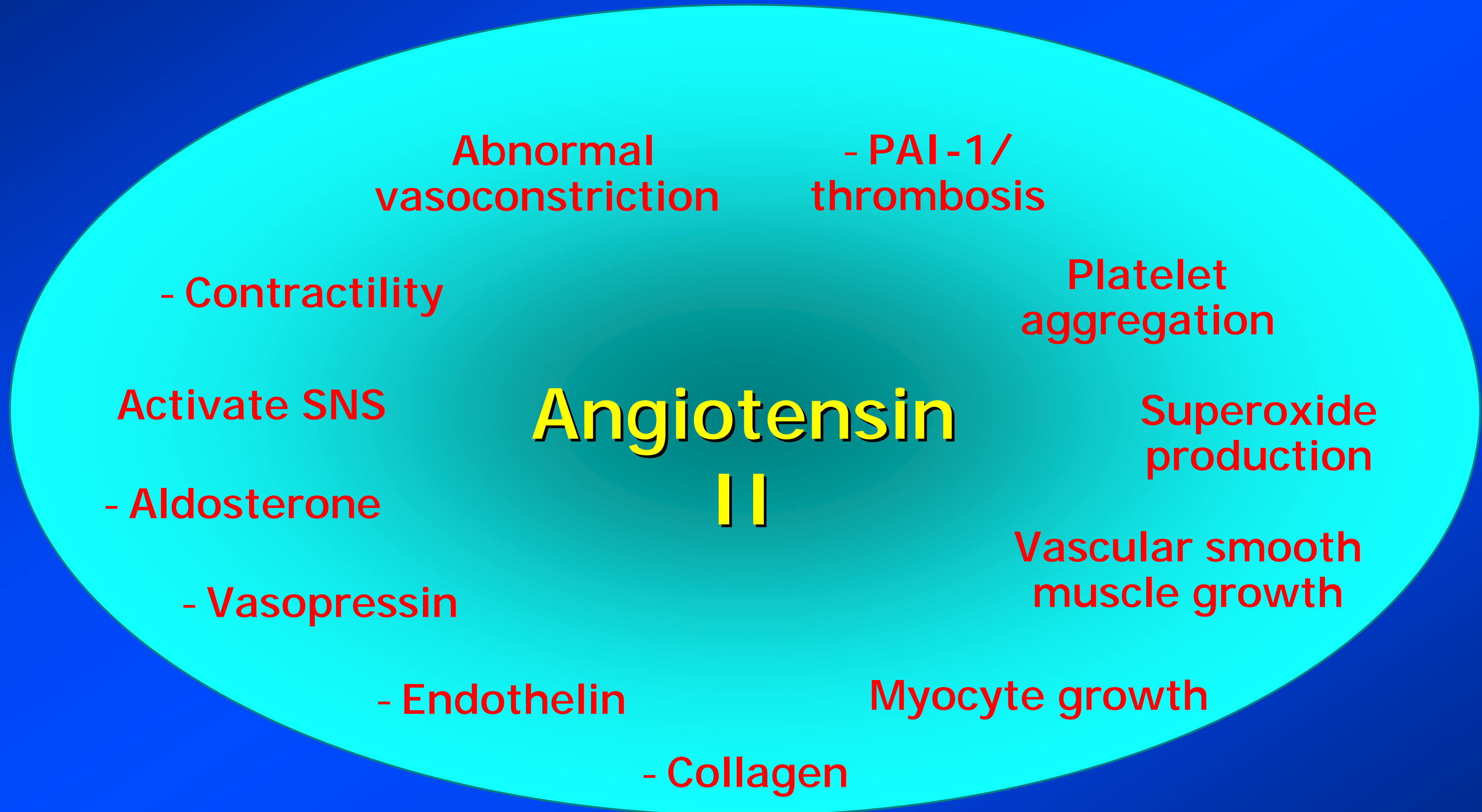


Jessup M. Brozena S. N Engl J Med. 2003:348:2007-18

Renin-Angiotensin Aldosterone System

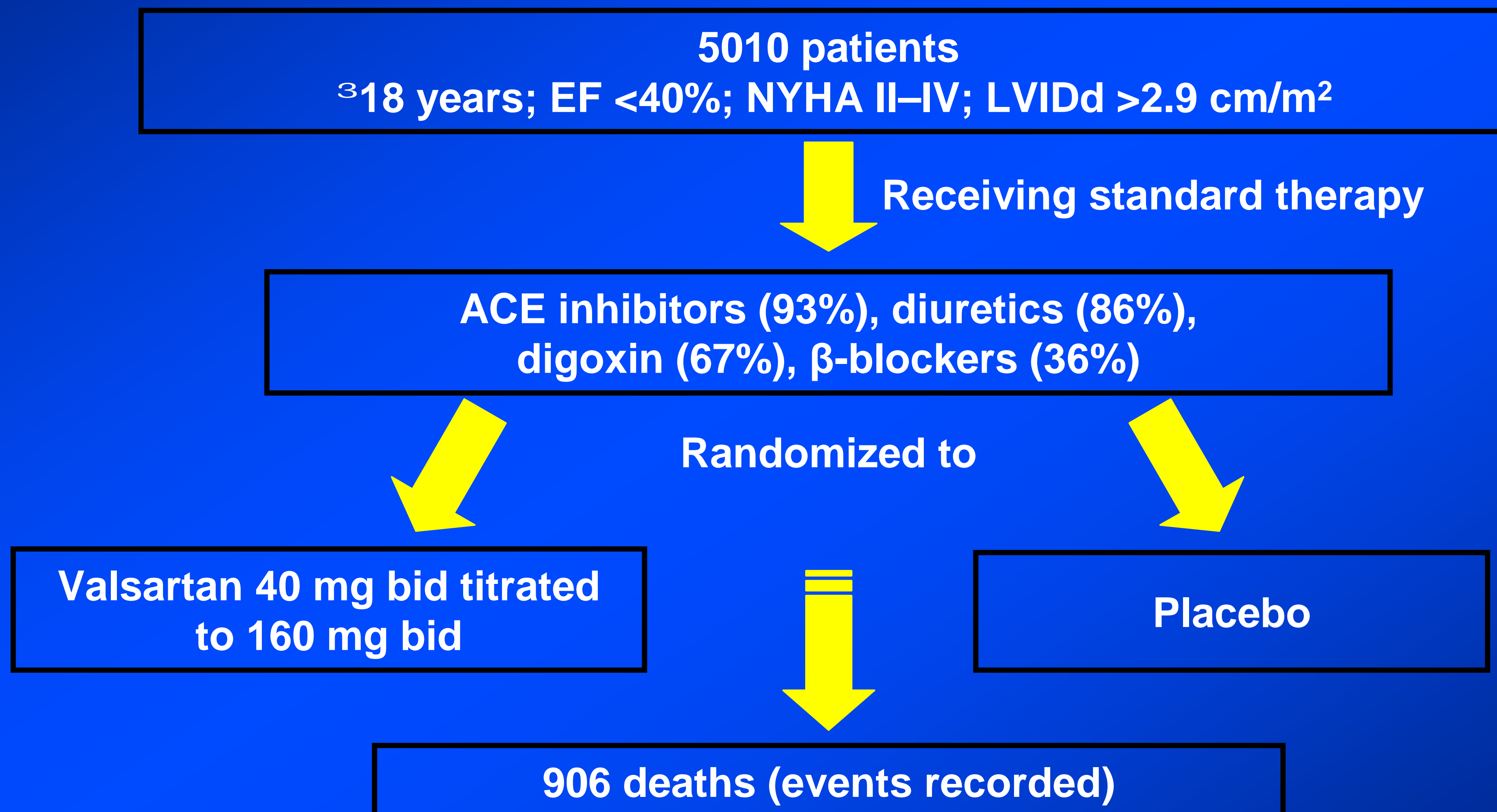


Pathophysiologic Effects of Angiotensin II



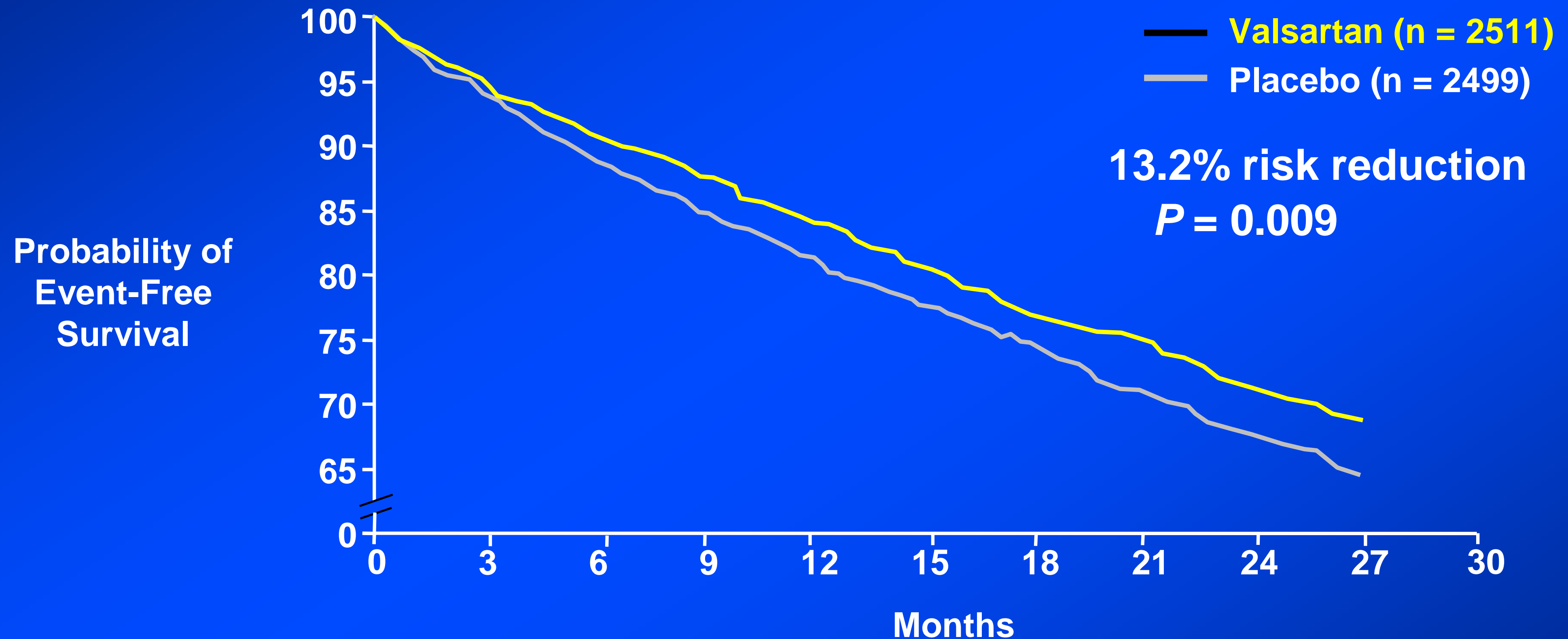
Burnier M, Brunner HR. Lancet. 2000;355:637–645.

Val-HeFT : *Valsartan + ACE-I in HF: Valsartan Heart Failure Trial*



EJ = ejection fraction; LVIDd = left ventricular internal diastolic diameter.
Cohn JN et al. *Eur J Heart Fail*. 2000;2:439-446.

Effect of Valsartan on Combined Mortality and Morbidity End Point* in Overall Population

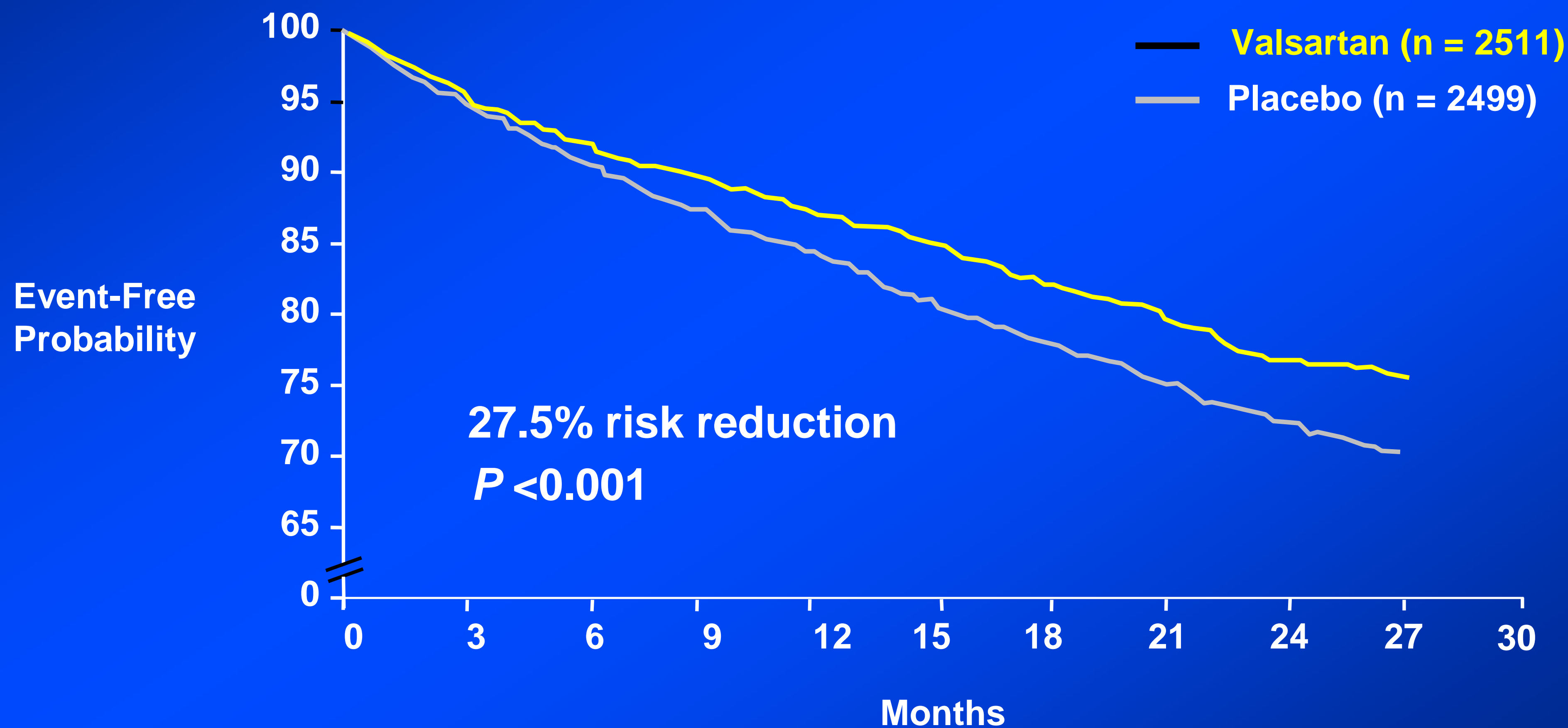


Valsartan significantly reduces the combined endpoint of mortality and morbidity and improves clinical signs and symptoms in patients with heart failure, when added to prescribed therapy.

*All-cause mortality, sudden death with resuscitation, hospitalization for worsening heart failure, or therapy with IV inotropes or vasodilators.

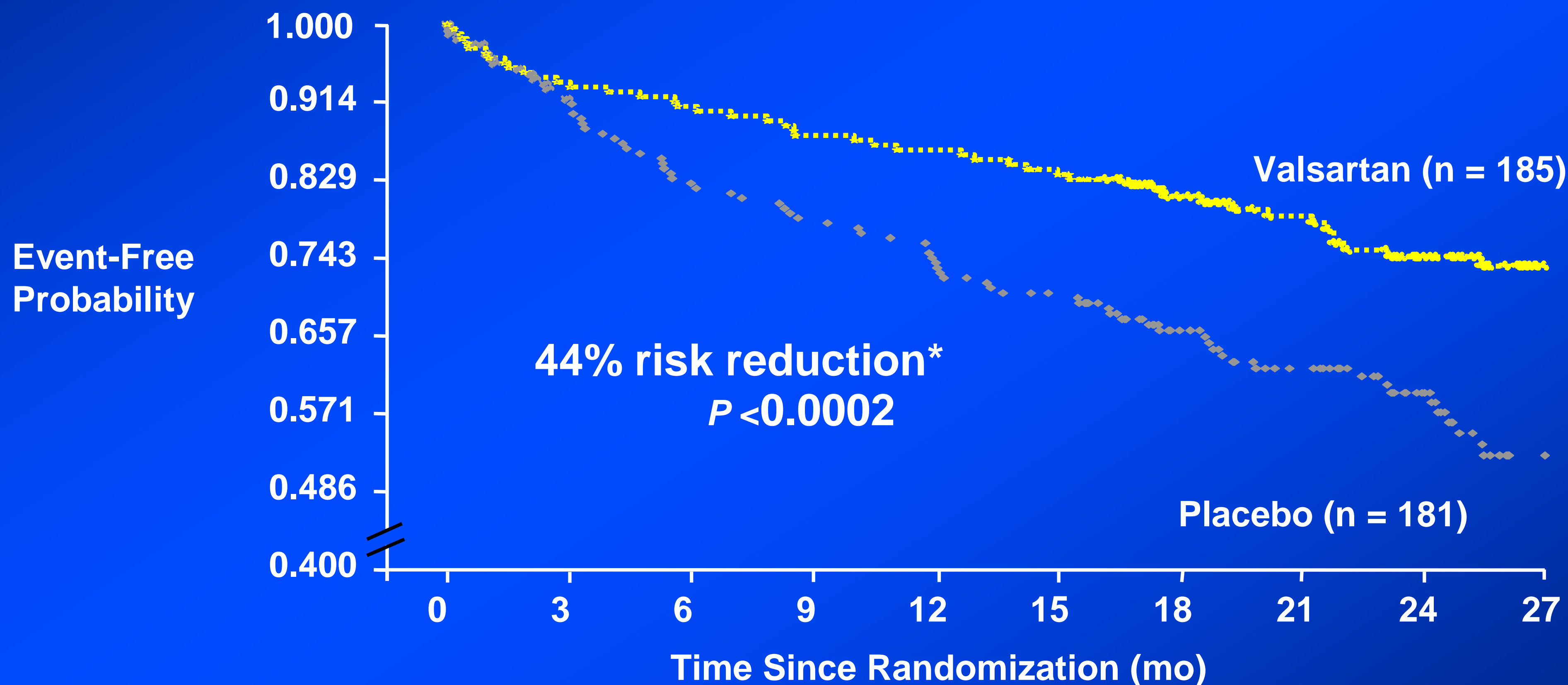
Cohn JN et al. *N Engl J Med.* 2001;345:1667-1675.

Val-HeFT: Heart Failure-Related Hospitalizations*



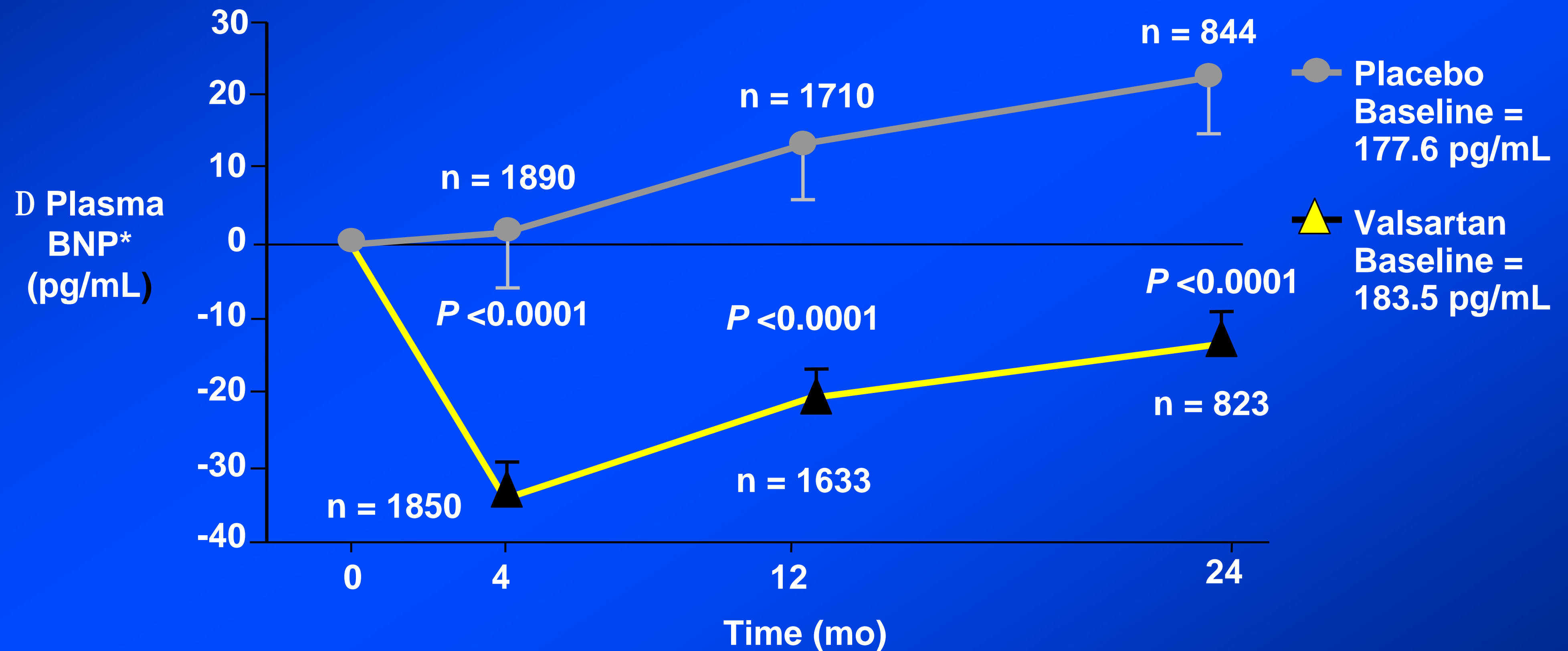
*First hospitalization.
Cohn JN et al. *N Engl J Med.* 2001;345:1667-1675.

Val-HeFT: Combined Morbidity and Mortality End Point



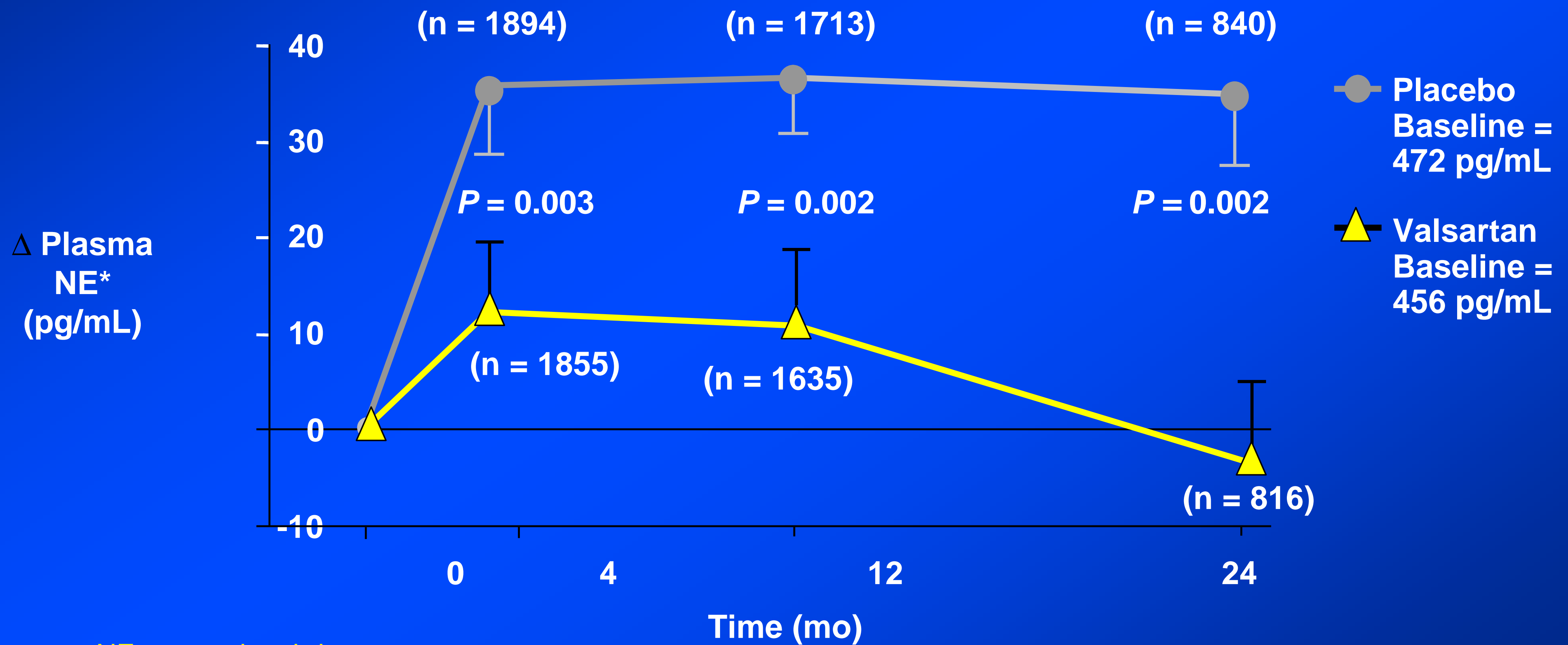
*For morbidity; 34% RR for mortality.
Adapted from Maggioni AP et al. *J Am Coll Cardiol*. 2002;40:1414-1421.

Val-HeFT: Change in Plasma Brain Natriuretic Peptide Over Time



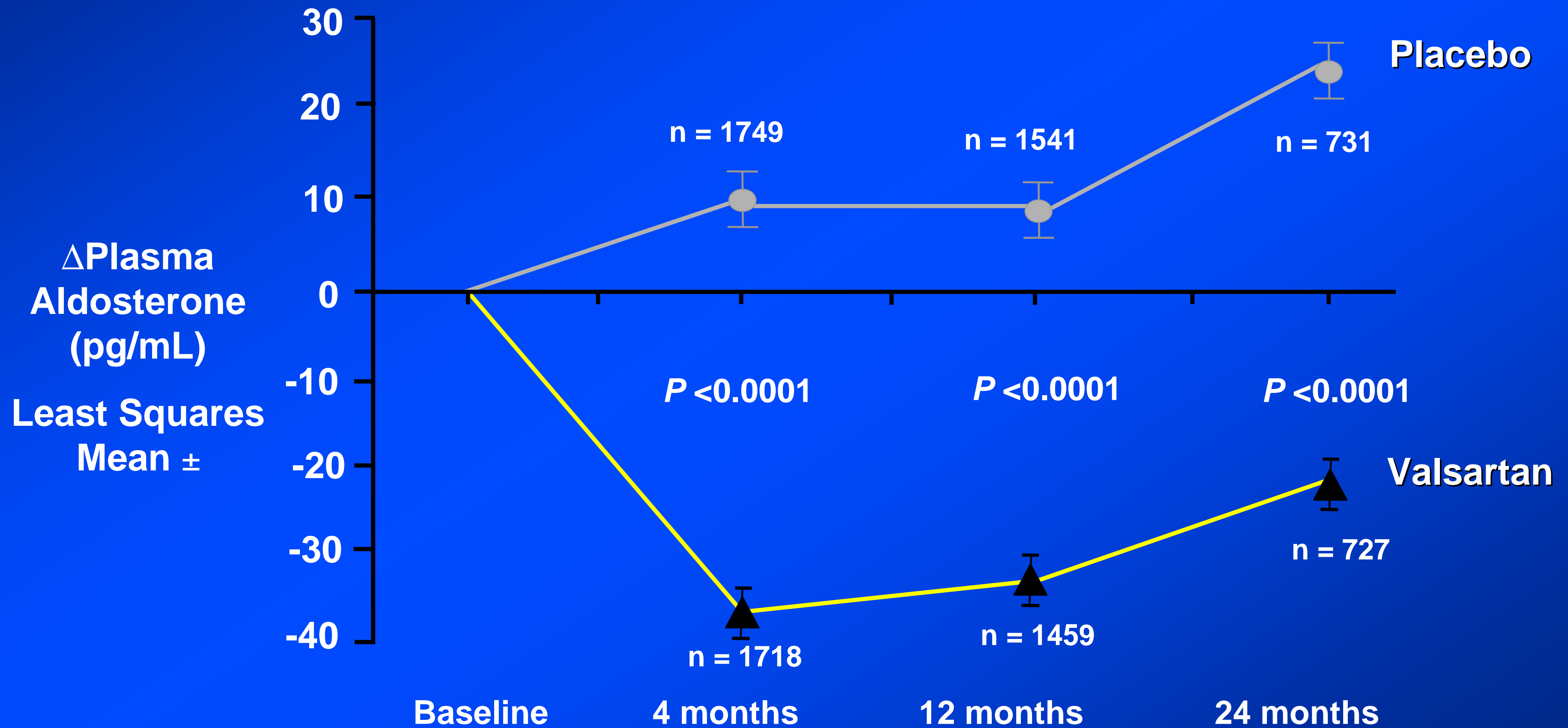
*R et Mean ± SEM.
Latini al. *Circulation*. 2002;106:2454-2458.

Val-HeFT: Neurohormones – Change in Plasma NE Over Time

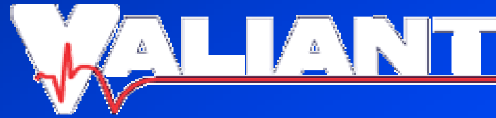


NE = norepinephrine.
*Mean ± SEM.
Latini R et al. *Circulation*. 2002;106:2454-2458.

Val-HeFT: Change From Baseline in Plasma Aldosterone



Anand I et al. AHA 75th Scientific Session. 2002;A1763.



Acute MI (0.5–10 days)—SAVE, AIRE or TRACE eligible
(either clinical/radiologic signs of HF or LV systolic dysfunction)

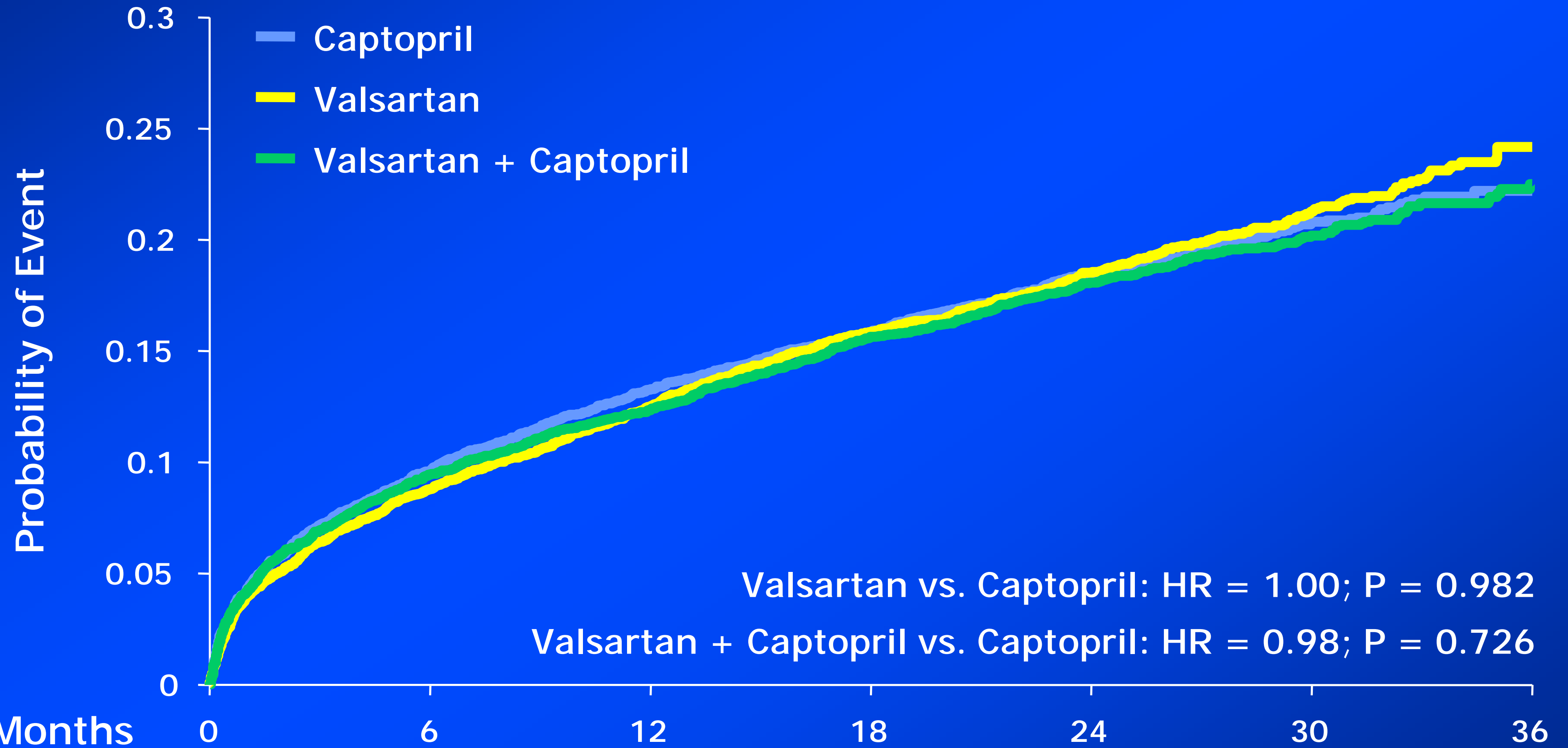
double-blind active-controlled

Captopril 50 mg tid (n = 4909)	Valsartan 160 mg bid (n = 4909)	Captopril 50 mg tid + Valsartan 80 mg bid (n = 4885)

median duration: 24.7 months
event-driven

Primary Endpoint:	All-Cause Mortality
Secondary Endpoints:	CV Death, MI, or HF
Other Endpoints:	Safety and Tolerability

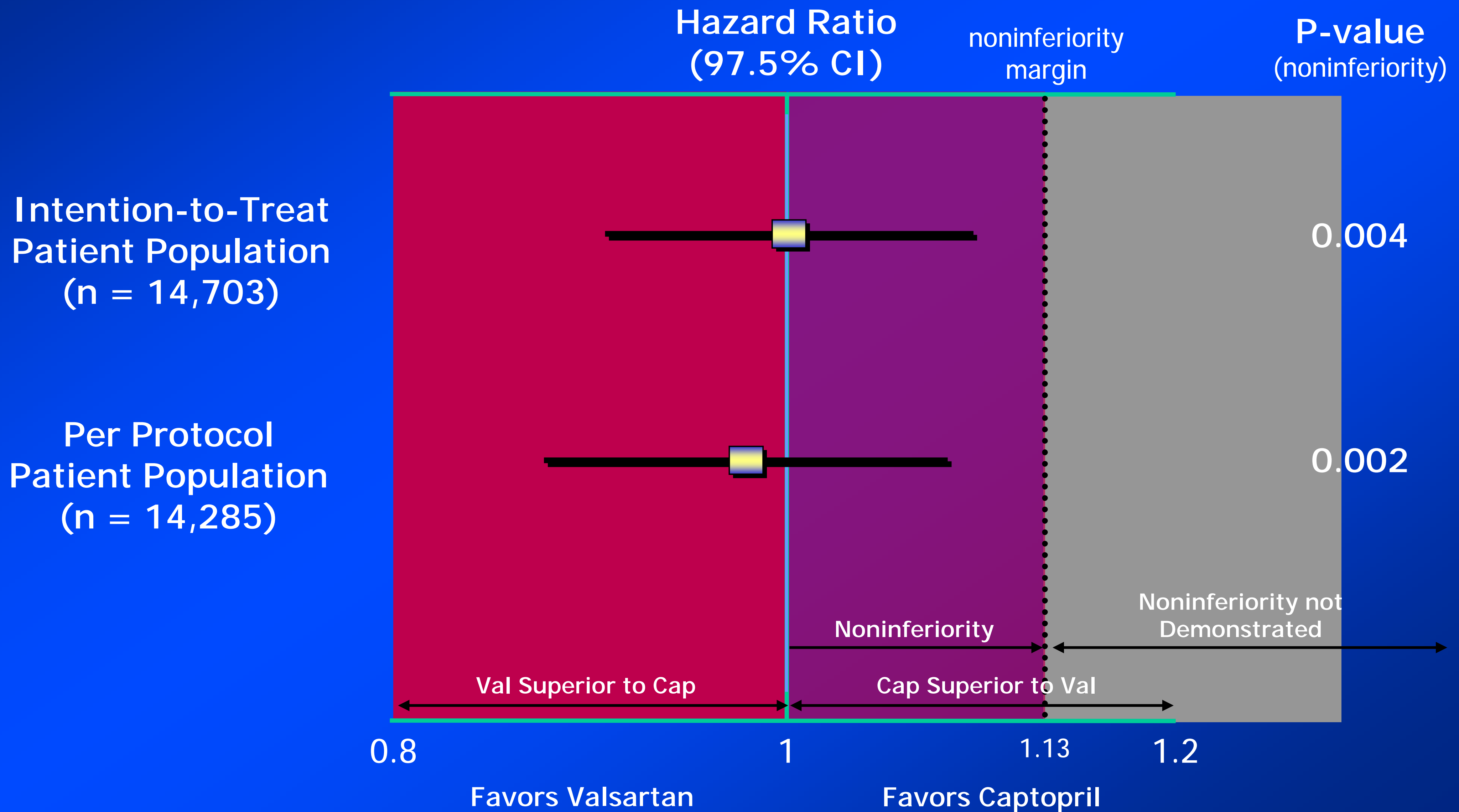
Mortality by Treatment



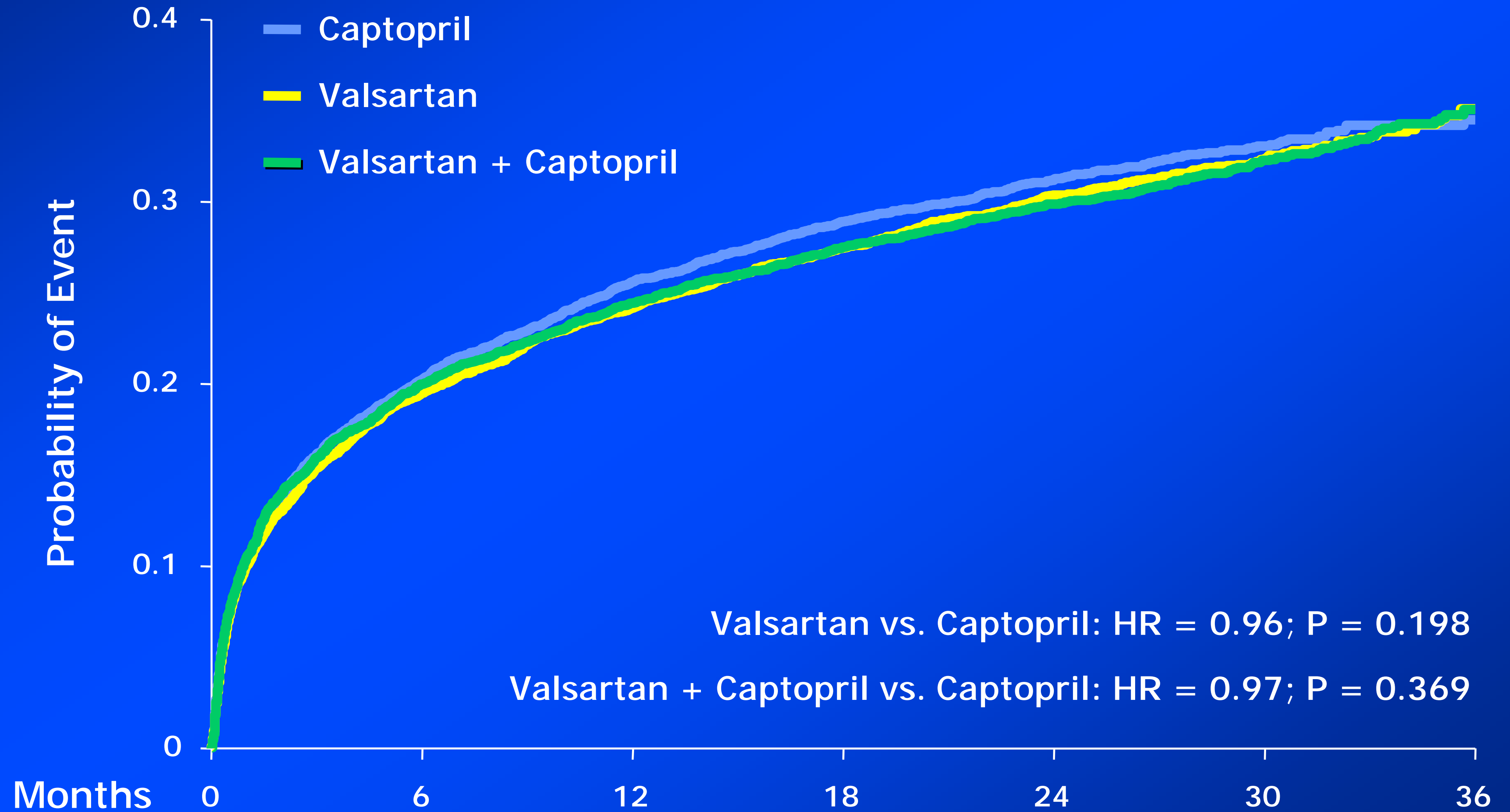
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

All-Cause Mortality: Non-Inferiority Analyses



CV Death, MI, or HF by Treatment



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

Hazard Ratios (95% CI) for CV Death, MI, or HF

Valsartan vs. Captopril:

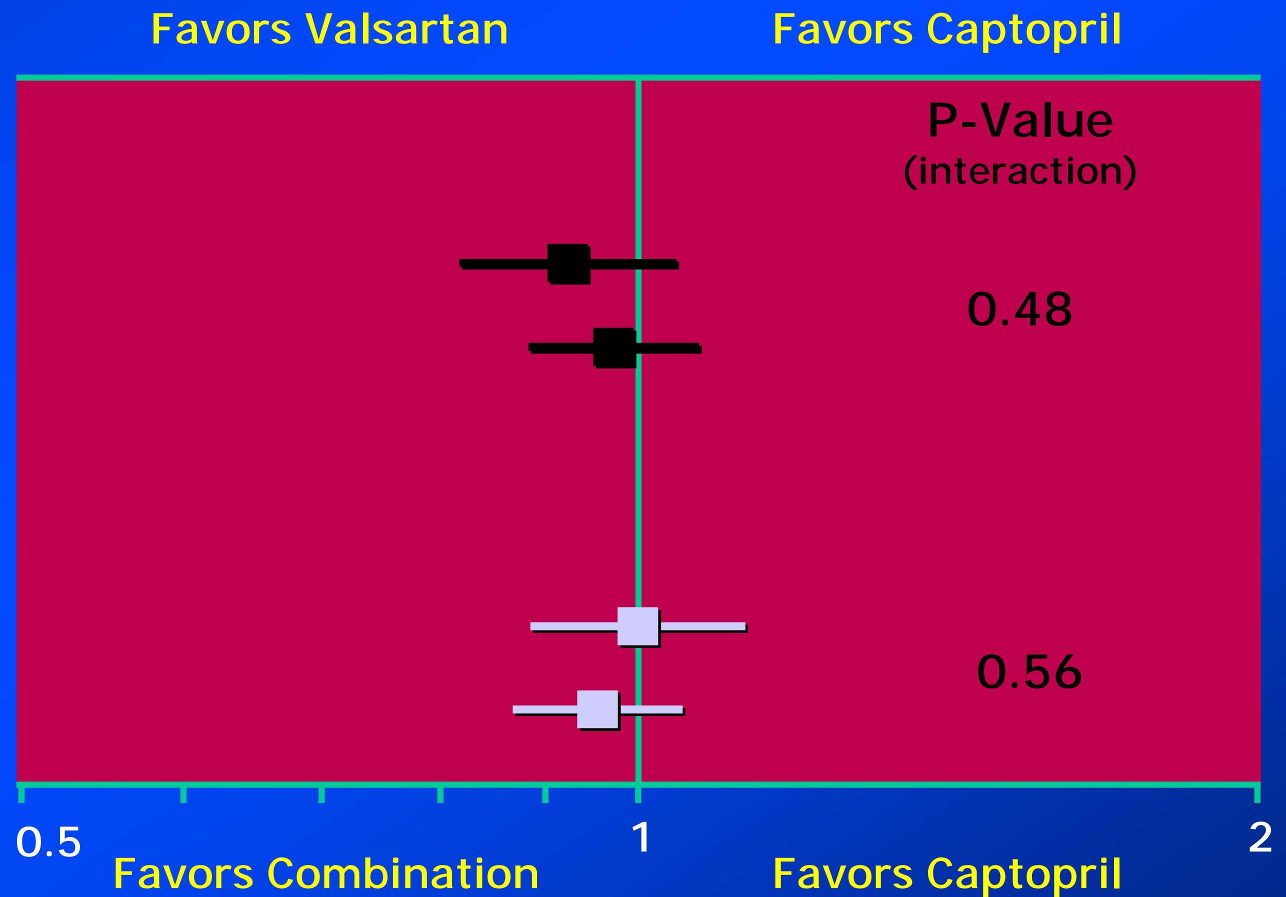
No Beta-Blocker (n = 2907)

Beta-Blocker (n = 6911)

Combination vs. Captopril:

No Beta-Blocker (n = 2910)

Beta-Blocker (n = 6882)



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349:1893–1906

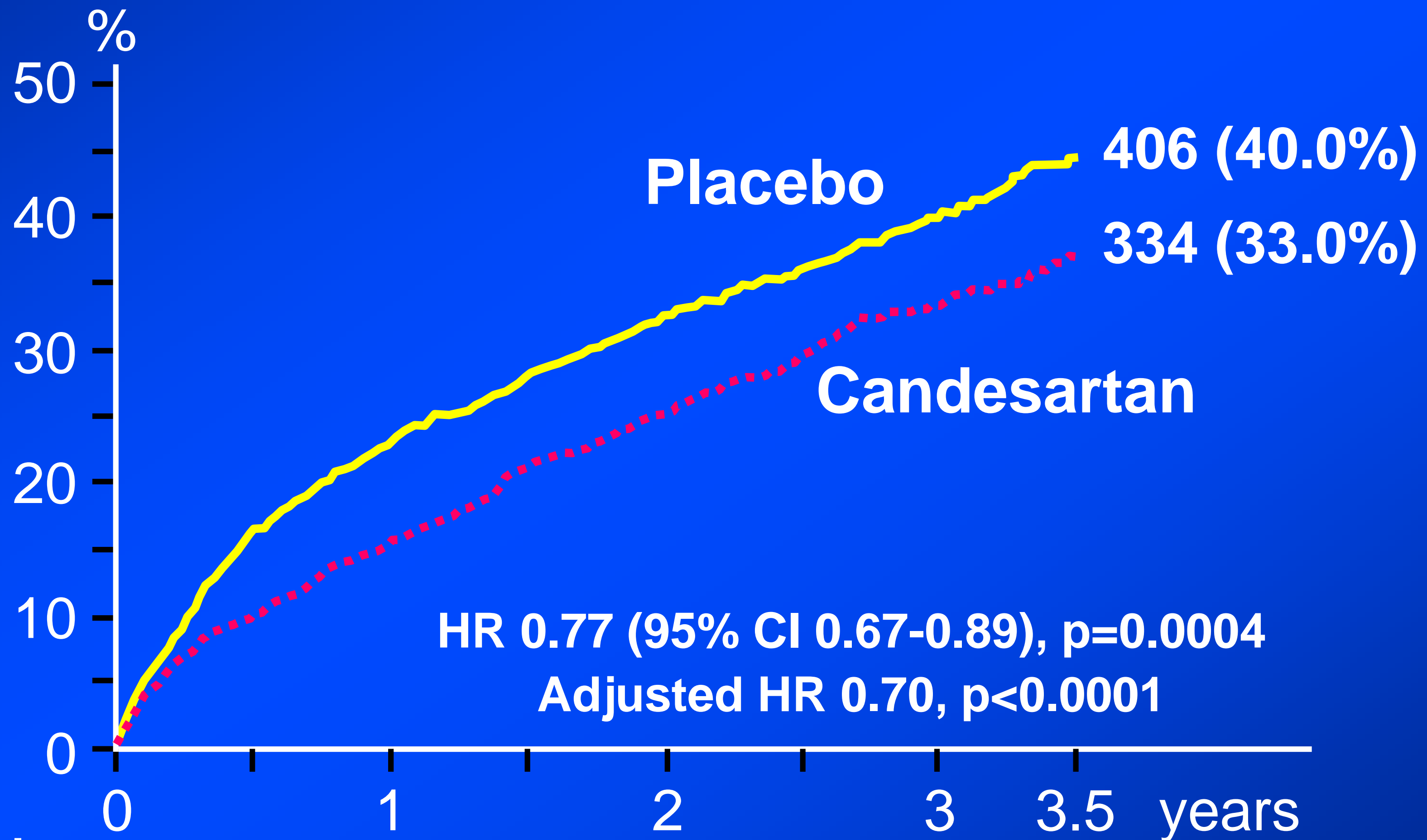
CHARM Programme

3 component trials comparing candesartan to placebo

Primary outcome:
CV death or CHF hosp

CHARM-Alternative: Primary outcome

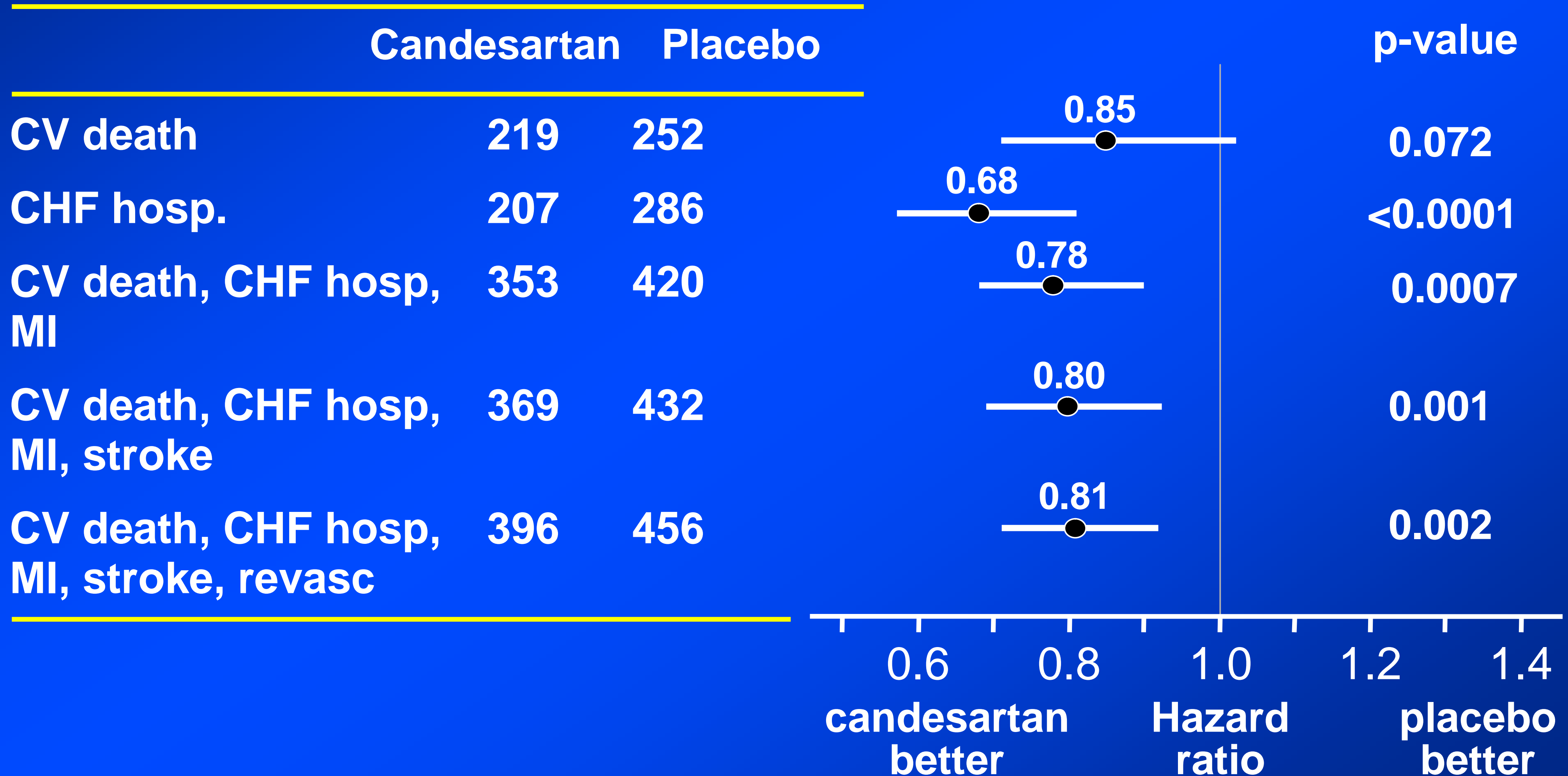
CV death or CHF hospitalisation



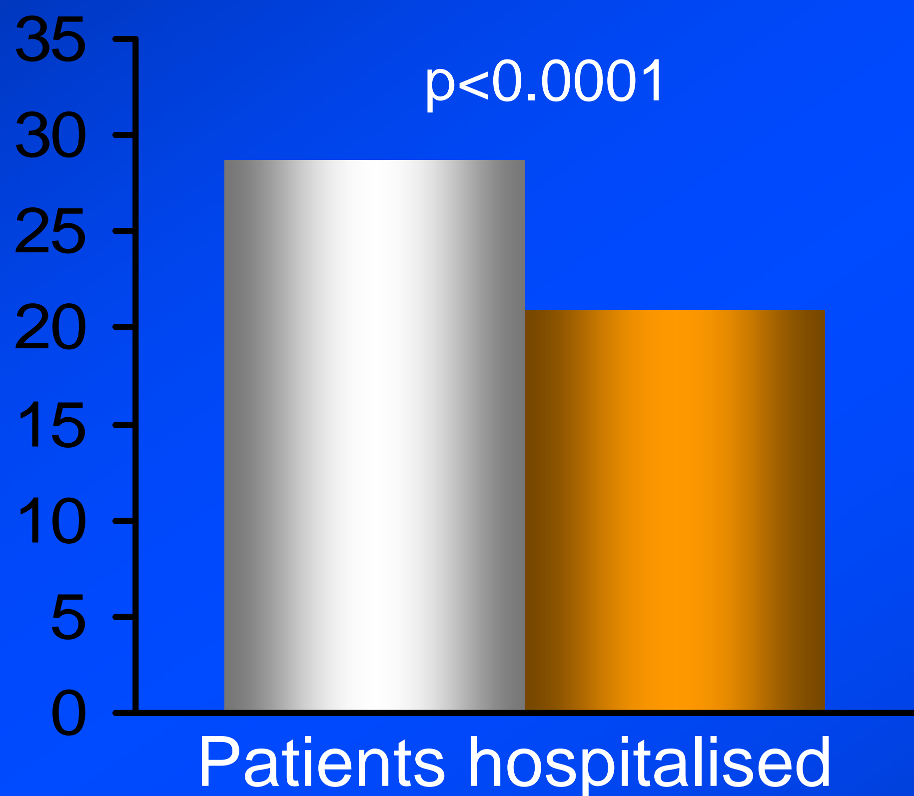
Number at risk

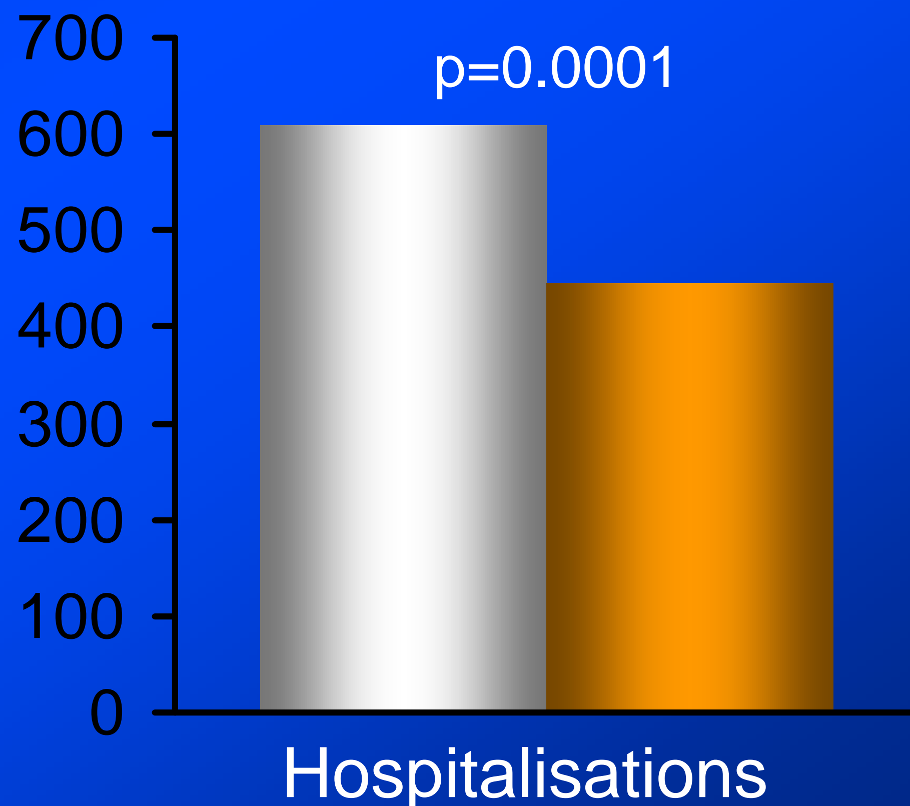
	0	1	2	3	3.5
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

CHARM-Alternative: Secondary outcomes



CHARM-Alternative
Investigator reported CHF hospitalisations





CHARM-Alternative
Conclusions

- Despite prior intolerance to another inhibitor of the renin-angiotensin-aldosterone system, candesartan
  was well tolerated
- In patients with symptomatic chronic heart failure and ACE-inhibitor intolerance, candesartan reduces cardiovascular mortality and morbidity

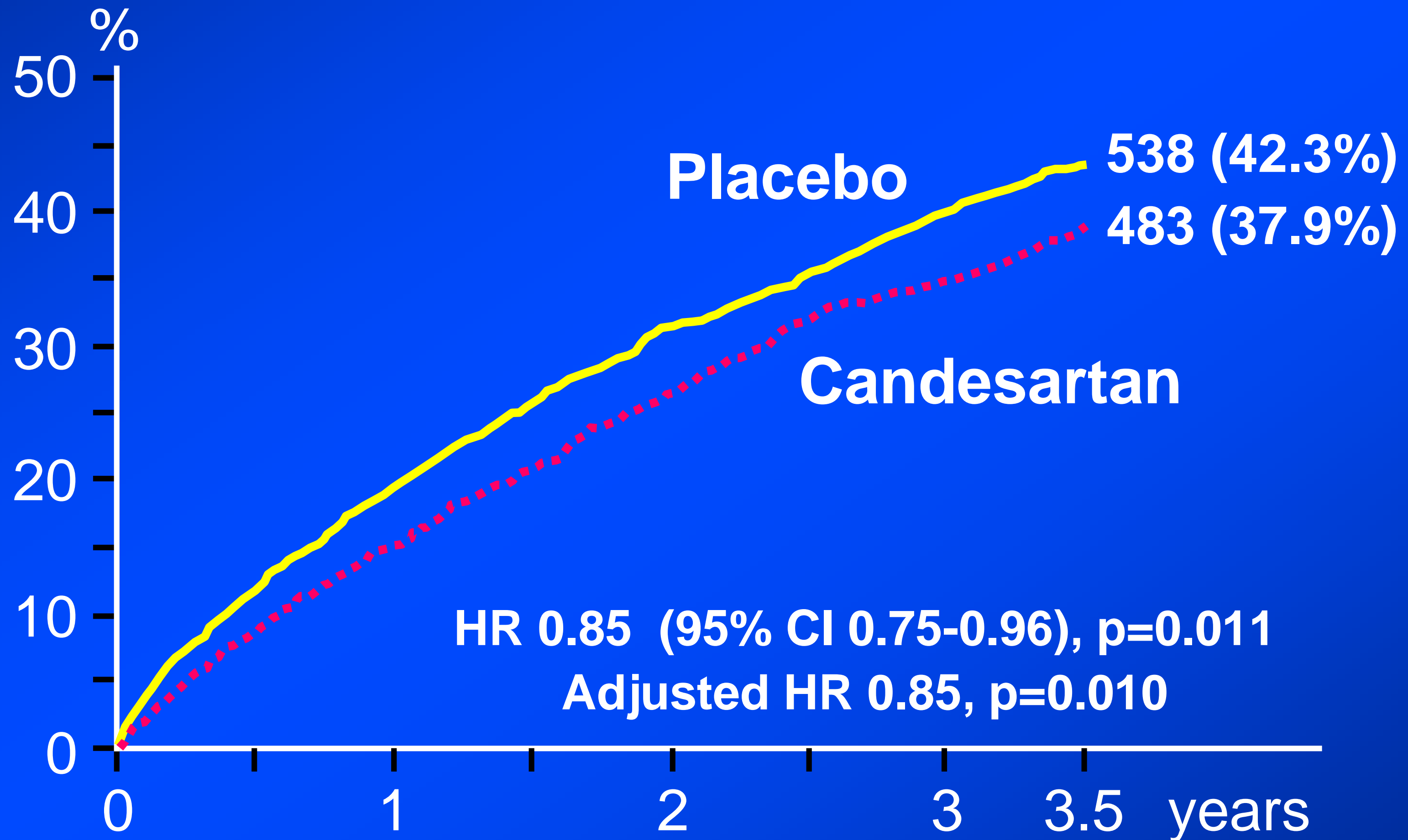
CHARM Programme

3 component trials comparing Candesartan to placebo

Primary outcome:

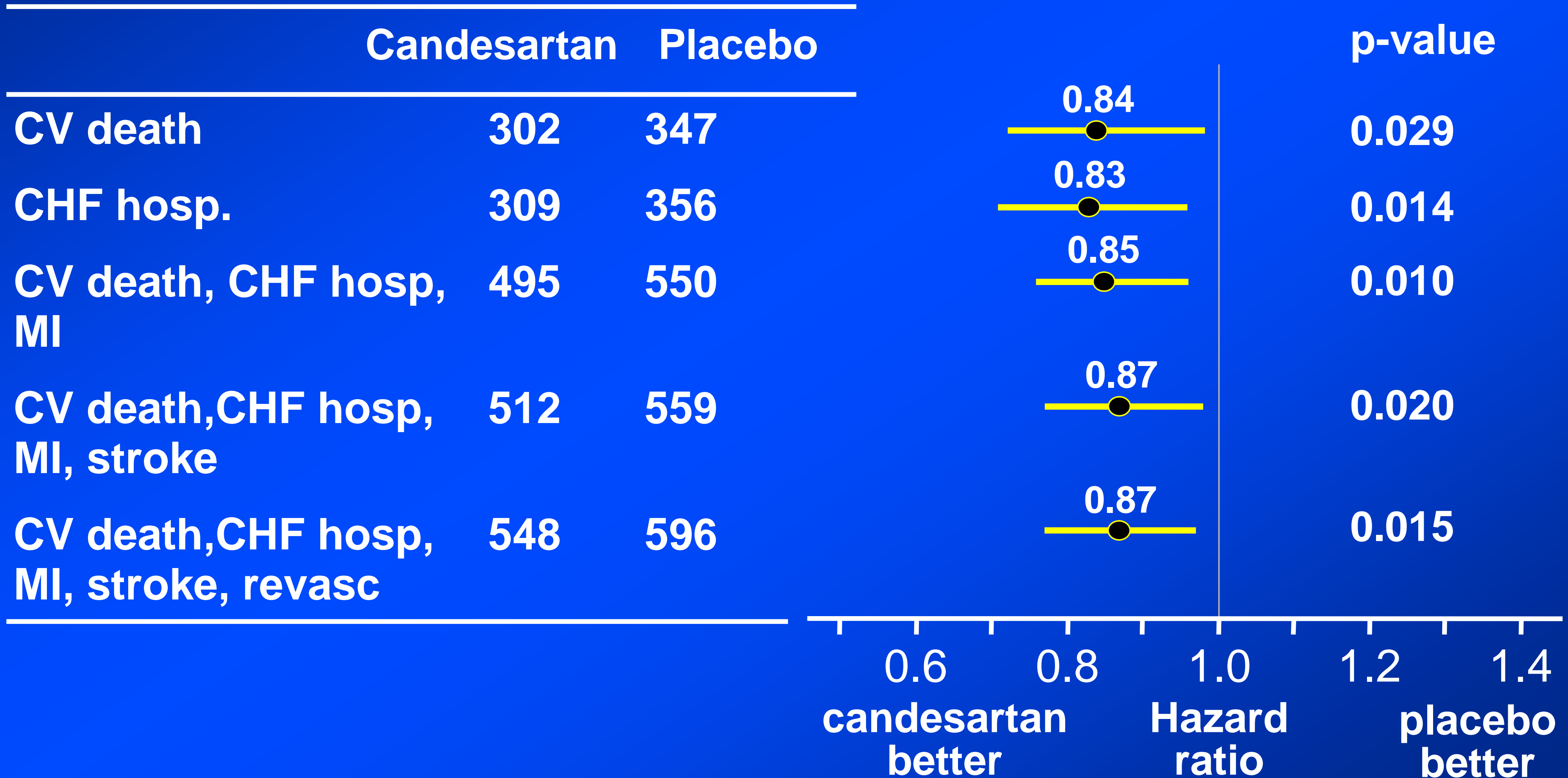
CV death or CHF hosp

CHARM-Added: Primary outcome
CV death or CHF hospitalisation



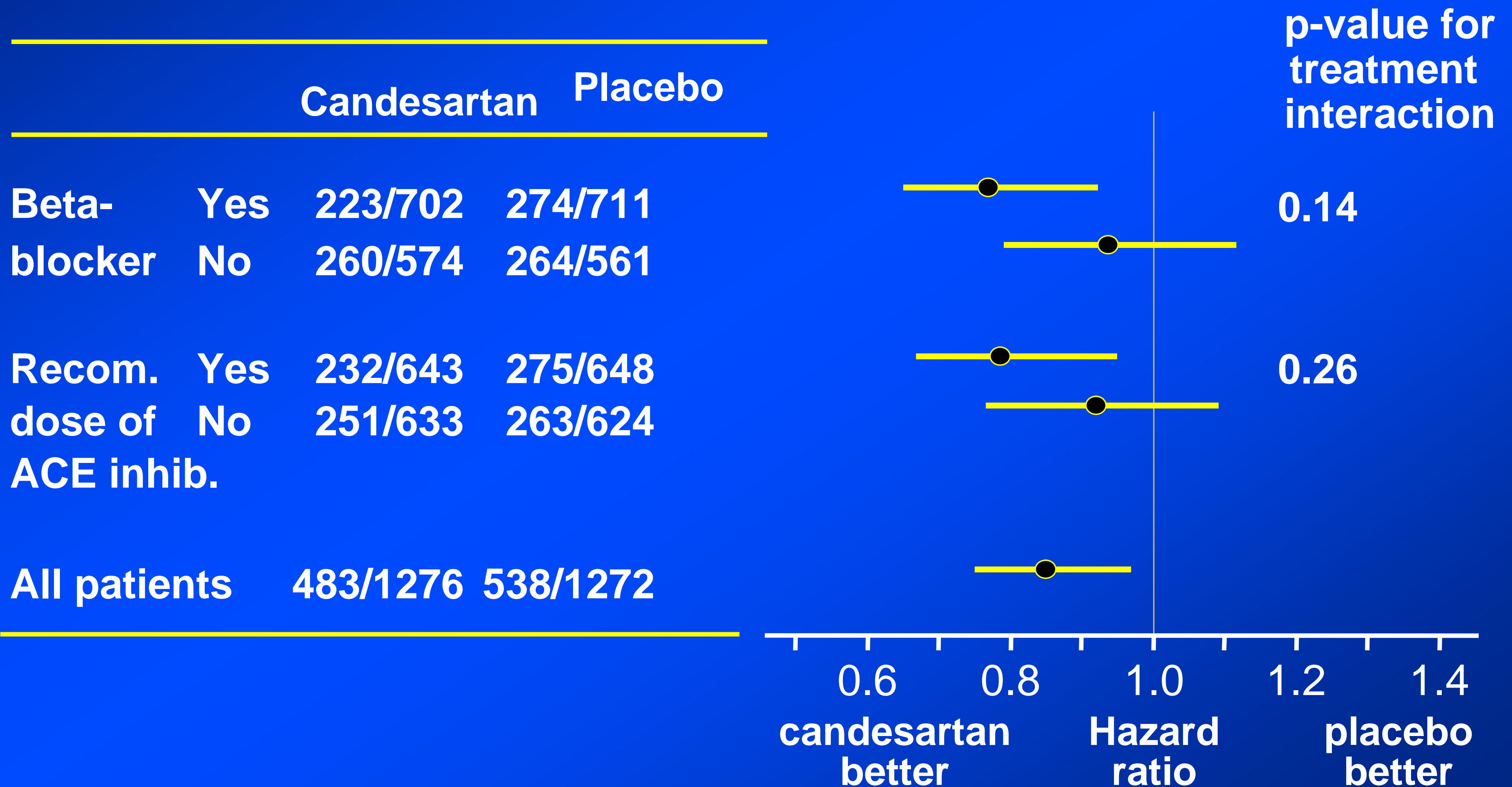
Number at risk					
Candesartan	1276	1176	1063	948	457
Placebo	1272	1136	1013	906	422

CHARM-Added
Secondary outcomes



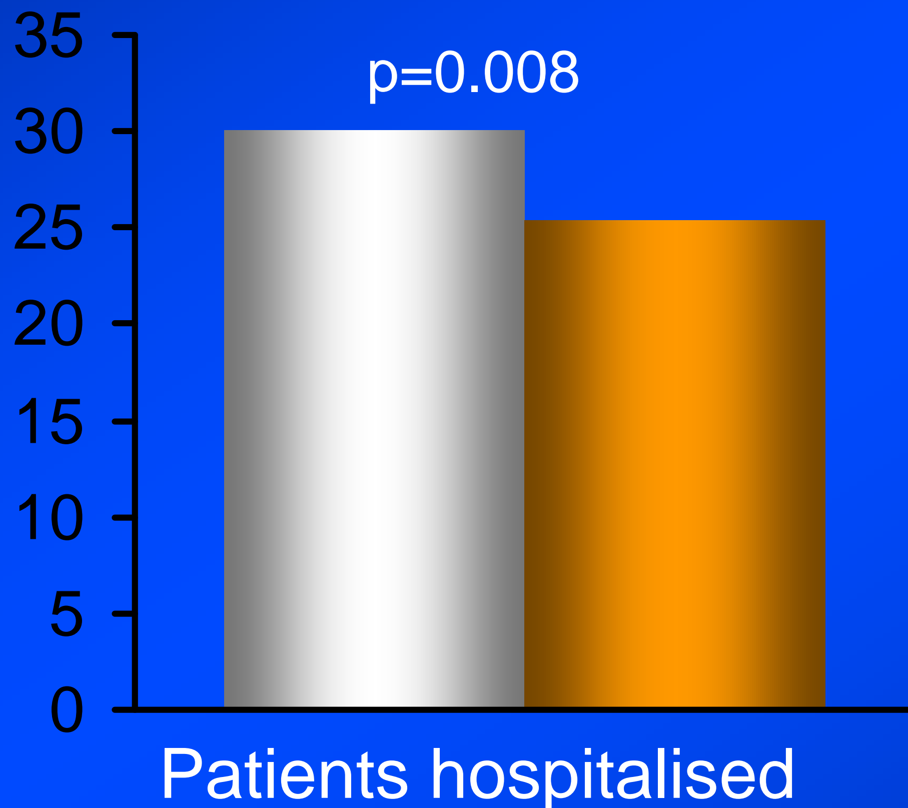
	Candesartan	Placebo	Hazard ratio	p-value
CV death	302	347	0.84	0.029
CHF hosp.	309	356	0.83	0.014
CV death, CHF hosp, MI	495	550	0.85	0.010
CV death,CHF hosp, MI, stroke	512	559	0.87	0.020
CV death,CHF hosp, MI, stroke, revasc	548	596	0.87	0.015

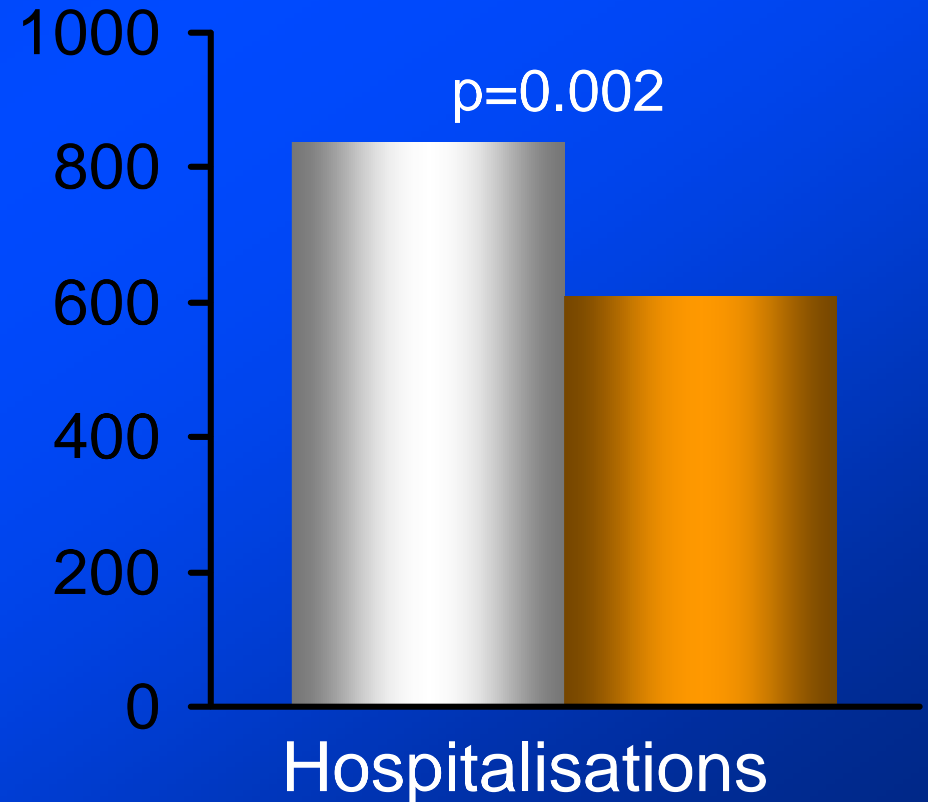
CHARM-Added
Prespecified subgroups, CV death or CHF hosp.



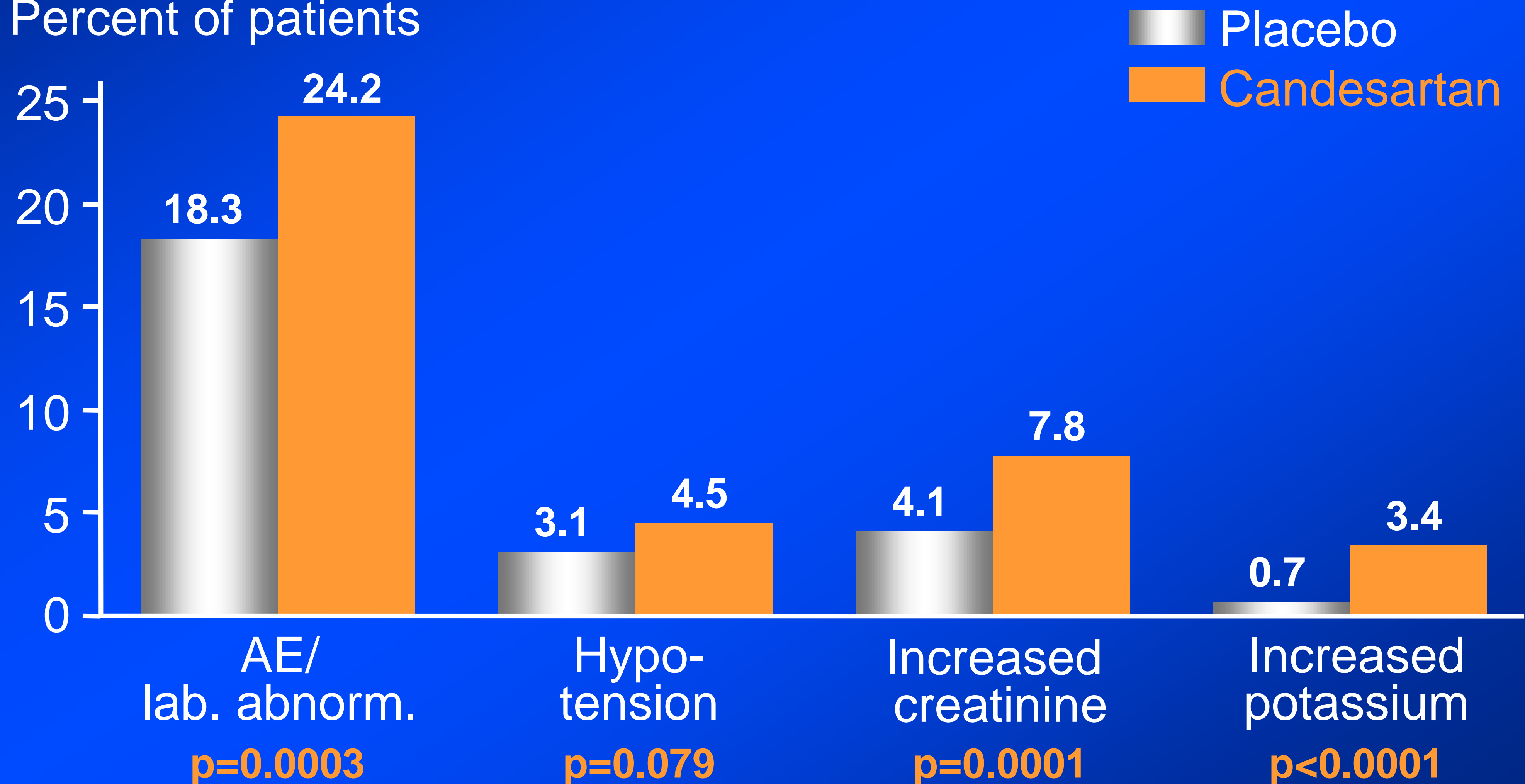
CHARM-Added
Investigator reported CHF hospitalisations

Placebo
Candesartan





CHARM-Added
Permanent study drug discontinuations



CHARM-Added
Conclusions

- Addition of candesartan to an ACE inhibitor (and beta-blocker) leads to a further and clinically important reduction in CV mortality and morbidity in patients with CHF

- This benefit is obtained with relatively few adverse effects, although there is an increased risk of hypotension, hyperkalaemia and renal dysfunction

Definition of Diastolic Dysfunction and HF

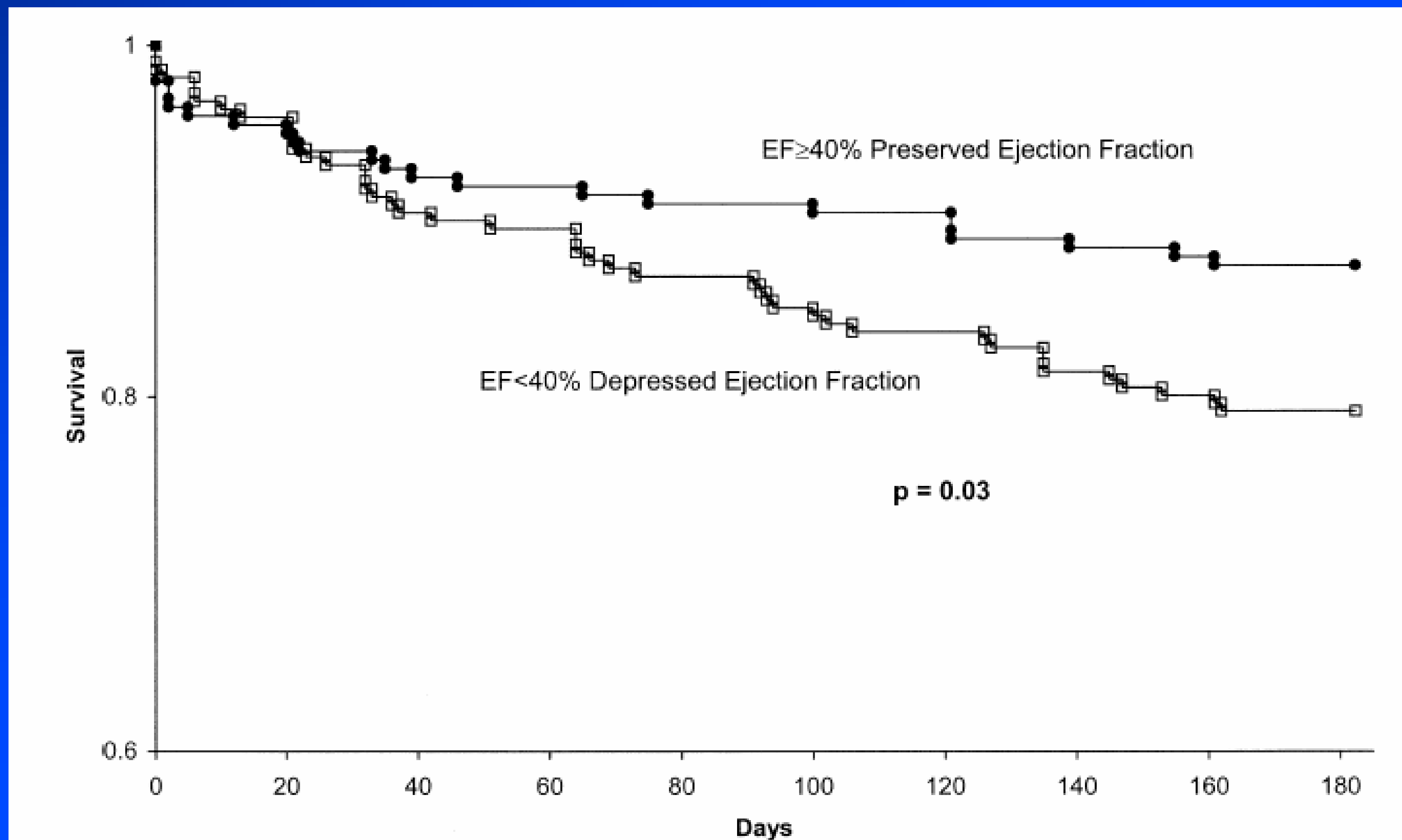
- Diastolic HF is a clinical syndrome characterized by the symptoms and signs of HF, a preserved EF and abnormal diastolic function.
- Diastolic dysfunction occurs when the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force, is prolonged, slowed or incomplete.
- Systolic and diastolic HF occurs when patients have a modest decrease in EF and a modest increase in end-diastolic volume but a marked increase in end-diastolic pressure and a diastolic pressure-volume relationship that reflects decreased chamber compliance.

Zile MR et al. Circulation 2002

Diastolic Heart Failure: Effects of Age on Prevalence and Prognosis

	Age, y		
	<50	50-70	>70
Prevalence	15	33	50
Mortality	15	33	50
Morbidity	25	50	50

Outcomes in Hf Patients with Preserved EF



Smith GL et al. J Am Coll Cardiol 2003

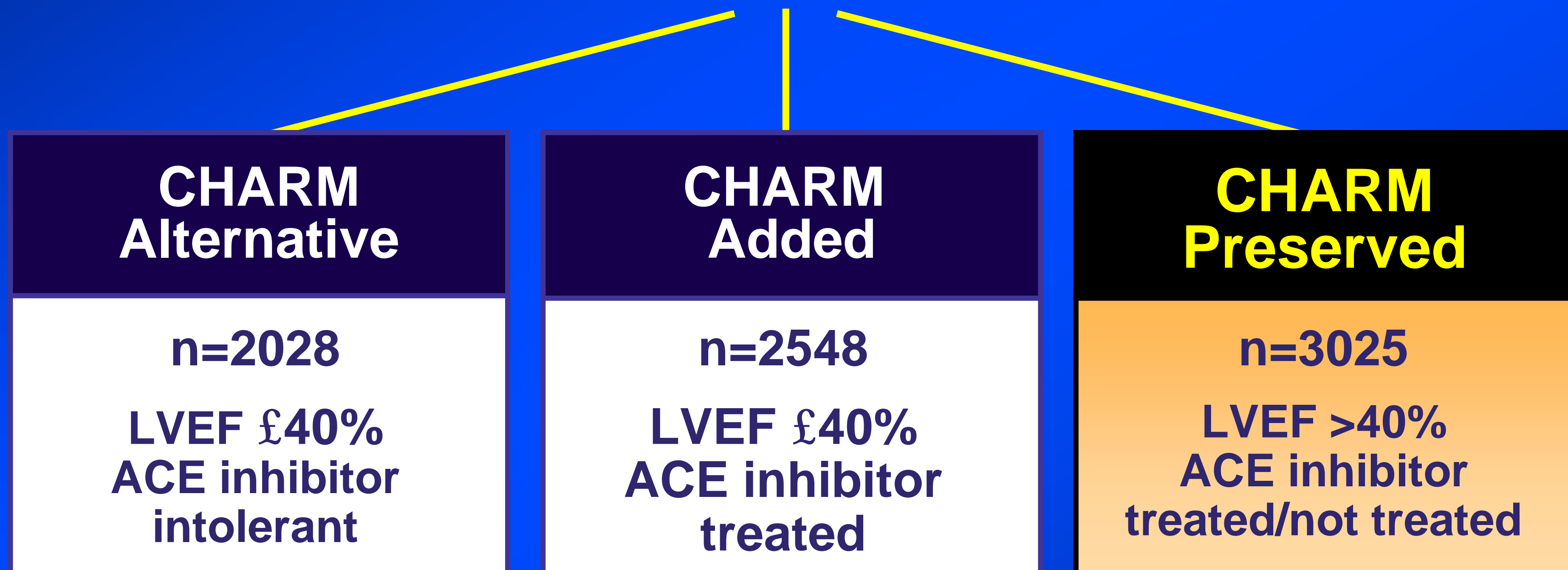
Patients with Preserved Versus Depressed EF

Clinical Outcomes	HR or OR	95% CI	p Value
Mortality*	0.51	0.27,0.96	0.04
All-cause readmission†	1.01	0.72,1.43	0.96
HF readmission†	0.77	0.38,1.56	0.46
Functional decline or death‡	0.98	0.57,1.69	0.63
Functional decline only (survivors: n = 316)‡	1.59	0.83,3.04	0.33

Smith et al.   J Am Coll Cardiol 2003

CHARM Programme

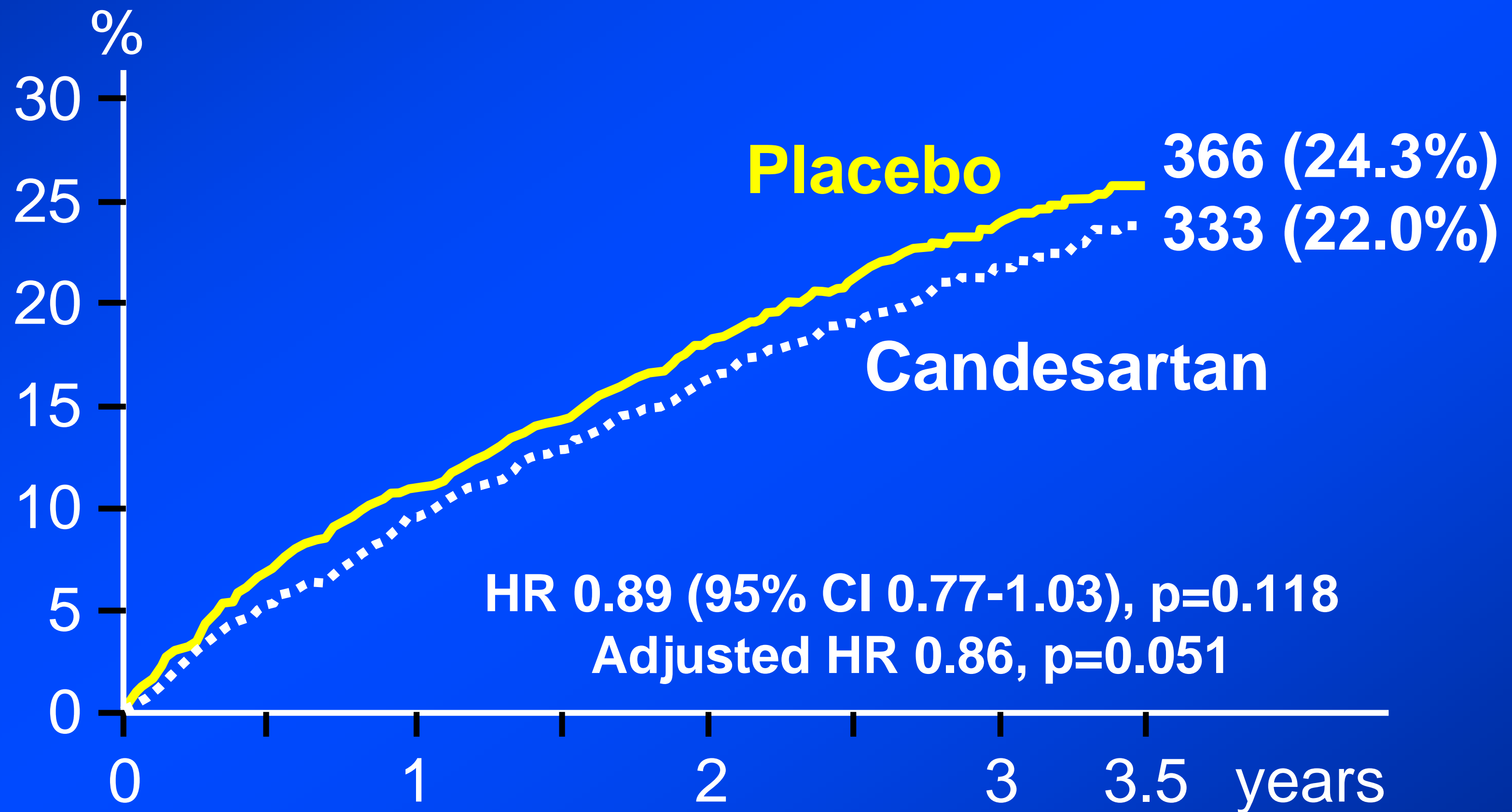
3 component trials comparing candesartan to placebo



Primary outcome:

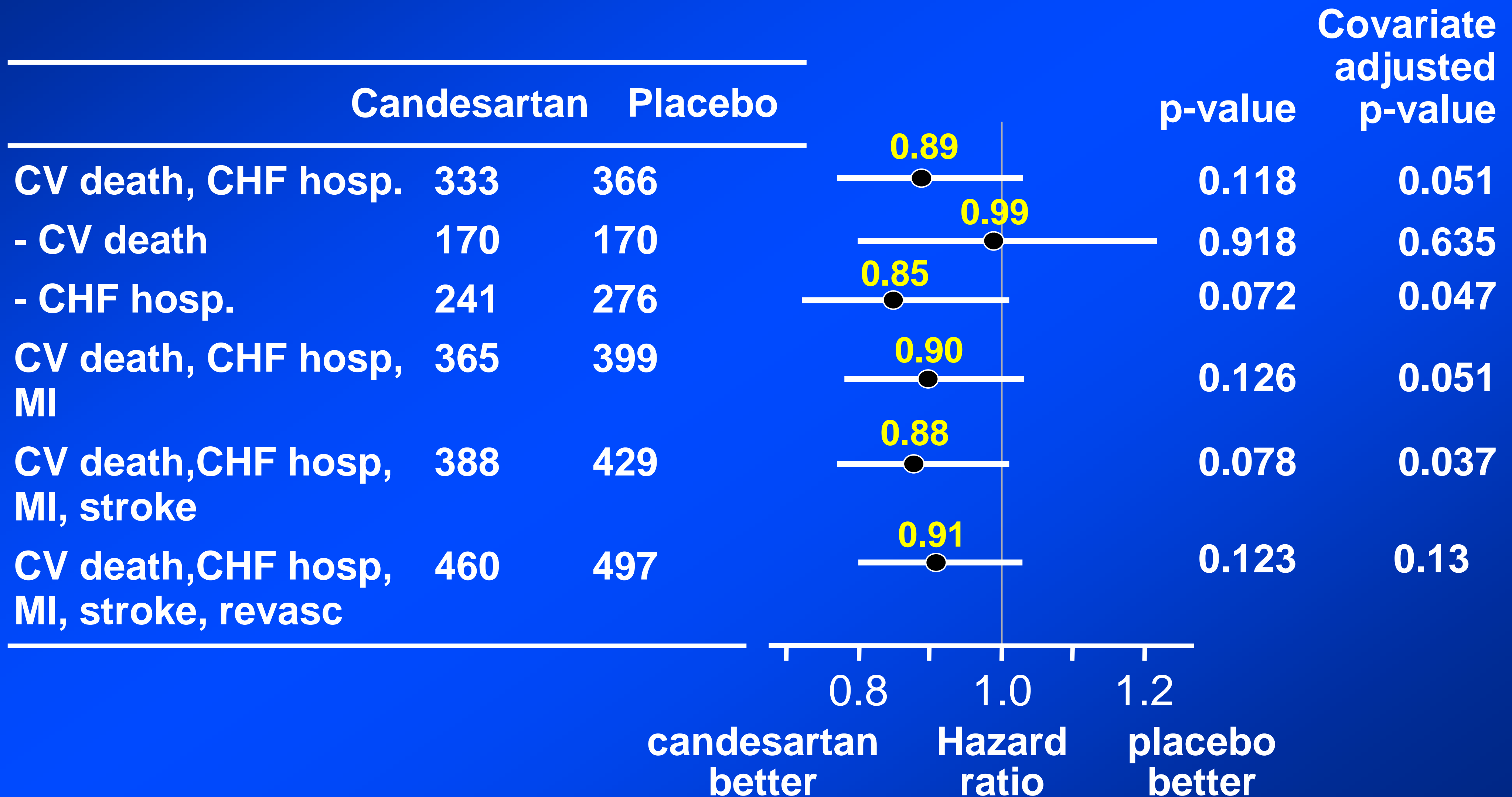
CV death or CHF hosp

CHARM-Preserved: Primary outcome CV death or CHF hospitalisation

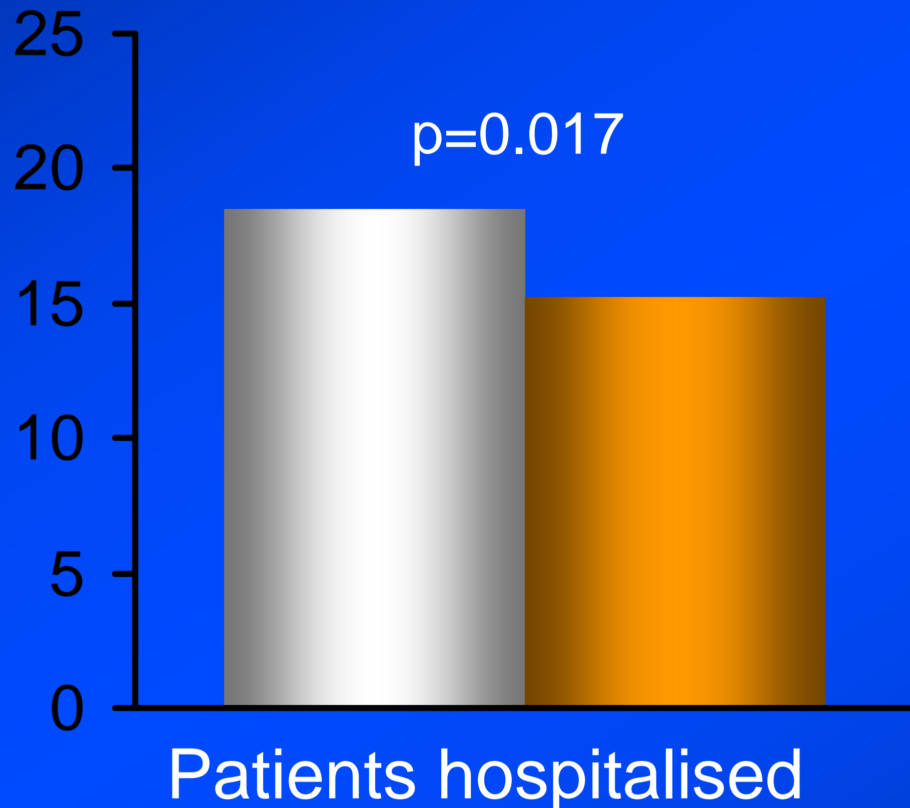


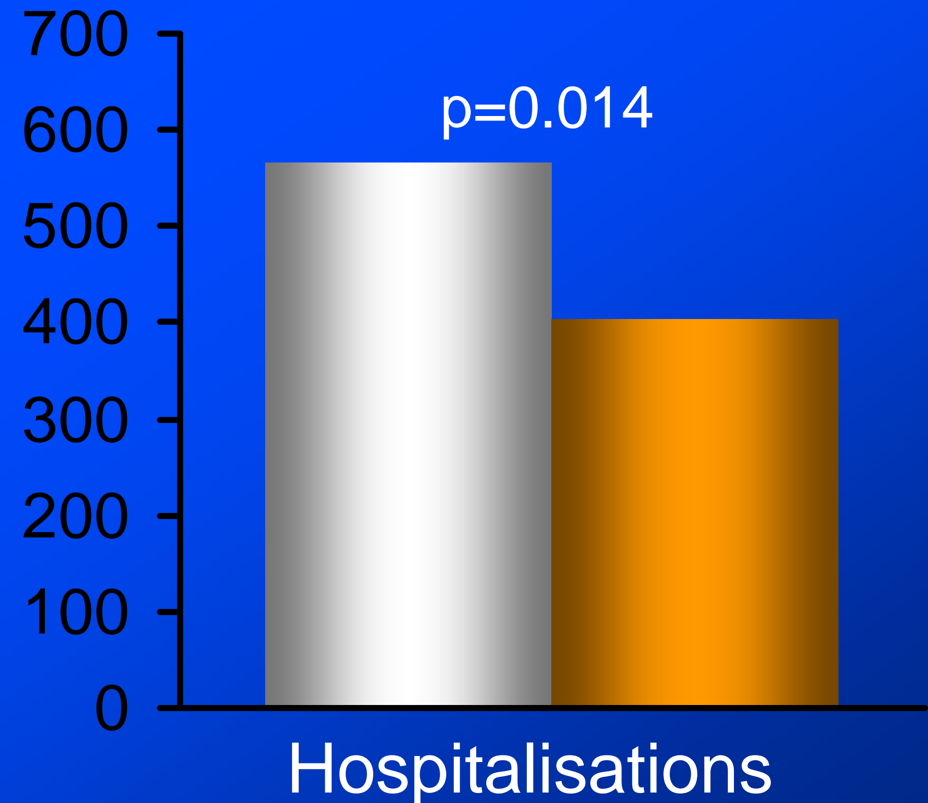
Number at risk

Candesartan	**1514**	**1458**	**1377**	**833**	**182**
Placebo	**1509**	**1441**	**1359**	**824**	**195**


CHARM-Preserved
Primary and secondary outcomes
Candesartan
Placebo
p-value
Covariate adjusted p-value
CV death, CHF hosp. 333 366 0.89 0.118 0.051
- CV death 170 170 0.99 0.918 0.635
- CHF hosp. 241 276 0.85 0.072 0.047
CV death, CHF hosp, MI 365 399 0.90 0.126 0.051
CV death,CHF hosp, MI, stroke 388 429 0.88 0.078 0.037
CV death,CHF hosp, MI, stroke, revasc 460 497 0.91 0.123 0.13
0.8
1.0
1.2
candesartan better
Hazard ratio
placebo better

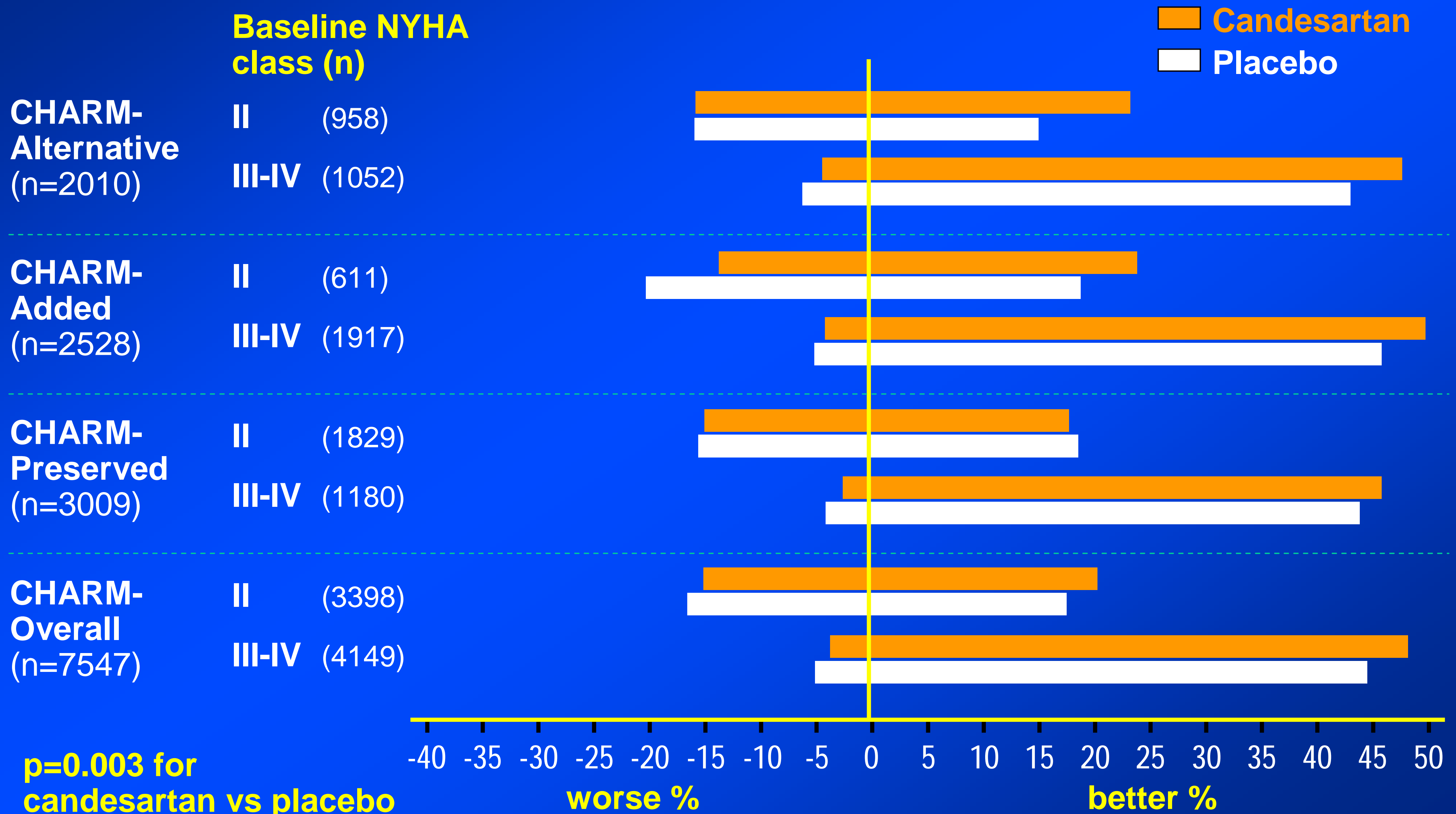
CHARM-Preserved
Investigator reported CHF hospitalisations

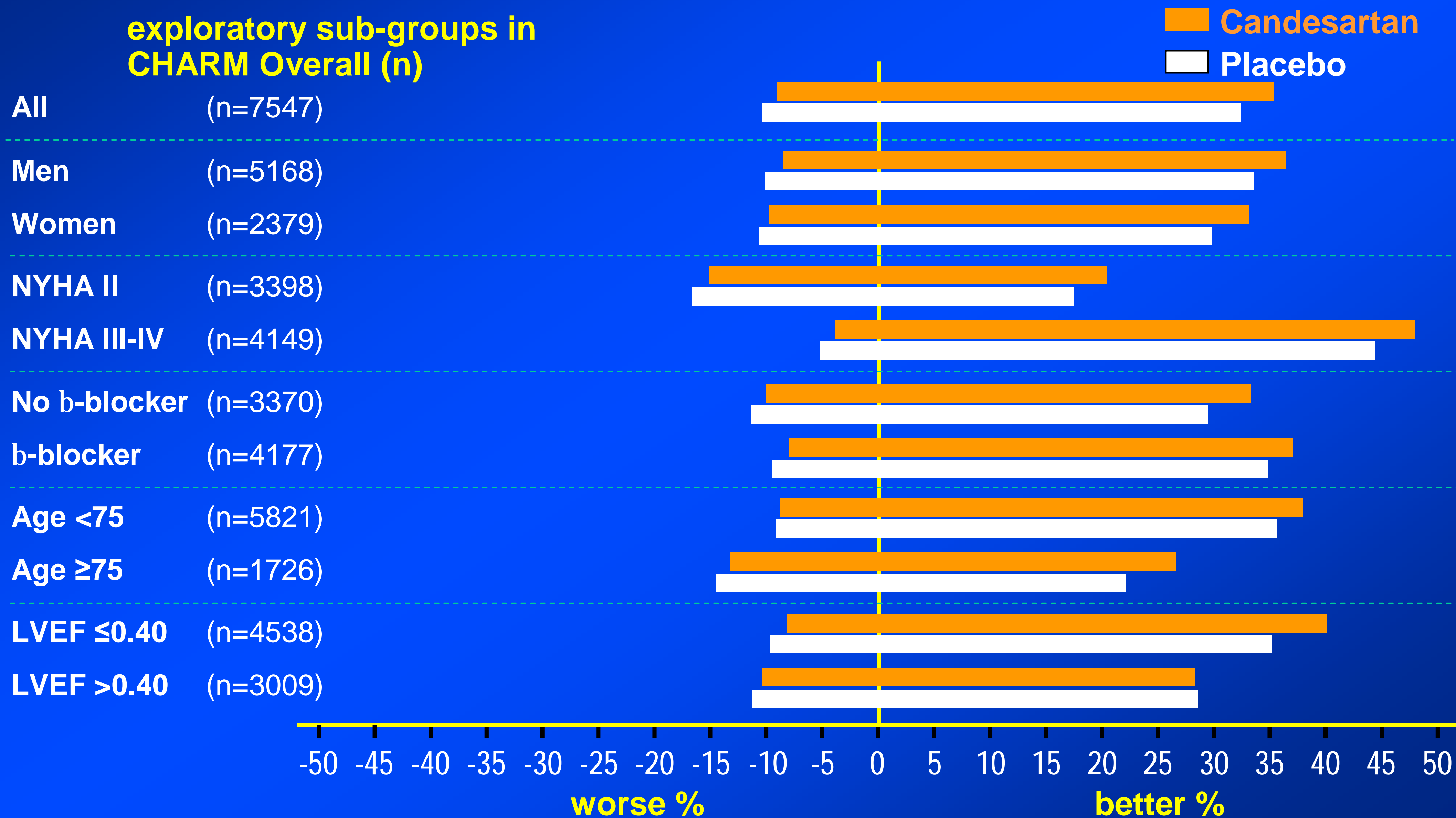




CHARM-Preserved
Conclusions

The CHARM Preserved trial provides supportive evidence that the ARB, candesartan can prevent CHF hospitalisations and can prevent the development of diabetes mellitus.


Change in NYHA class from baseline to end of study, last visit carried forward
O'Meara E. et al. Eur Heart J 2004
Baseline NYHA class (n)
Candesartan
Placebo
CHARM-Alternative (n=2010)
II (958)
III-IV (1052)
CHARM-Added (n=2528)
II (611)
III-IV (1917)
CHARM-Preserved (n=3009)
II (1829)
III-IV (1180)
CHARM-Overall (n=7547)
II (3398)
III-IV (4149)
-40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45 50
worse %
better %
p=0.003 for candesartan vs placebo



Change in NYHA class from baseline to end of study,
last visit carried forward
exploratory sub-groups in
CHARM Overall (n)
Candesartan
Placebo
All (n=7547)
Men (n=5168)
Women (n=2379)
NYHA II (n=3398)
NYHA III-IV (n=4149)
No b-blocker (n=3370)
b-blocker (n=4177)
Age <75 (n=5821)
Age ≥75 (n=1726)
LVEF ≤0.40 (n=4538)
LVEF >0.40 (n=3009)
-50 -45 -40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45 50
worse %
better %

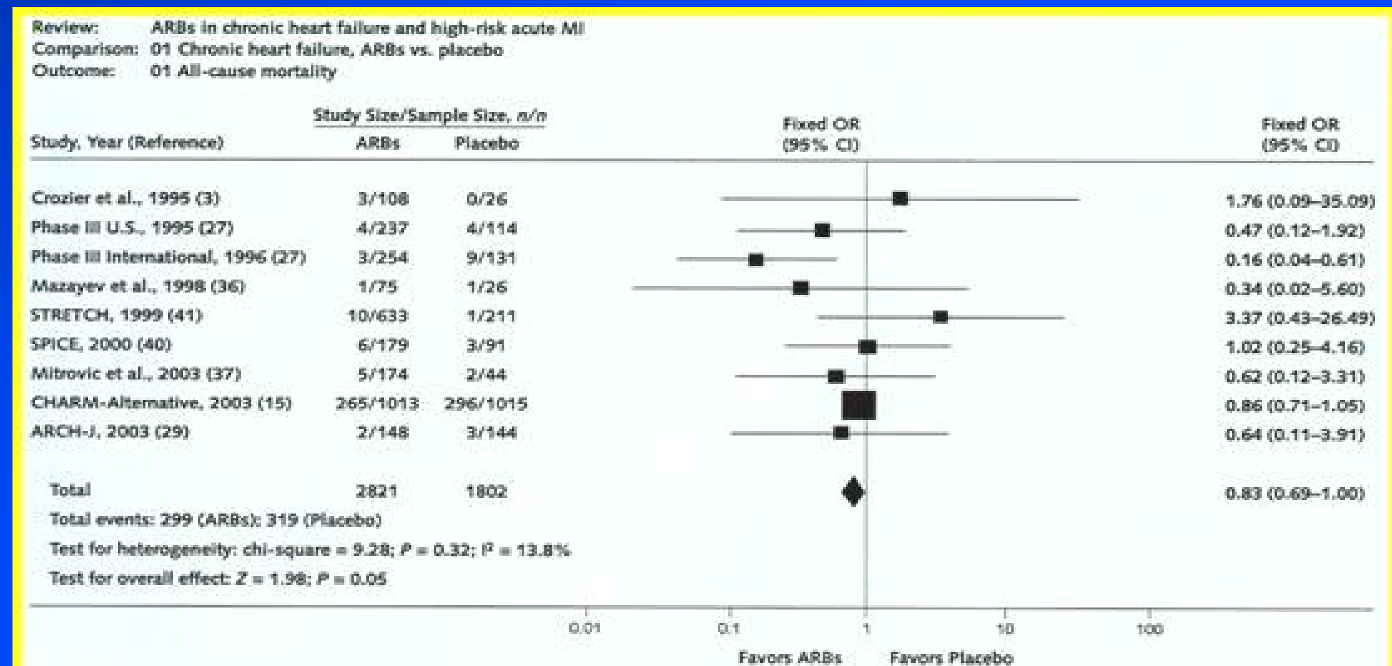
Effects of Candesartan on NYHA functional class. Results of the CHARM programm

- The ARB candesartan improved overall NYHA class in patients with CHF and left ventricular systolic dysfunction
- This benefit was seen even in patients treated with full conventional therapy
- The benefit observed was similar in magnitude to that observed with other treatments for CHF
- Candesartan improves symptoms, reduces hospital admissions for CHF and increases survival in patients with CHF and left ventricular systolic dysfunction

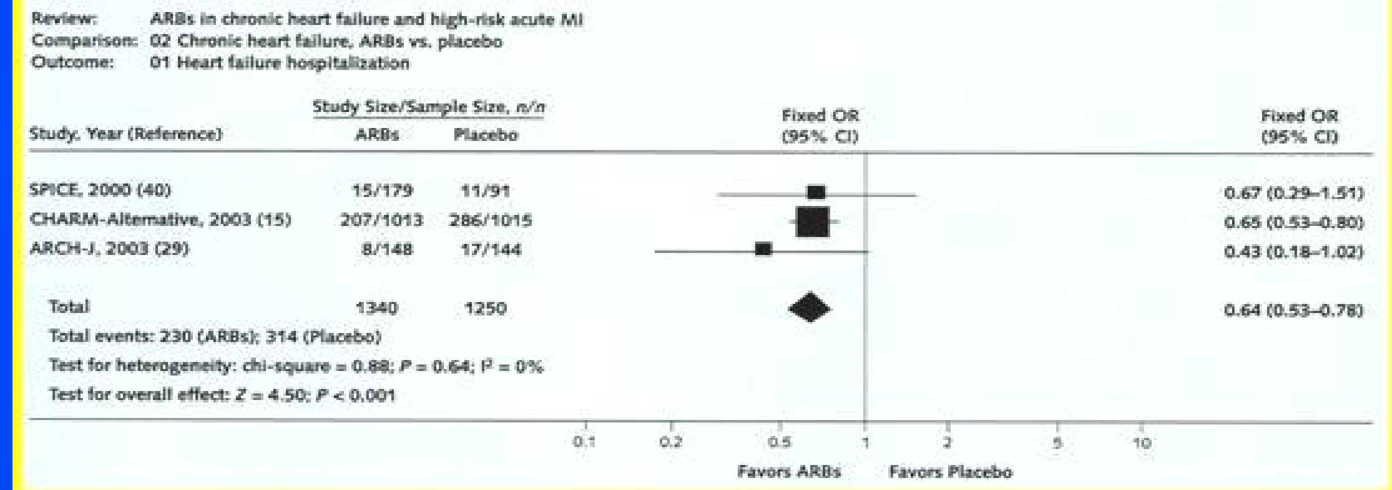
O'Meara E. et al. Eur Heart J 2004

ARBs vs Placebo in Patients with Chronic Heart Failure

All cause mortality



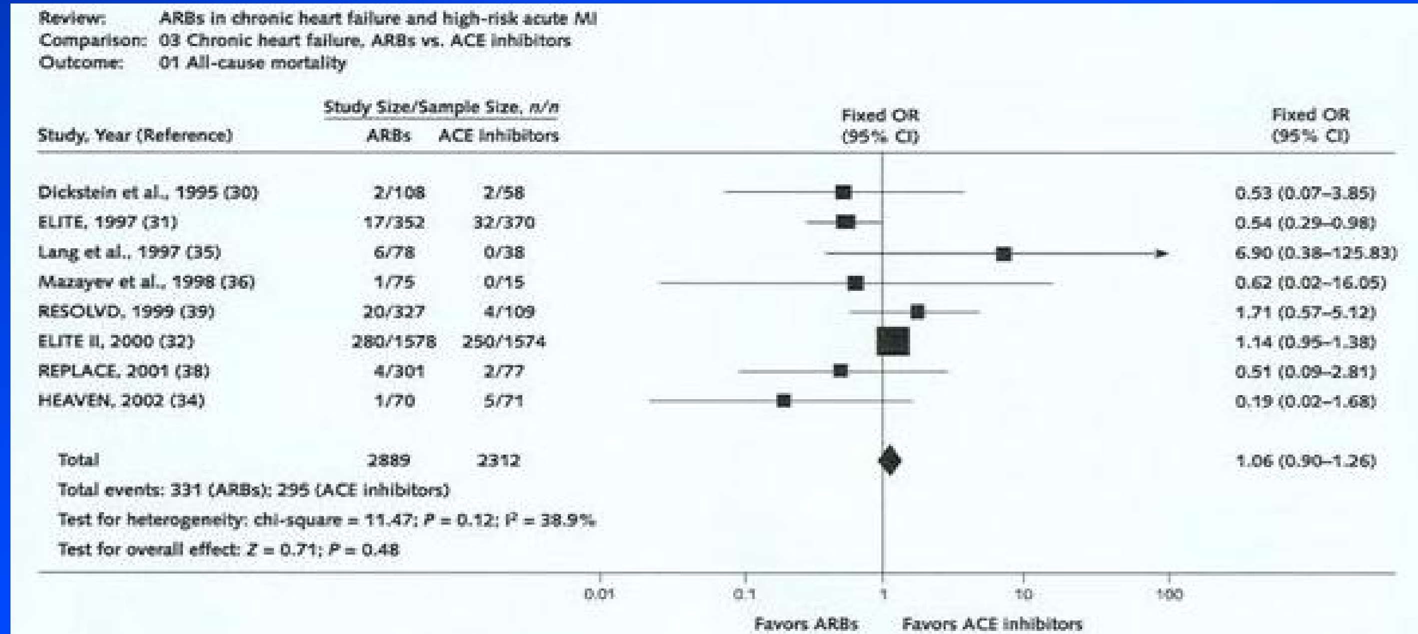
Hospitalisations



Ann Intern Med. 2004; 141:693-704

ARBs vs ACE inhibitors in patients with CHF

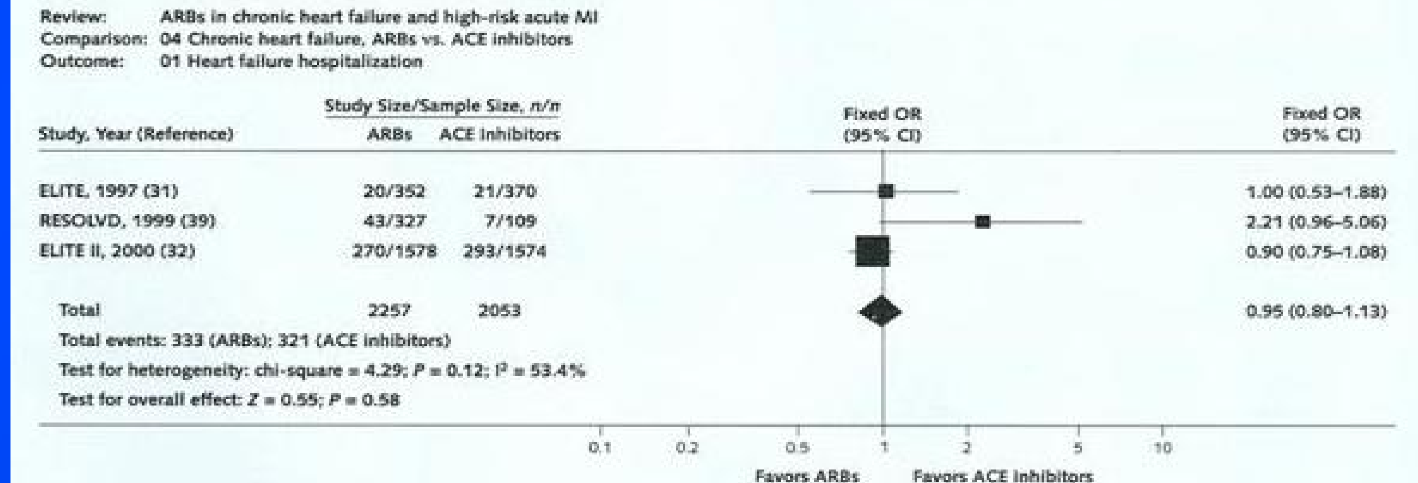
All cause mortality


Review: ARBs in chronic heart failure and high-risk acute MI
Comparison: 03 Chronic heart failure, ARBs vs. ACE inhibitors
Outcome: 01 All-cause mortality

Study, Year (Reference)	Study Size/Sample Size, n/n: ARBs	ACE Inhibitors	Fixed OR (95% CI)
Dickstein et al., 1995 (30)	2/108	2/58	0.53 (0.07–3.85)
ELITE, 1997 (31)	17/352	32/370	0.54 (0.29–0.98)
Lang et al., 1997 (35)	6/78	0/38	6.90 (0.38–125.83)
Mazayev et al., 1998 (36)	1/75	0/15	0.62 (0.02–16.05)
RESOLVD, 1999 (39)	20/327	4/109	1.71 (0.57–5.12)
ELITE II, 2000 (32)	280/1578	250/1574	1.14 (0.95–1.38)
REPLACE, 2001 (38)	4/301	2/77	0.51 (0.09–2.81)
HEAVEN, 2002 (34)	1/70	5/71	0.19 (0.02–1.68)
Total	2889	2312	1.06 (0.90–1.26)

Total events: 331 (ARBs); 295 (ACE inhibitors)
Test for heterogeneity: chi-square = 11.47; $P = 0.12$; $I^2 = 38.9\%$
Test for overall effect: $Z = 0.71$; $P = 0.48$

Hospitalisations


Review: ARBs in chronic heart failure and high-risk acute MI
Comparison: 04 Chronic heart failure, ARBs vs. ACE inhibitors
Outcome: 01 Heart failure hospitalization

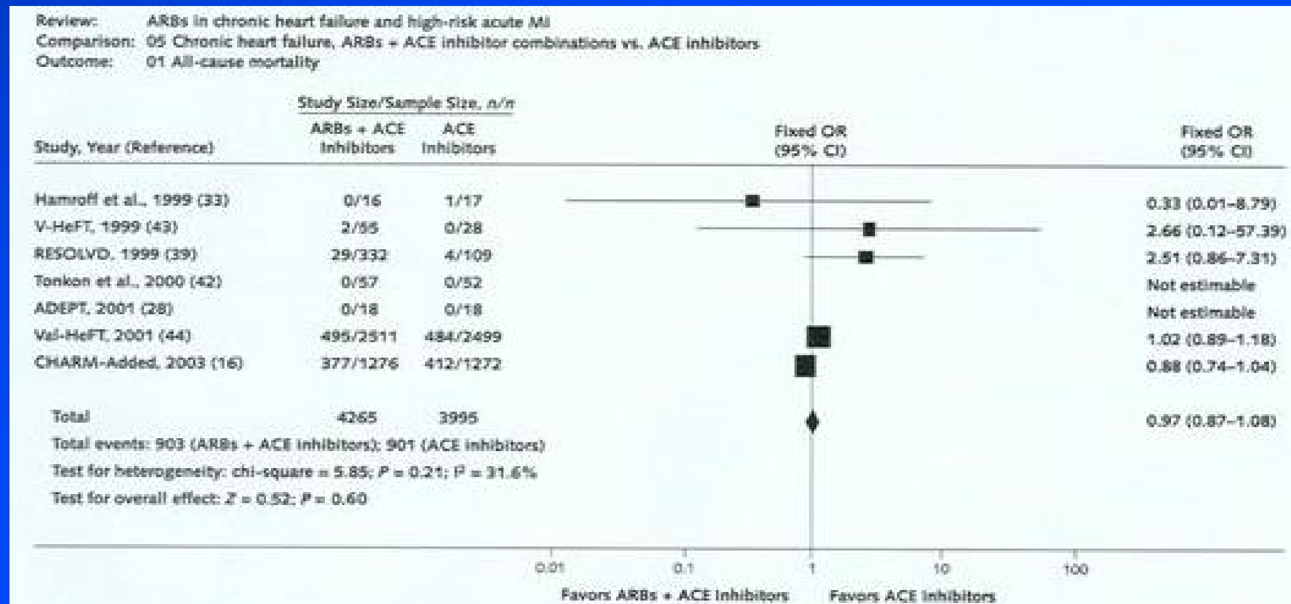
Study, Year (Reference)	Study Size/Sample Size, n/n: ARBs	ACE Inhibitors	Fixed OR (95% CI)
ELITE, 1997 (31)	20/352	21/370	1.00 (0.53–1.88)
RESOLVD, 1999 (39)	43/327	7/109	2.21 (0.96–5.06)
ELITE II, 2000 (32)	270/1578	293/1574	0.90 (0.75–1.08)
Total	2257	2053	0.95 (0.80–1.13)

Total events: 333 (ARBs); 321 (ACE inhibitors)
Test for heterogeneity: chi-square = 4.29; $P = 0.12$; $I^2 = 53.4\%$
Test for overall effect: $Z = 0.55$; $P = 0.58$

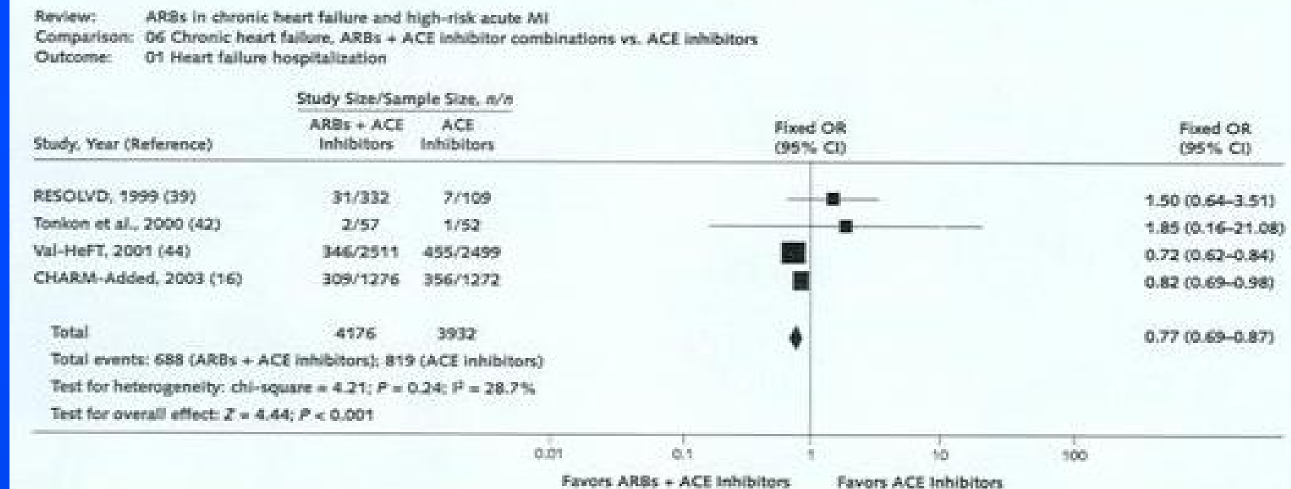
Ann Intern Med. 2004; 141:693-704

ARB and ACE inhibitor combinations vs ACE inhibitors in patients with chronic heart failure.

All cause mortality

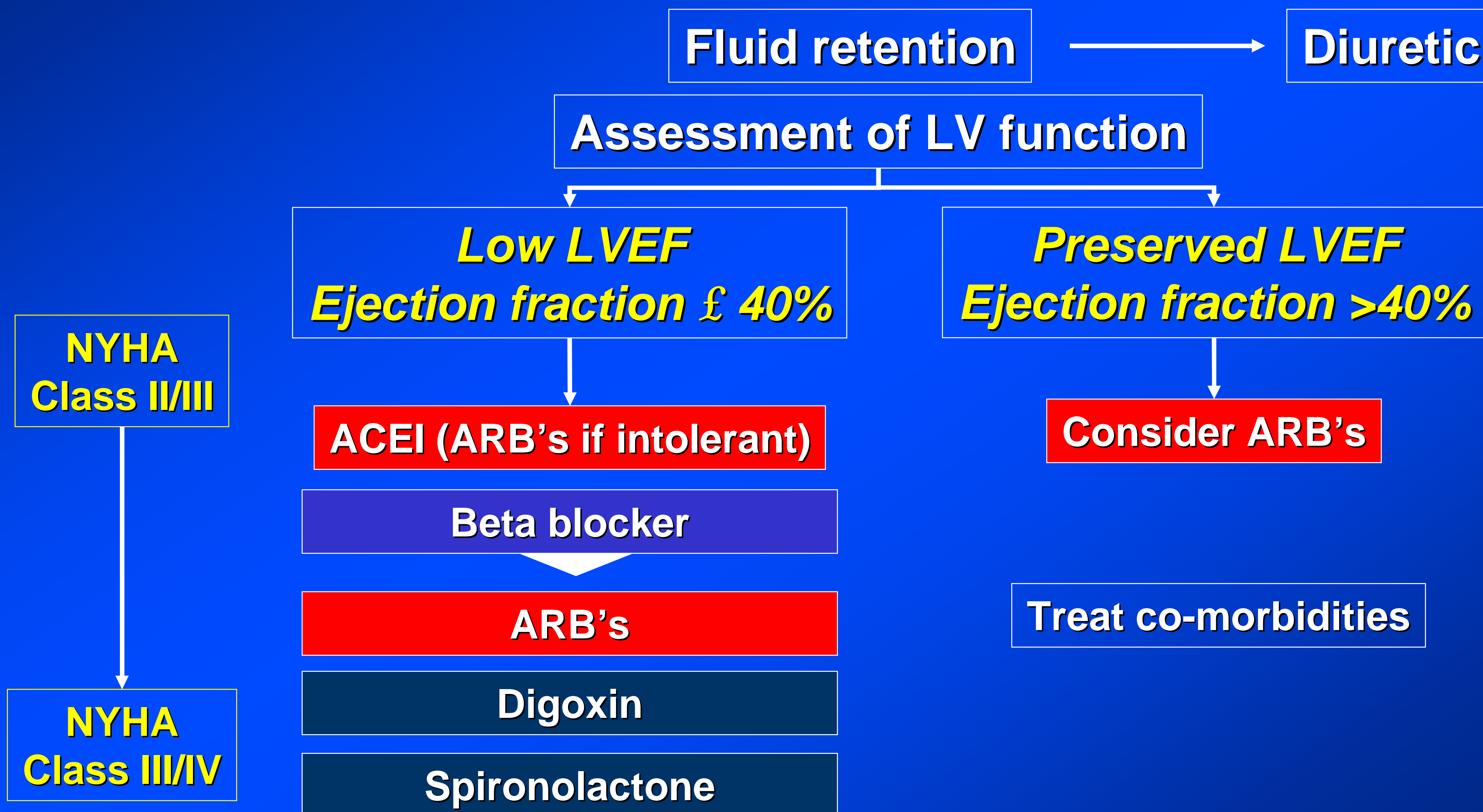


Hospitalisations



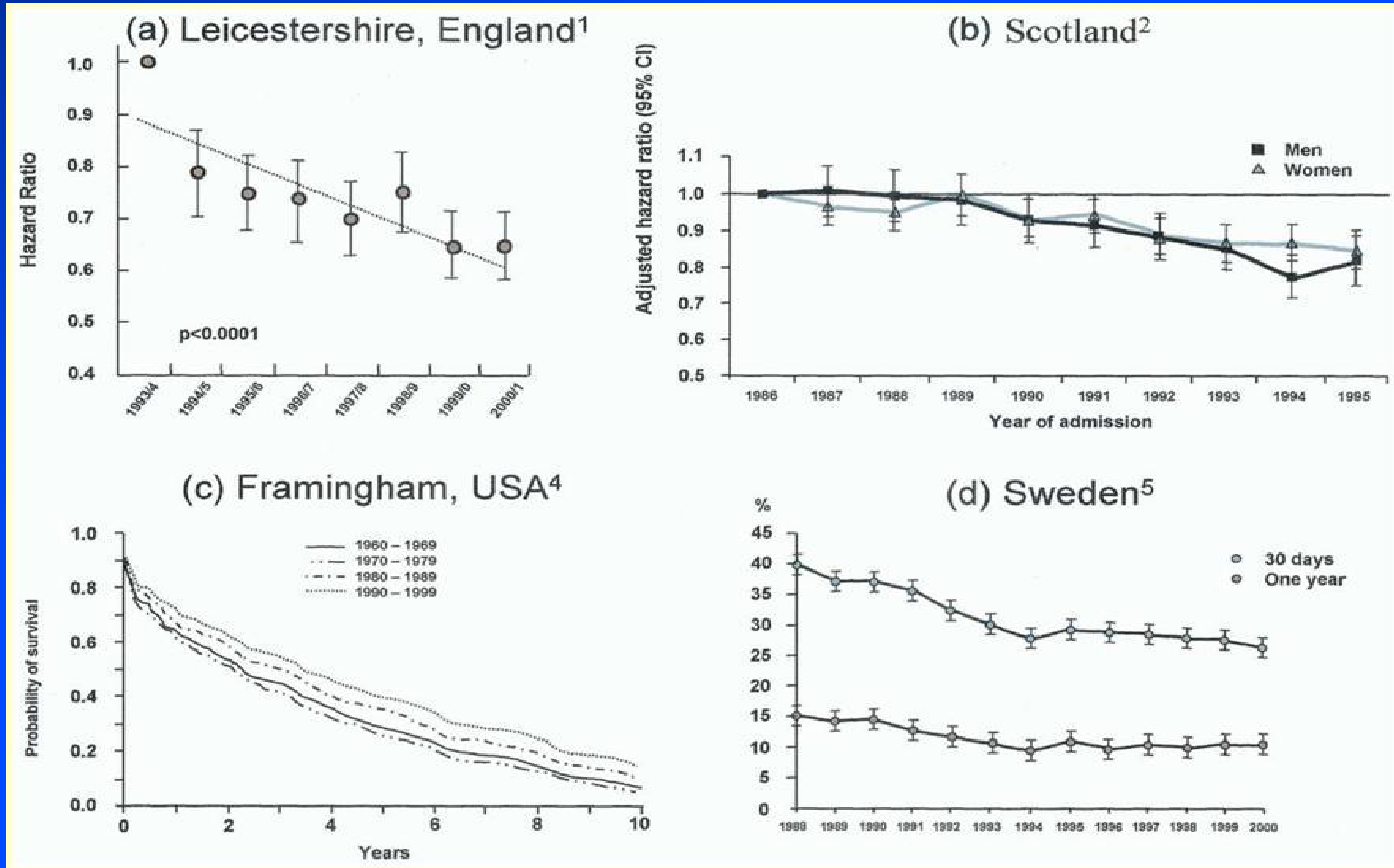
Ann Intern Med. 2004; 141:693-704

Approaches to the patient with heart failure: implications from recent trials



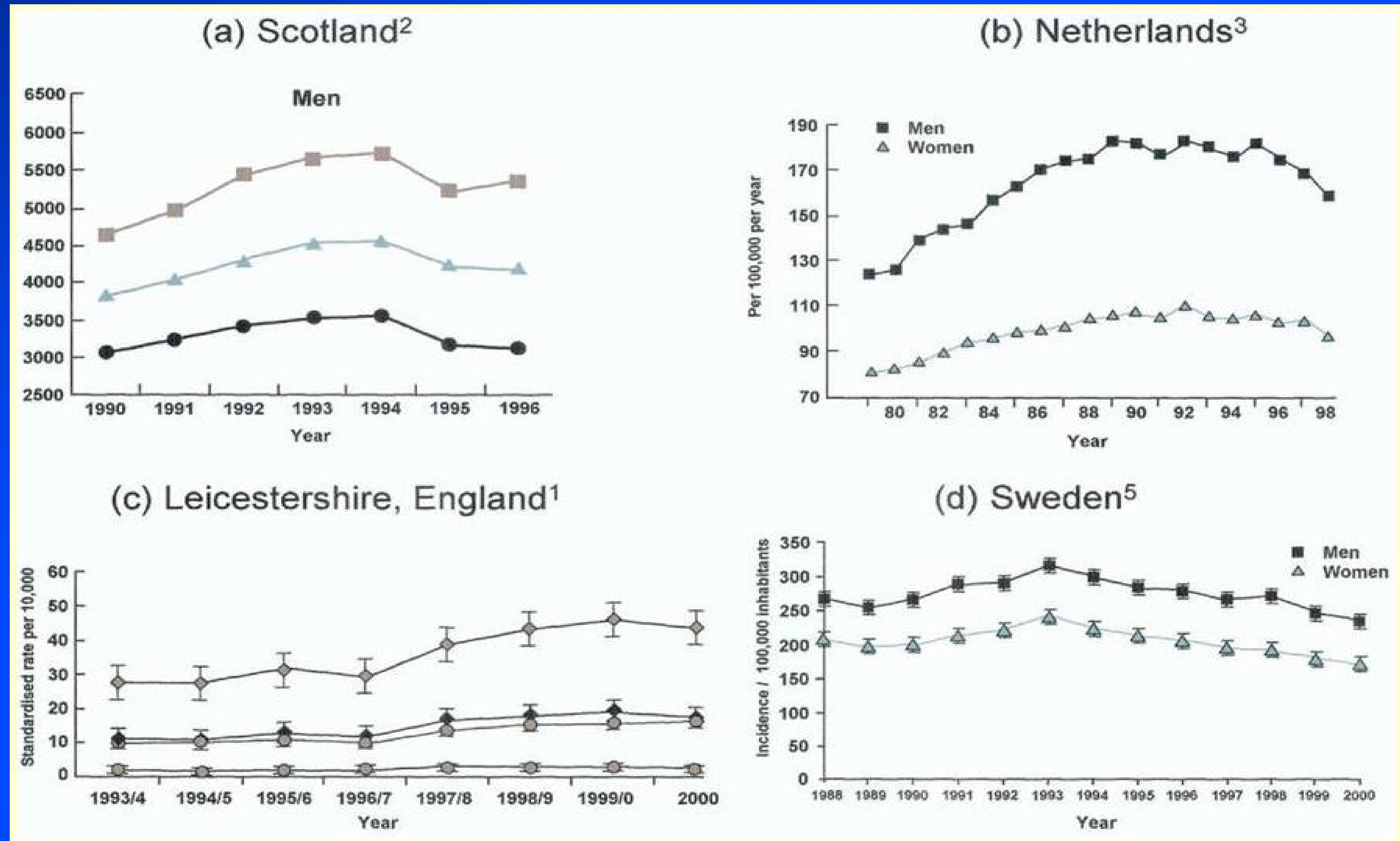
European Heart Journal Sup (2004) 6 (Sup H), H55-H60

Evidence of improving survival from heart failure in the general population



JACC Vol. 44, No. 12, 2004: 2398-405

Recent trends in hospital admissions for heart failure demonstrating recent plateau or decline



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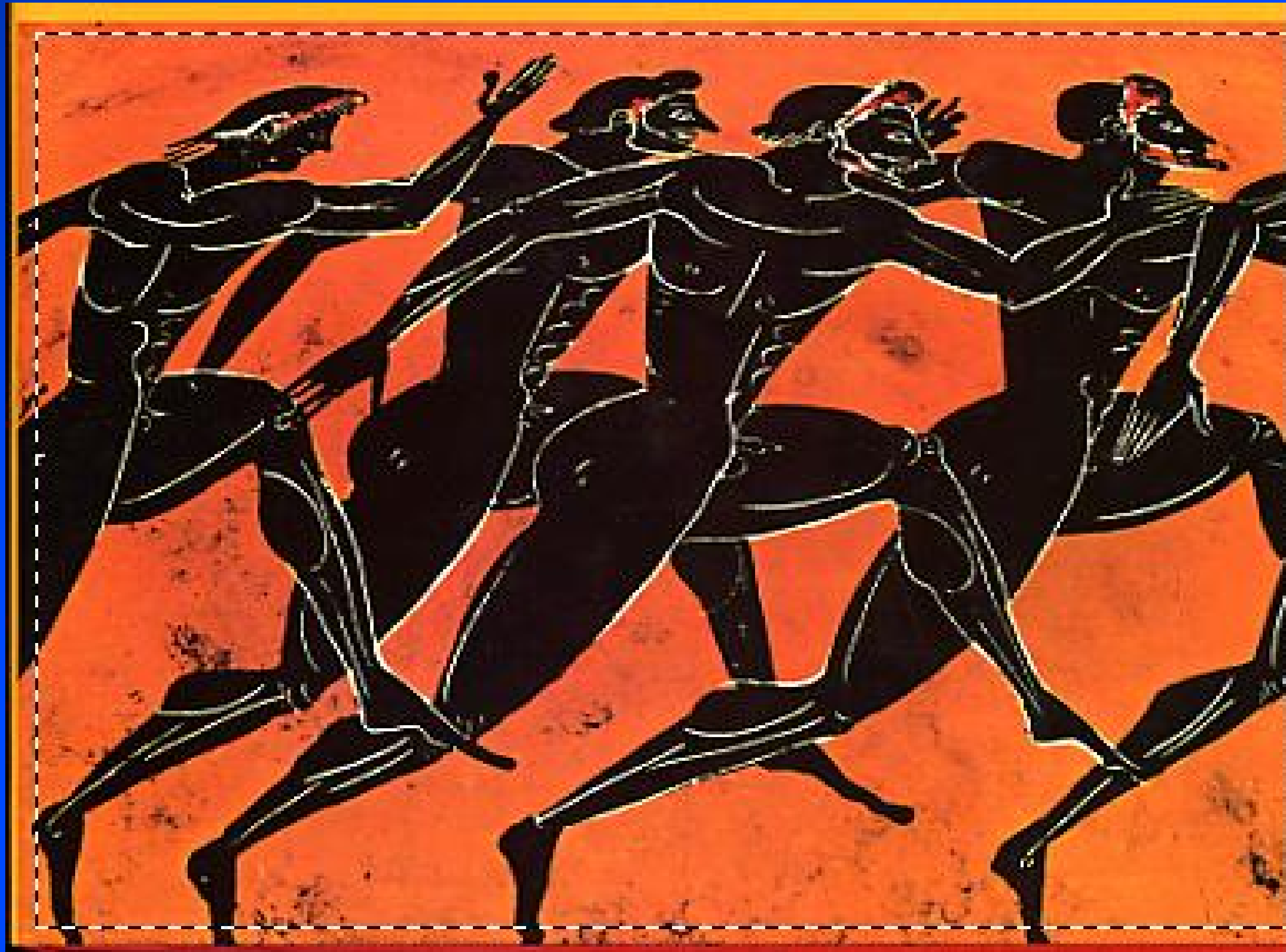

2004: The Year in Heart Failure

- Η Καρδιακή ανεπάρκεια παραμένει ένα δυναμικό πεδίο
- Η θεραπεία συνεχίζει να βελτιώνεται, και επιτέλους το όφελος που παρατηρήθηκε στις μεγάλες μελέτες φαίνεται να περνά και στο γενικό πληθυσμό.
- Πέρα από τους β-αναστολείς και τους ΑΜΕΑ, δύο επιπλέον ομάδες φαρμάκων, **οι ανταγωνιστές υποδοχέων της αγγειοτασίνης** και οι ανταγωνιστές της αλδοστερόνης απέδειξαν αναμφίβολα την ωφέλειά τους στη θεραπεία της καρδιακής ανεπάρκειας.

McMurray JJ, Pfeffer MA. J Am Coll Cardiol 2004

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