The Therapeutic Potential of Novel Approaches to RAAS Inhibition in Heart Failure

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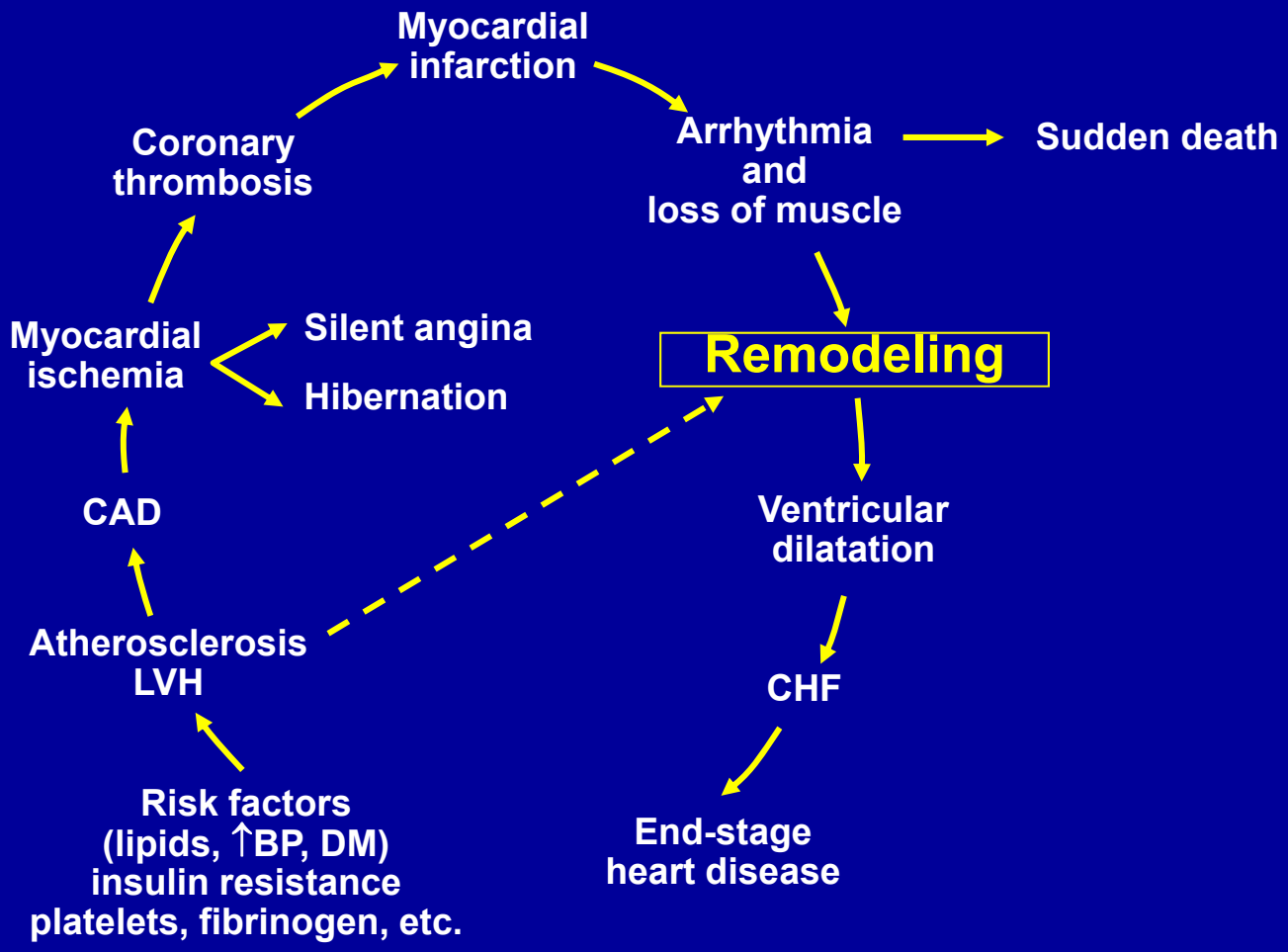
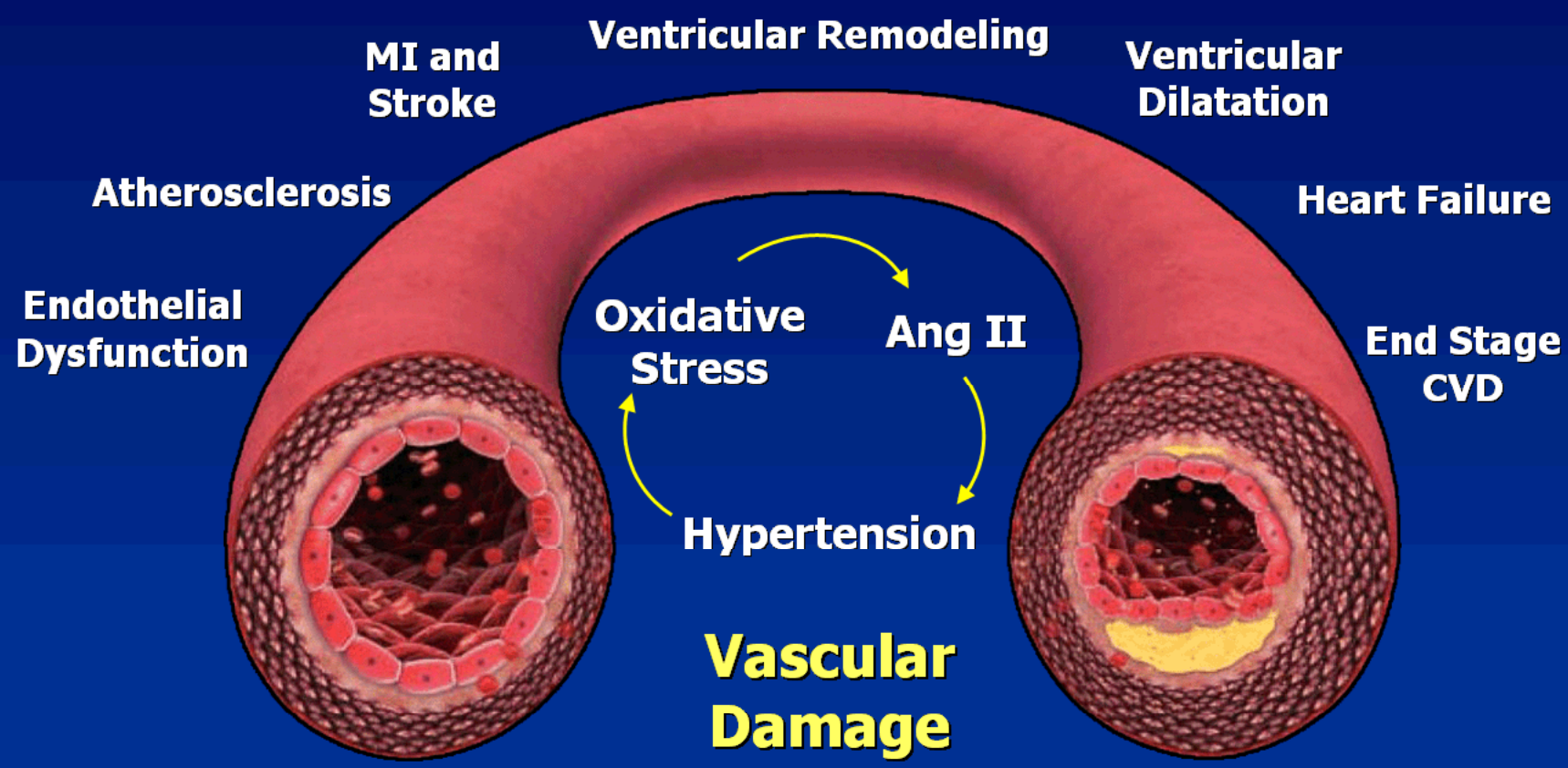
Chain of Events Leading to End-Stage Heart Failure



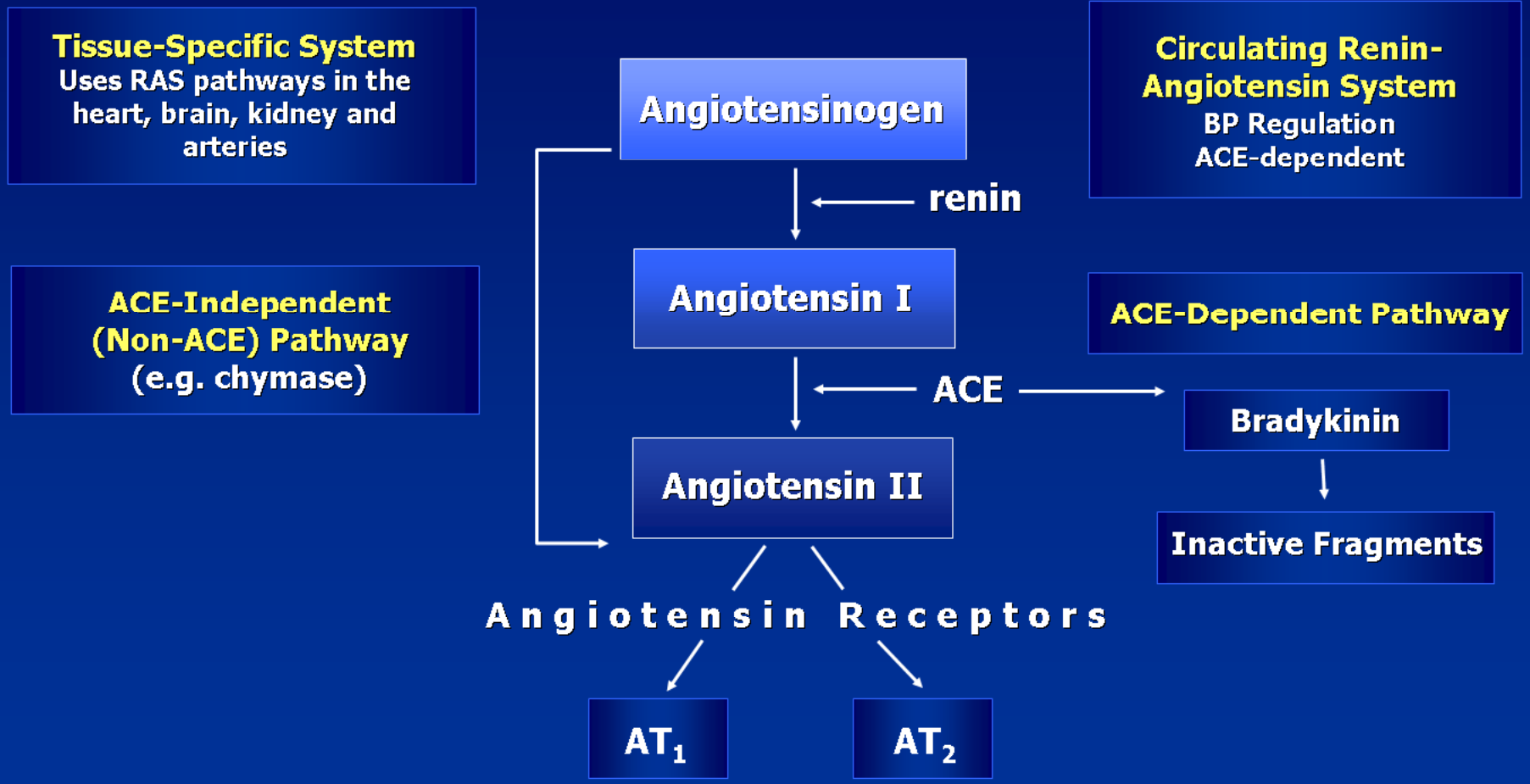
Dzau and Braunwald. *Am Heart J.* 1991;121(4 part 1):1244.

Ang II and Cardiovascular Risk



Adapted from Dzau V. *J Hypertens Suppl*. 2005;23:S9–S17.

The RAAS Cascade: Formation of Angiotensin II



ACE=angiotensin-converting enzyme; RAAS=renin-angiotensin-aldosterone system.
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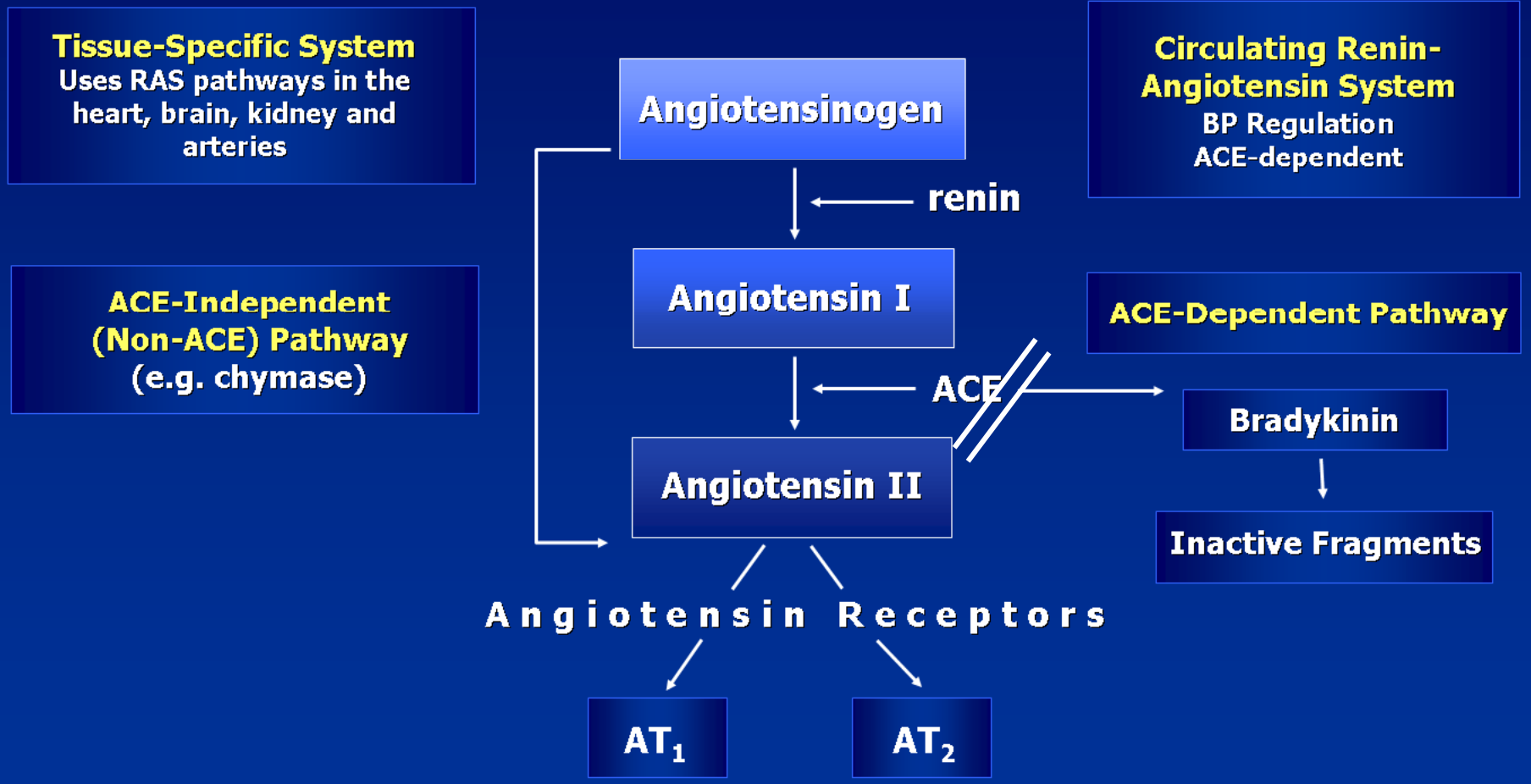

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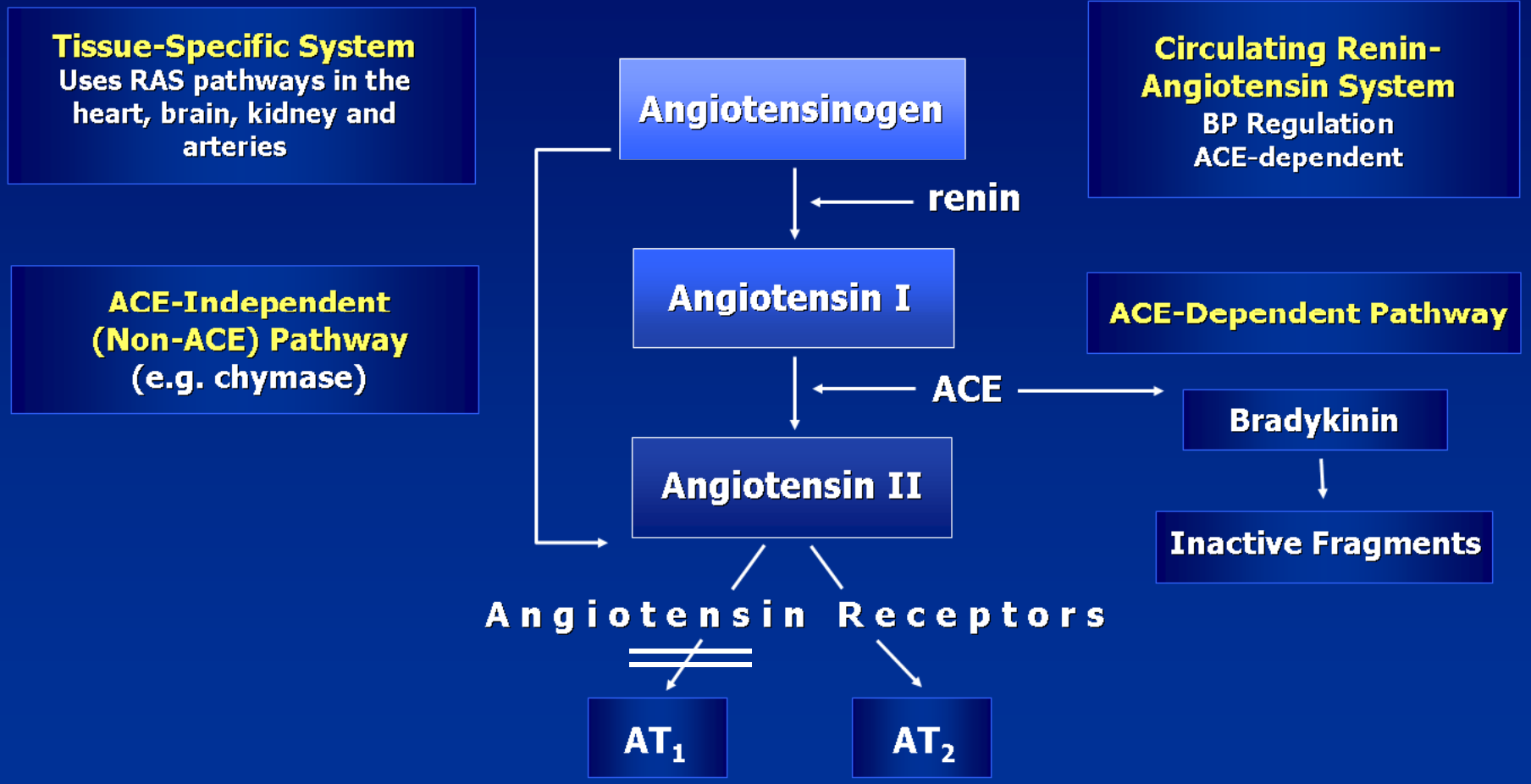

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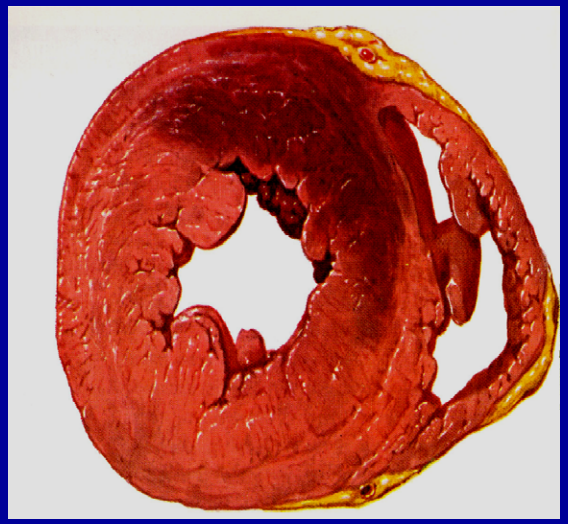
Angiotensin Receptors

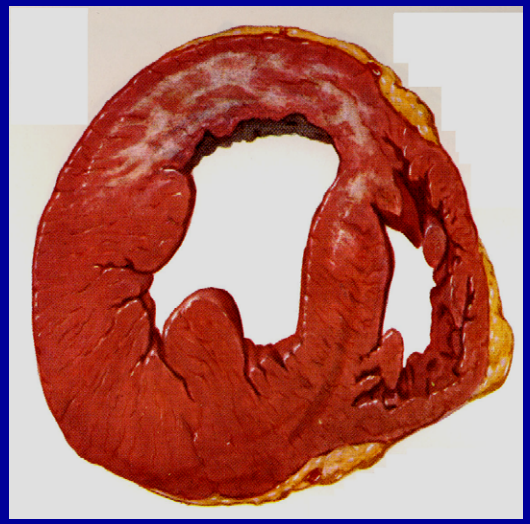
- The AT_1 receptor is responsible for most effects of Ang II.
- AT_1 stimulation results in salt/water retention, arterial vasoconstriction, release of secondary growth factors (e.g. TGF-β, ET-1), myocyte hypertrophy and fibroblast activation.
- AT_1 receptor density is increased in the post-MI and failing heart.

Structural Remodeling Post-MI

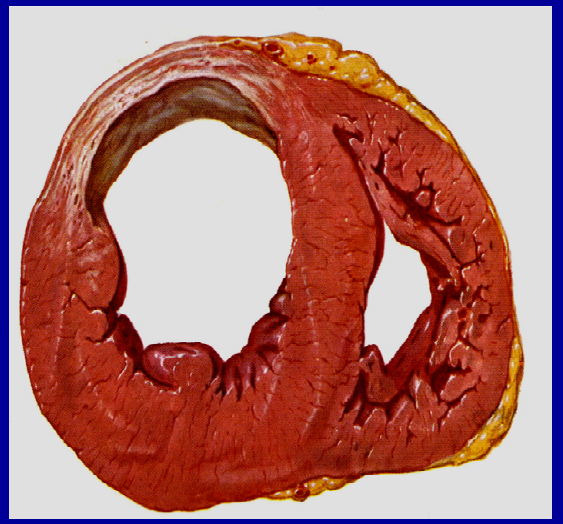
Days → Weeks → Months - Years



MI due to coronary occlusion

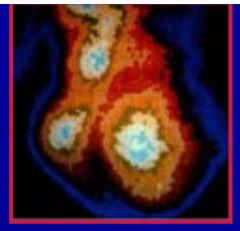


Scarring and reshaping of the heart (remodeling)

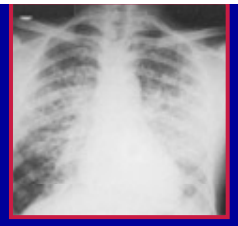


Heart enlarges and leads to congestive heart failure

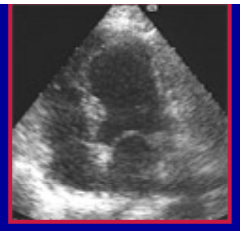
F. Netter CIBA



SAVE
Radionuclide
EF ≤ 40 %

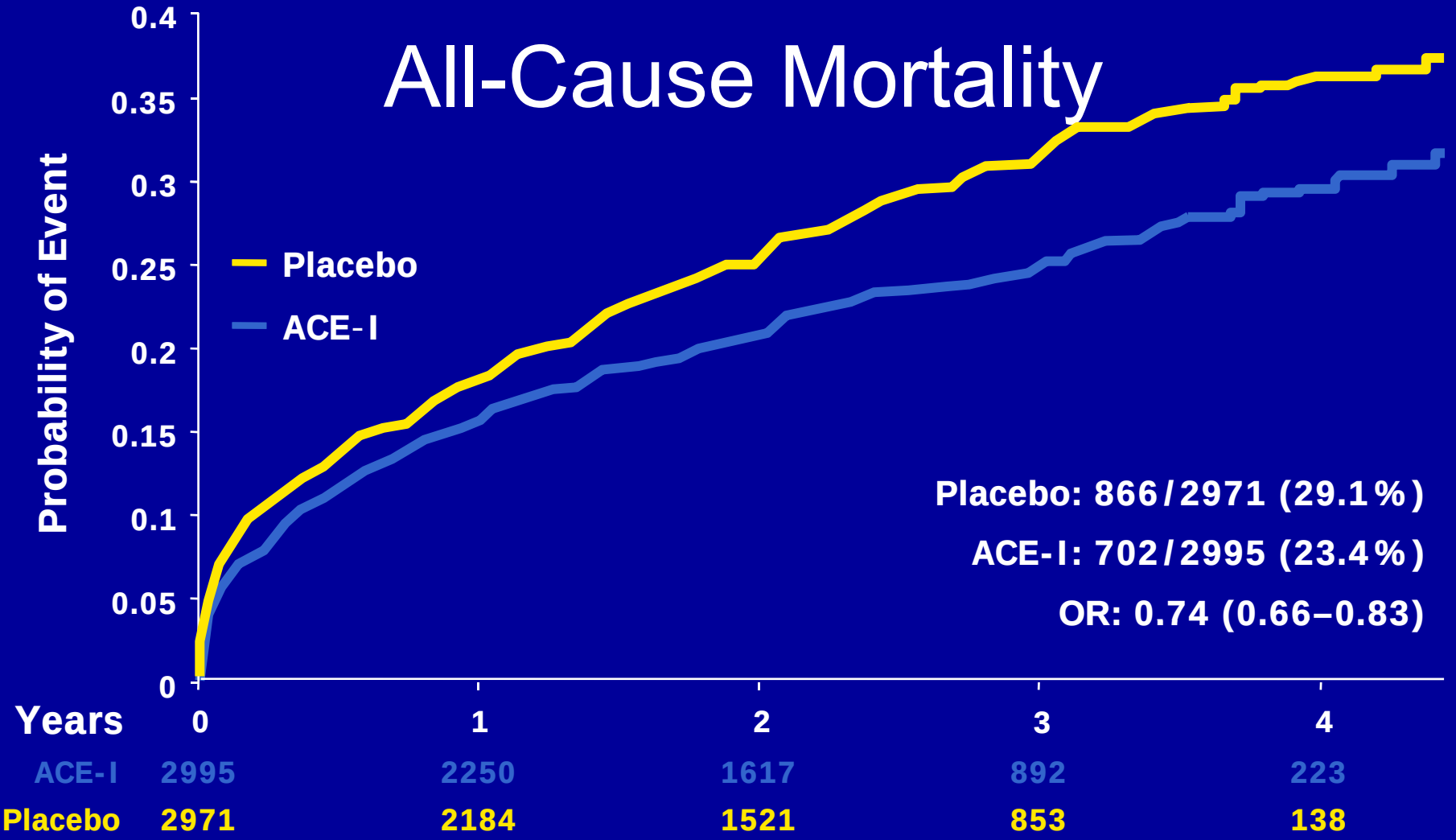


AIRE
Clinical and/or
radiographic
signs of HF



TRACE
Echocardiographic
EF ≤ 35 %

All-Cause Mortality



Flather MD, et al. Lancet. 2000;355:1575–1581

VALIANT

Objective

- VALIANT was designed as a mortality trial in high-risk MI patients (SAVE, AIRE, TRACE) who derived particular benefits from an ACE inhibitor.
- To determine whether:

  Diovan was superior to captopril in improving survival

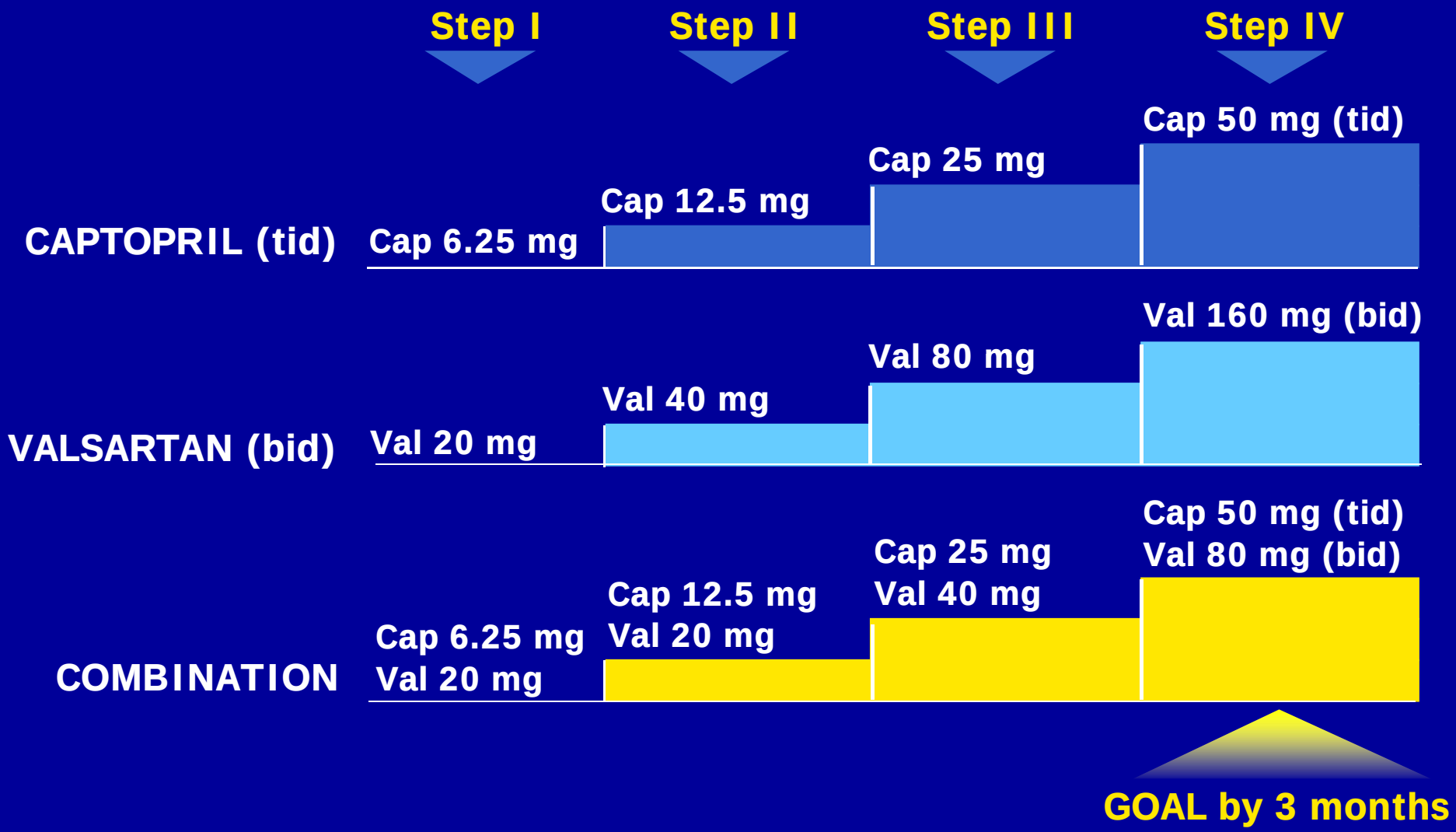
  and with equal statistical power

  the addition of the Diovan to captopril was superior to the proven dose of captopril in improving survival

- If Diovan was not superior to captopril, a non-inferiority analysis was prespecified to determine whether Diovan could be considered “as effective as” captopril

VALIANT

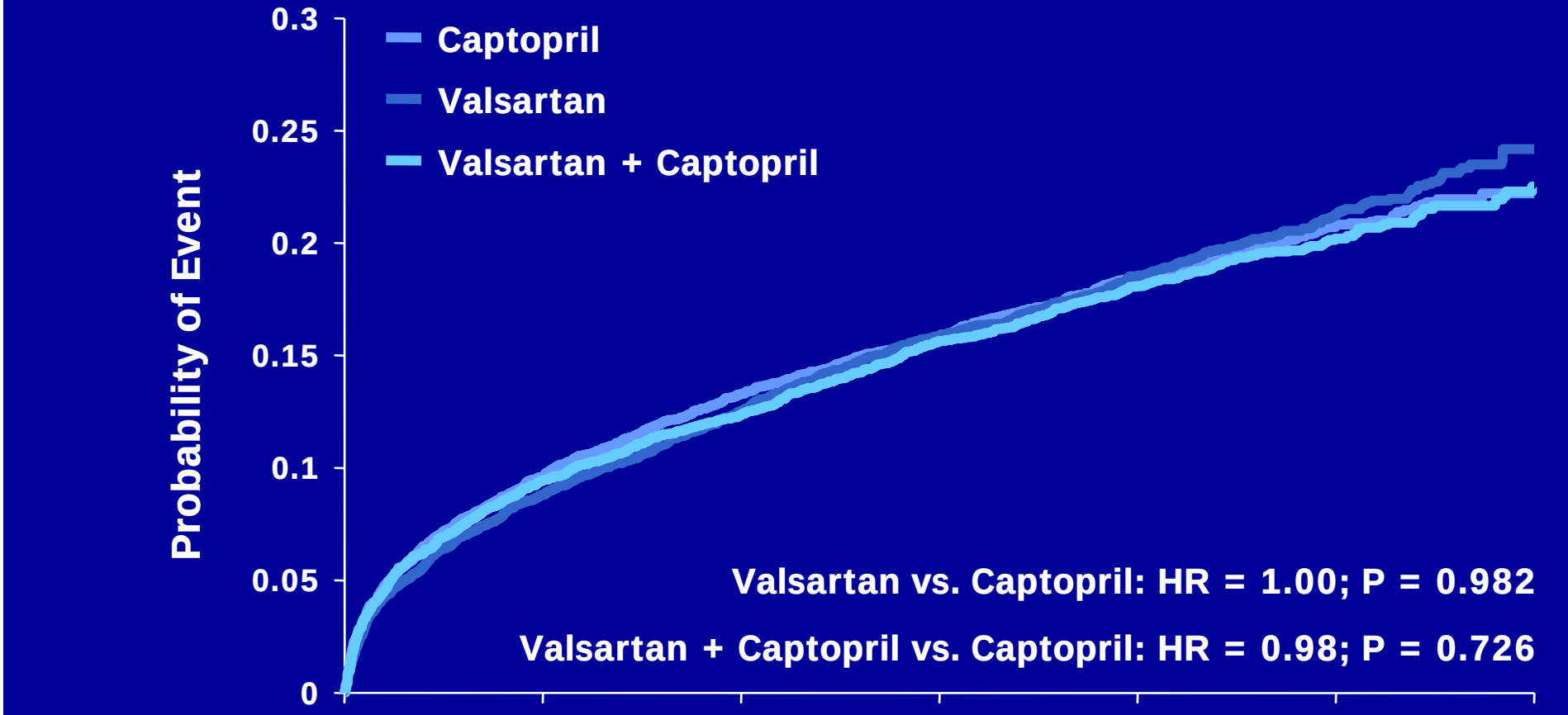
Study Drug Dose Titration



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

VALIANT

Mortality by Treatment

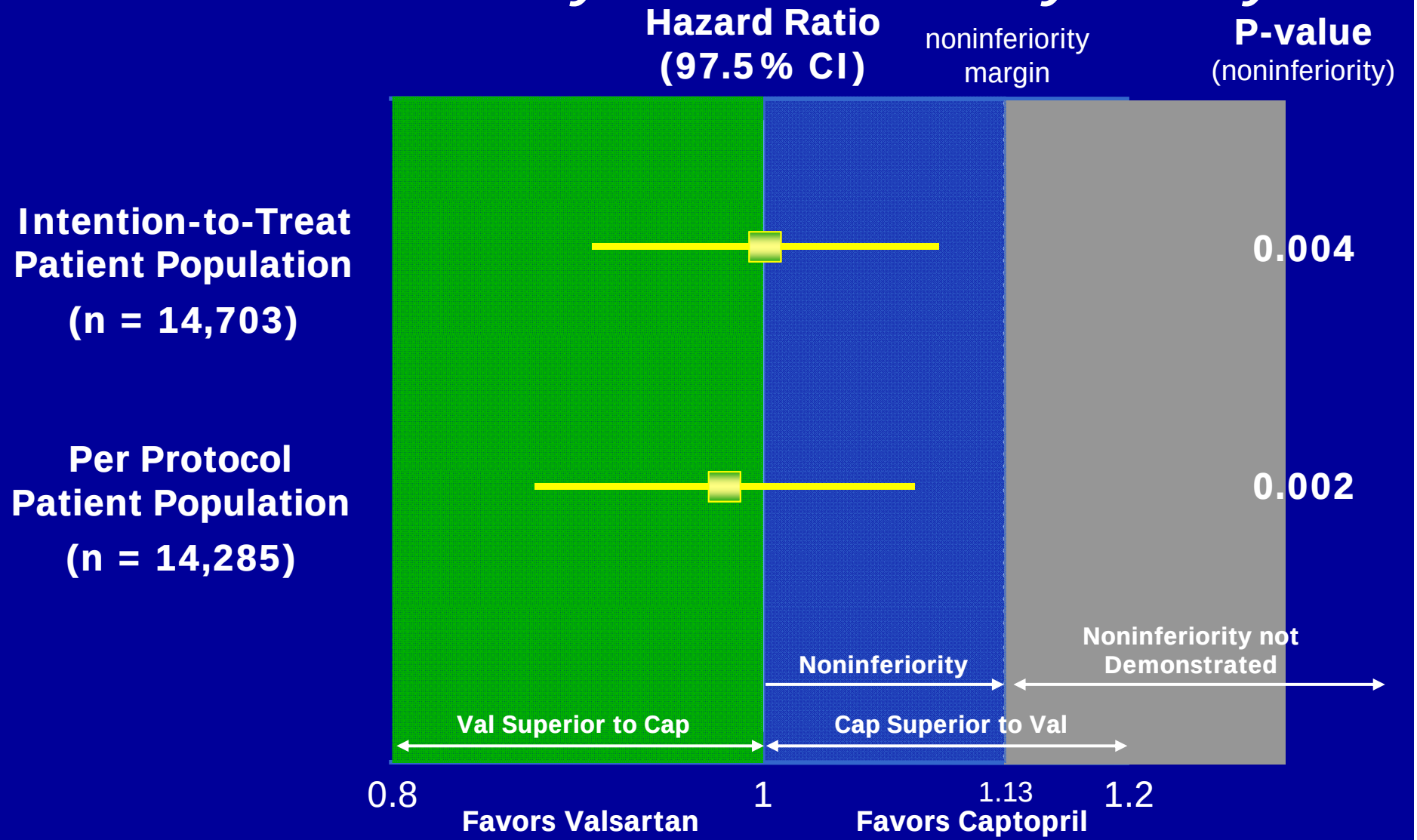


Months	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

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

VALIANT

All Cause Mortality Non-inferiority Analysis



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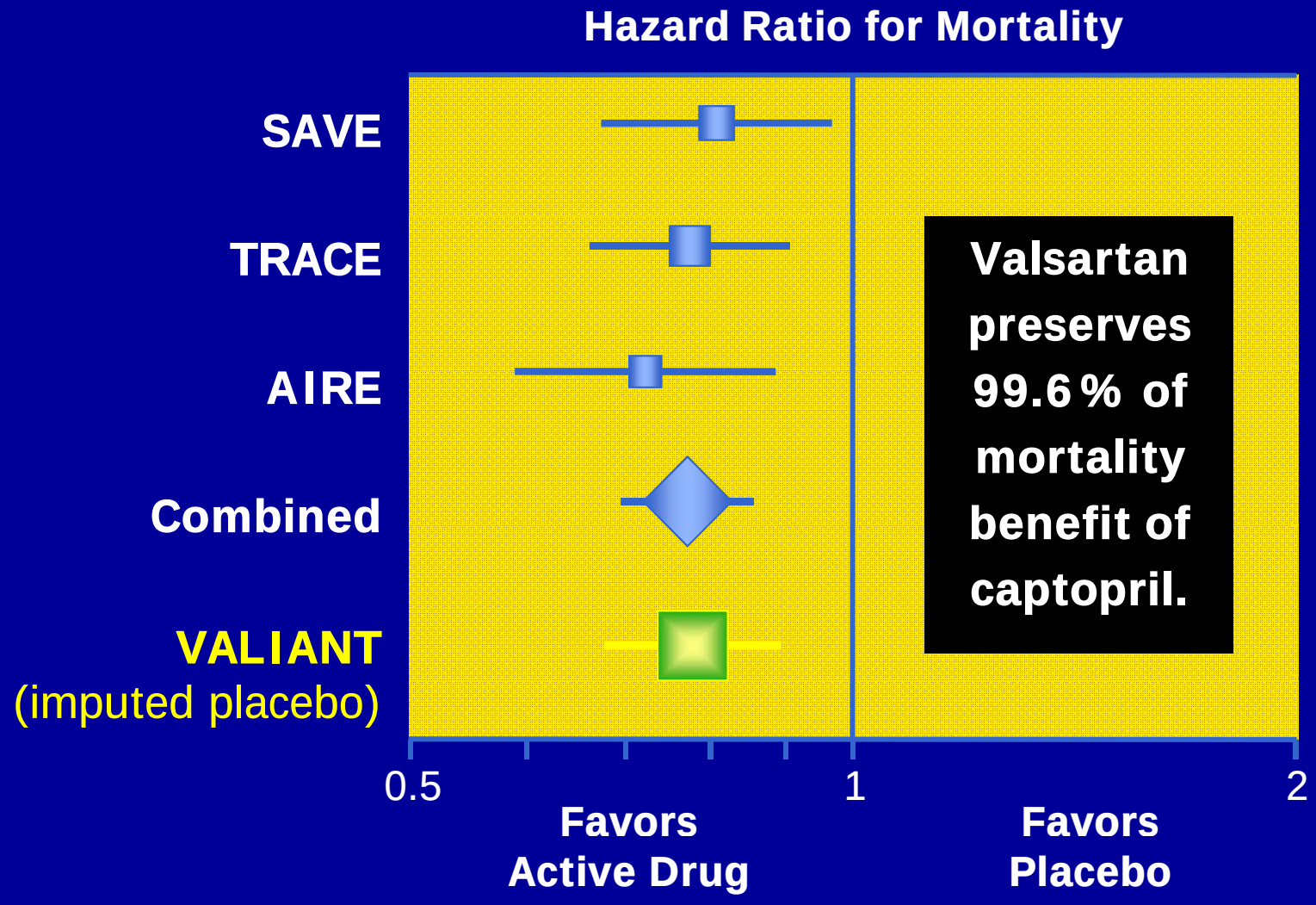
VALIANT

Mortality in SAVE, TRACE, AIRE, VALIANT



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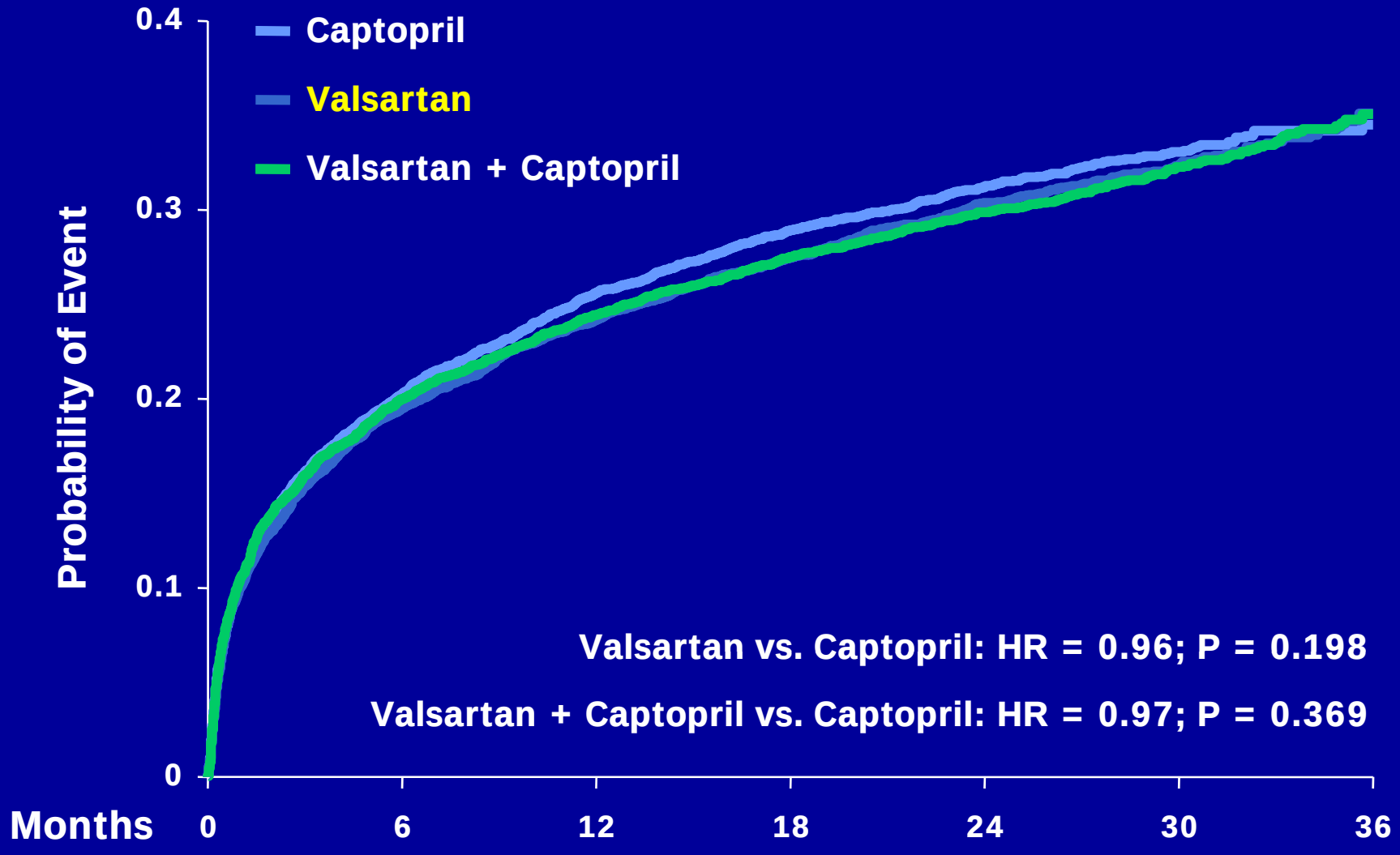
VALIANT

CV Death, MI, or HF by Treatment



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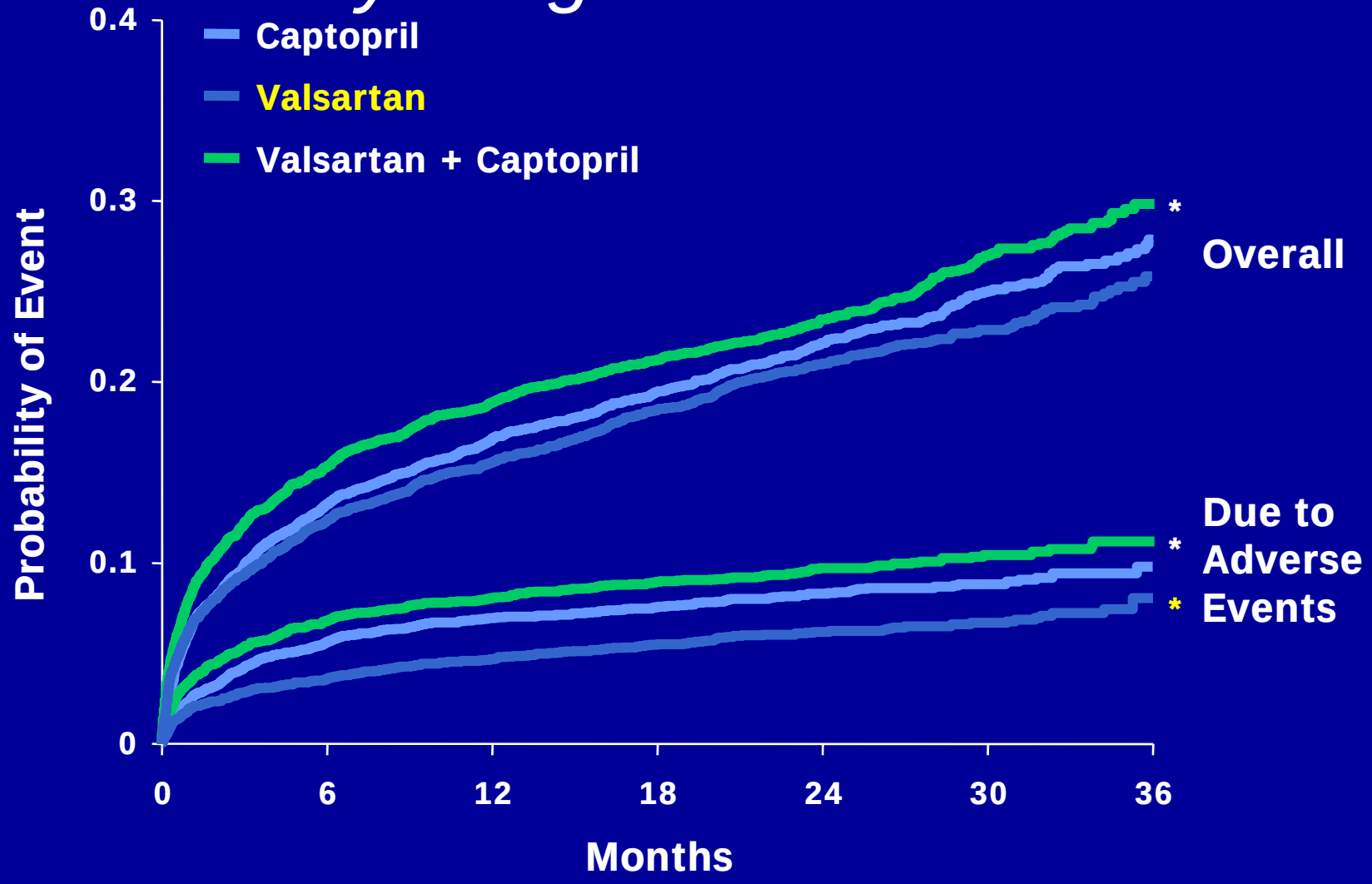
VALIANT

Study Drug Discontinuation



***P < 0.05 vs Captopril**

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

CMS/JCAHO Now Recommend Either ARB or ACEI for HF and AMI

- Premise for changes based on expert opinion:

✓ "…accumulating evidence has provided the impetus to include ARBs as acceptable alternatives to ACE inhibitors."

✓ "…all patients with HF and LVSD, including those post-MI, should be treated with either an ACEI or an ARB unless there is documentation of a specific absolute contraindication or drug intolerance to both ACEIs and ARBs."

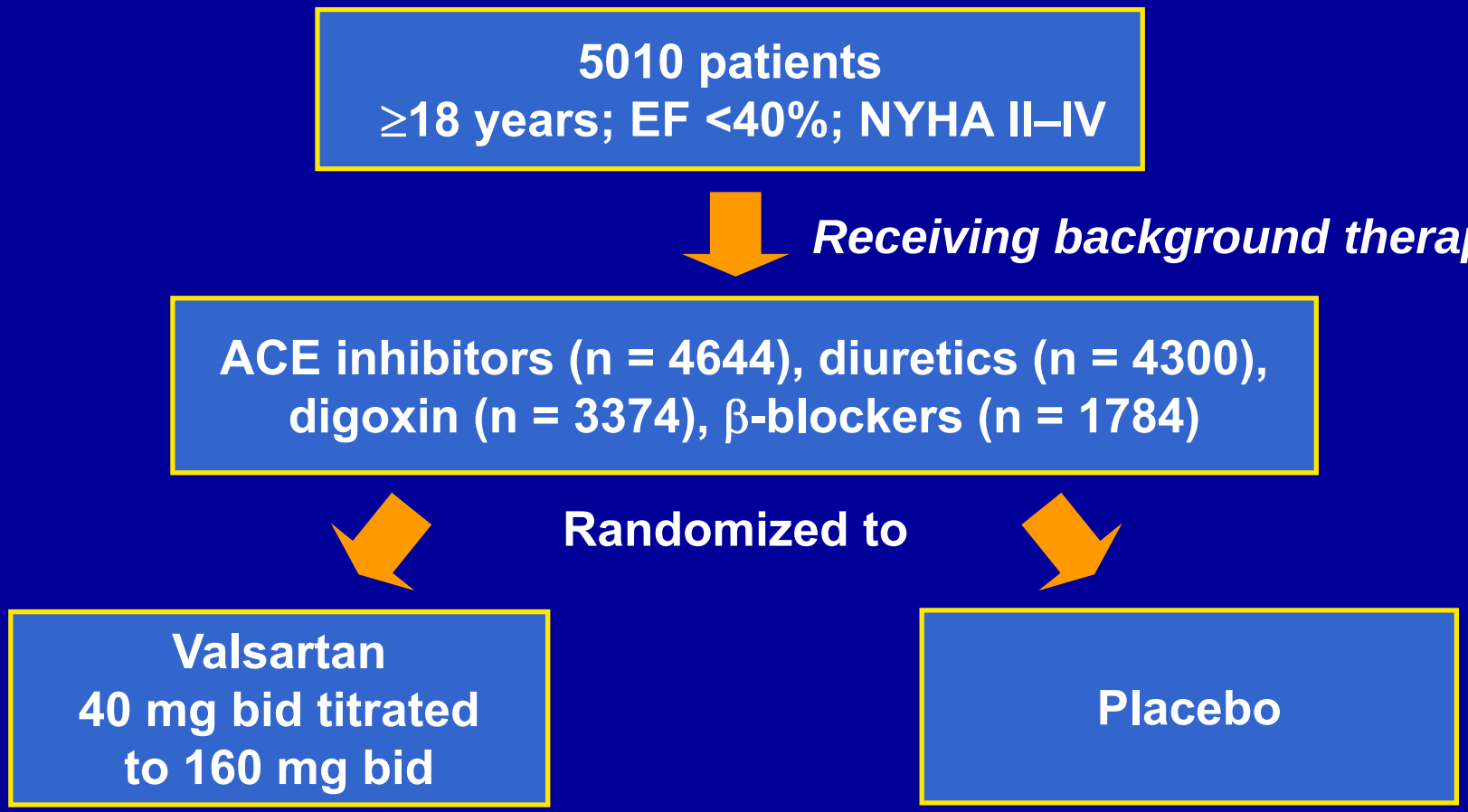
CMS=Centers for Medicare & Medicaid Services.
JCAHO=Joint Commission on Accreditation of Healthcare Organizations.

Joint Commission on Accreditation of Healthcare Organizations. Change in ACEI for LVSD measures (HF-3, AMI-3): Incorporation of ARBs.

Accessed at http://www.jcaho.org/pms/core+measures/changeinaceiforlvsdmeasuresincorparbs.pdf on February 1, 2005.

Val-HeFT

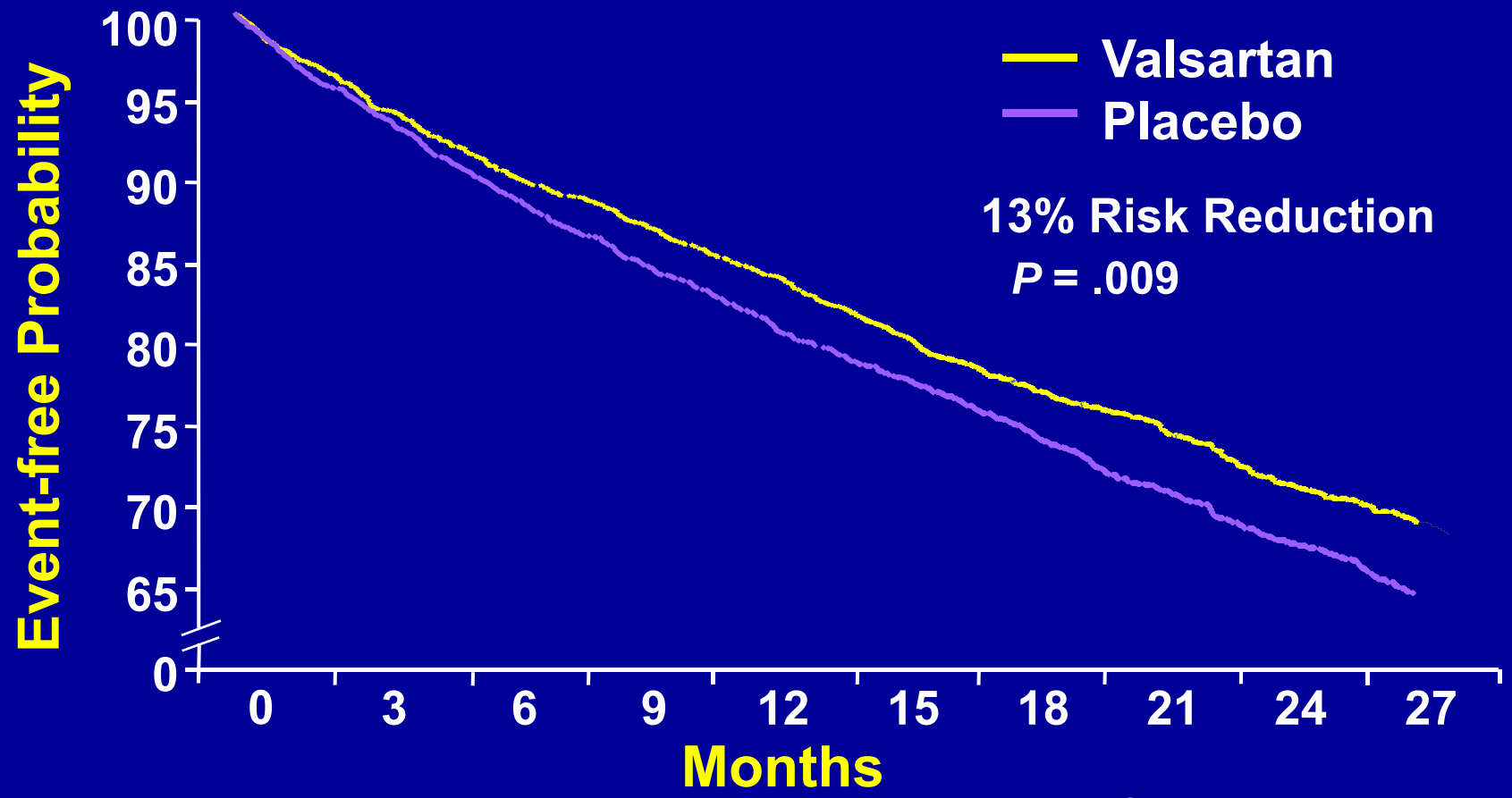
Study Design



Cohn JN et al. For the Valsartan Heart Failure Trial Investigators. *N Engl J Med.* 2001;345:1667–1675.

Val-HeFT

*Combined Morbidity Endpoint**

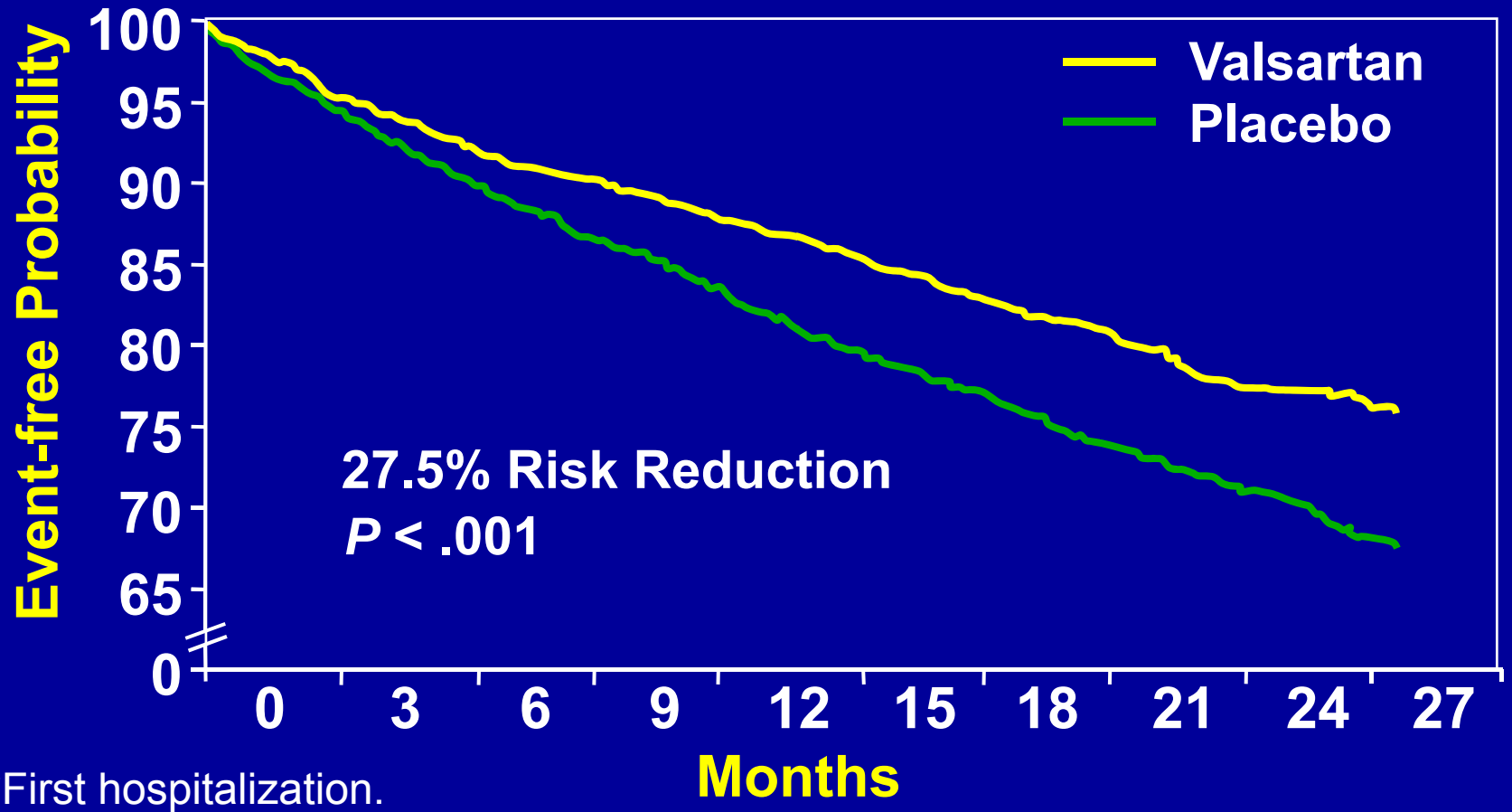


*All-cause mortality, sudden death with resuscitation, hospitalization for worsening HF, or therapy with IV inotropes or vasodilators.

(Cohn JN, et al. *N Engl J Med.* 2001)

Val-HeFT

*Heart Failure Hospitalizations**



*First hospitalization.

Cohn JN, et al. *N Engl J Med.* 2001

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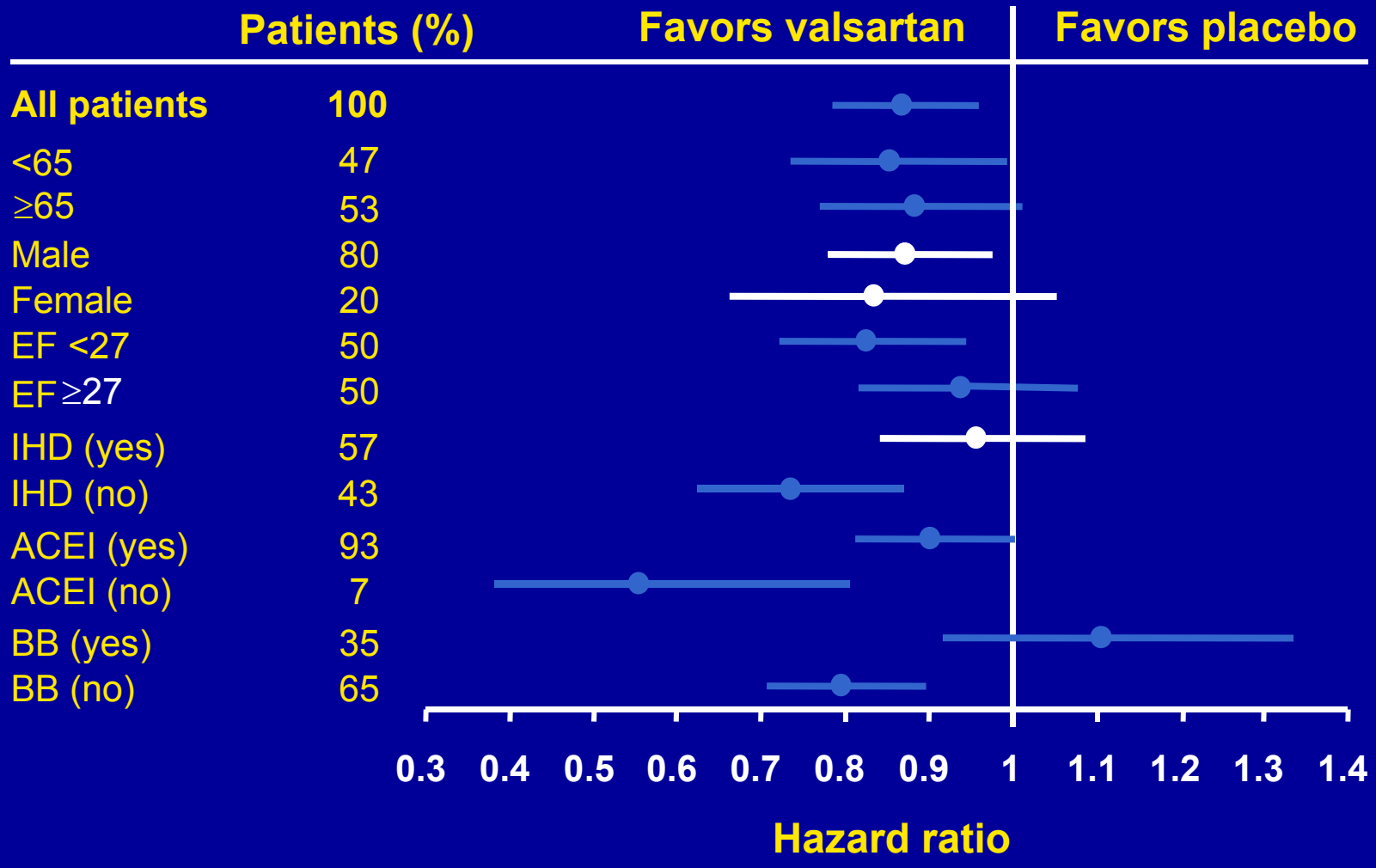
Subgroup Combined Mortality/Morbidity



Cohn JN. *Circulation*. 2000;102:2672-2676.

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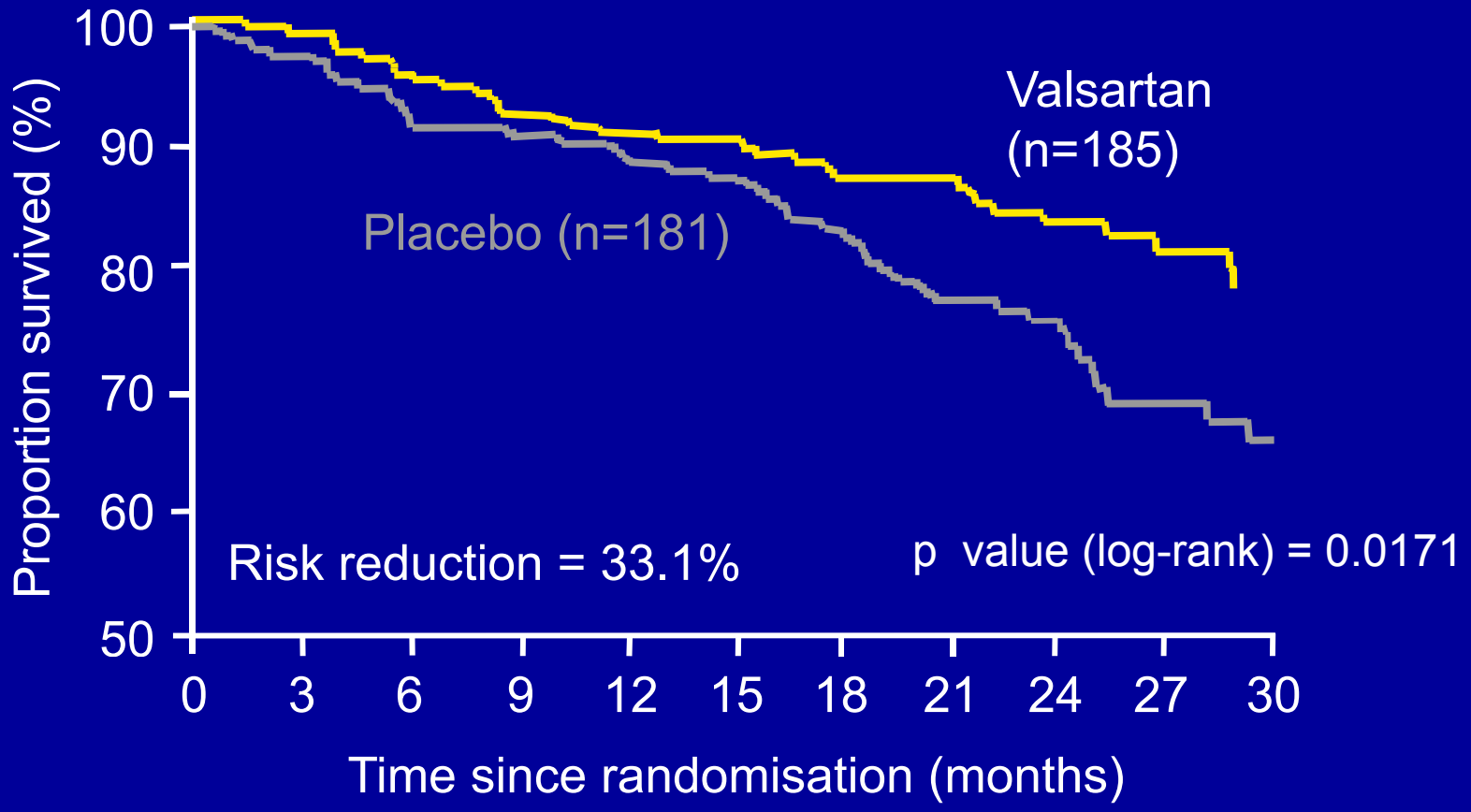
Subgroup not Receiving ACE-Is: Reduction in Mortality



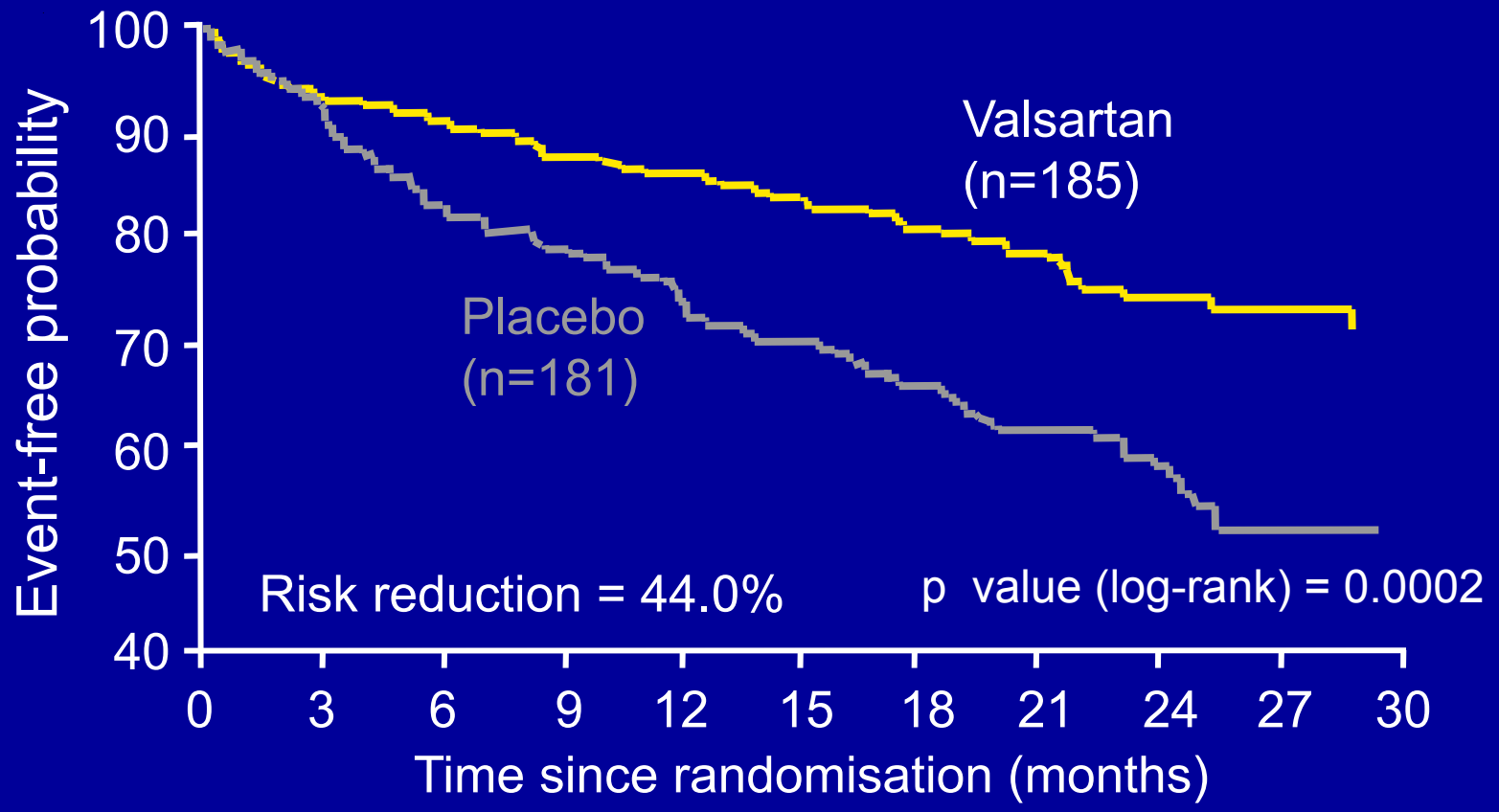
Hazard ratio (Cox model): 0.6694

Maggioni AP et al. J Am Coll Cardiol 2002;40:1414–21

Val-HeFT

*Subgroup not Receiving ACE-Is: Reduction in Combined Morbidity Endpoint**

Subgroup without ACE-I background therapy

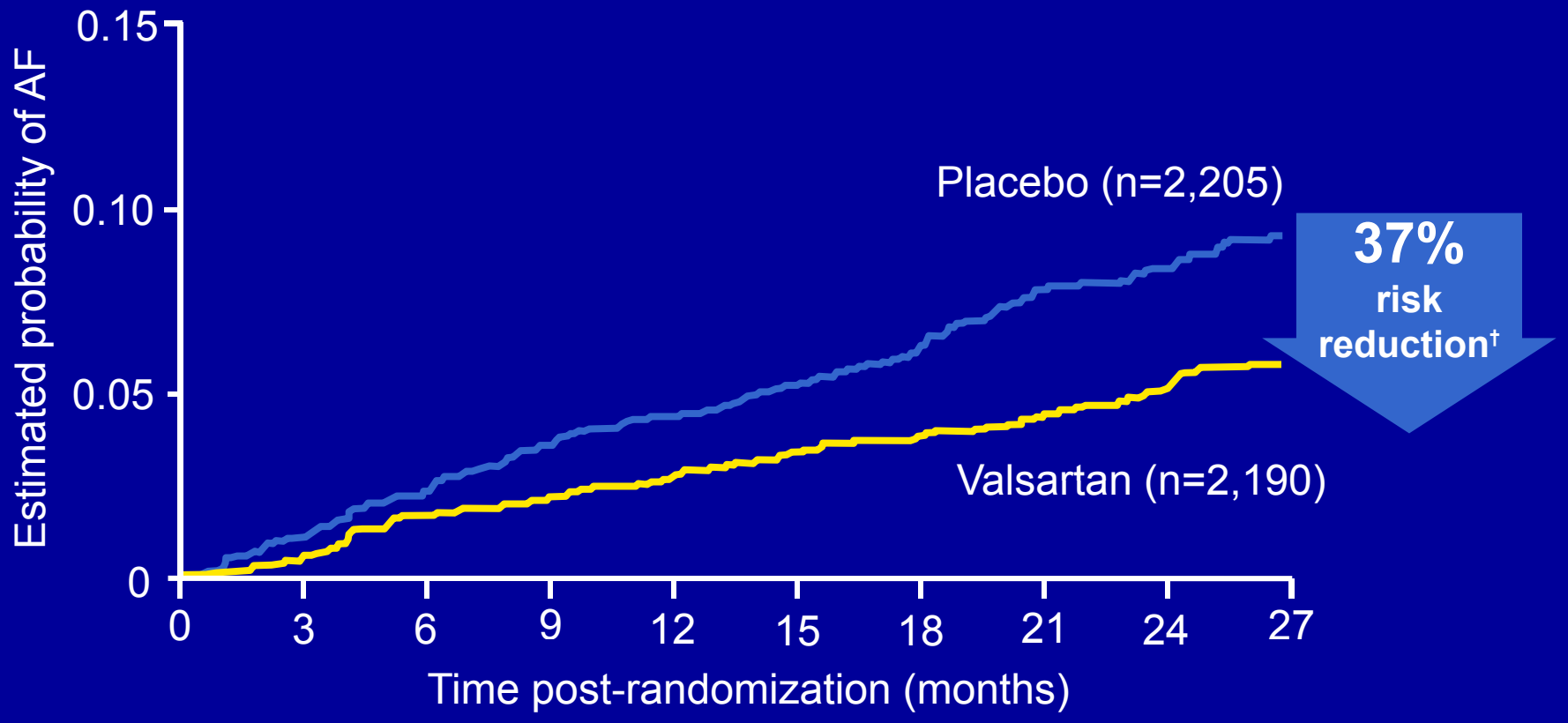


*p<0.001 for morbidity/mortality;
33% relative risk (RR; p=0.017) for all-cause mortality
Randomised, double blind, parallel group trial

Maggioni AP et al. J Am Coll Cardiol 2002;40:1414–21

Val-HeFT AF Sub-study

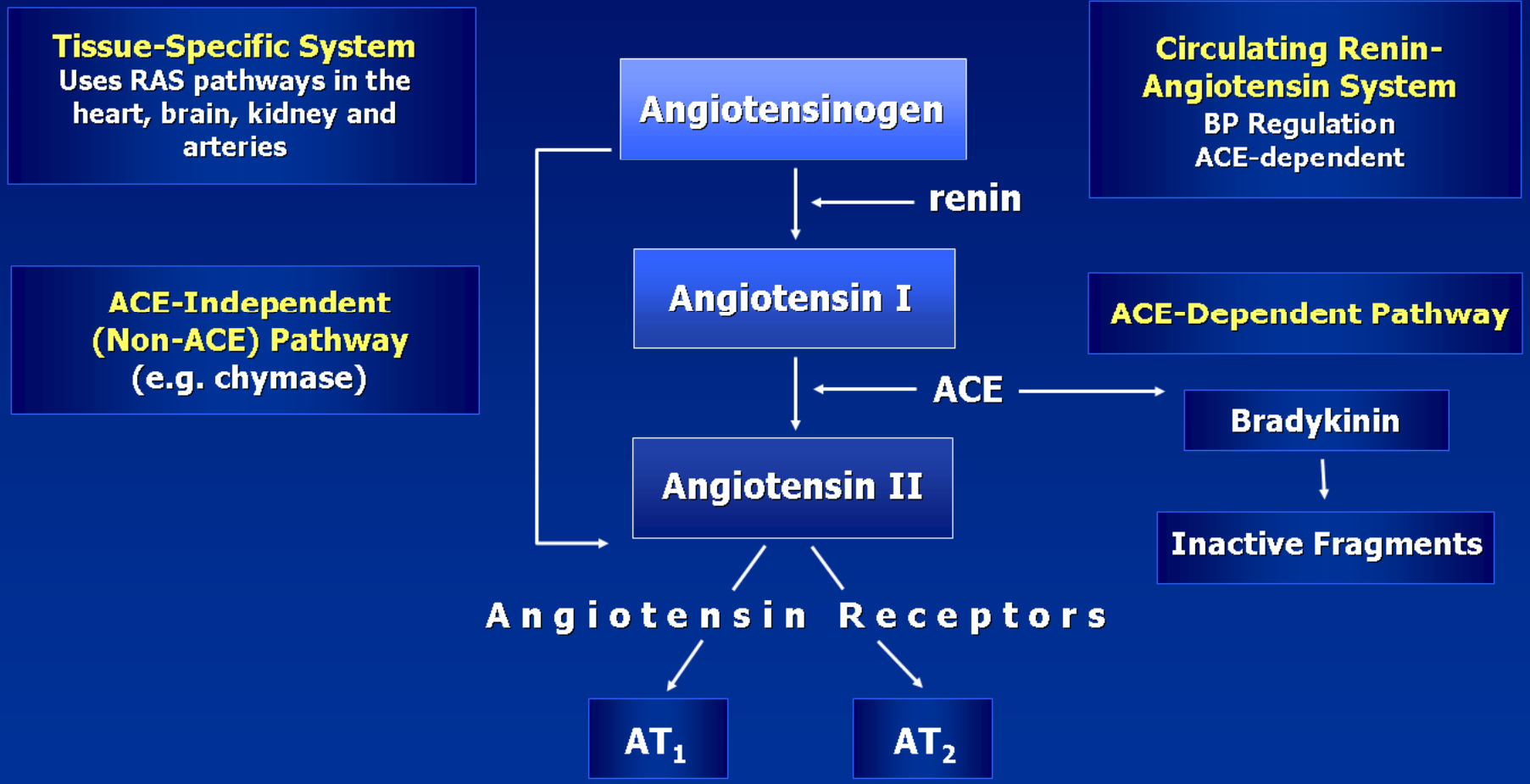
Risk of New Onset AF



†p=0.003

Maggioni AP et al. Am Heart J 2005;149:548–57

The RAAS Cascade: Formation of Angiotensin II



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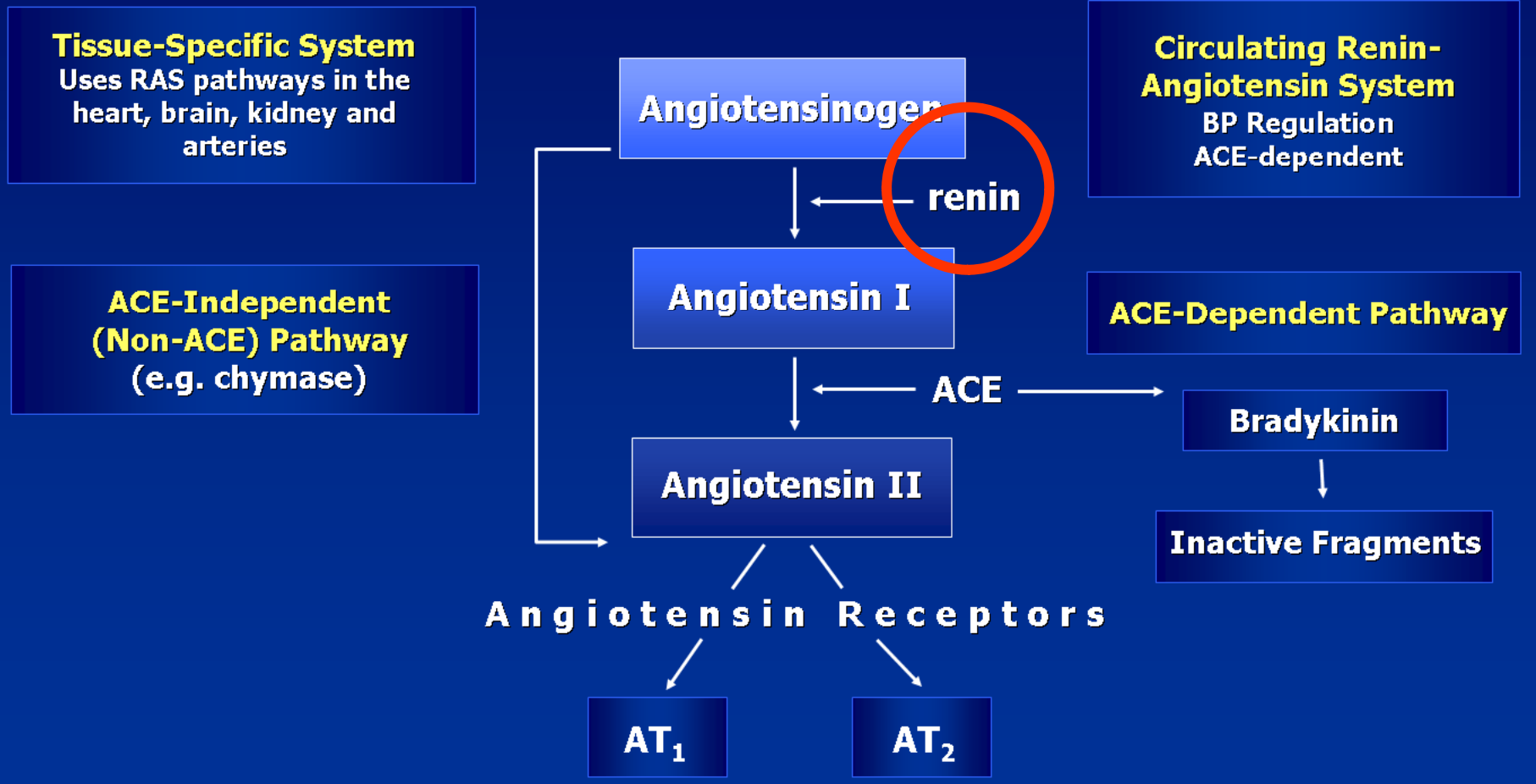

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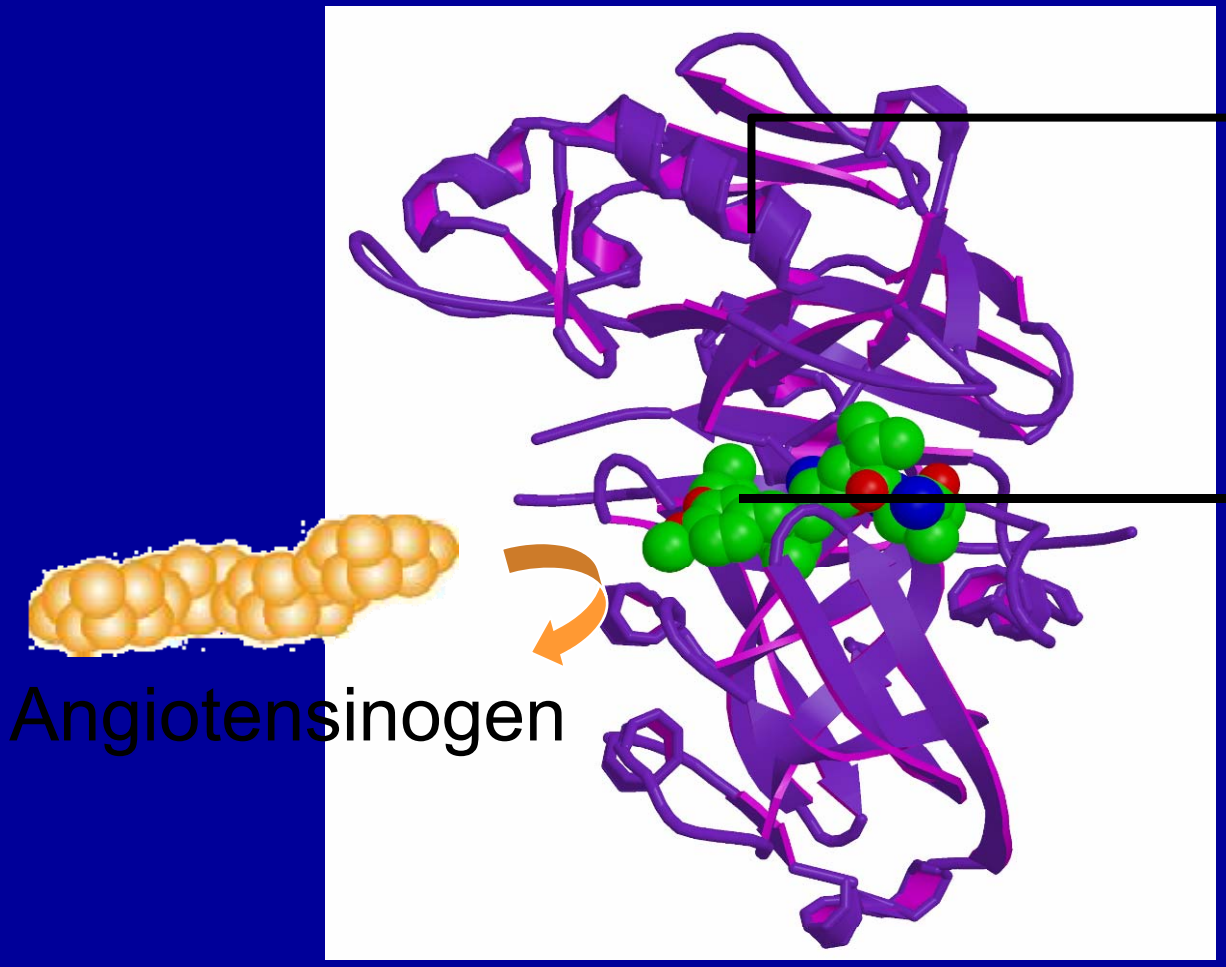
Aliskiren Binds to the Active Site of the Renin Molecule



Aliskiren binds to a pocket in the renin molecule, blocking cleavage of angiotensinogen to angiotensin I

Adapted from Wood JM, *et al.* 2003

Drug Effects on the RAS

Class	PRA	Ang I	Ang II
ACEI	↑	↑	↓
ARB	↑	↑	↑
Direct Renin Inhibitor (DRI)	↓	↓	↓

Increased peptide levels have not been shown to overcome the blood pressure–lowering effect of these agents.
ACEI, angiotensin-converting enzyme inhibitor; Ang, angiotensin; ARB, angiotensin receptor blocker;
PRA, plasma renin activity.

1. Johnston CI. *Blood Press Suppl*. 2000;1:9(suppl 1):9-13.
2. Widdop RE et al. *Hypertension*. 2002;40:516-520.
3. Lin C et al. *Am Heart J*. 1996;131:1024-1034.

ALOFT: Objectives

Primary objective:

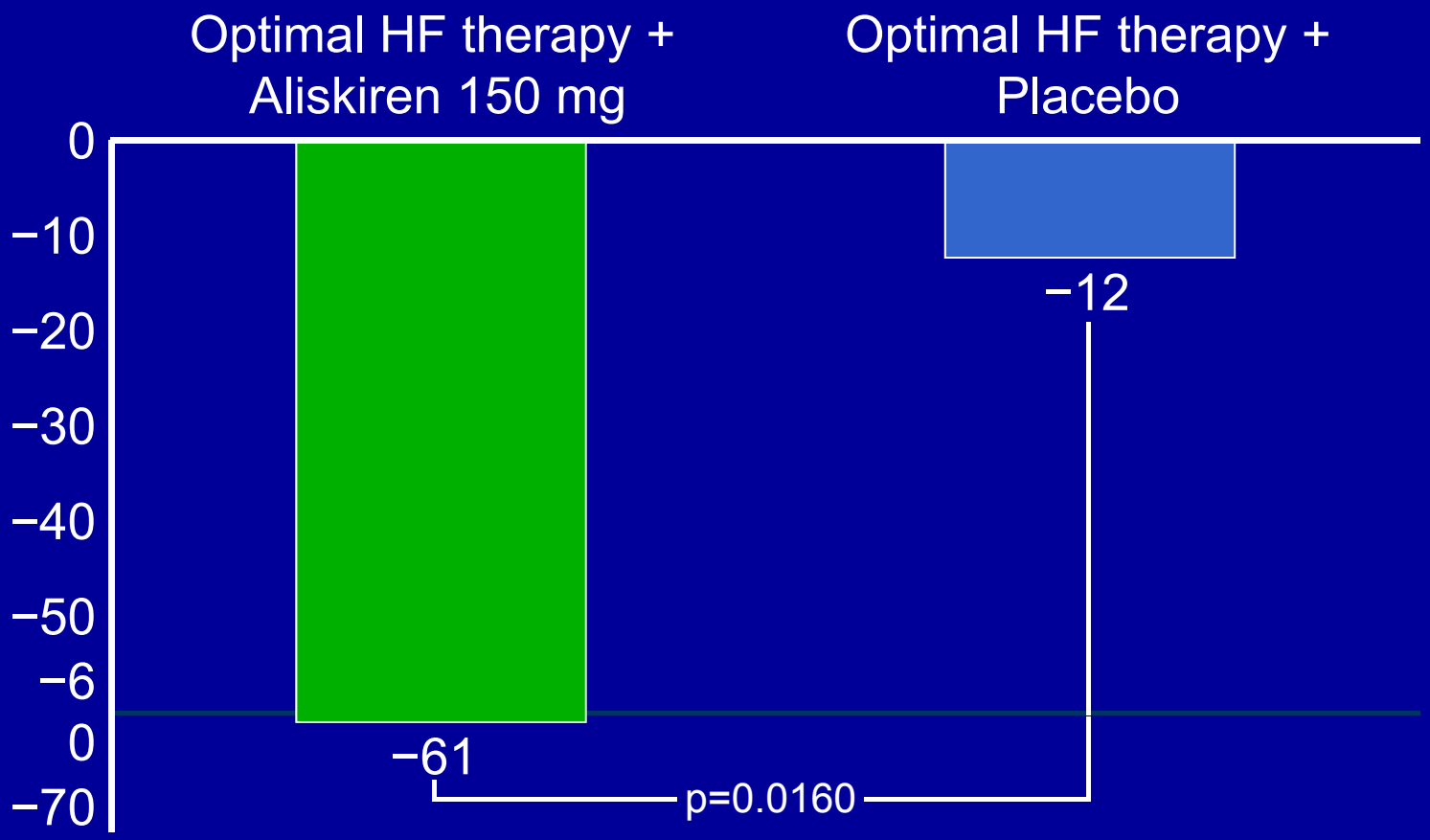
- Evaluate the safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in patients with hypertension and stable HF

Secondary objectives included:

- Effect of aliskiren on BNP, N-terminal proBNP (NT-proBNP) and aldosterone
- Effect of aliskiren on echocardiographic measures of left ventricular (LV) function
- Effect of aliskiren on improvement in signs and symptoms of HF
- Effect of aliskiren on BP

McMurray JJV. *Circ Heart Failure*. 2008;1:17-24

ALOFT
Reductions in BNP levels



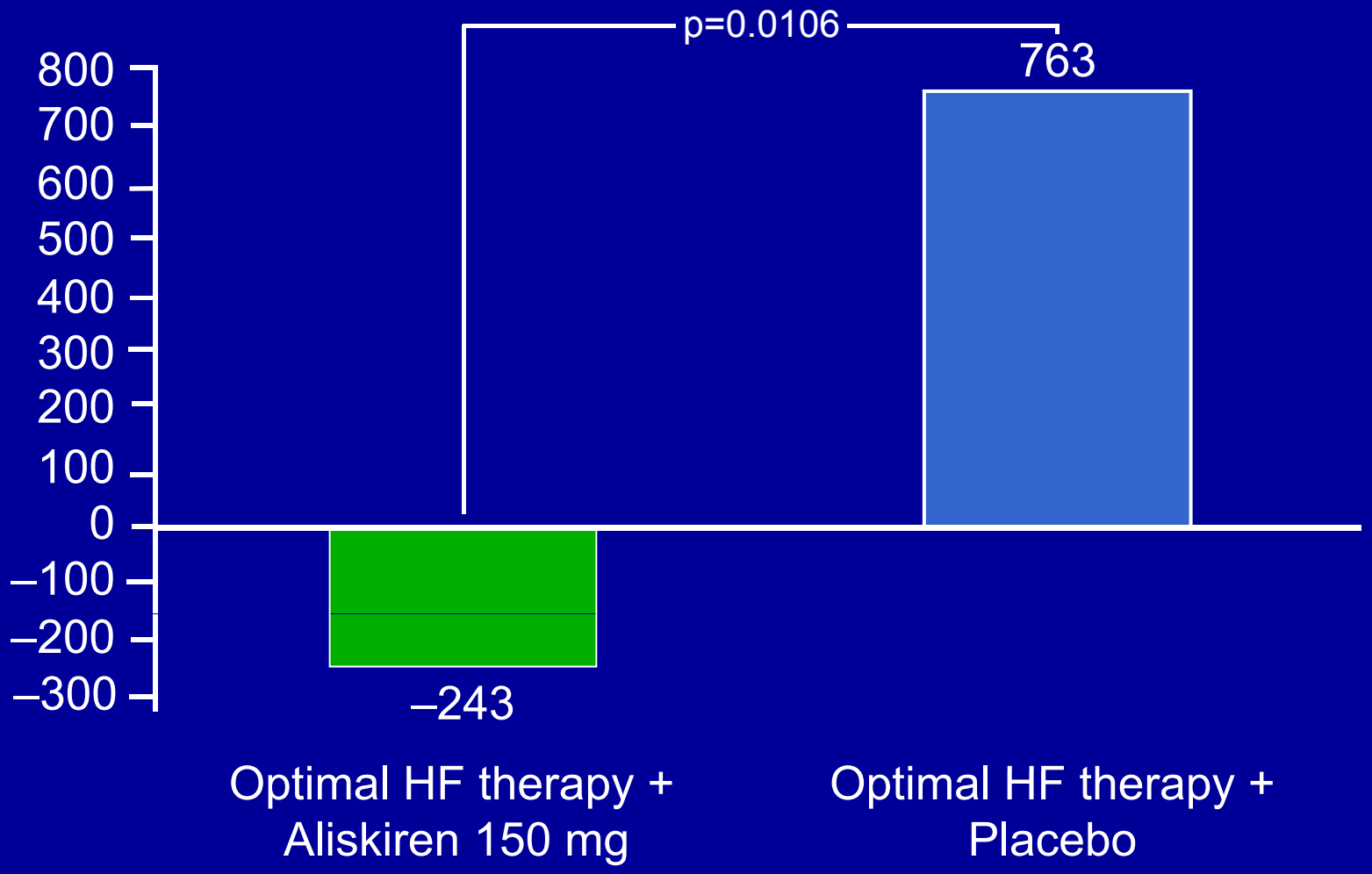
Mean change from baseline in BNP at Week 12 (pg/mL)

Baseline BNP concentration = 301 pg/mL for aliskiren and 273 for placebo.

McMurray JJV. *Circ Heart Failure*. 2008;1:17-24

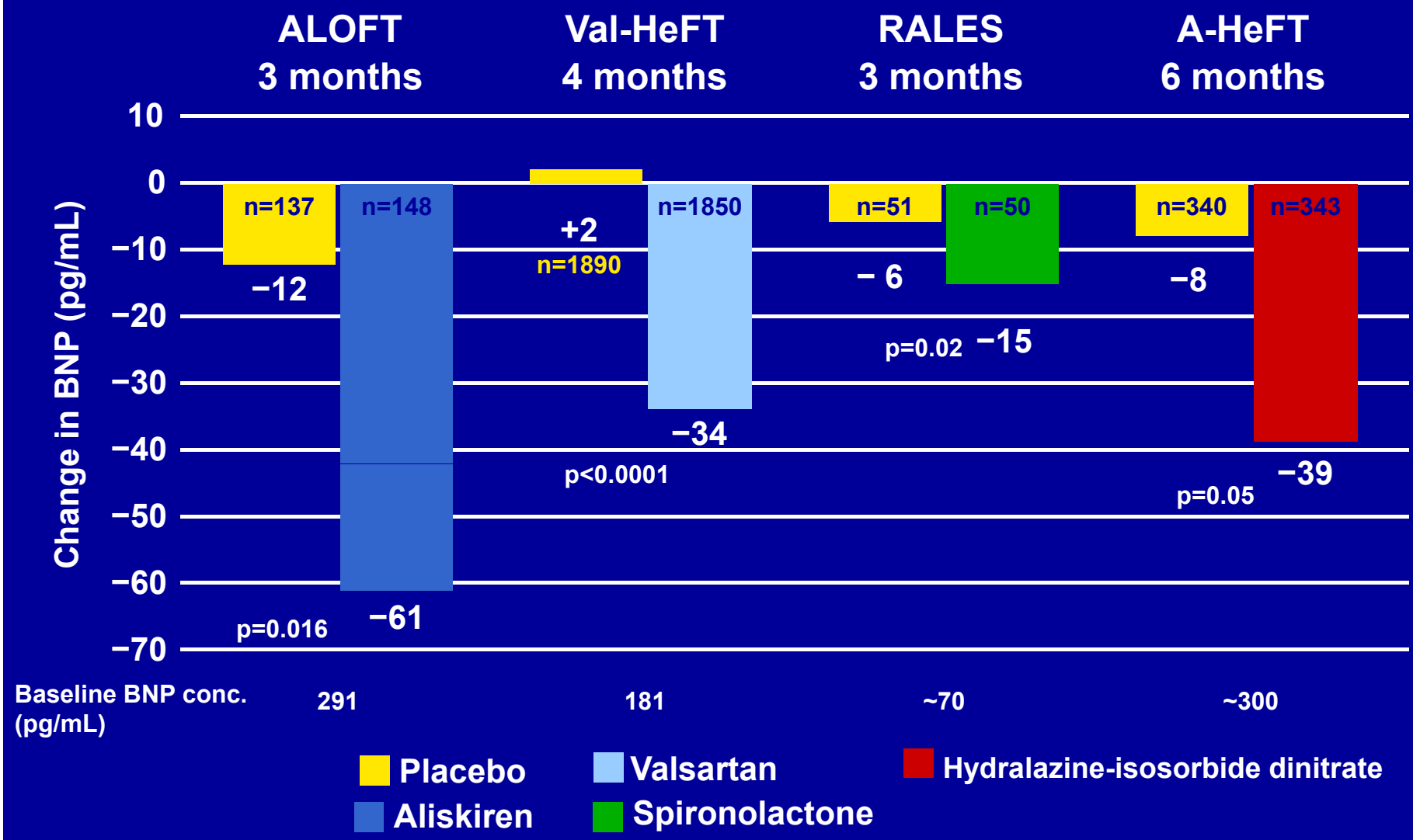
ALOFT
Reductions in NT-proBNP levels

Mean change from baseline in NT-proBNP at Week 12 (pg/mL)



McMurray JJV. *Circ Heart Failure*. 2008;1:17-24

Perspectives from other Outcome Studies



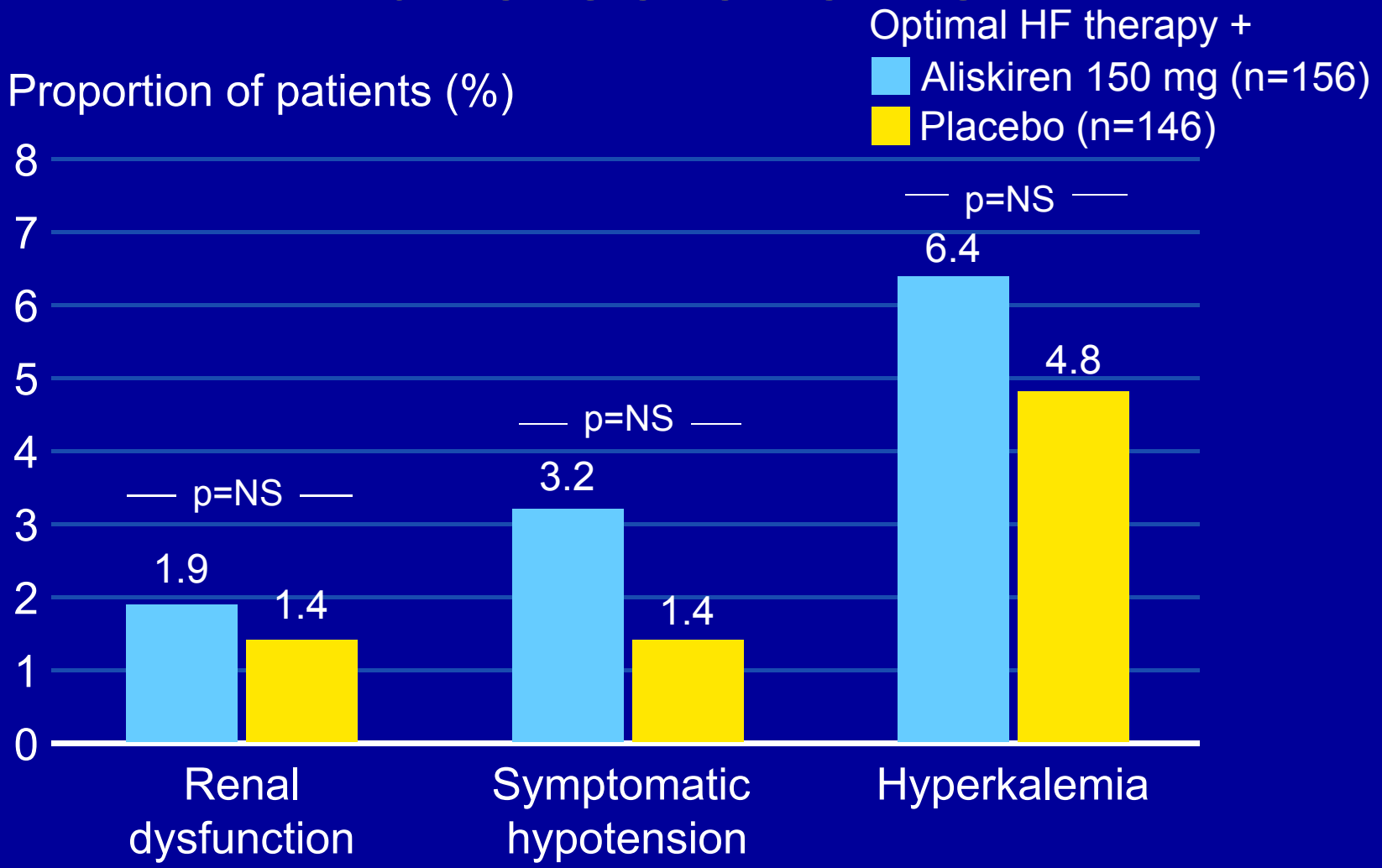
ALOFT: Echo End-points

	Optimal HF therapy + Aliskiren 150 mg (n=156)	Optimal HF therapy + Placebo (n=146)	Adjusted p (between Groups)
EDV index, mL/m^2	−2.7 (6.7)	−3.4(12.9)	0.56
ESV index, mL/m^2	−4.0 (8.1)	−4.3 (10.7)	0.67
LVEF, %	1.7 (3.1)	1.6 (2.9)	0.96
MR/LA area ratio	−4.1 (10.1)	1.3 (10.1)	0.0006
*E/E’	−0.83 (8.0)	0.11 (6.9)	0.047

*Post hoc analysis. EDV, End diastolic volume; ESV, End systolic volume; MR, mitral regurgitation; LA, left atrial; E, early diastolic peak transmitral flow velocity; E’ mitral annular relaxation velocity

McMurray JJV. *Circ Heart Failure*. 2008;1:17-24

ALOFT
Adverse events



NS – non-significant

McMurray JJV. *Circ Heart Failure*. 2008;1:17-24

Summary Conclusions

- Ang II plays an important role in the pathogenesis of CV diseases.
- AT_1 receptor blockade with valsartan is equally effective as an ACEI in reducing mortality in patients with post-MI LVD.
- AT_1 receptor blockade with valsartan improves outcomes in heart failure patients with LVD.
- DRIs provide a new strategy for blocking the effects of the RAS.
- Emerging data indicates that aliskiren will favorably affect outcomes in hypertension and heart failure.