ARB Role in Post-MI
: High dose is better?

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The Catholic University of Korea

TOPIC

- ARB Role in Post MI
- High Dose is better ?

I. ARB Role in Post MI

- Reduced LV Remodelling
- Reduced Cardiac mortality, morbidity
- Reduced HF rehospitallization

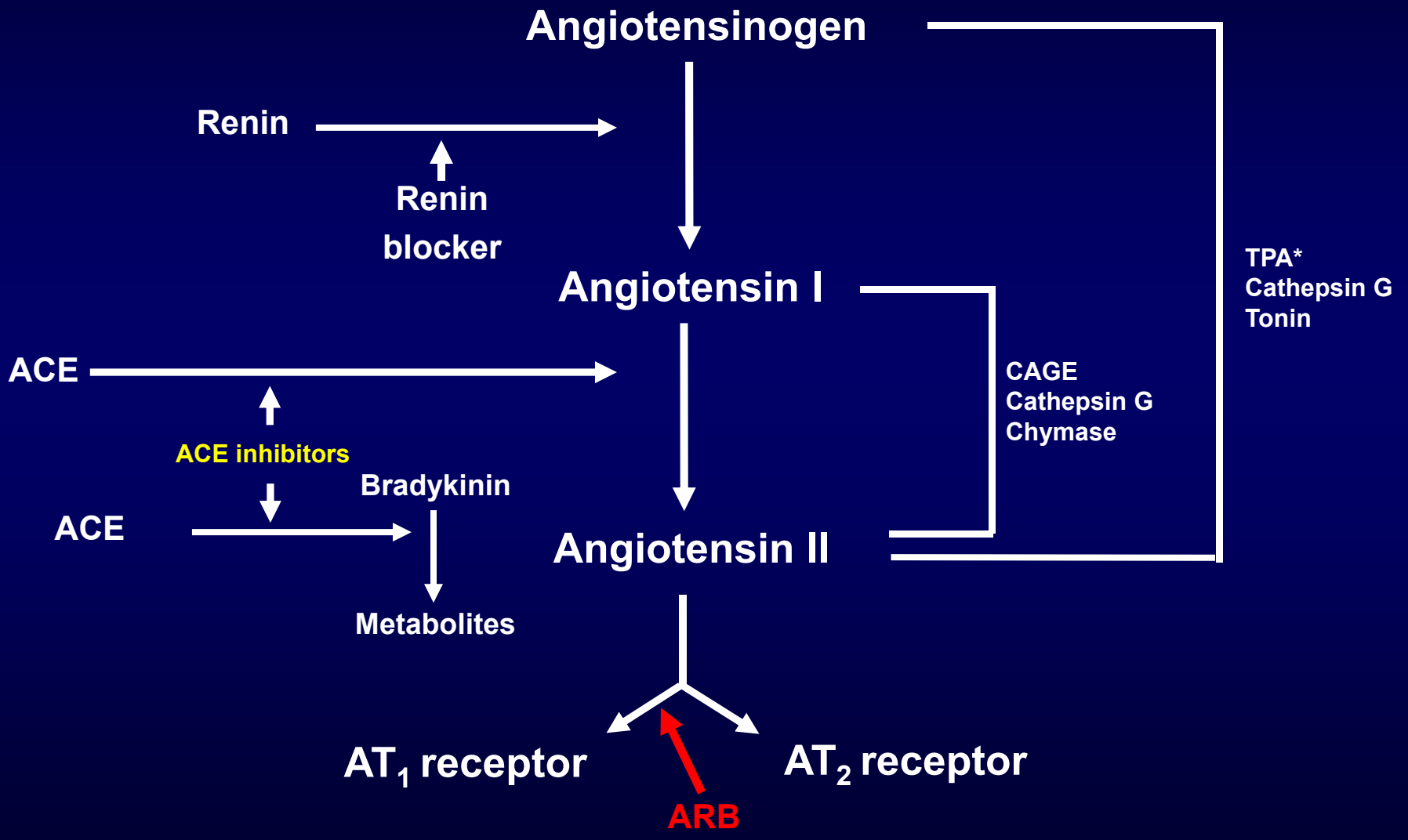
ARB: Mechanism of Action

- Angiotensin II type 1 (AT1) receptor blockers provide a pharmacologically distinct mechanism of inhibiting the renin-angiotensin-aldosterone system

- AT1-receptor blockers offer the potential to produce further clinical improvements above and beyond ACE inhibitors as well as an alternative for those previously intolerant to an ACE inhibitor

Pfeffer et al, Lancet 2003

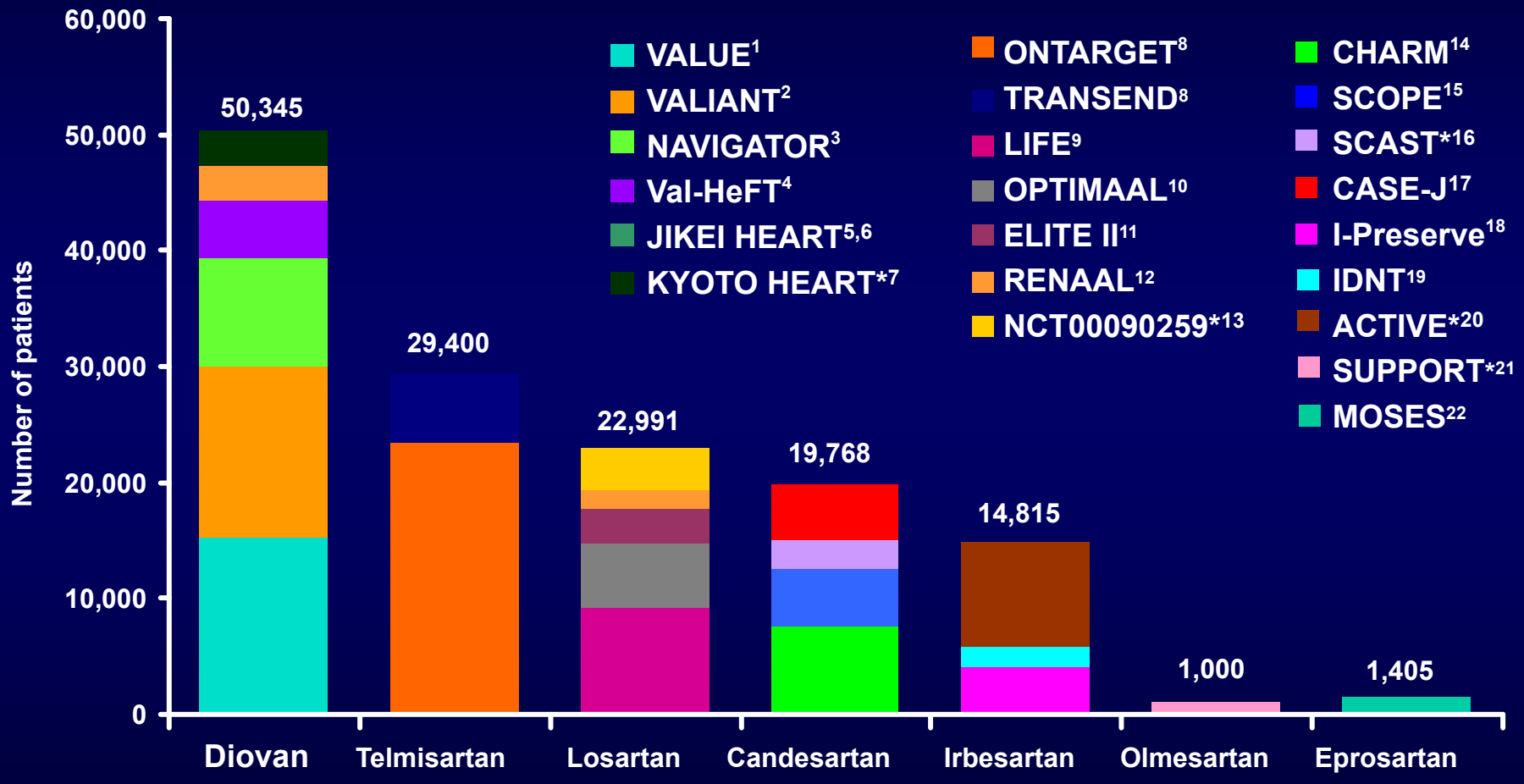
ARB: Mechanism of Action



* TPA = tissue plasminogen activator

The broadest and widest evidence of ARB

: Mortality and Morbidity Endpoint Trials with ARB



[1]Julius et al. Lancet 2004;363:2022–31; [2]Pfeffer et al. NEJM 2003;349:1893–906; [3]www.novartis.com; [4]Cohn et al. NEJM 2001;345:1667–75; [5]Mochizuki et al. J Hypertens 2006;24(Suppl. 4):S31; [6]Mochizuki et al. Cardiovasc Drugs Ther 2004;18:305–9; [7]http://clinicaltrials.gov (NCT00149227) [8]www.ontarget-micardis.com; [9]Dahlof et al. Lancet 2002;359:955–1003; [10]Dickstein et al. Lancet 2002;360:752–60; [11]Pitt et al. Lancet 2000;355:1582–7; [12]Brenner et al. NEJM 2001;345:861–9; [13]http://clinicaltrials.gov (NCT00090259) [14]www.atacand.com; [15]Papademetriou et al. J Am Coll Cardiol 2004;44:1175–80; [16]http://clinicaltrials.gov (NCT00120003); [17]Ogihara J Hypertens 2006;24(Suppl. 4):S30; [18]Carson et al. J Card Fail 2005;11:576–85; [19]Lewis et al. NEJM 2001;345:851–60; [20]http://clinicaltrials.gov (NCT00249795); [21]http://clinicaltrials.gov (NCT00417222); [22]Schrader et al. Stroke 2005;36:1218–26

*Expected enrolment

Clinical Trials with ARBs

	Losartan	Diovan	Irbesartan	Candesartan	Telmisartan
HTN including diabetic Subgroups	LIFE (9193)	VALUE (15,314)		SCOPE (4 000)	ONTARGET (23,400) TRASCEND
Heart Failure	ELITE II (3152)	Val-HeFT (5010)	I-PRESERVE (~3000)	CHARM (~7000)	–
Post-MI	OPTIMAAL (5000)	VALIANT (14,500)	–	–	–
Diabetic Nephropathy	RENAAL (1513)		IDNT (1715)	–	DETAIL
Microalbum.		MARVAL (332) SMART DROP	IRMA II (590)		
IGT	–	NAVIGATOR (9518)	–	–	–

VALsartan In Acute myocardial iNfarcTion

Marc A. Pfeffer, M.D., Ph.D. (Chair), John J.V. McMurray, M.D. (Co-Chair),
Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D.,
Harvey D. White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S.,
Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D.,
for the VALIANT Investigators

Other Steering Committee Members:
P. Aylward, P. Armstrong, S. Barvik, Y. Belenkov, A. Dalby, R. Diaz, H. Drexler, G. Ertl, G. Francis, J. Hampton, A. Harsanyi, J. Kvasnicka, V. Mareev, J. Marin-Neto, J. Murin, M. Myers, R. Nordlander, G. Opolski, J. Soler-Soler, J. Spac, T. Stefenelli, D. Sugrue, W. Van Gilst, S. Varshavsky, D. Weaver, F. Zannad.

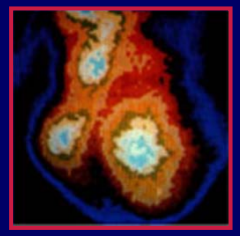
Dr. Pfeffer is named as a coinventor on a patent awarded to the Brigham and Women's Hospital regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis Pharmaceuticals and the Brigham and Women's Hospital, which is not linked to sales.

Supported by a grant from Novartis Pharmaceuticals

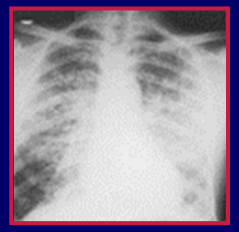
ACE Inhibitor MI Mortality Trials

VALIANT

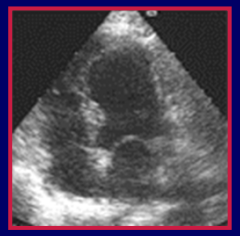
Broad (short term)	Selective (higher risk, long term)	
CONSENSUS II	SAVE	(EF ≤ 40%)
GISSI-3	AIRE	(clinical HF)
ISIS-4	SMILE	(anterior MI, no lytic)
Chinese-Cap	TRACE	(wall motion score, EF ≤ 35%)



SAVE
Radionuclide
EF ≤ 40 %

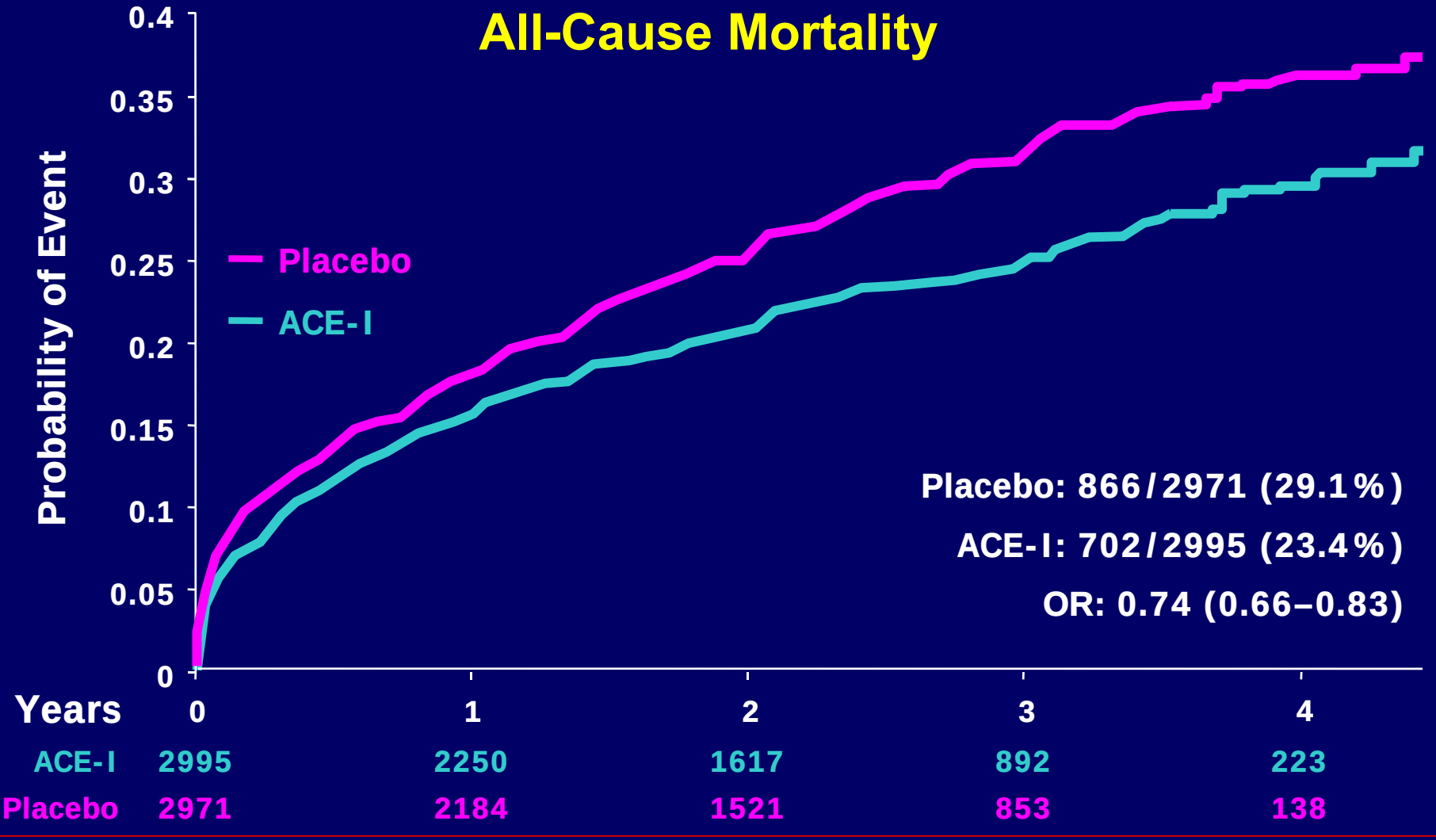


AIRE
Clinical and/or radiographic signs of HF

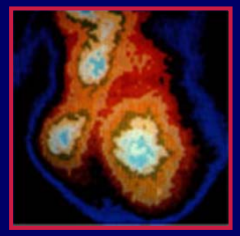


TRACE
Echocardiographic
EF ≤ 35 %

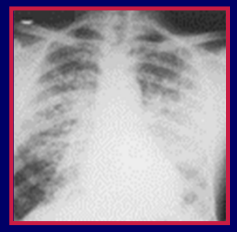
All-Cause Mortality



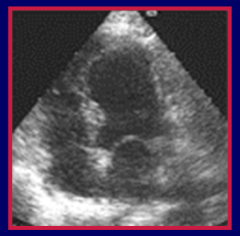
Flather MD, et al. *Lancet*. 2000;355:1575–1581



SAVE
Radionuclide
EF ≤ 40 %

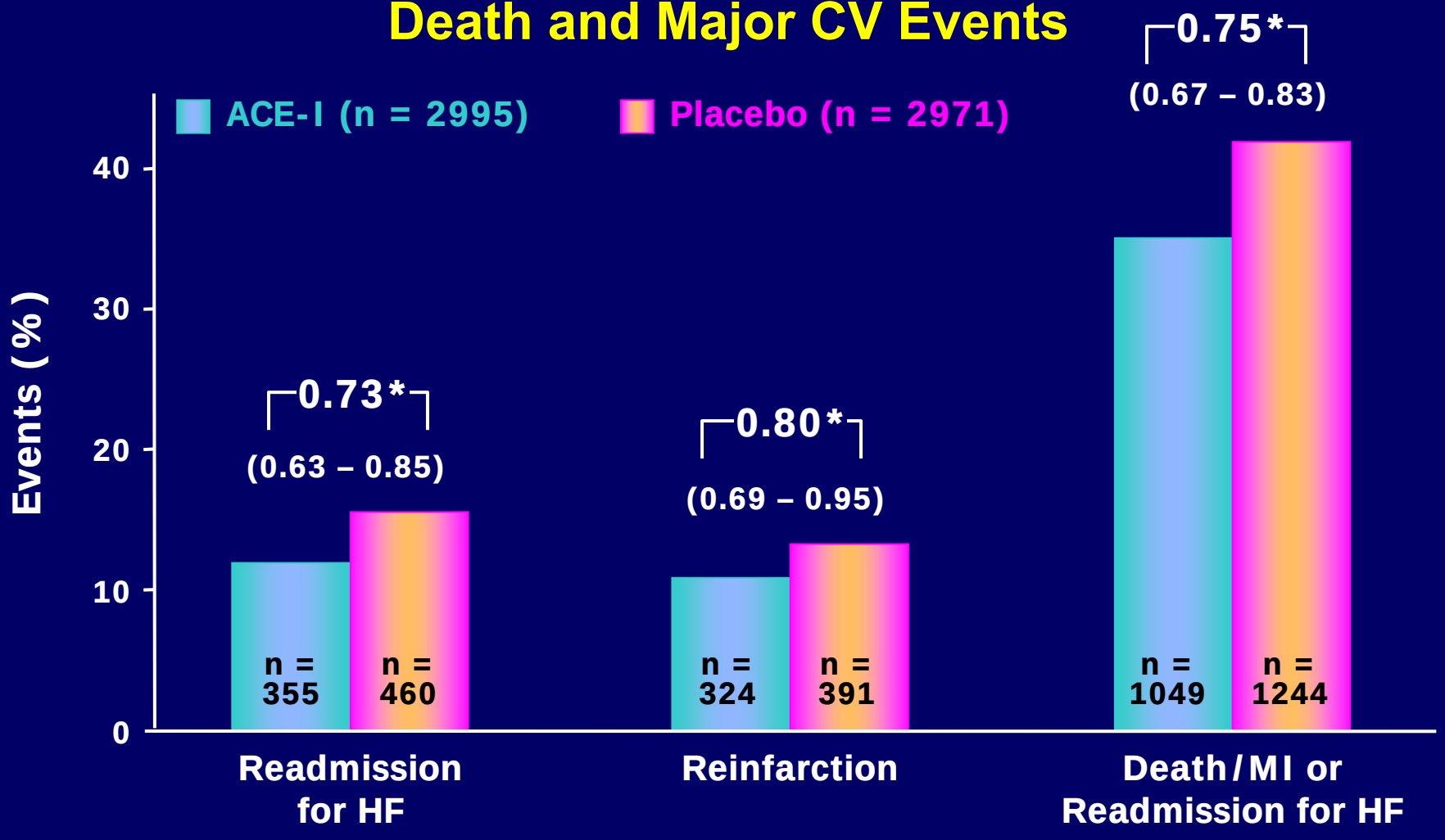


AIRE
Clinical and/or
radiographic
signs of HF



TRACE
Echocardiographic
EF ≤ 35 %

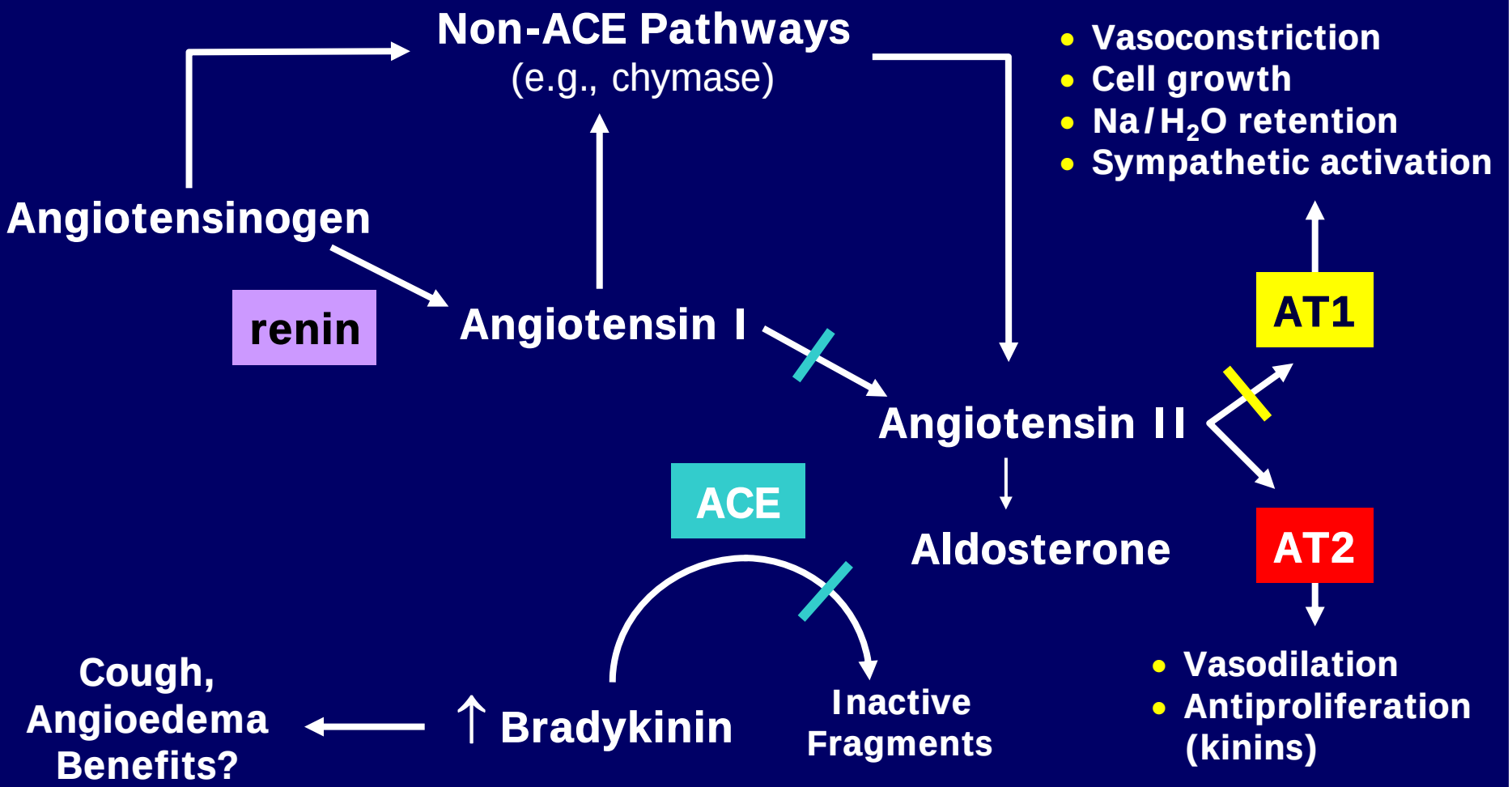
Death and Major CV Events



*odds ratio (95% CI)

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

Renin-Angiotensin Aldosterone System



Aims

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

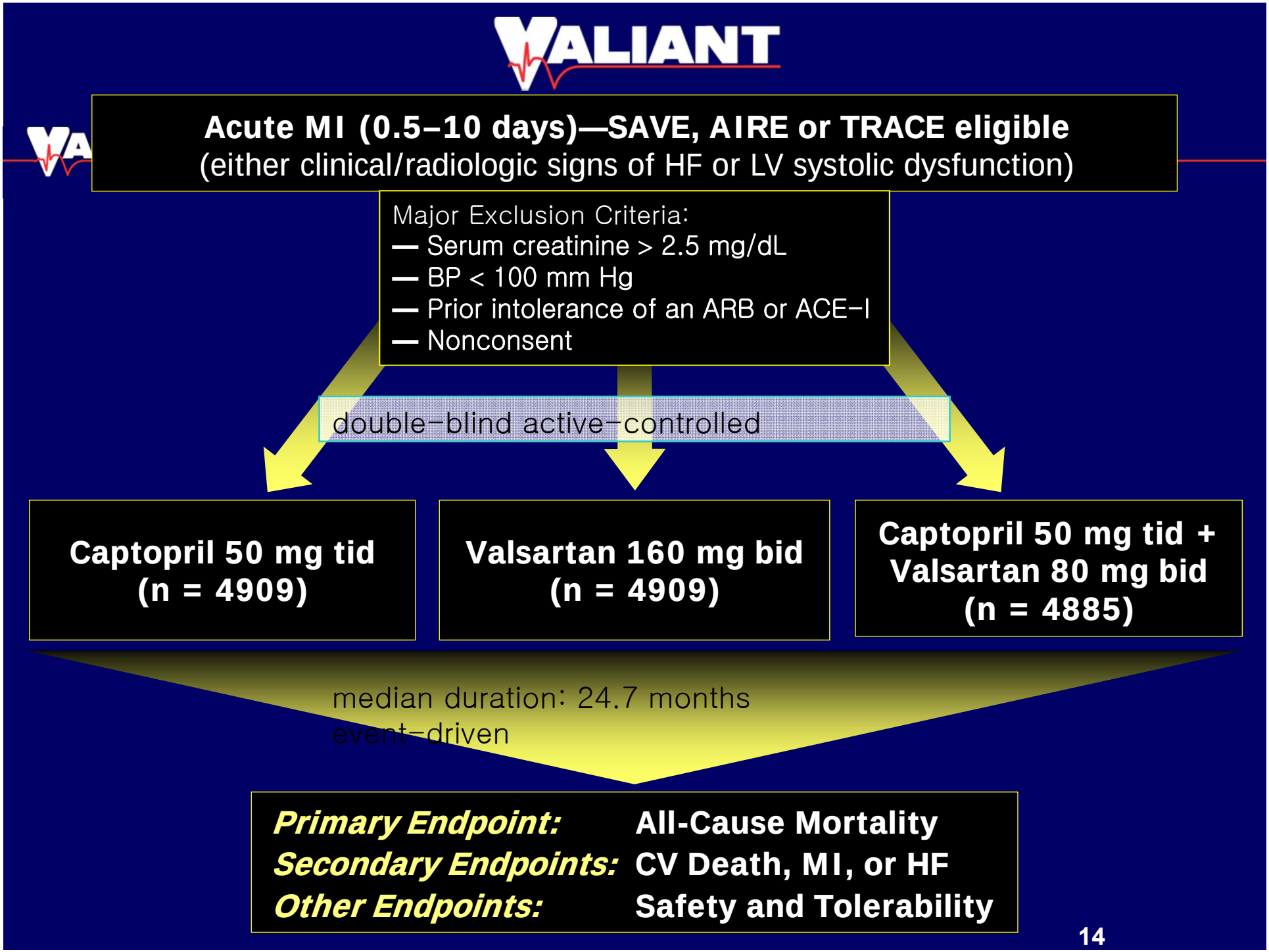
To determine whether:

- the ARB valsartan was superior to captopril in improving survival

and with equal statistical power

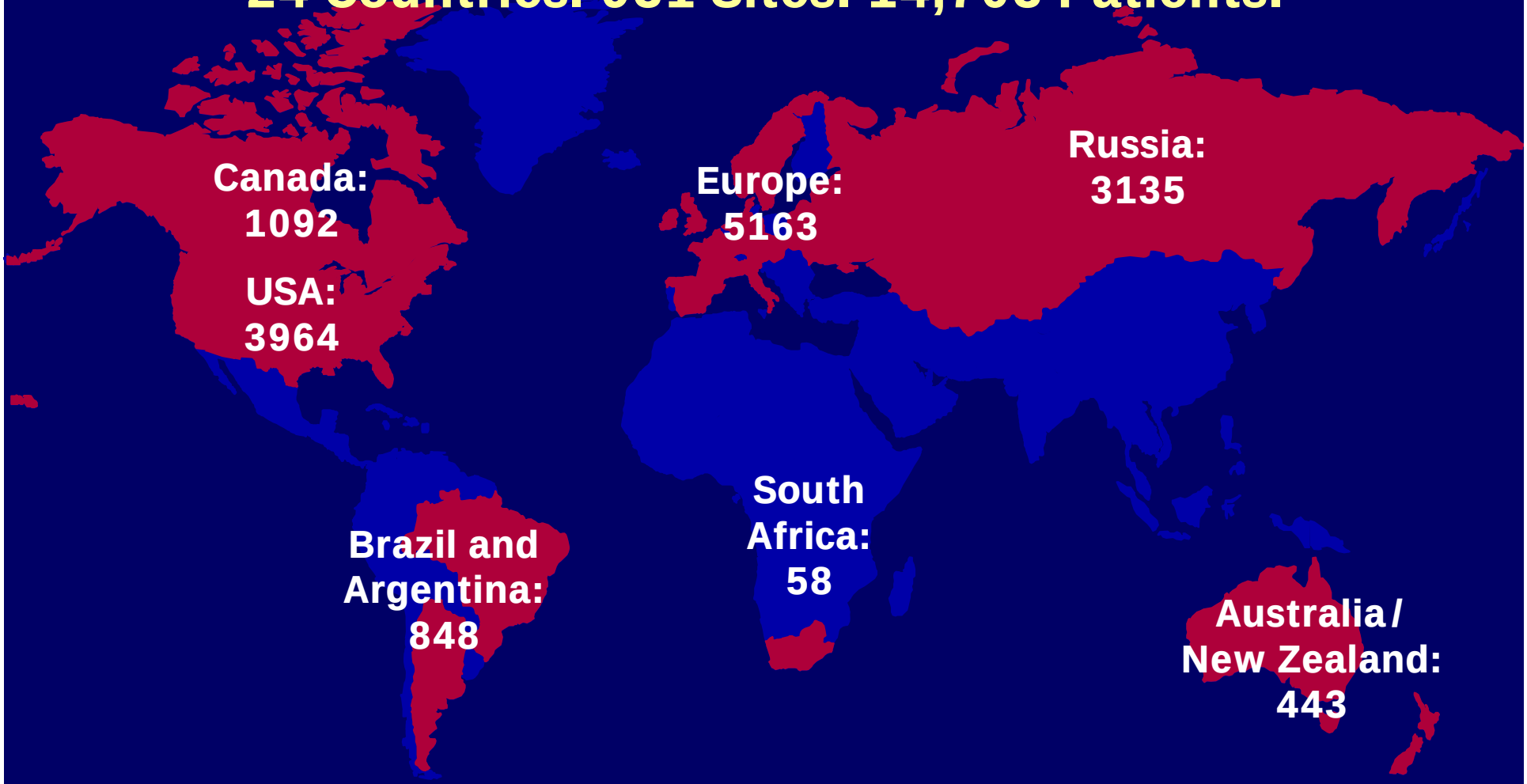
- the addition of the ARB valsartan to captopril was superior to the proven dose of captopril in improving survival

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

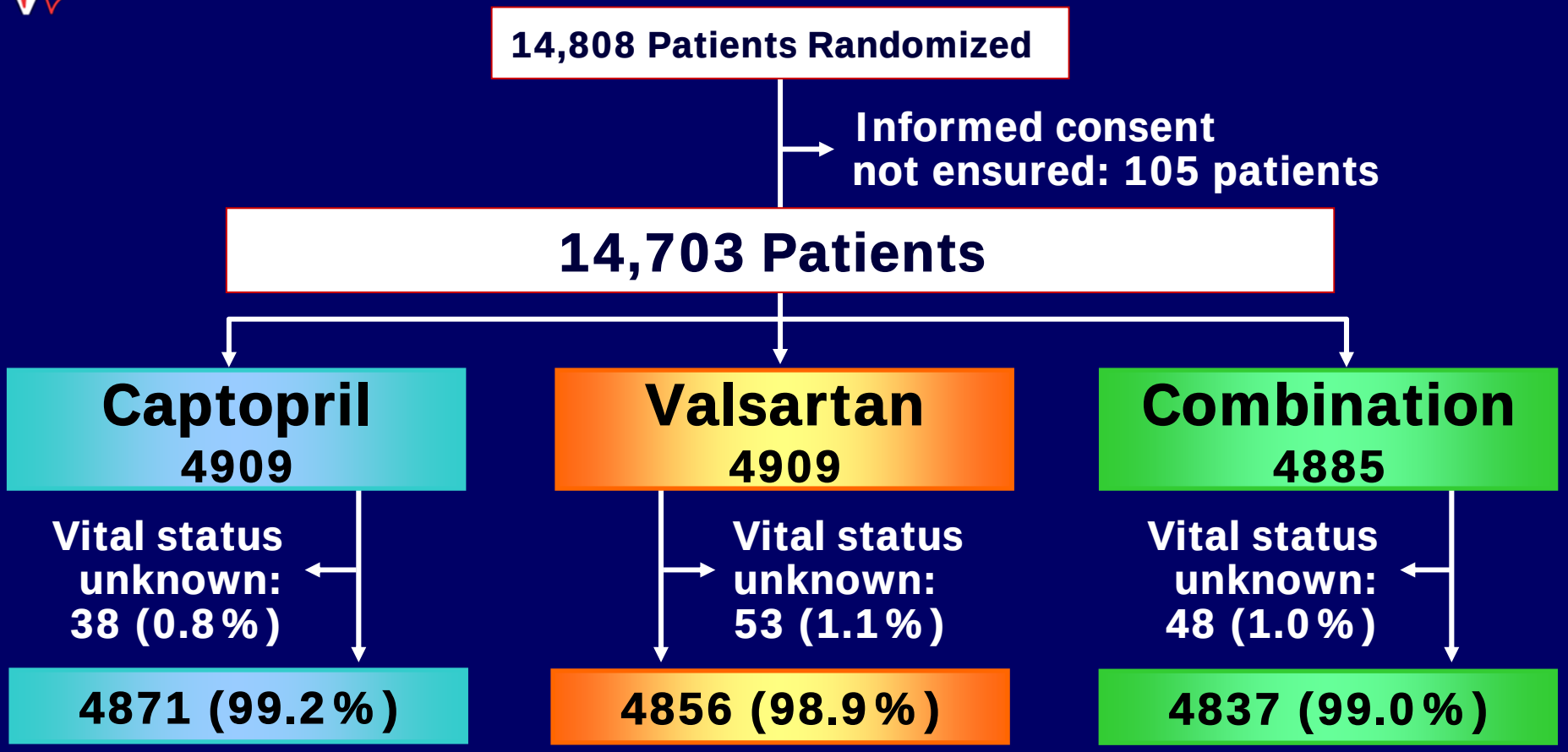

VALIANT
Acute MI (0.5–10 days)—SAVE, AIRE or TRACE eligible
(either clinical/radiologic signs of HF or LV systolic dysfunction)
Major Exclusion Criteria:
— Serum creatinine > 2.5 mg/dL
— BP < 100 mm Hg
— Prior intolerance of an ARB or ACE-I
— Nonconsent
double-blind active-controlled
Captopril 50 mg 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

Enrollment

24 Countries. 931 Sites. 14,703 Patients.



Enrollment and Follow-up



Median follow-up: 24.7 months

Vital status ascertained in 14,564 patients (99.05%)
Vital status not ascertained in 139 patients (0.95%)
(lost to follow-up at 1 year: 0.4%; 2 years: 0.7%)

Baseline Characteristics

VALIANT

Mean age **(years)**		64.8
Women **(%)**		31.1
Mean BP **(mm Hg)**		123/72
Killip class **(%)**	I	28.0
	II	48.3
	III	17.3
	IV	6.4
Mean LVEF* (%)		**35.3**
Creatinine		1.1 mg/dL 98 µmol/L
Time to randomization **(d)**	4.9	

Thrombolytic therapy **(%)**	35.2
Primary PCI **(%)**	14.8
Other PCI after MI, prior to randomization **(%)**	19.8
Qualifying MI site **(%)**	
Anterior	59.4
Inferior	34.4
Qualifying MI type **(%)**	
Q wave	66.6
Non Q wave	31.9

*data on LVEF were available for 11,338 patients

Baseline Characteristics

Medical History (%):	
Diabetes mellitus	23.1
Hypertension	55.2
Smoking	31.7
Prior:	
Myocardial infarction	27.9
Heart failure	14.8
Stroke	6.1
CABG	7.0
PCI	7.3

Baseline Medications (%):	
ACE inhibitor*	39.6
ARB*	1.2
Beta-blocker	70.4
Aspirin	91.3
Other antiplatelet	24.8
Potassium-sparing diuretic	9.0
Other diuretic	50.3
Statin	34.1

*stopped prior to randomization

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

Baseline Characteristics

VALIANT

Characteristic	Valsartan (n = 4909)	Valsartan + Captopril (n = 4885)	Captopril (n = 4909)
Age (yr)	65.0 ± 11.8	64.6 ± 11.9	64.9 ± 11.8
Race			
Caucasian	4604 (93.8%)	4553 (93.2%)	4591 (93.5%)
Black	125 (2.5%)	137 (2.8%)	145 (3.0%)
Asian	**44 (0.9%)**	**53 (1.1%)**	**44 (0.9%)**
Other	136 (2.8%)	142 (2.9%)	129 (2.6%)
Females	1544 (31.5%)	1490 (30.5%)	1536 (31.3%)
Blood pressure (mm Hg)			
Systolic	122.7 ± 16.8	122.5 ± 17.1	122.8 ± 17.0
Diastolic	72.3 ± 11.3	72.3 ± 11.4	72.4 ± 11.2
Heart rate (beats/min)	76.2 ± 13.0	76.2 ± 12.7	76.2 ± 12.8

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

Baseline Characteristics

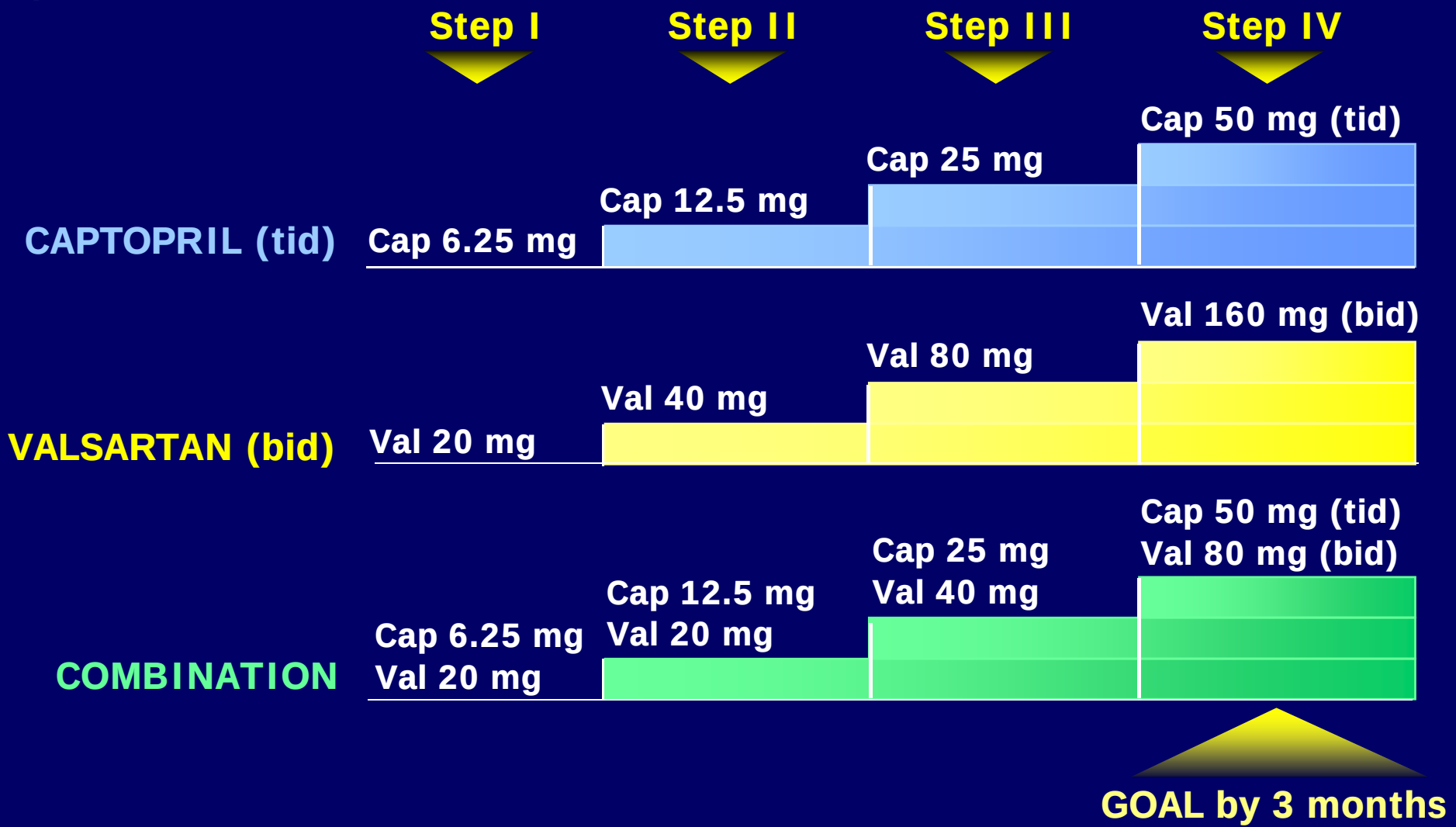
VALIANT

Characteristic	Valsartan (n = 4909)	Valsartan + Captopril (n = 4885)	Captopril (n = 4909)
BMI (kg/m²) (median)	27.34	27.24	27.14
(25th, 75th percentile)	(24.69, 30.47)	(24.62, 30.35)	(24.54, 30.22)
LVEF* (%)	35.3 ± 10.4	35.3 ± 10.3	35.3 ± 10.4
Killip class			
I	1294 (26.5%)	1381 (28.4%)	1424 (29.1%)
II	2401 (49.2%)	2329 (47.9%)	2346 (48.0%)
III	874 (17.9%)	842 (17.3%)	813 (16.6%)
IV	313 (6.4%)	312 (6.4%)	306 (6.3%)
Days from MI to randomization	4.8	4.9	4.9
Serum creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.4

*measured in 11,338 (77.1%) of the patients

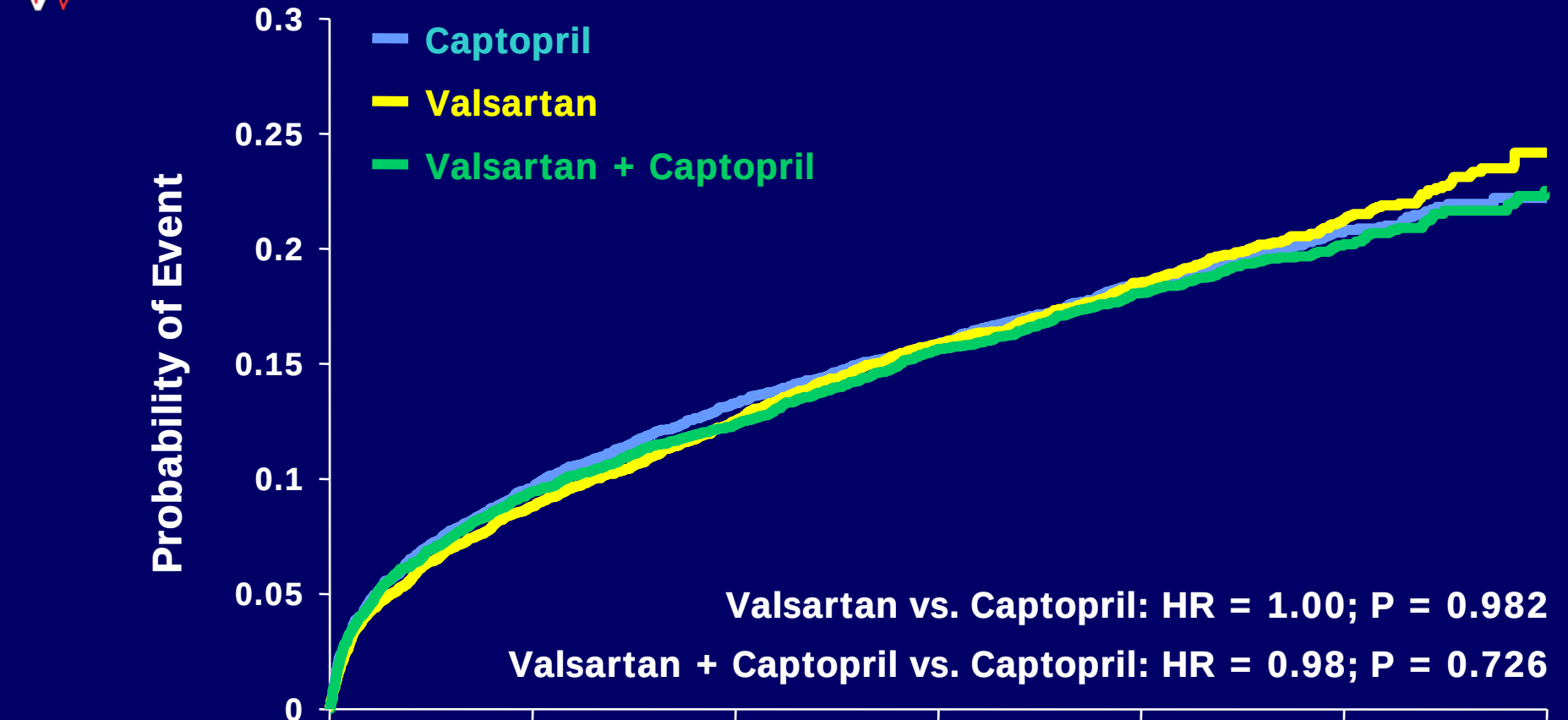
Study Drug Dose Titration

VALIANT



Am Heart J. 2000;140:727–734.

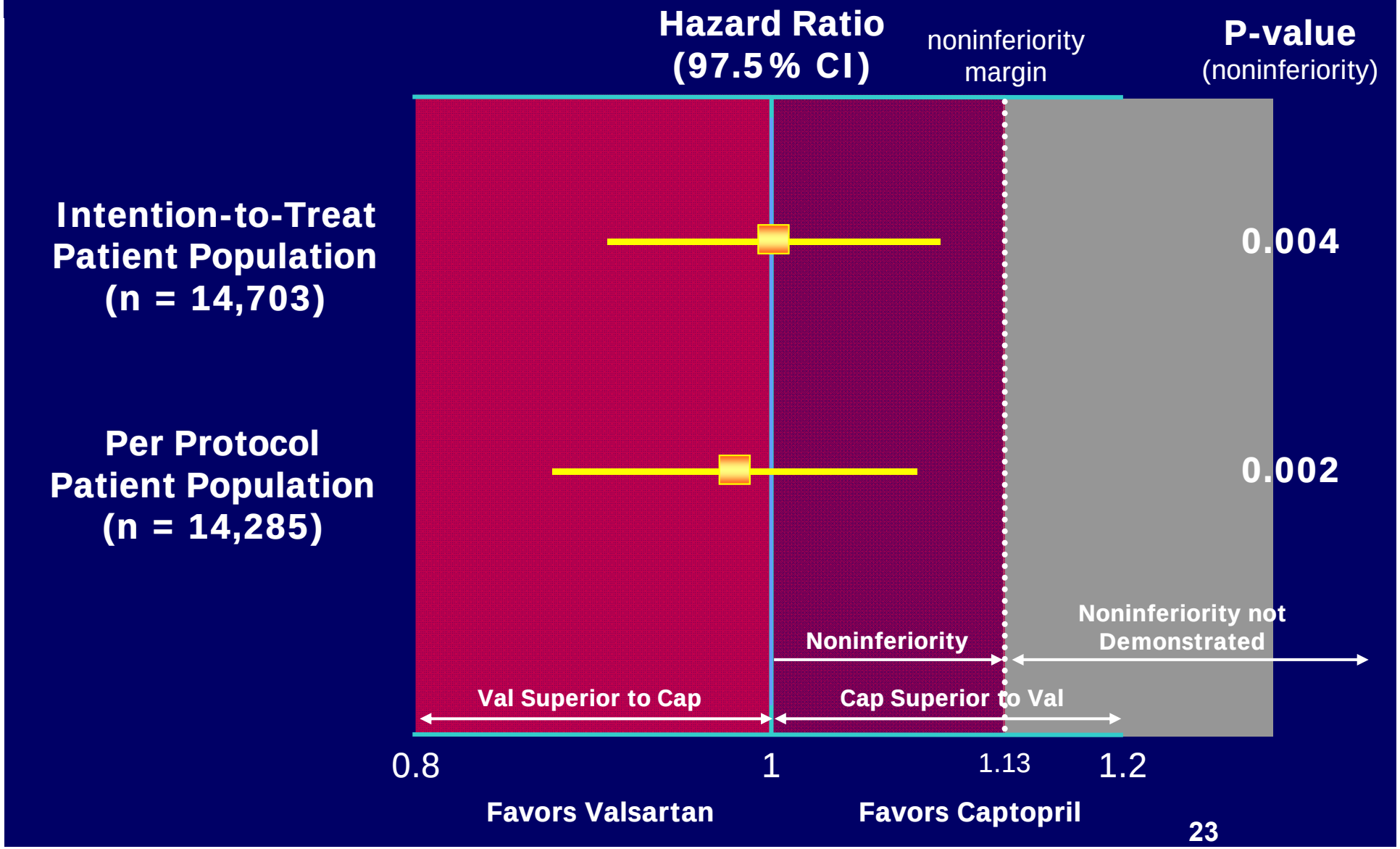
Mortality by Treatment



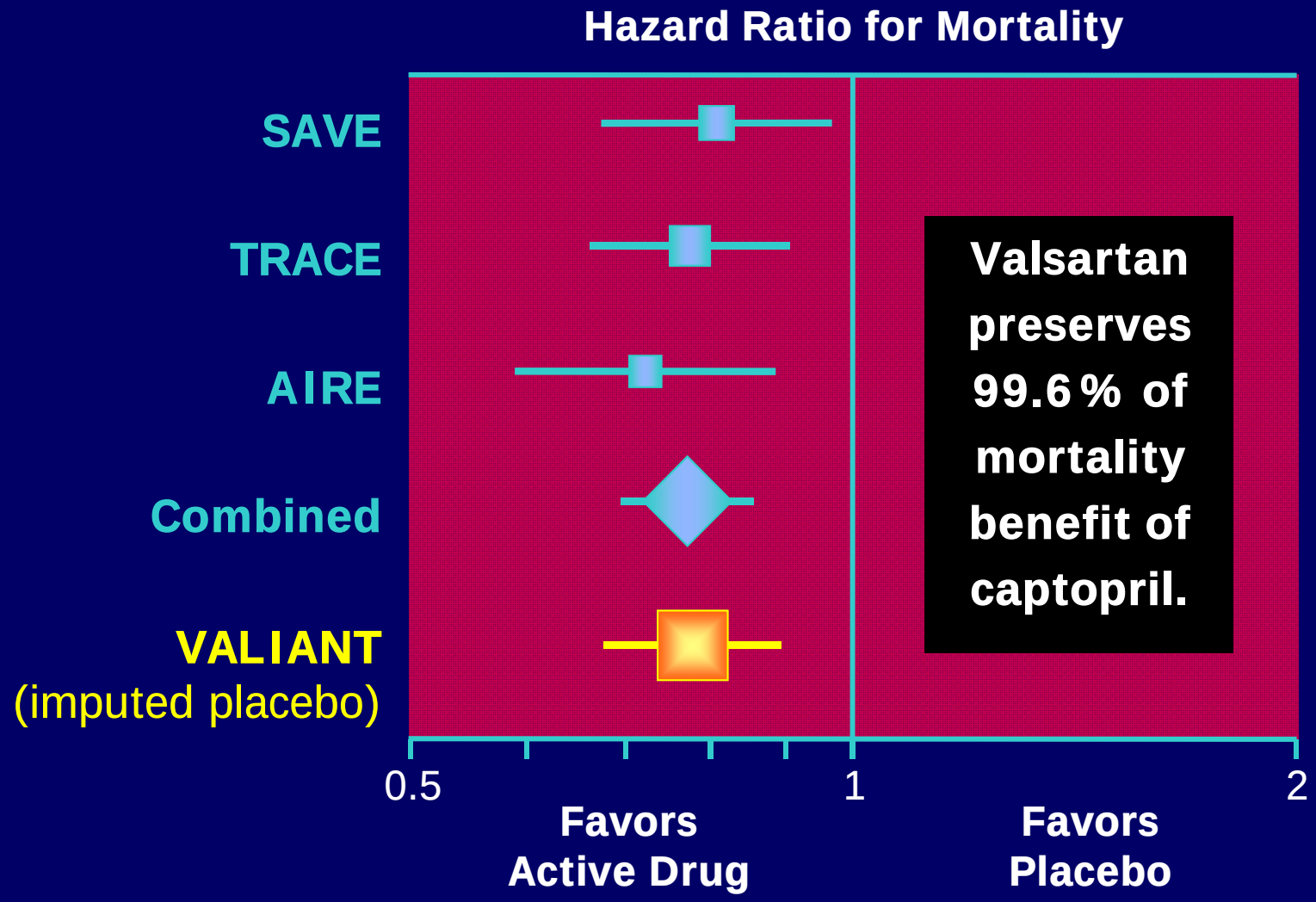
Months	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

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

All-Cause Mortality: Non-Inferiority Analyses



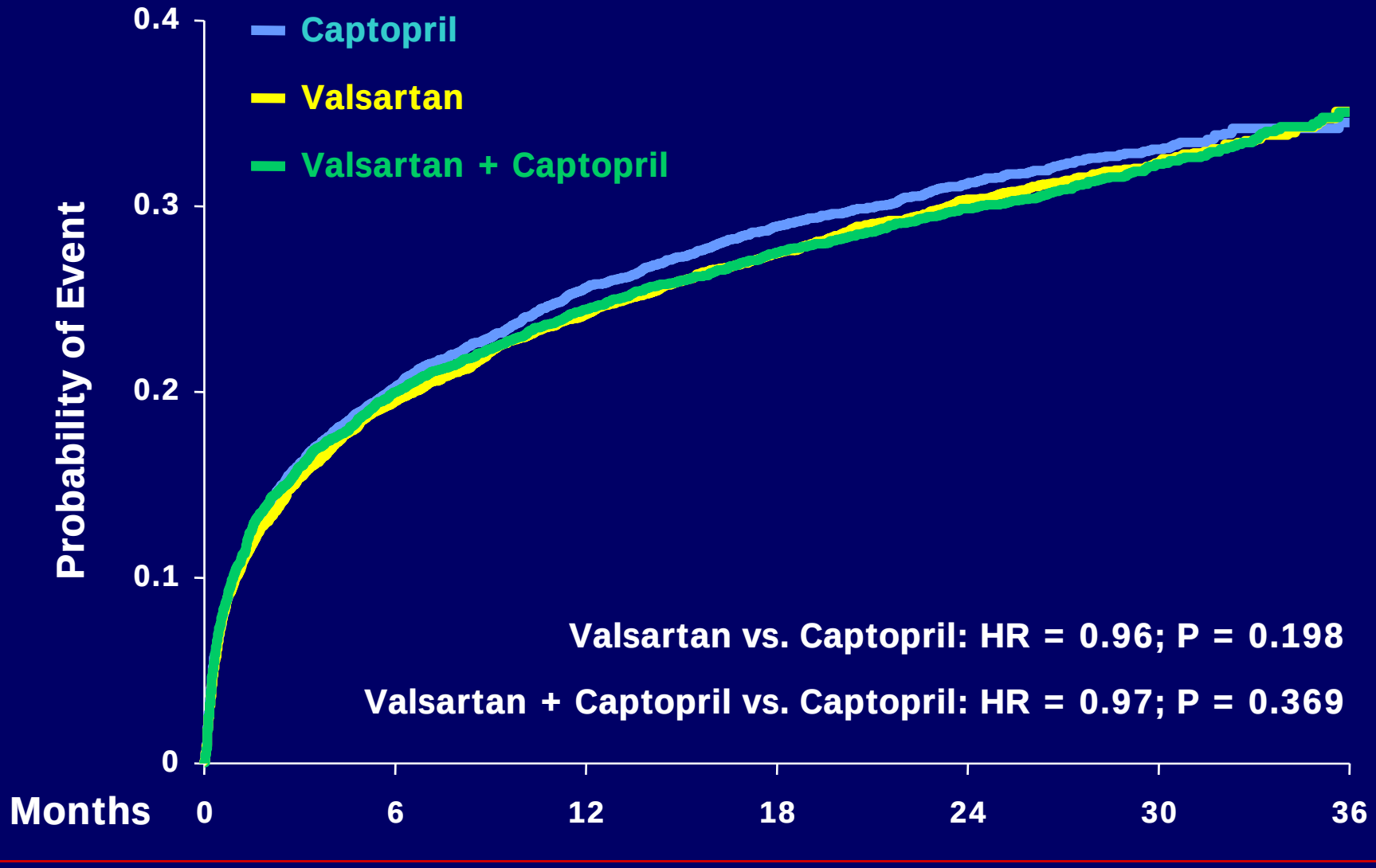
Mortality in SAVE, TRACE, AIRE, and VALIANT



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

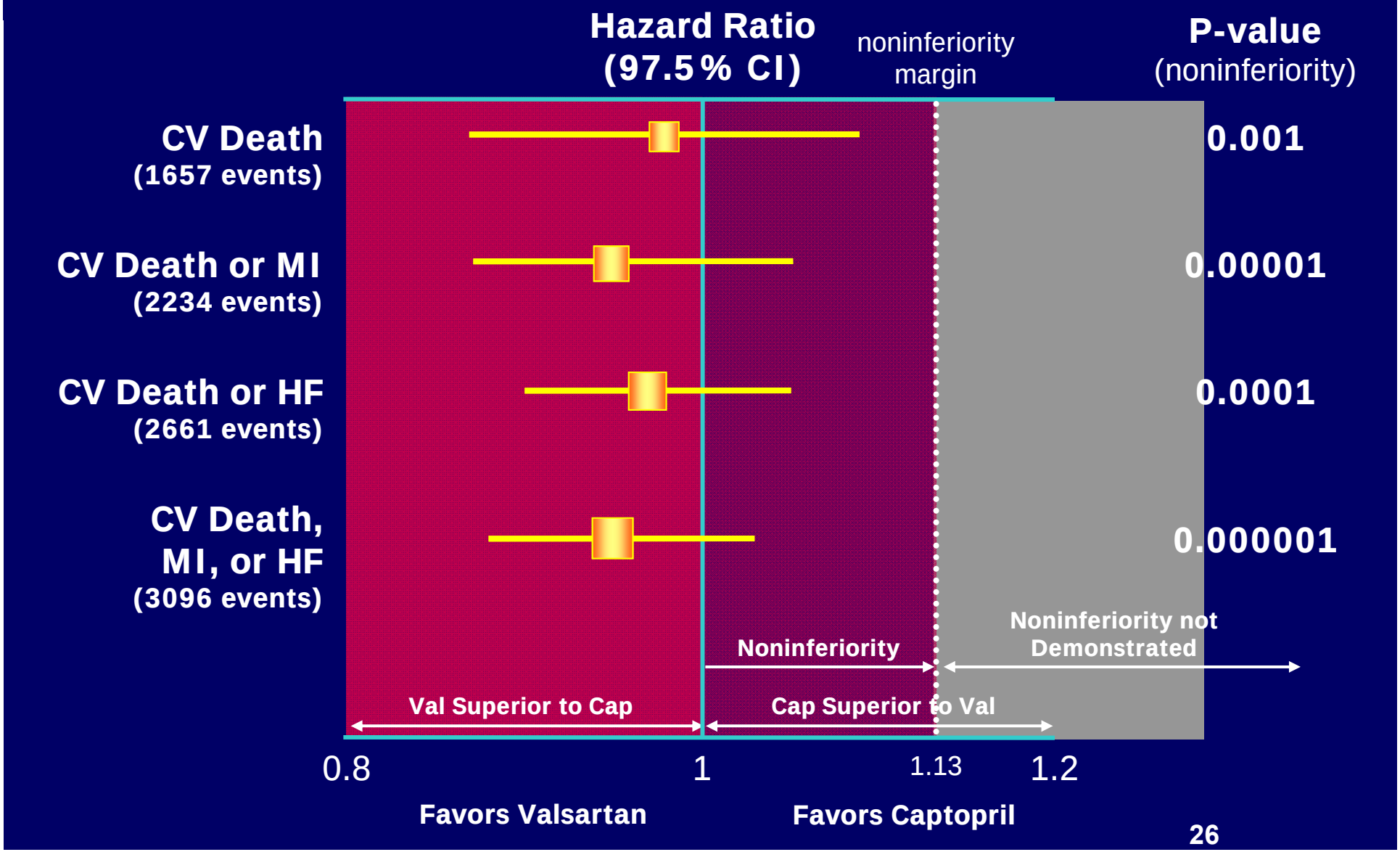
CV Death, MI, or HF by Treatment

VALIANT



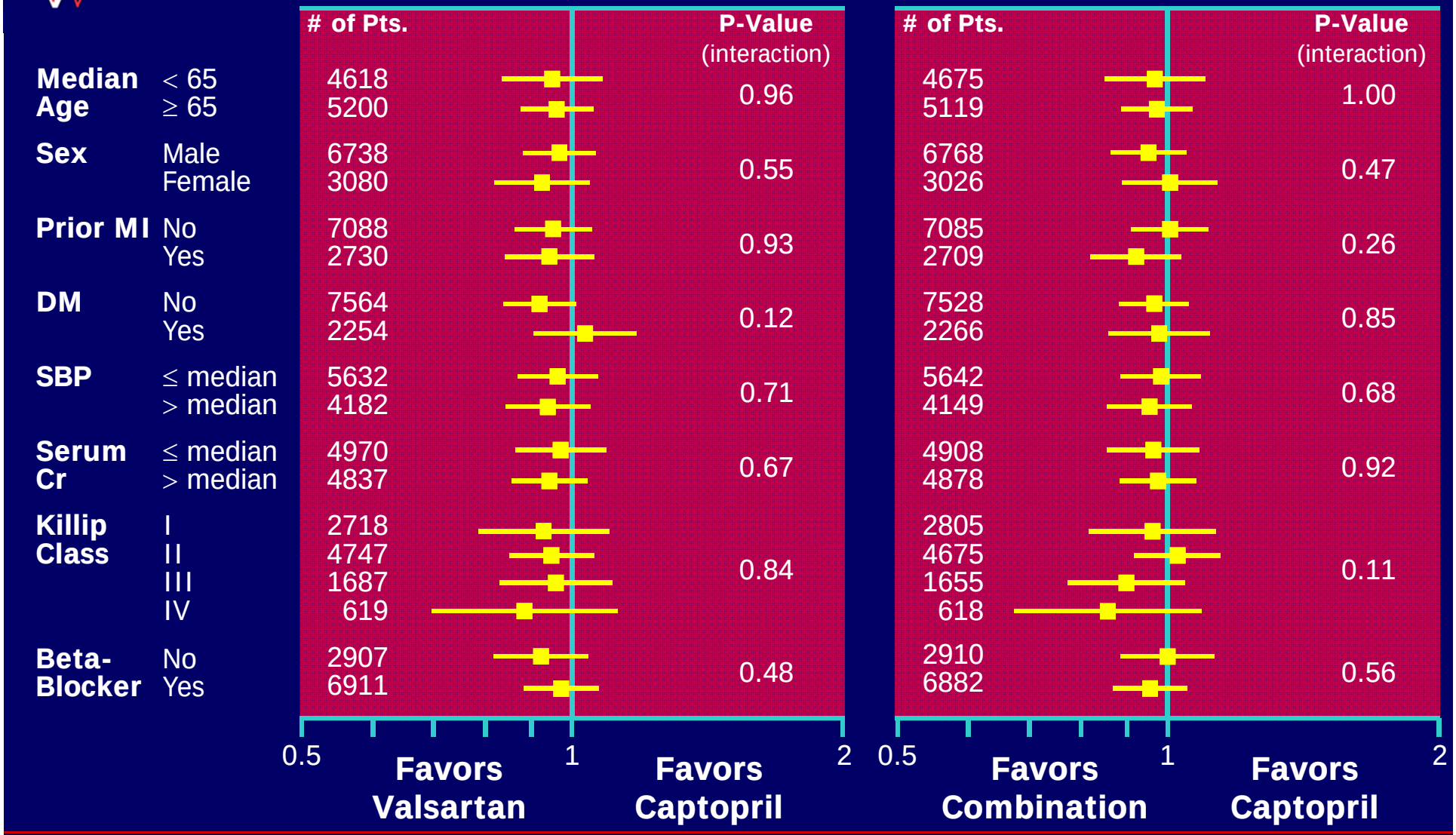
Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

Cardiovascular Mortality and Morbidity



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

VALIANT



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

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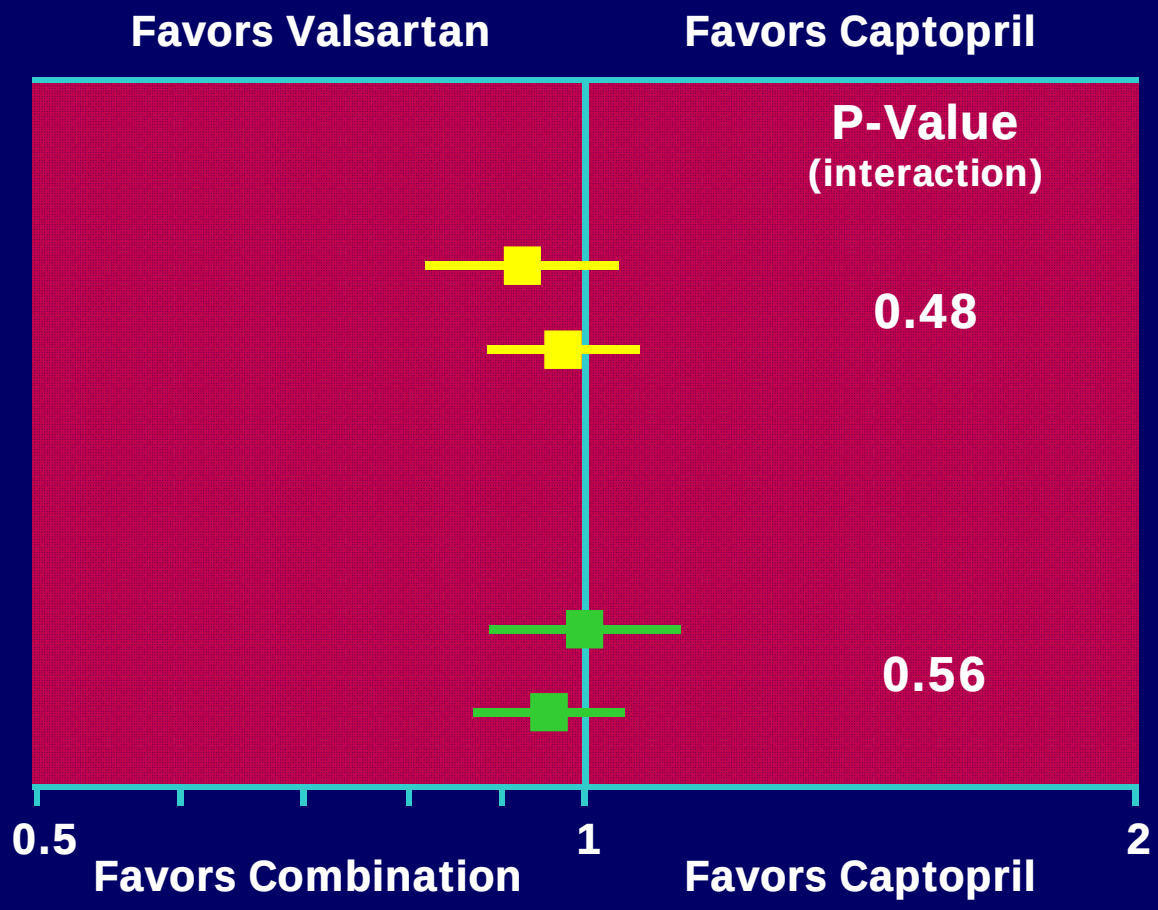


Valsartan vs. Captopril:

No Beta-Blocker (n = 2907)

Beta-Blocker (n = 6911)

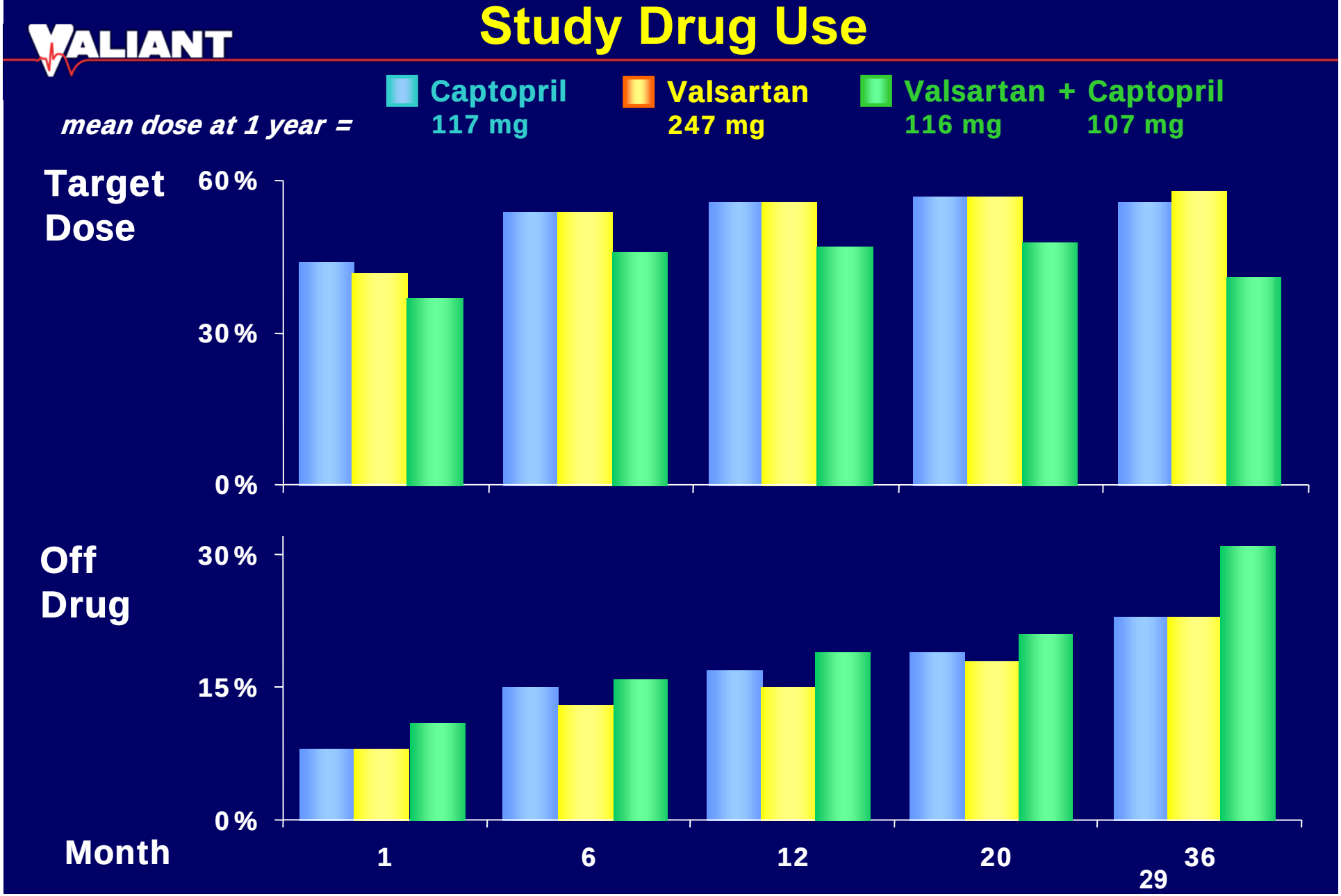
Combination vs. Captopril:

No Beta-Blocker (n = 2910)

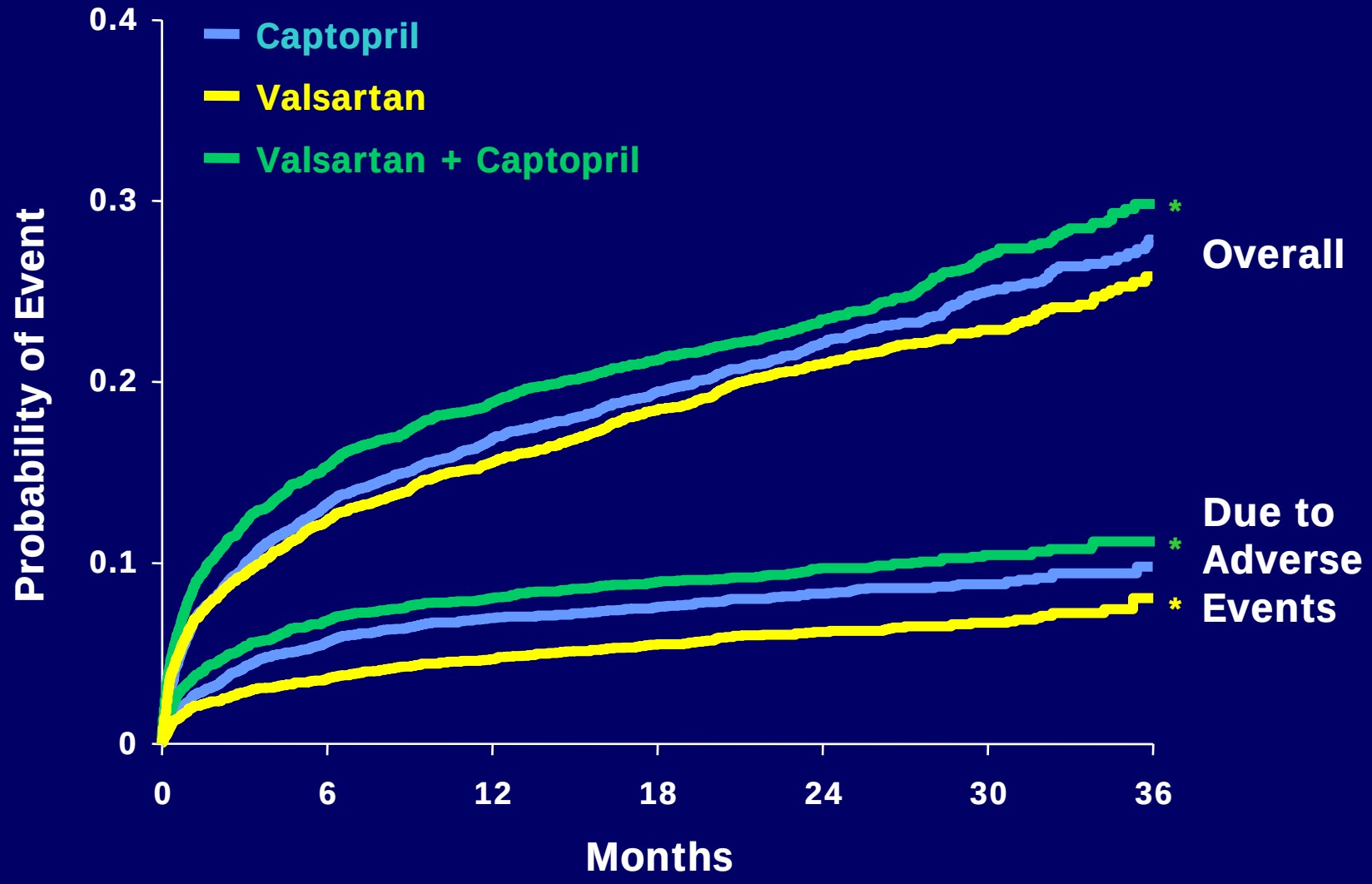
Beta-Blocker (n = 6882)

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

Study Drug Use



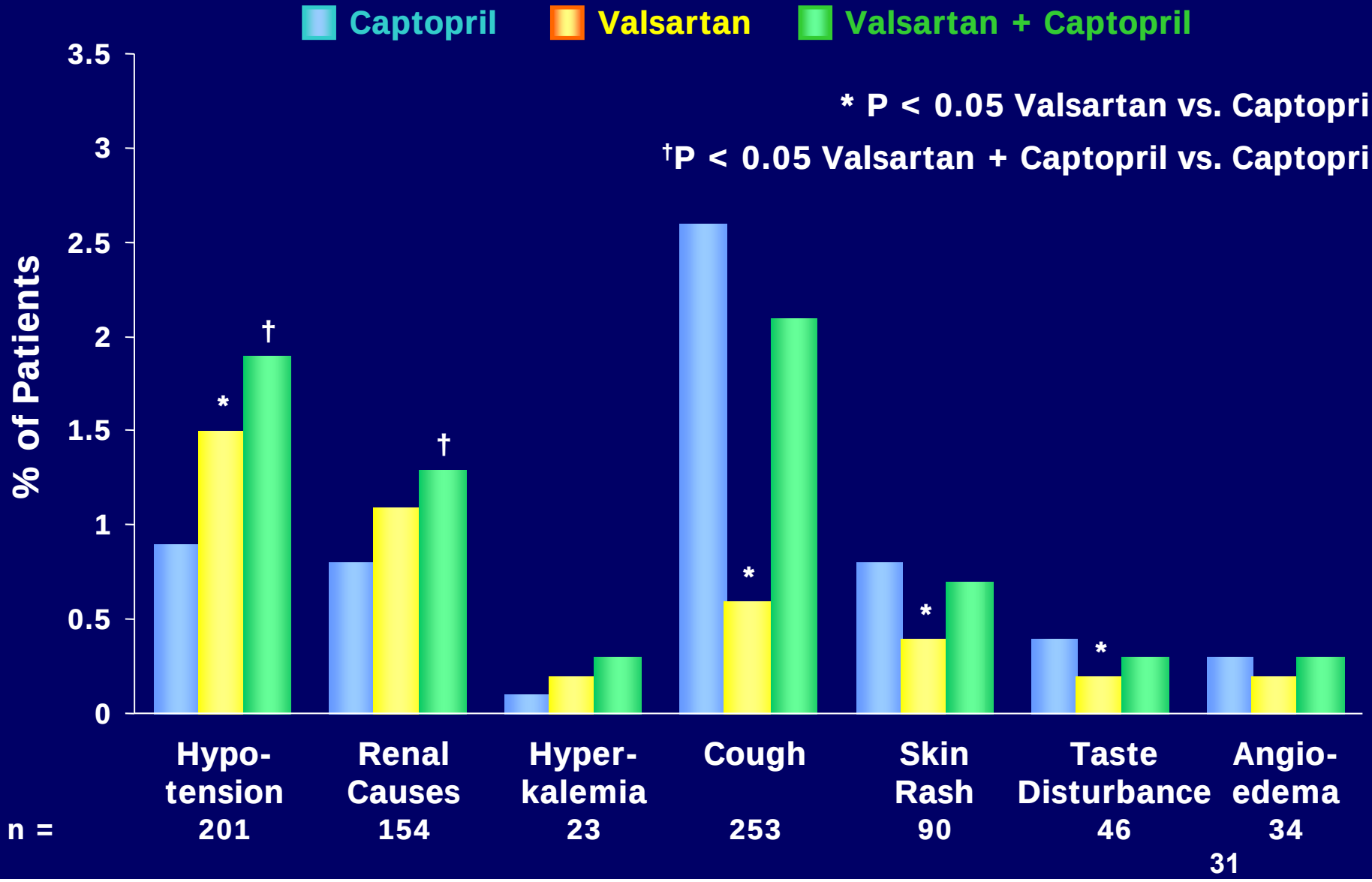
Study Drug Discontinuation



*P < 0.05 vs Captopril

Adverse Experience Leading to Study Drug Discontinuation

VALIANT



Conclusion

In patients with MI complicated by heart failure, left ventricular dysfunction or both:

- Valsartan is as effective as a proven dose of captopril in reducing the risk of:
  - Death
  - CV death or nonfatal MI or heart failure admission
- Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.

Implications:
In these patients, valsartan is a clinically effective alternative to an ACE inhibitor.

OPTIMAAL

OPtimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan

Steering Committee

J. Kjekshus (Chair), K. Dickstein (Coordinator),
S. G. Ball, A. J. S. Coats, R. Dietz, A. Kesäniemi, E. S. P. Myhre,
M. S. Nieminen, K. Skagen, K. Swedberg, K. Thygesen, H. Wedel,
R. Willenheimer, A. Zeiher, J. C. Fox and K. Kristianson

Endpoint Committee

J. G. F. Cleland and M. Romo

Data Safety and Monitoring Board

D. Julian (Chair), A. Bayés de Luna, D. L. DeMets,
C. D. Furberg, W. W. Parmley and L. Rydén

Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Rationale

- ACE inhibitors reduce mortality in high risk post MI patients
- Selective A II Receptor Antagonists are an alternative because of more complete blockade of tissue RAAS
- Better tolerability

Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Hypothesis

Losartan (50 mg) is superior or non-inferior to captopril (150 mg) in decreasing all-cause mortality in high-risk patients following AMI.

Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Study Design

- Double-blind randomised, parallel, investigator initiated, no placebo control
- Event driven (all-cause death = 937)
- Multicentre (Denmark, Finland, Germany,Ireland, Norway, Sweden, UK)

Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Prespecified Endpoints

1. All-cause death
2. SCD / RCA
3. Reinfarction

- Reinfarction / all-cause death
- Cardiovascular death
- Stroke
- Revascularisation
- First all-cause hospitalization
- Safety and tolerability

Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Inclusion Criteria

- Documented AMI
- Age ≥ 50 years

  and

- heart failure

  or

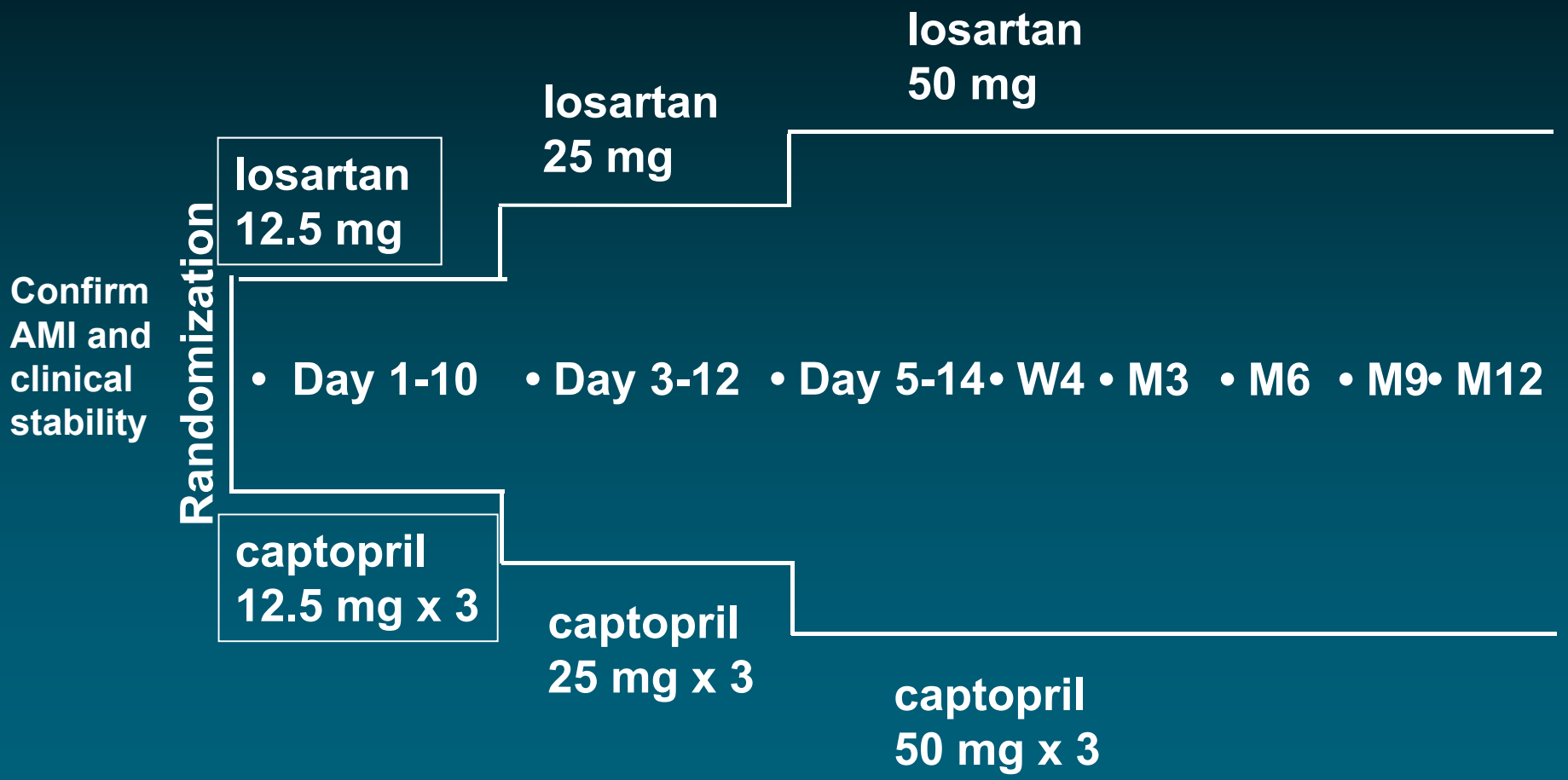
- new anterior Q-wave

  reinfarction with previous anterior Q-wave

(ACE I / A II antagonists excluded)

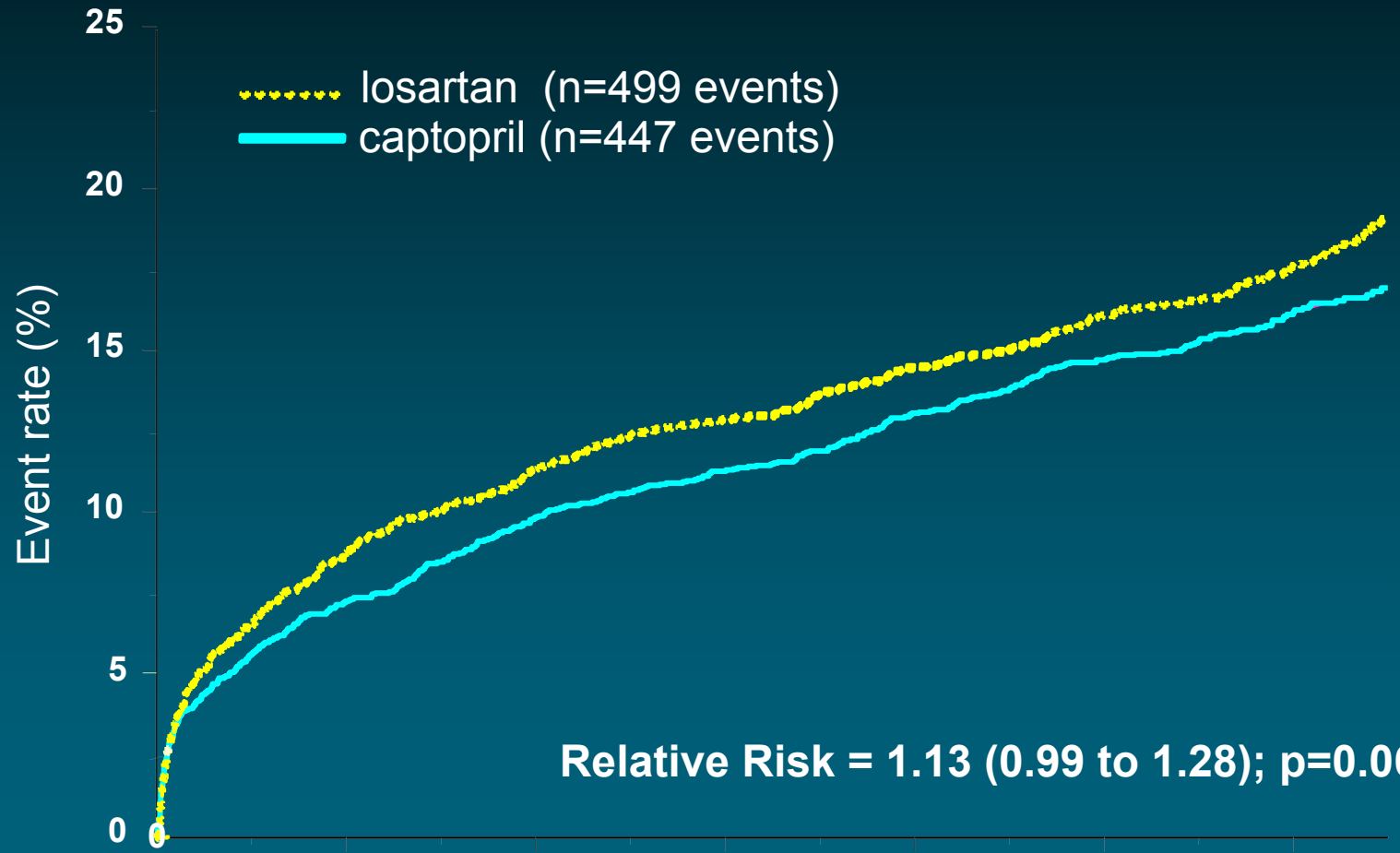
Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Study Design



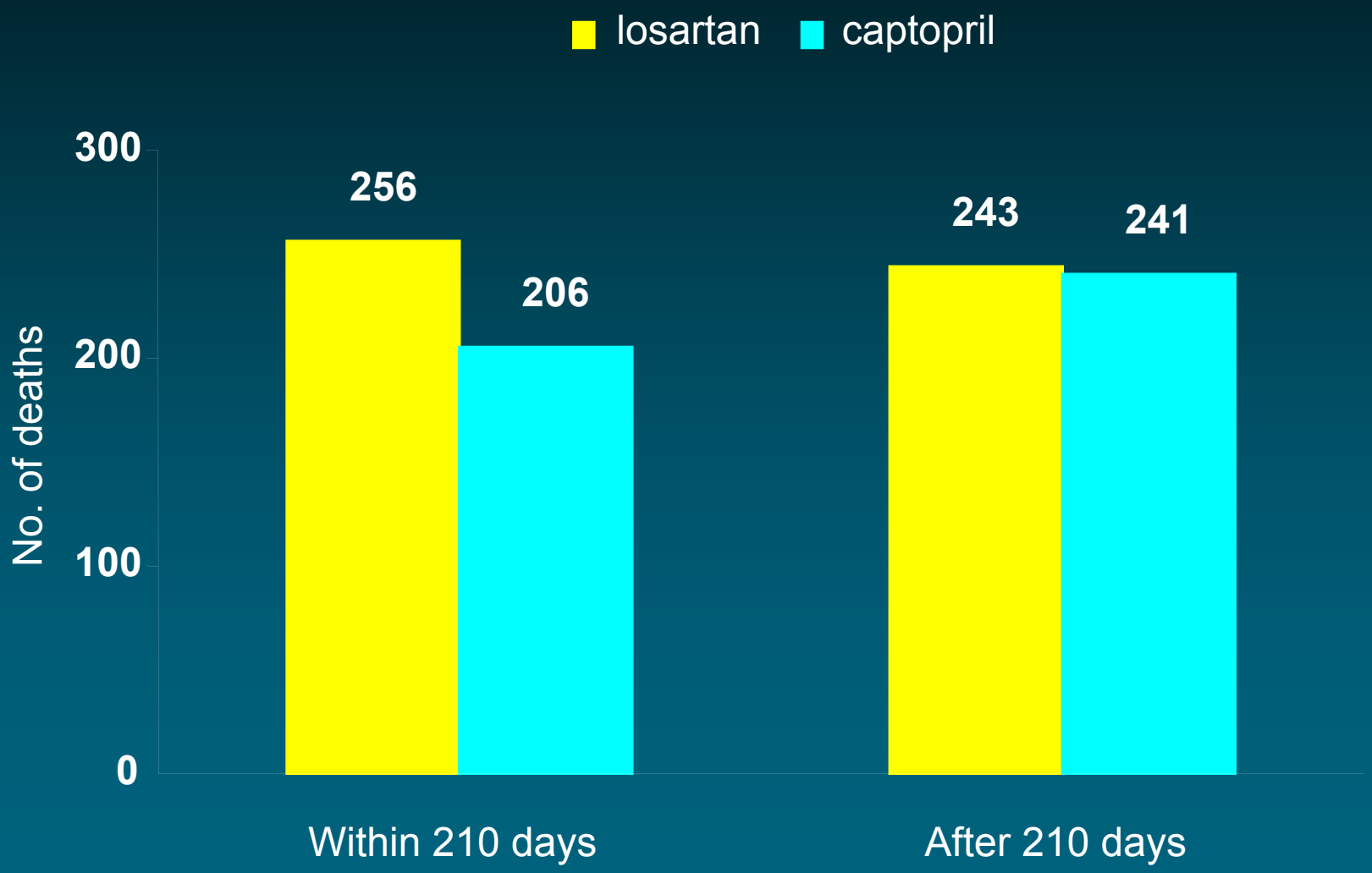
Dickstein et al. *Am J Cardiol* 1999; 83:477-481.

OPTIMAAL:
Primary Endpoint: All-cause Mortality

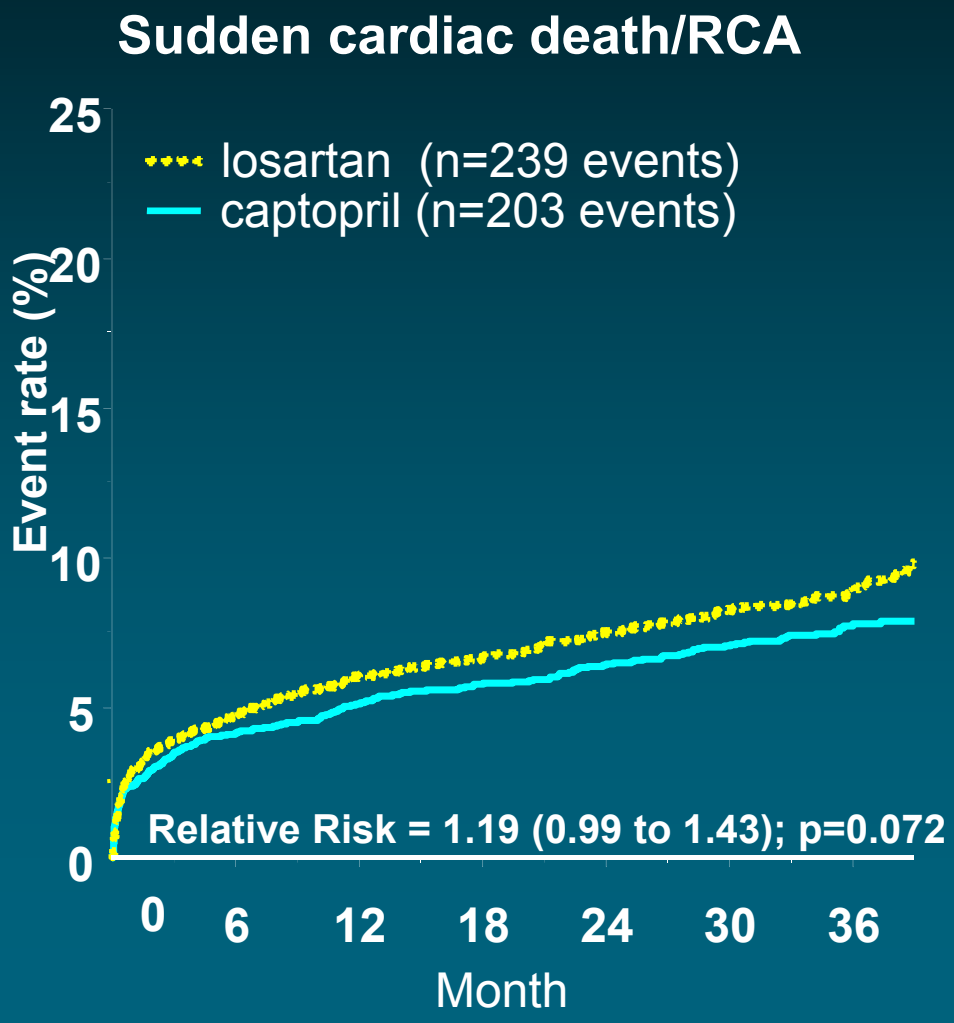


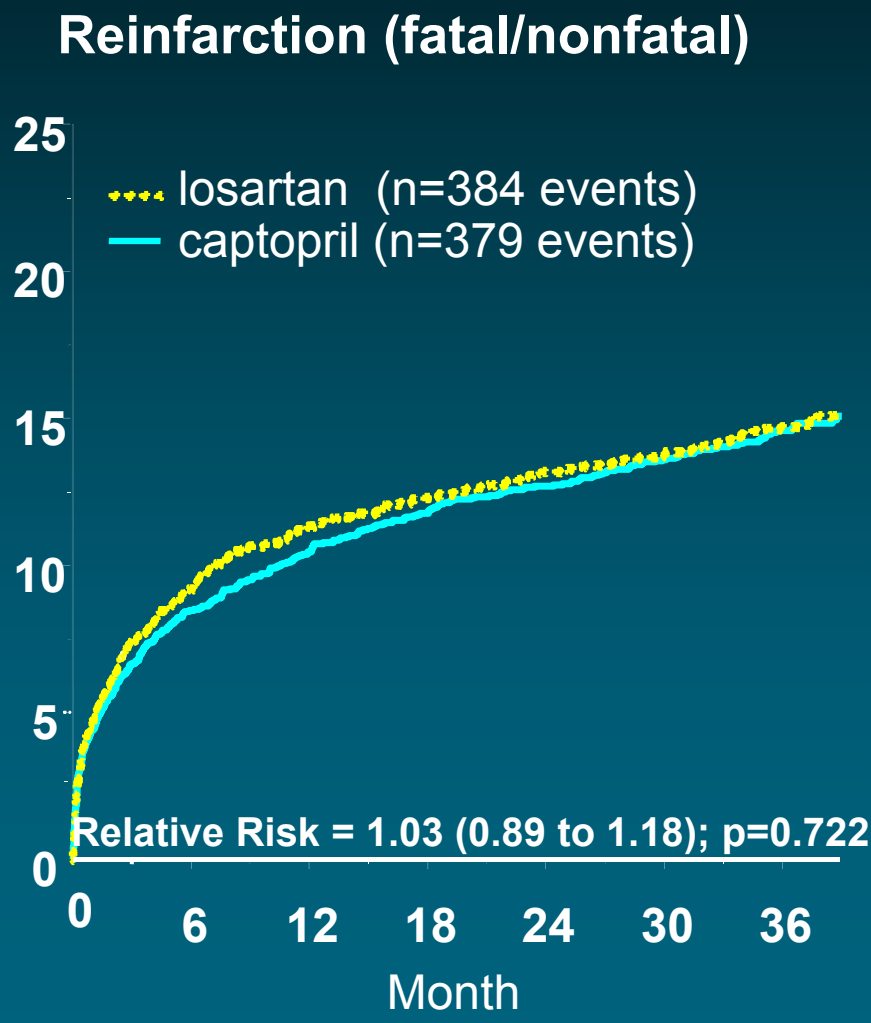
losartan (n)	2744	2504	2432	2390	2344	2301	1285
captopril (n)	2733	2534	2463	2423	2374	2329	1309

All-cause mortality: early vs late



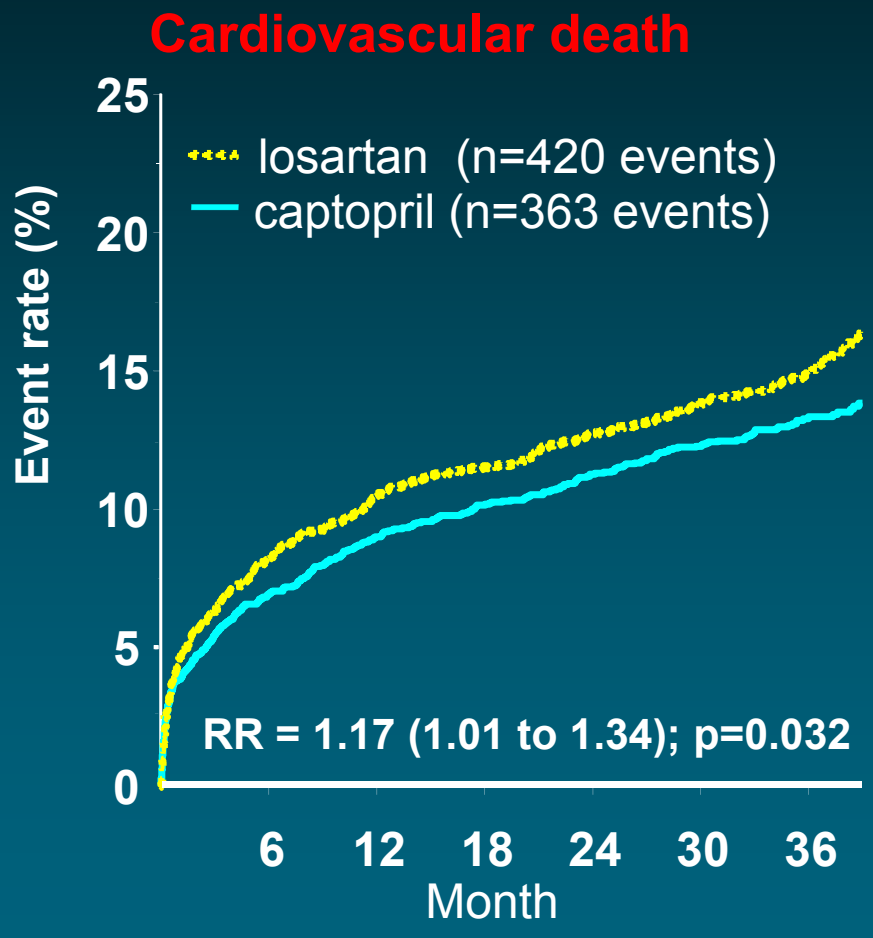
OPTIMAAL:
Secondary and Tertiary Endpoints

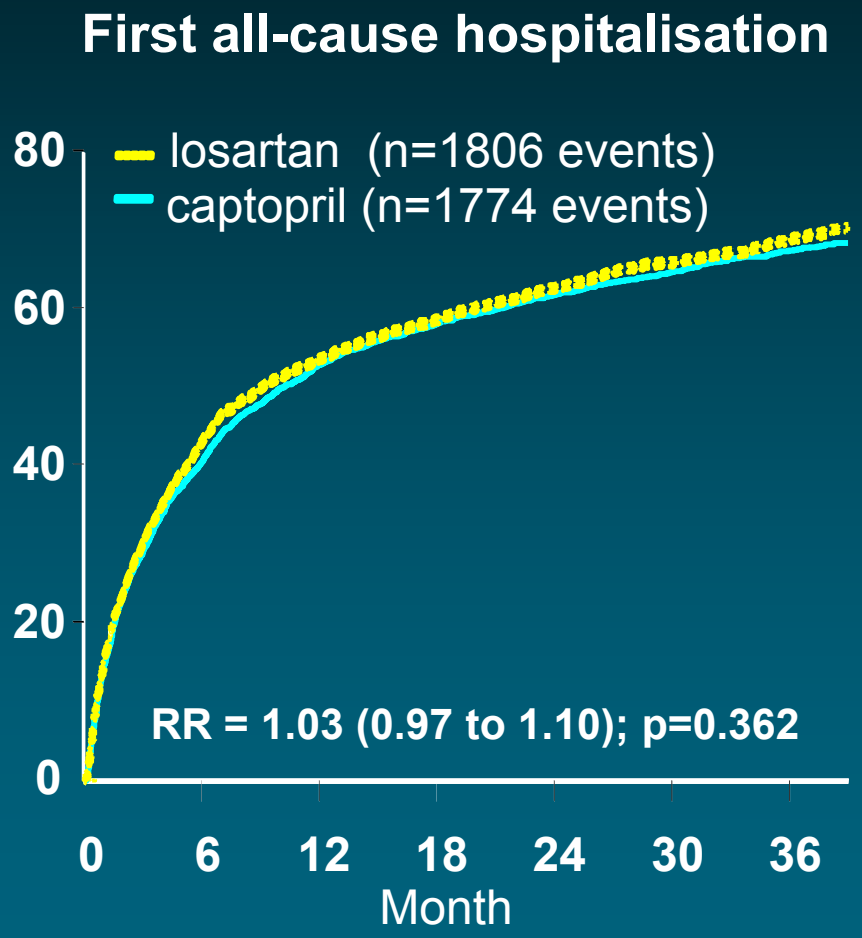




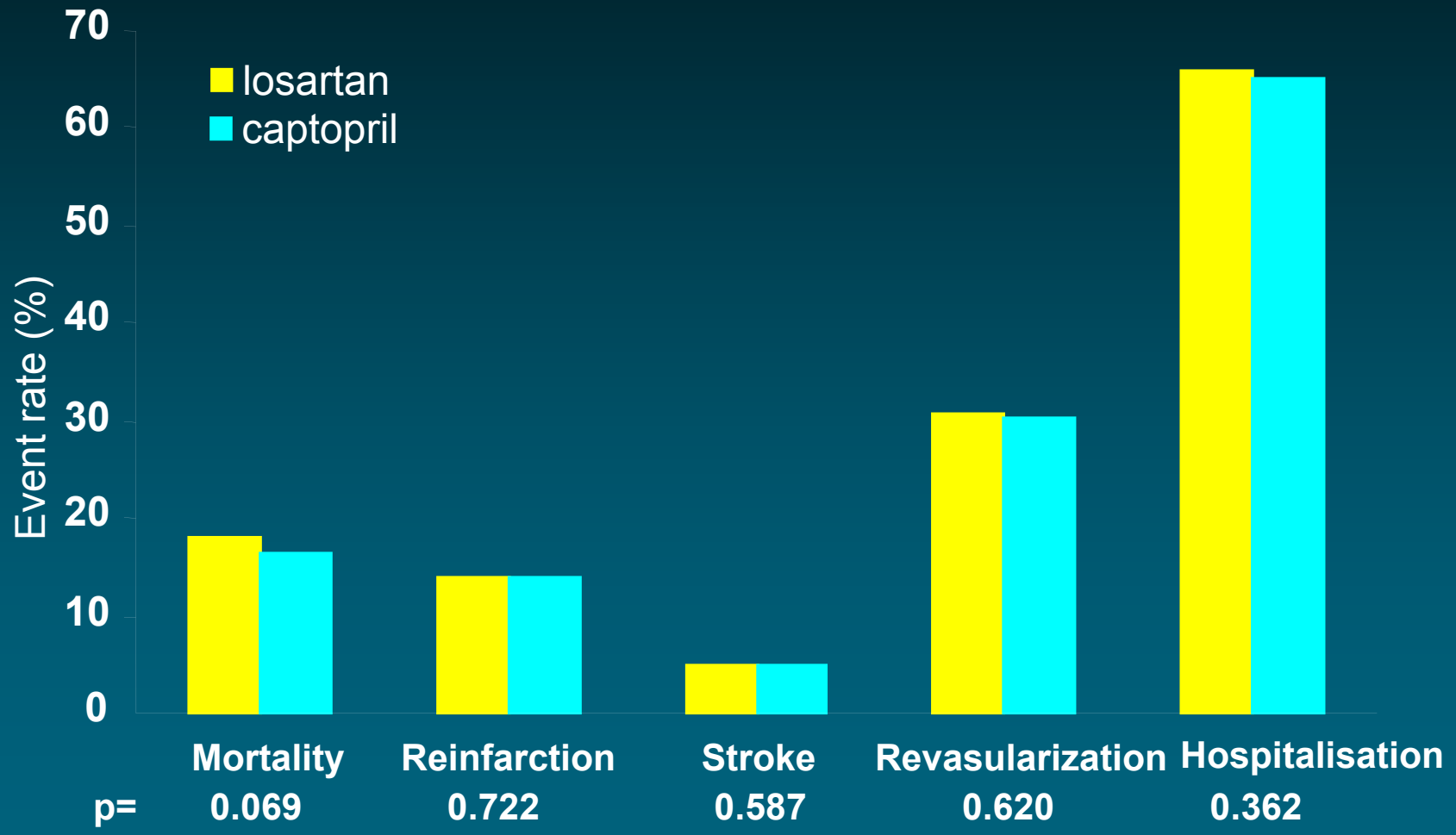
Dickstein et al. *Lancet* 2002;360:752-760.

OPTIMAAL: Exploratory Endpoints

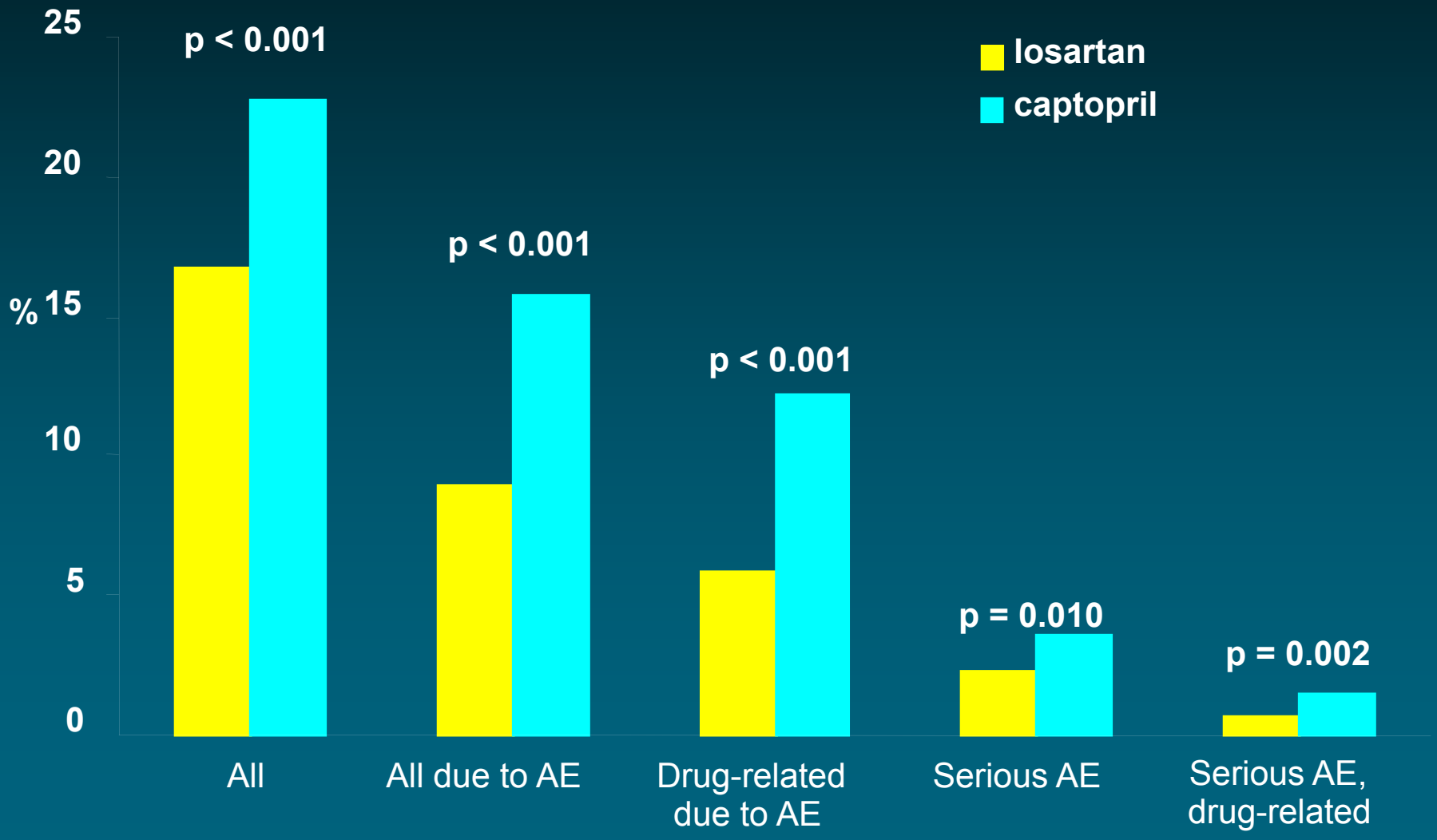




OPTIMAAL: Endpoints



OPTIMAAL: Discontinuations



Dickstein et al. *Lancet* 2002;360:752-760.

Understanding the OPTIMAAL Trial

- Very specific patient population:
  - Patients enrolled had AMI plus documented signs or symptoms of heart failure or Q waves
  - Patients with prior treatment with ACE inhibitors or AII antagonists were excluded
- No placebo control arm (2 active agents)
- Dosing regime based on ELITE study:
  Were the doses of losartan and captopril equivalent?

Effect of losartan

	Rel. Risk	% change
ACE Inhibit. vs. placebo*	0.805	- 19.5
losartan vs. captopril (OPTIMAAL)	1.126	12.6
losartan vs. putative placebo (0.805 x 1.126)	0.906	- 9.4

* Based on a prospective meta-analysis of the following placebo-controlled trials:

SAVE, AIRE. TRACE, SMILE, GISSI III, CONSENSUS II and ISIS IV

Dickstein et al. *Lancet* 2002;360:752-760.

What is the correct dose of COZAAR in the acute MI patient?

ELITE II in HF patients
mean dose: 41 mg

RENAAL in HTN patients with DM and nephropathy
mean dose: 86 mg

HEAAL in ACEI intolerant HF patients
losartan 50 mg vs. 150 mg

OPTIMAAL in AMI patients
mean dose:
45 mg
captopril: 132 mg

LIFE in HTN patients
mean dose:
82 mg

Pitt B et al. Lancet 2000;355:1582-1587; Brenner B et al. N Engl J Med 2001;345:861-869; Dickstein et al *Lancet* 2002; 360:752-760; Dahlof et al. Lancet 2002;359:995-1003.

OPTIMAAL: Summary

- Losartan (50 mg daily) compared with captopril (150 mg daily) in high risk acute MI patients:
- Neither the superiority nor the non-inferiority of losartan (50 mg/day) vs. captopril (150 mg/day) in total mortality was demonstrated, non-significant trend in all-cause mortality in favor of captopril
- Essentially identical results for the secondary and tertiary endpoints: sudden cardiac death/resuscitated cardiac arrest and reinfarction
- Essentially identical results for other prespecified endpoints: eg stroke, revascularization, all-cause hospitalization and NYHA class, only exception a higher incidence of CV mortality ($p=0.032$)
- Losartan demonstrated better tolerability with significantly fewer discontinuations for adverse events

OPTIMAAL: Interpretation

"Since we showed a non-significant difference in total mortality in favor of captopril, ACE inhibitors should remain first-choice treatment in patients after complicated acute myocardial infarction.

Losartan cannot be generally recommended in this population.

However, it was better tolerated than captopril, and was associated with significantly fewer discontinuations.

Although the role of losartan in patients intolerant of ACE inhibition is not clearly defined, it can be considered in such patients."

(Dickstein et al. *Lancet* 2002;360:752-760.)

II. High Dose is better ?

- HYPOTHESIS: Increased ARB dose is associated with improved clinical outcomes in heart failure and acute MI
- HYPOTHESIS: Increased ARB dose is associated with improved LV function in acute MI
- HYPOTHESIS: Increased ARB dose is associated with improved clinical outcomes in Oriental population

Comparison of Low-Dose Versus High-Dose Losartan Treatment on Morbidity and Mortality in Angiotensin-Converting-Enzyme-Inhibitor-Intolerant Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction: Results of the HEAAL* Study

Marvin A. Konstam, James D. Neaton, Kenneth Dickstein, Helmut Drexler, Michel Komajda, Felipe A. Martinez, Gunter A.J. Riegger, Ronald D. Smith, William Malbecq, Soneil Guptha, Philip A. Poole-Wilson for the HEAAL investigators

* Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan

Lancet 2009; **374:** 1840–48

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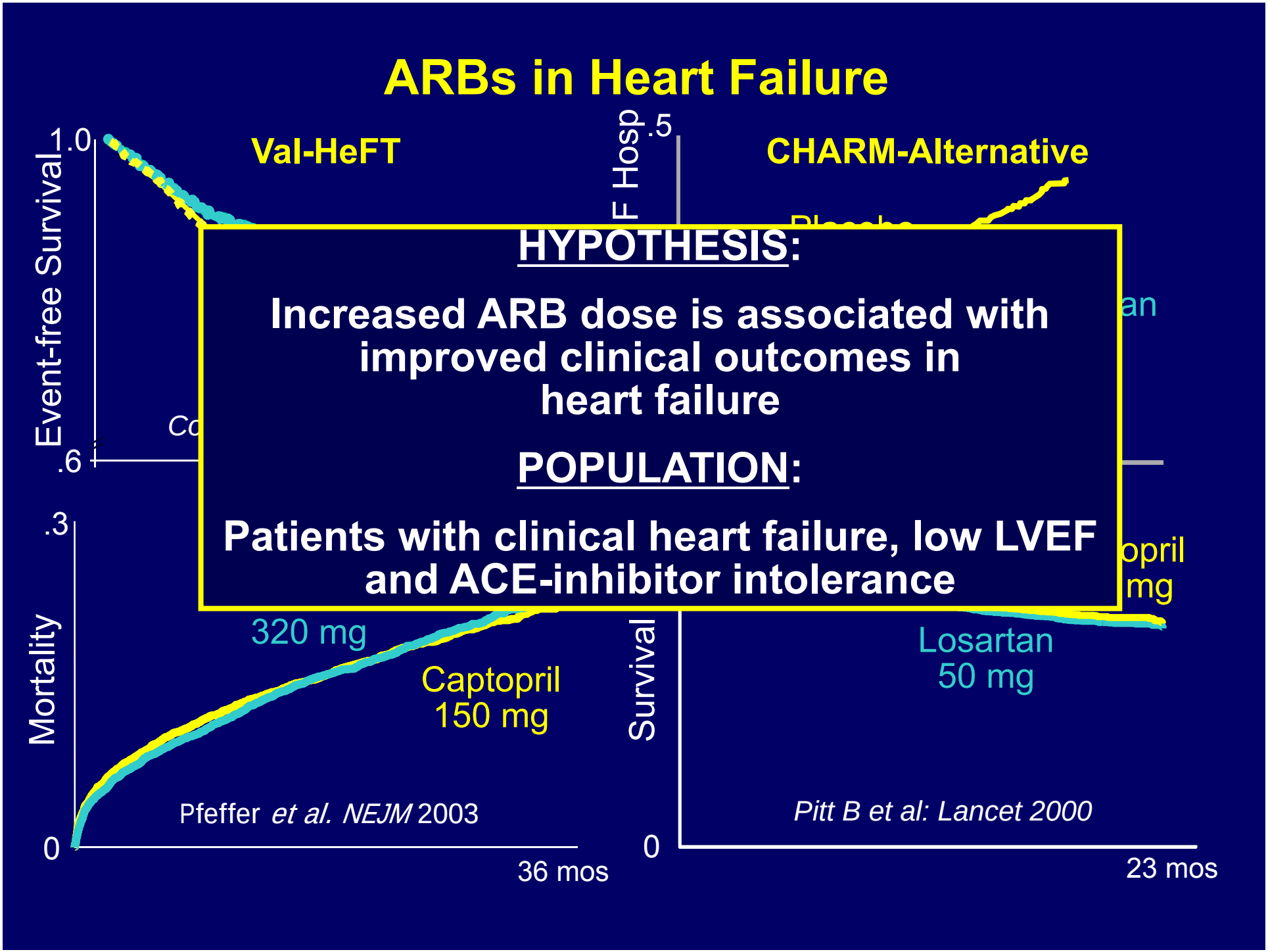
ARBs in Heart Failure

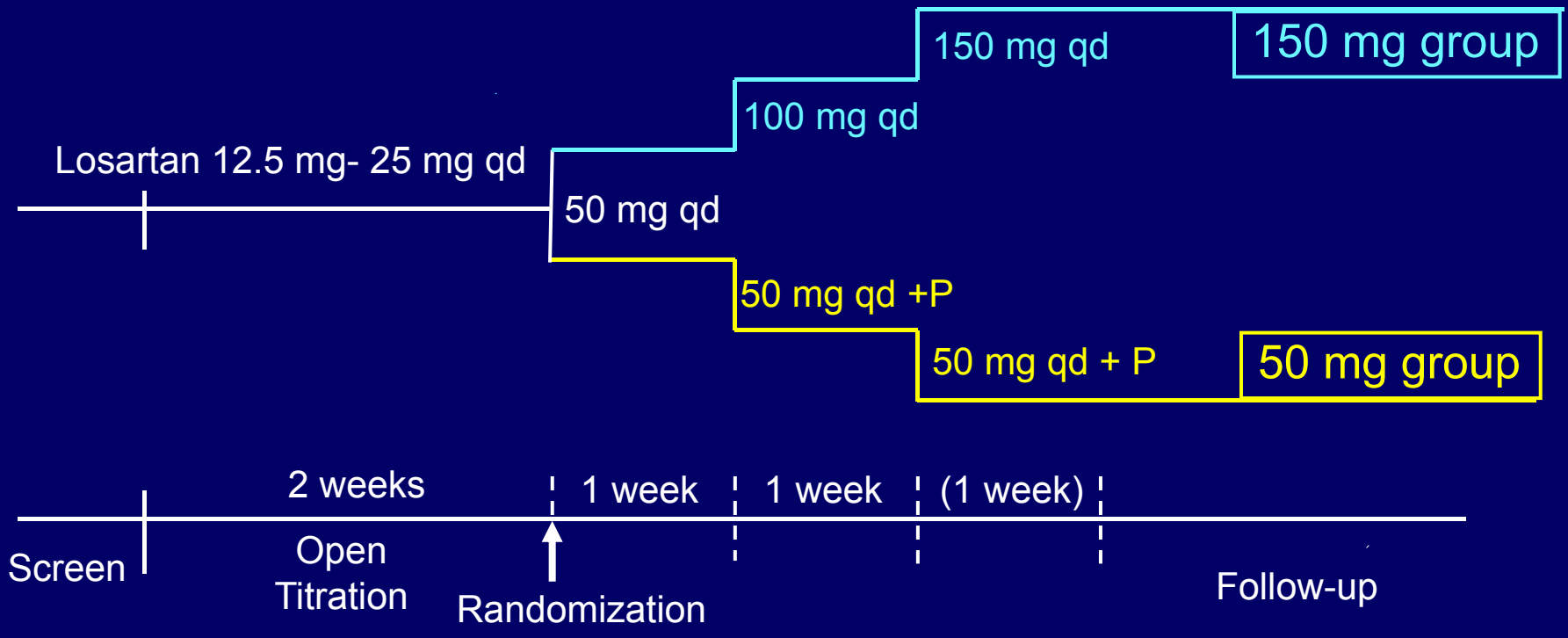


Inclusion Criteria

- Inclusion
  - NYHA II-IV Heart Failure
  - LVEF ≤40%
  - Intolerance to ACEI
- Exclusion
  - Known intolerance to ARBs
  - Systolic BP < 90 mm Hg
  - Myocarditis, pericarditis, or stenotic valvular disease
  - MI, unstable angina, PTCA, or CABG within prior 12 wks
  - CVA or TIA within prior 12 weeks

Konstam MA et al, Lancet 2009; **374:** 1840–48

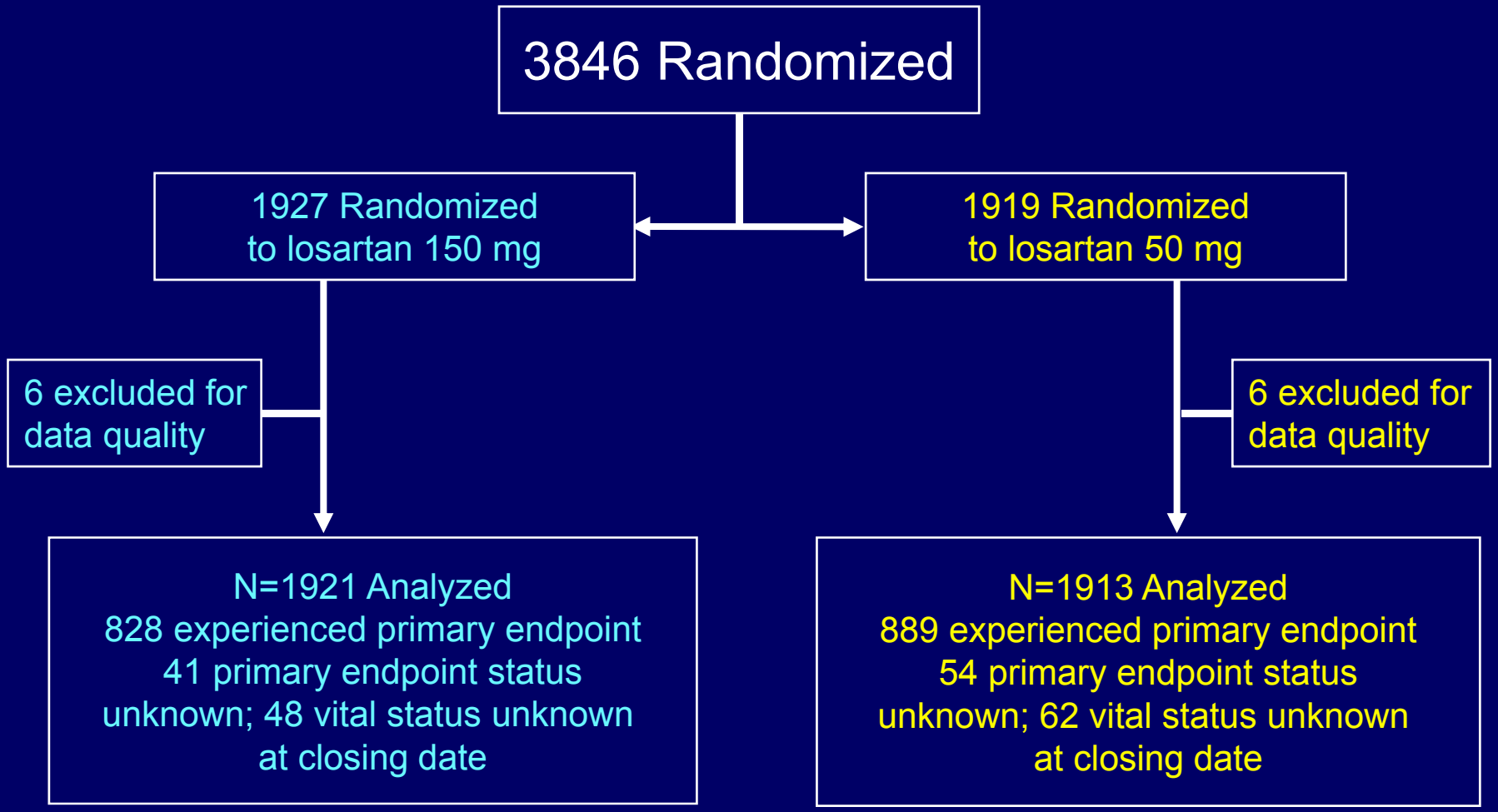
Study Design and Sample Size



- Primary endpoint: death or hospitalization for HF
- 1710 patients with primary endpoint events provided 95% power for HR = 0.837 for superiority with 2-sided α = 0.043

Konstam MA et al, Lancet 2009; **374:** 1840–48

Disposition of Patients



Konstam MA et al, Lancet 2009; **374:** 1840–48

Baseline Characteristics

	Losartan 150 mg (N=1921)	Losartan 50 mg (N=1913)
Age, mean (years)	64.4	64.1
Gender (% male)	69.7	70.7
Atrial fibrillation (%)	27.9	28.0
Ischemic heart disease (%)	63.6	64.6
Hypertension (%)	59.8	59.7
Diabetes (%)	31.0	31.6
NYHA Class (% II/III/IV)	69/30/1	70/30/1
Ejection fraction, mean (%)	31.6	31.6
Serum creatinine (mg/dL)	1.2	1.1
ARB (at screening) (%)	77.2	76.2
Beta-blocker (%)	72.3	71.9
Diuretics (%)	76.9	75.6
Aldosterone Antagonists (%)	37.9	38.4

Konstam MA et al, Lancet 2009; **374:** 1840–48

Patient Follow-up and Dosing

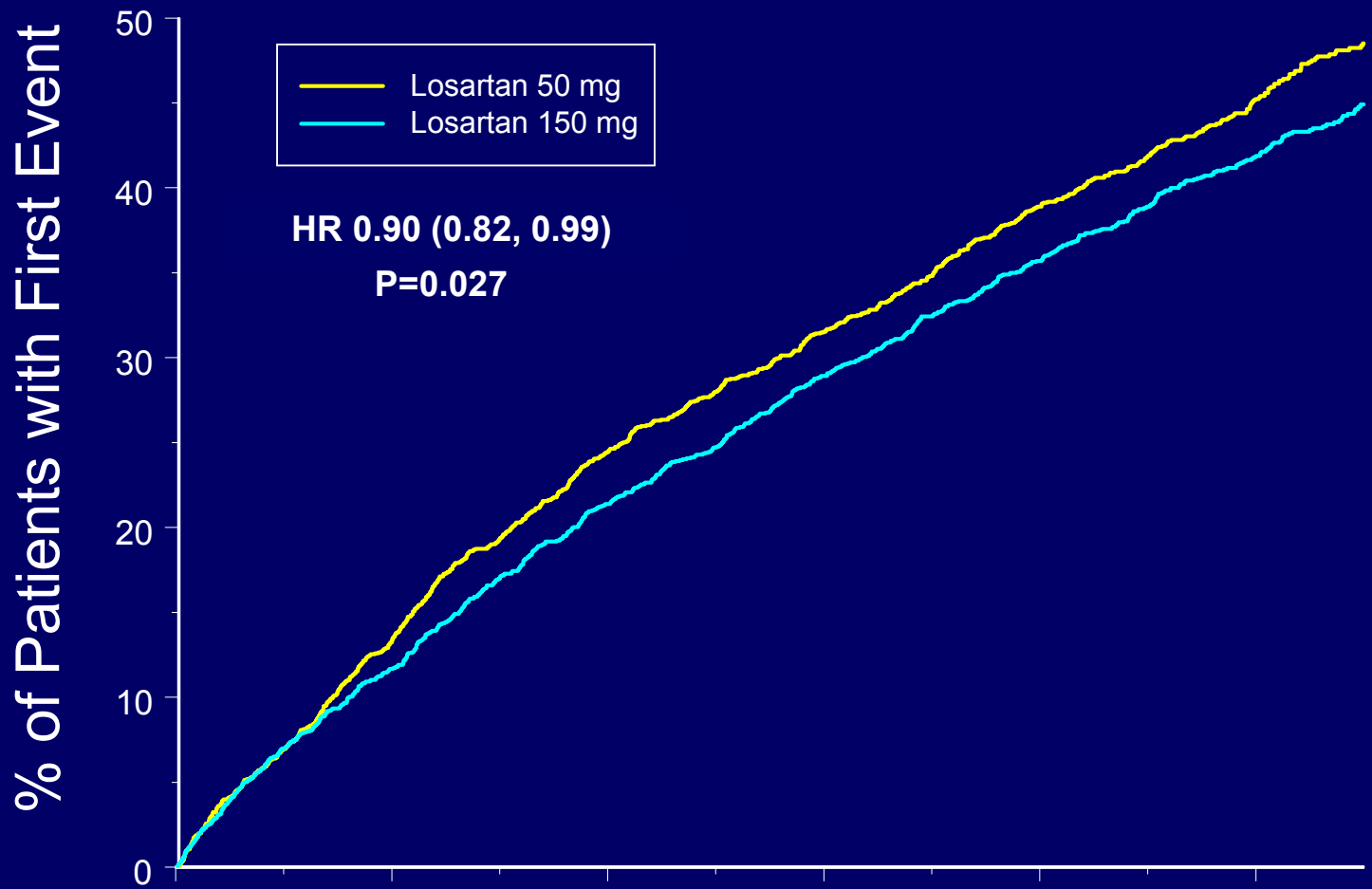
	Losartan 150 mg	Losartan 50 mg
Median follow-up time (yrs)*	4.7	4.7
Discontinuations (%)	28.3	27.3
Discontinuations for AE (%)	7.7	7.0
Mean dose (mg/day)**	128.9	45.6

*Follow up = time from randomization to study end or primary endpoint

**Including time off drug

Konstam MA et al, Lancet 2009; **374:** 1840–48

Primary Endpoint
Death or Hospitalization for HF

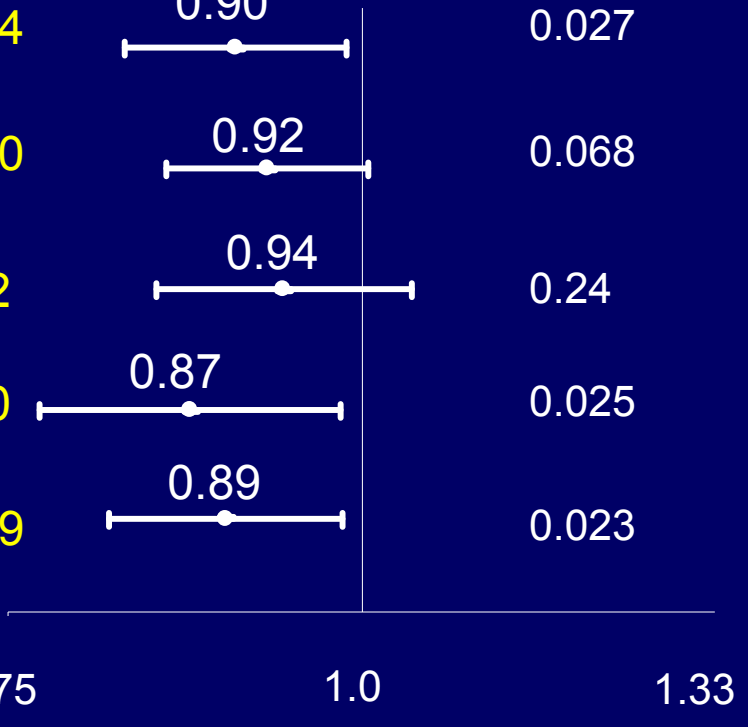


Number of patients at risk					
Losartan 50 mg	1646	1422	1277	1126	644
Losartan 150 mg	1684	1493	1344	1205	711

Konstam MA et al, Lancet 2009; **374:** 1840–48

Primary and Major Secondary Endpoints and Components

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or HF hospitalization	828	11.1	889	12.4	0.90	0.027
Death or CV hospitalization	1037	15.6	1085	17.0	0.92	0.068
Death	635	7.6	665	8.2	0.94	0.24
HF hospitalization	450	6.0	503	7.0	0.87	0.025
CV hospitalization	762	11.5	826	12.9	0.89	0.023

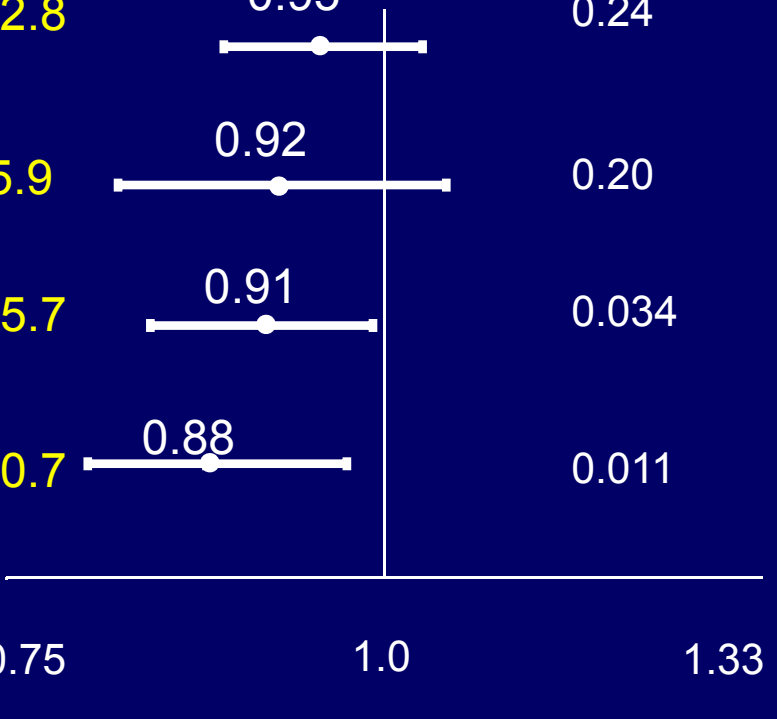


*Rate per 100 person years

Konstam MA et al, Lancet 2009; **374:** 1840–48

Other Outcomes

	Losartan 150mg		Losartan 50mg		Hazard Ratio (95%CI)	P-value
	No.	Rate*	No.	Rate*		
Death or all cause hospitalization	1237	21.6	1269	22.8	0.95	0.24
CV death	448	5.4	478	5.9	0.92	0.20
CV death or CV hospitalization	942	14.2	1003	15.7	0.91	0.034
CV death or HF hospitalization	698	9.3	771	10.7	0.88	0.011

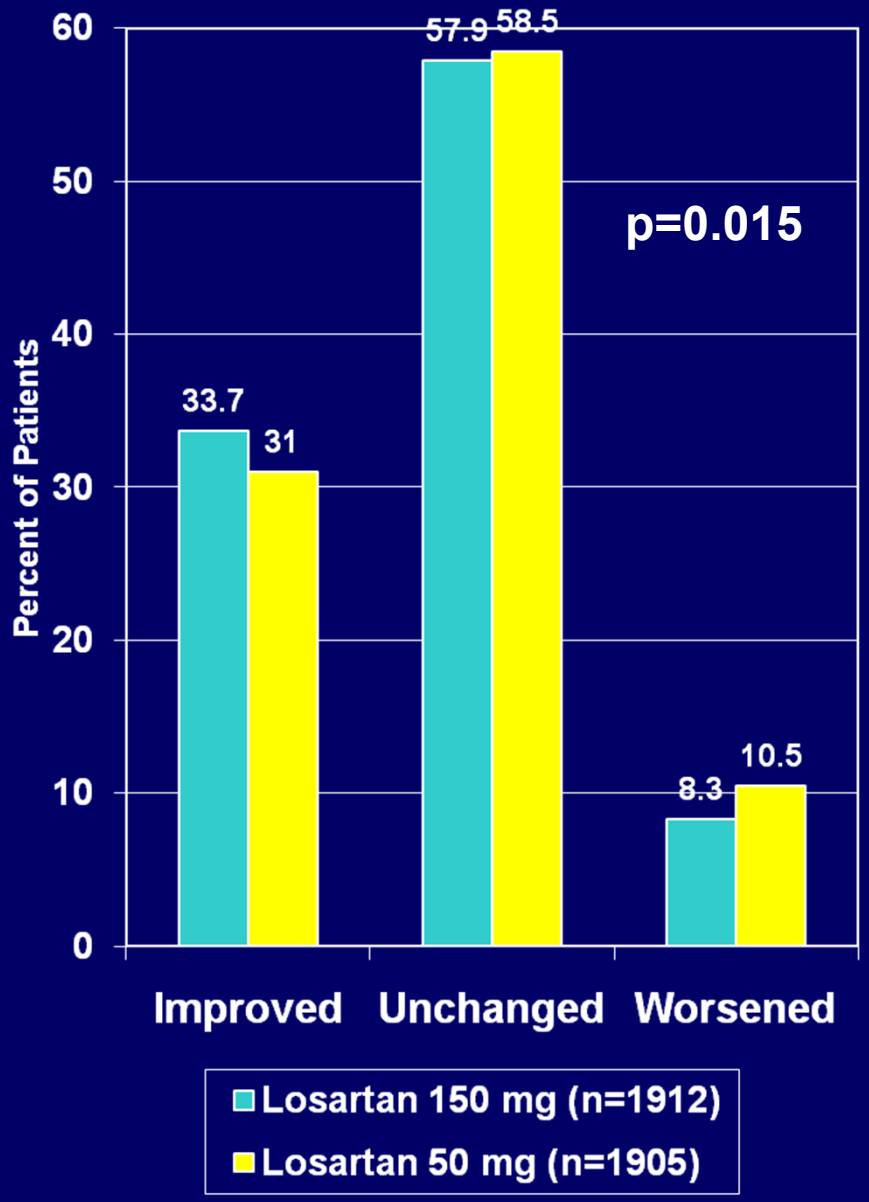


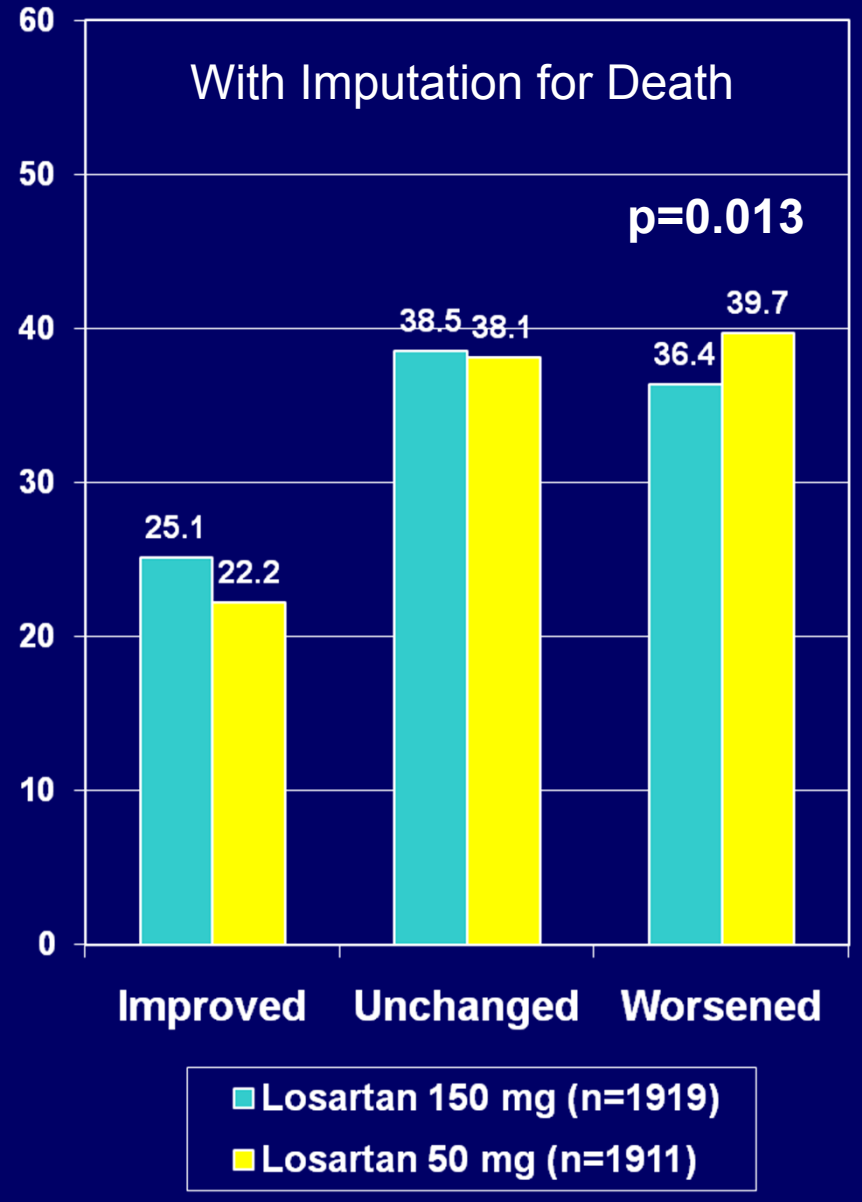
*Rate per 100 person years

Konstam MA et al, Lancet 2009; **374:** 1840–48

Change in NYHA Class*

Percent of Patients





*From baseline to last available data

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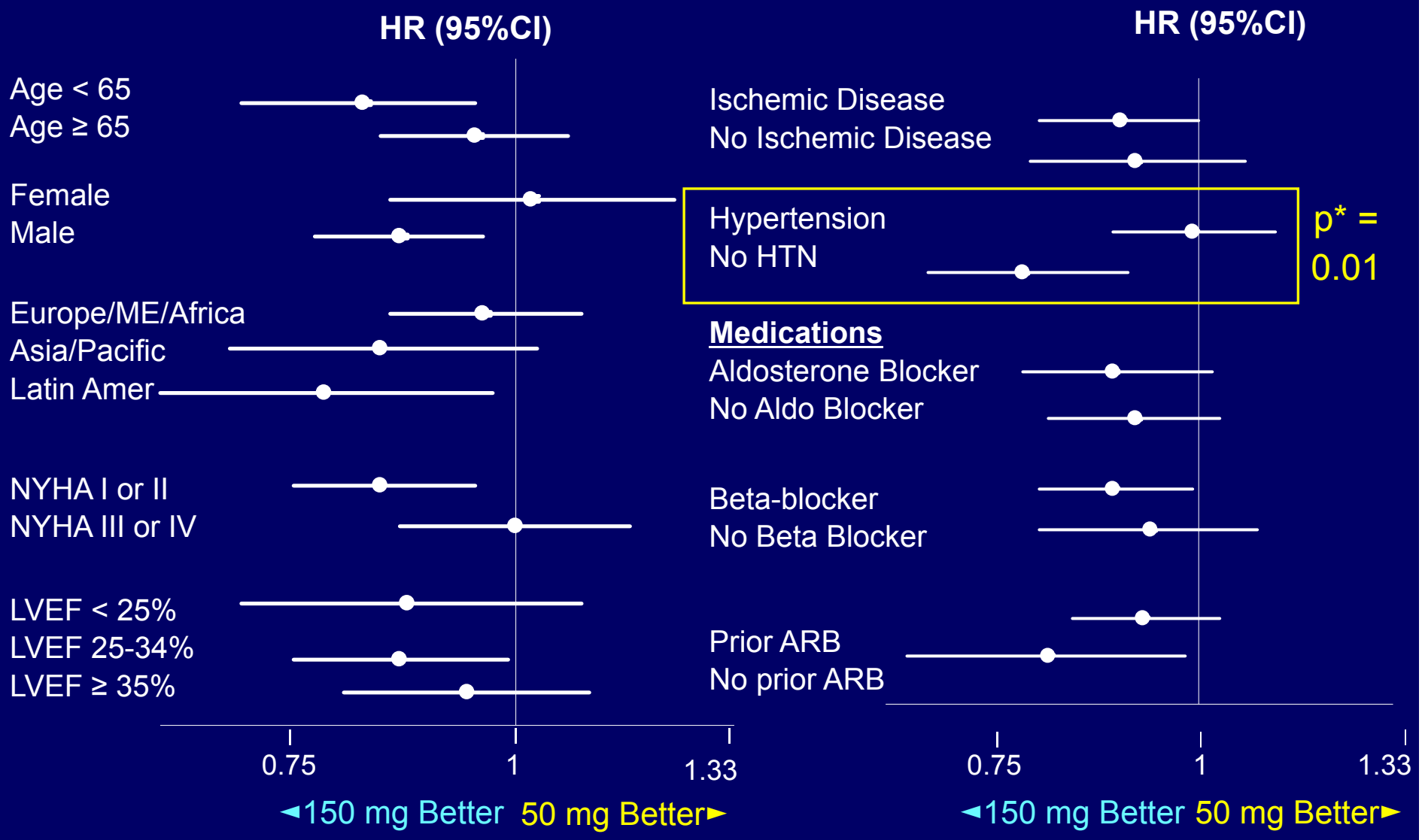
Primary Endpoint: Selected Subgroups

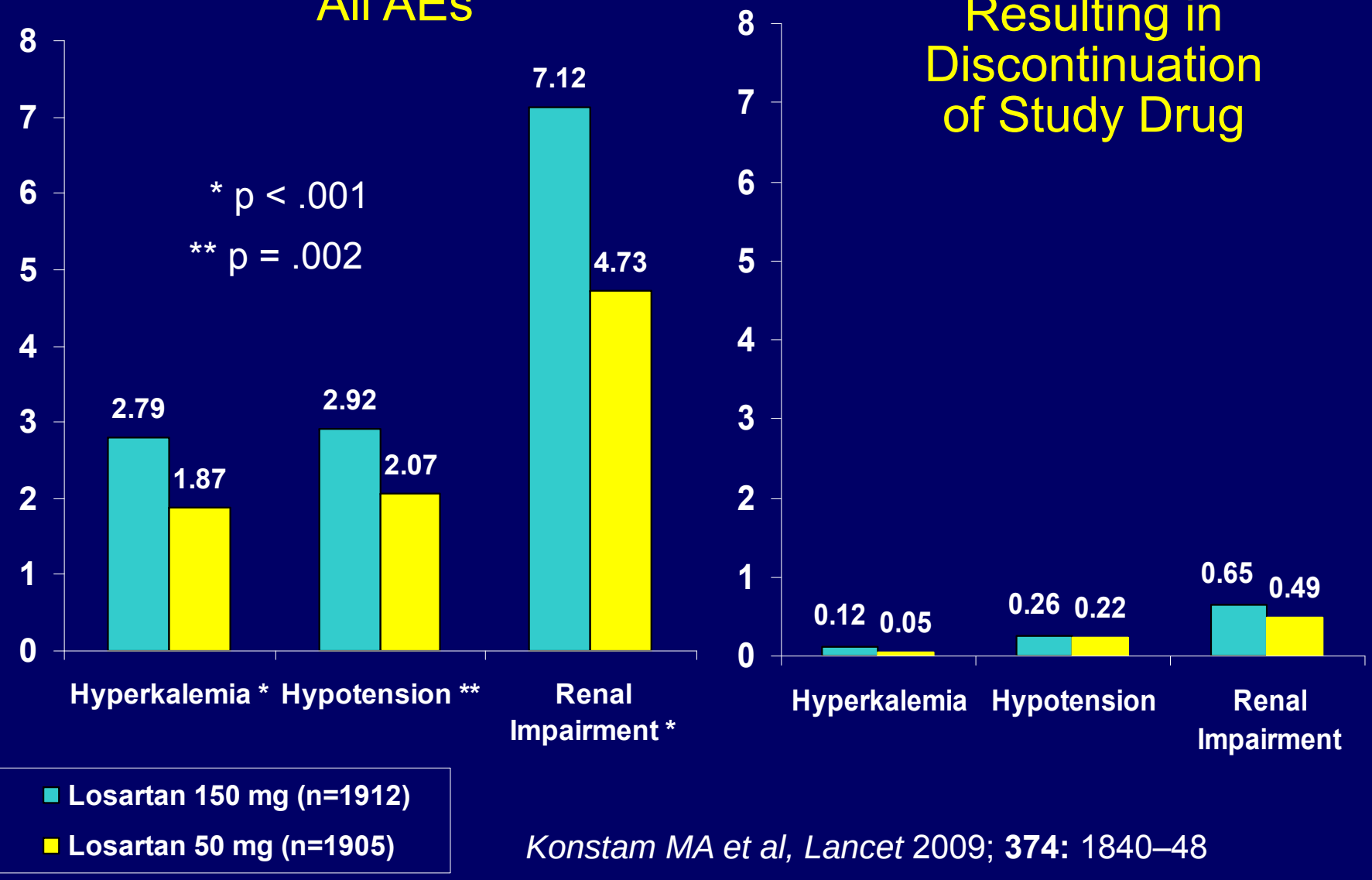


Konstam MA et al, Lancet 2009; **374:** 1840–48

* p for interaction

Selected Adverse Events

Rate / 100 person-years



Konstam MA et al, Lancet 2009; **374:** 1840–48

Summary

- HEAAL represents the first study to investigate the dose-response of an ARB on clinical outcomes in patients with HF.
- Compared with losartan 50 mg daily, losartan 150 mg daily reduced the rate of the combined endpoint of all-cause mortality or HF hospitalization
- The 150 mg dose was associated with higher rates of hypotension, hyperkalemia, and renal impairment, although the overall rates of clinically relevant adverse events were small.

Conclusions

- In patients with HF, reduced LVEF, and ACE inhibitor intolerance, incremental value is derived from up-titrating ARB doses to levels demonstrated to confer benefit on clinical outcomes.
- Our findings confirm the view that incremental inhibition of the renin-angiotensin system, within the range explored in HF trials to date, achieves a progressively favorable impact on clinical outcomes.

Evaluation of Cardiac Function by Transthoracic Echocardiography in Subjects with ST-segment Elevation Myocardial Infarction Following Primary Percutaneous Coronary Intervention According to Valsartan Dose – The Valsartan One Center Trial

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J Cardiovasc Ultrasound 2010;18(3):77-83

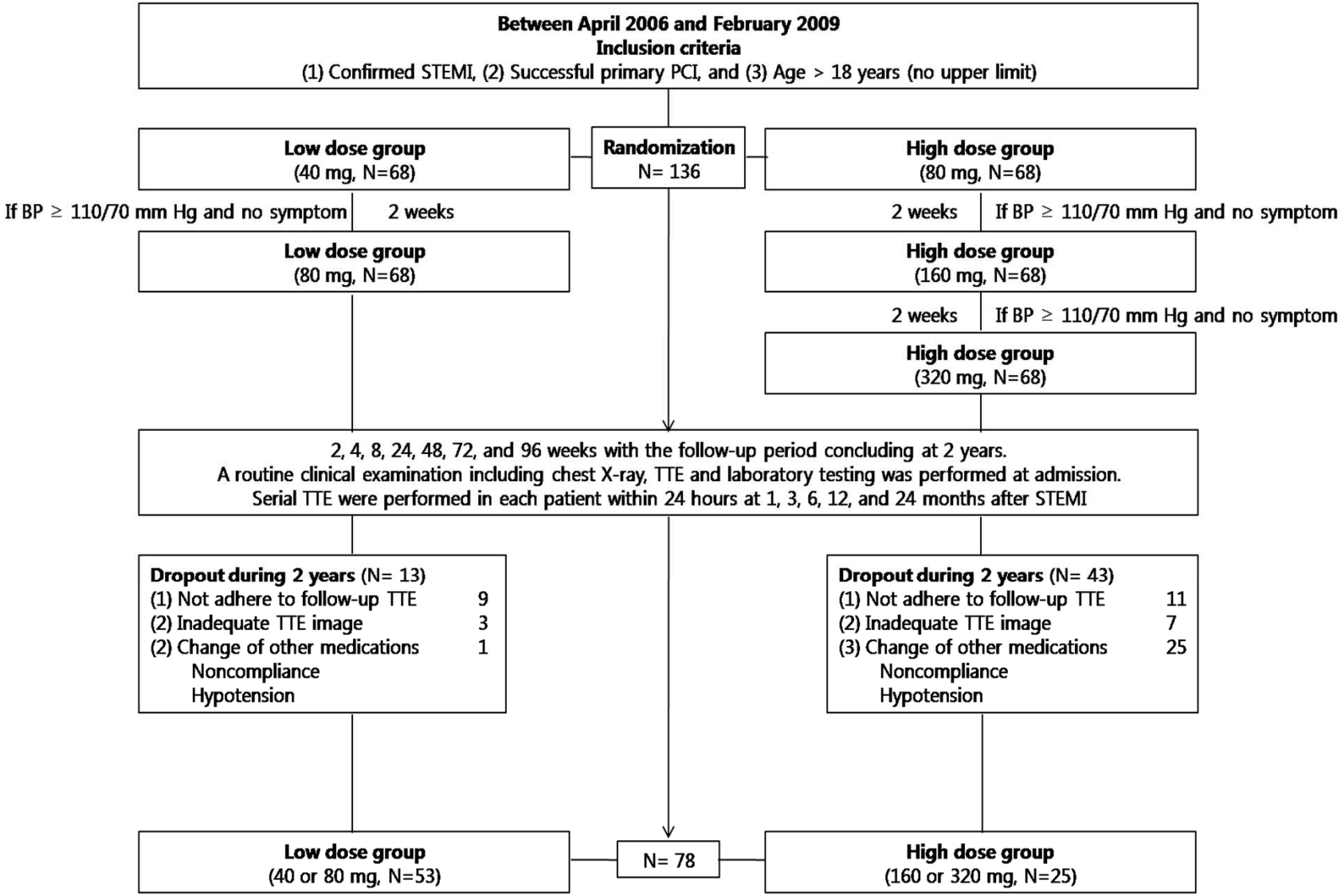
Background

- **Left ventricular (LV) remodeling and angiotensin receptor blocker (ARB) treatment after acute myocardial infarction (AMI) are important in mortality and morbidity.**
- **But little is known about long-term data of transthoracic echocardiography (TTE) in patient with ST elevation myocardial infarction (STEMI) underwenting primary percutaneous coronary intervention (PCI).**

Aim

- **The aim of this study was to evaluate the mid-term changes in cardiac function by transthoracic echocardiogram (TTE) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) according to valsartan dose.**

Subjects & Methods



STEMI; ST-segment elevation myocardial infarction, PCI; percutaneous coronary intervention, BP; blood pressure, TTE; transthoracic echocardiography.

Results

Baseline characteristics

N = 78	Low dose group (40 or 80mg, n=53)	High dose group (160 or 320mg, n=25)	*p* value
Clinical findings			
Age, years	58 ± 11	54 ± 14	0.15
Male sex, n (%)	48 (91)	23 (92)	0.84
Systolic blood pressure, mm Hg	133 ± 28	141 ± 30	0.25
Diastolic blood pressure, mm Hg	82 ± 17	84 ± 19	0.70
Hypertension, n (%)	19 (36)	10 (40)	0.72
Diabetes mellitus, n (%)	11 (21)	5 (20)	0.94
Dyslipidemia, n (%)	11 (27)	4 (17)	0.39
Cigarette smoking, n (%)	36 (68)	9 (36)	<0.01
Obesity [BMI (W/H^2) ≥ 25], n (%)	18 (34)	9 (36)	0.86
Door to balloon time, hour	1.3 ± 0.9	1.3 ± 0.8	0.96
Medical history			
Mean valsartan dose, mg	73.9 ± 14.5	176 ± 73.1	<0.01
ʙ-bocker, n (%)	52 (98.1)	23 (92)	0.82
Calcium channel blocker, n (%)	5 (9)	5 (20)	0.19
Diuretics, n (%)	8 (15)	2 (8)	0.38
Statins, n (%)	47 (89)	23 (92)	0.65

J Cardiovasc Ultrasound 2010;18(3):77-83

Angiographic findings				
Infarct-related artery	LAD, n (%)	30 (56)	10 (40)	0.23
	LCx, n (%)	3 (6)	3 (12)	0.38
	RCA, n (%)	20 (38)	12 (48)	0.46
No. of vessels	1 vessel disease, n (%)	32 (60)	11 (44)	0.23
	2 vessels disease, n (%)	15 (28)	10 (40)	0.31
	3 vessels disease, n (%)	6 (12)	4 (16)	0.72
Laboratory findings				
CK-MB, ng/ml		44.1 ± 94.1	22.9 ± 45.6	0.19
Troponin-T, ng/ml		1.2 ± 3.5	0.6 ± 1.4	0.47
BNP, pg/ml		110 ± 187	85 ± 113	0.99
BUN, mg/dl		14.3 ± 4.3	13.6 ± 3.7	0.79
Creatinine, mg/dl		1.2 ± 1.2	0.9 ± 0.2	0.31
CRP, mg/dl		2.9 ± 3.2	2.1 ± 3.1	0.08
Total cholesterol, mg/dl		176 ± 49	168 ± 36	0.74
Triglyceride, mg/dl		130 ± 72	105 ± 55	0.31
HDL, mg/dl		39 ± 10	37 ± 7	0.38
LDL, mg/dl		105 ± 52	107 ± 31	0.47
Hb_{A1c}, %		6.4 ± 1.2	6.6 ± 1.6	0.88

LAD; left anterior descending artery, LCx; left circumflex artery, RCA; right coronary artery.

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The change of TTE parameters between initial and final follow-up TTE

N = 78	Initial	Final follow-up	*p* value
Wall motion score index	1.45 ± 0.30	1.33 ± 0.32	<0.01
Fractional shortening, %	26.9 ± 10.5	28.8 ± 10.1	0.18
LVIDd, mm	47.2 ± 5.8	48.1 ± 6.3	0.04
LVIDs, mm	34.6 ± 6.6	34.6±6.8	0.91
Ejection fraction, %	52.7 ± 8.1	55.2±8.4	<0.01
LVEDV, mL	103.8 ± 39.1	103.2 ± 38.9	0.85
LVESV, mL	49.8 ± 27.0	47.5 ± 24.9	0.32
Left atrium volume, mL	51.9 ± 18.0	48.4 ± 18.5	0.09
E velocity, m/s	67.5 ± 20.0	62.9 ± 17.5	0.09
A velocity, m/s	72.8 ± 25.3	71.2 ± 18.4	0.57
Deceleration time, ms	189 ± 56	222 ± 71	<0.01
e' velocity (septal), m/s	5.8 ± 2.0	6.0 ± 1.9	0.32
e' velocity (lateral), m/s	7.9 ±3.1	8.2 ± 2.6	0.59
E/e' (average)	12.2 ± 5.2	10.1 ± 4.9	<0.01

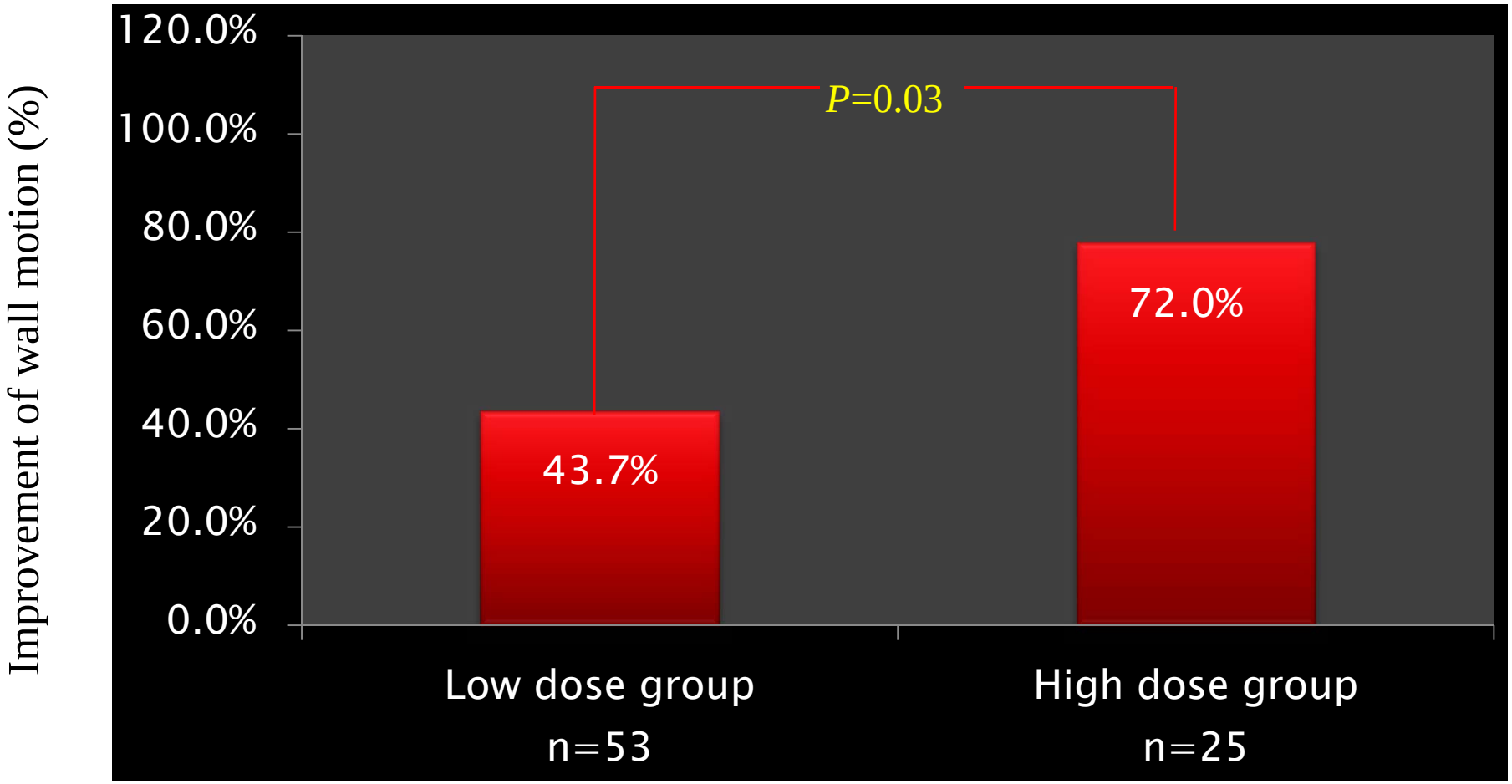
IVSd; interventricular septum [illegible]nsion, PWd; posterior wall dimension, LVEDd; left ventricular end diastolic dimension
LVESd; left ventricular end systolic dim[illegible] LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end systolic volume.

The change of TTE parameters according to valsartan dose

N = 78	Low dose group (40 or 80mg, n=53)	High dose group (160 or 320mg, n=25)	p value
Δ Wall motion score index	- 0.12 ± 0.22	- 0.17 ± 0.20	0.25
Δ Fractional shortening, %	2.3 ± 12.4	2.1 ±14.5	0.96
Δ LVEDd, mm	2.2 ± 6.5	2.2 ± 5.2	0.19
Δ LVEDs, mm	0.5 ± 6.3	- 0.8 ± 6.8	0.45
Δ Ejection fraction, %	2.1± 8.4	3.9 ± 8.4	0.38
Δ LVEDV, mL	3.8 ± 30.0	- 9.6 ± 31.2	0.08
Δ LVESV, mL	- 1.0 ± 20.7	- 5.7 ± 17.6	0.34
Δ Left atrium volume, mL	- 2.8 ± 18.0	- 5.1 ±16.5	0.60
Δ E velocity, m/s	- 4.1 ± 24.7	- 6.6 ± 23.0	0.68
Δ A velocity, m/s	- 1.2 ± 25.5	1.2 ± 21.6	0.69
Δ Deceleration time, ms	33 ± 84	44 ± 79	0.60
Δ e' velocity(septal), m/s	0.4 ± 2.0	- 0.2 ± 2.0	0.21
Δ e' velocity(lateral), m/s	0.1 ± 2.0	0.5 ± 3.3	0.74
Δ E/e' (average)	- 1.4 ± 5.3	- 1.8 ± 4.2	0.75

LVEDd; left ventricular end diastolic dimension, LVESd; left ventricular end systolic dimension, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end systolic volume.

Comparison of the percent of patients according to improvement of wall motion in the injured myocardium between low- and high-dose valsartan groups



Improvement in injured myocardium was defined as increase in wall motion score of ≥ 1 grade in more than two injured myocardial segments at follow-up TTE

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Summary

- **The mean follow-up TTE duration was 24± 8 months. Deceleration time (DT) (188.6±56.3msec vs. 221.5±71.3msec, *p*=0.01), E/e' (12.24±5.2 vs. 10.1±4.9, *p*=0.002), ejection fraction (EF) (52.7±8% vs. 55.2±8.4%, *p*<0.01), and wall motion score index (WMSI) (1.45±0.30 vs. 1.33±0.32, *p*<0.01) showed significant changes during the follow-up period.**
- **Wall motion improvement in injured myocardial segments was significantly more frequently observed in the high-dose valsartan group compared to the low-dose group (18/25, 72% vs. 24/53, 43.7%, *p*=0.03).**
- **There was no significant difference in the changes in cardiac dimensions and function between the low and high dose valsartan group.**

Conclusion

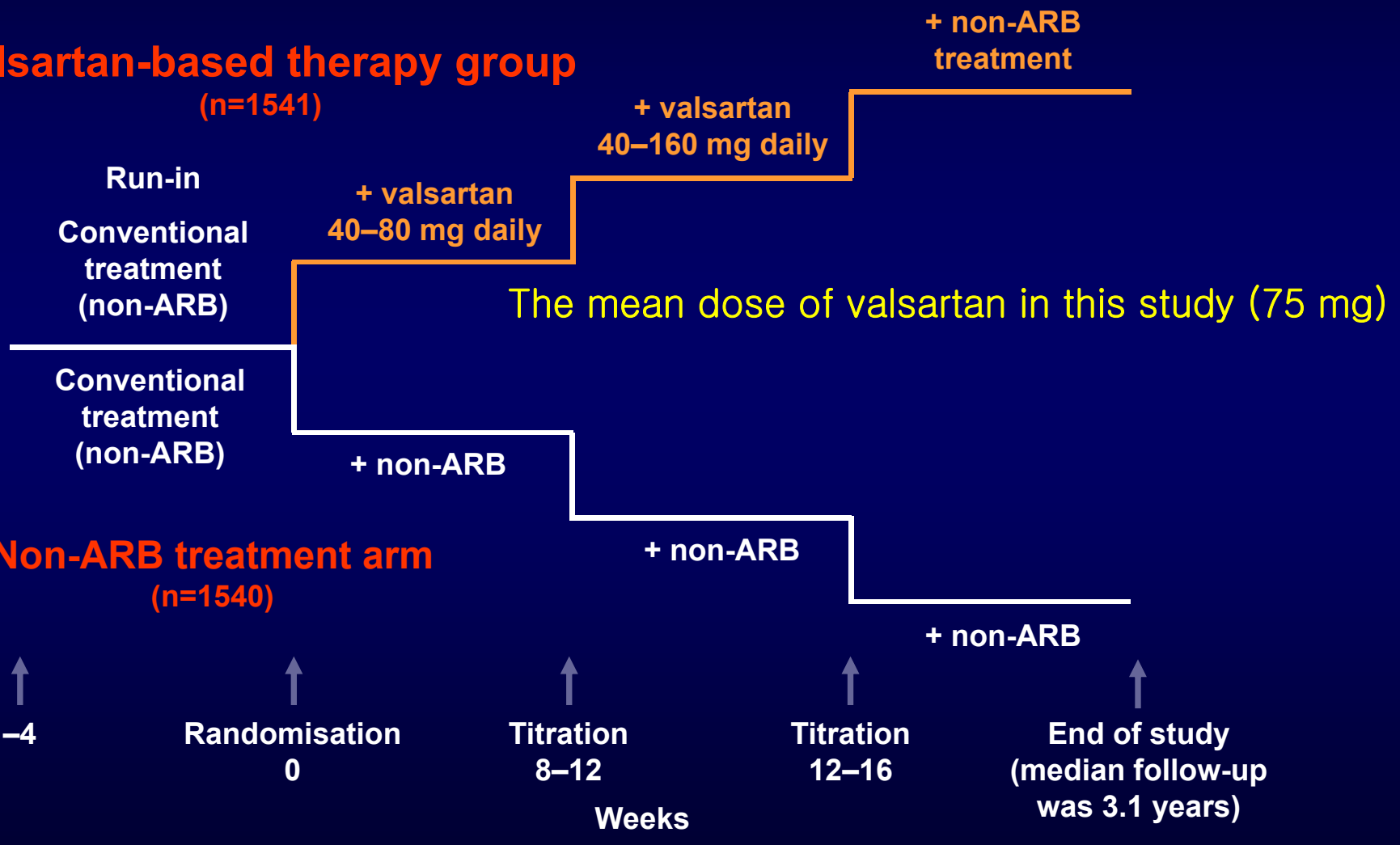
- **In patients with STEMI who undergoing primary PCI, high-dose valsartan treatment may be more helpful than low-dose in improving wall motion in the injured myocardium.**

Effects in Oriental Population

JIKEI

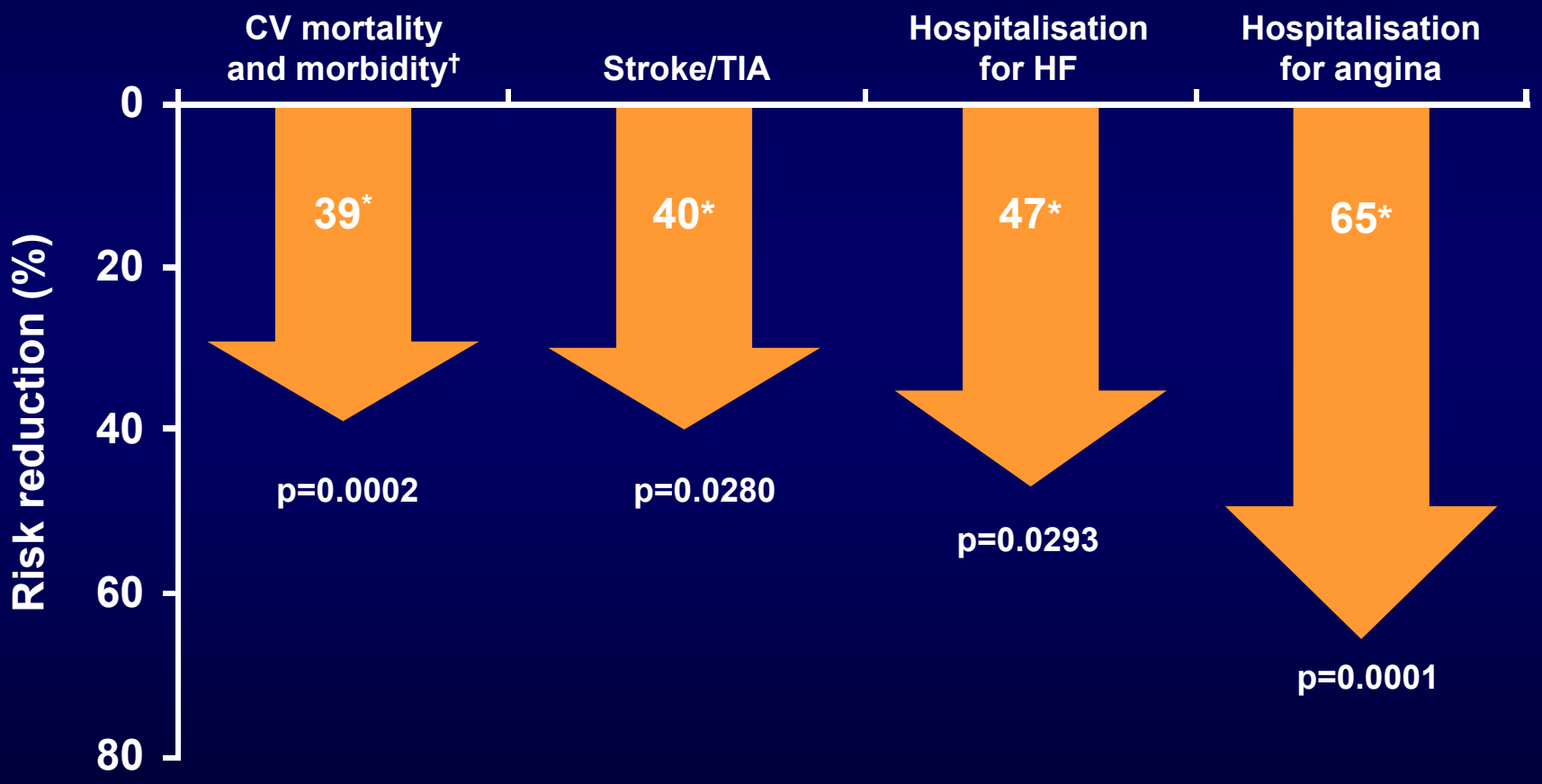
SMART

JIKEI HEART : Valsartan-based Therapy Improved Outcomes in Japanese Patients with HT and/or Coronary Heart Disease and/or HF



Mochizuki et al. Lancet 2007;369:1431–9

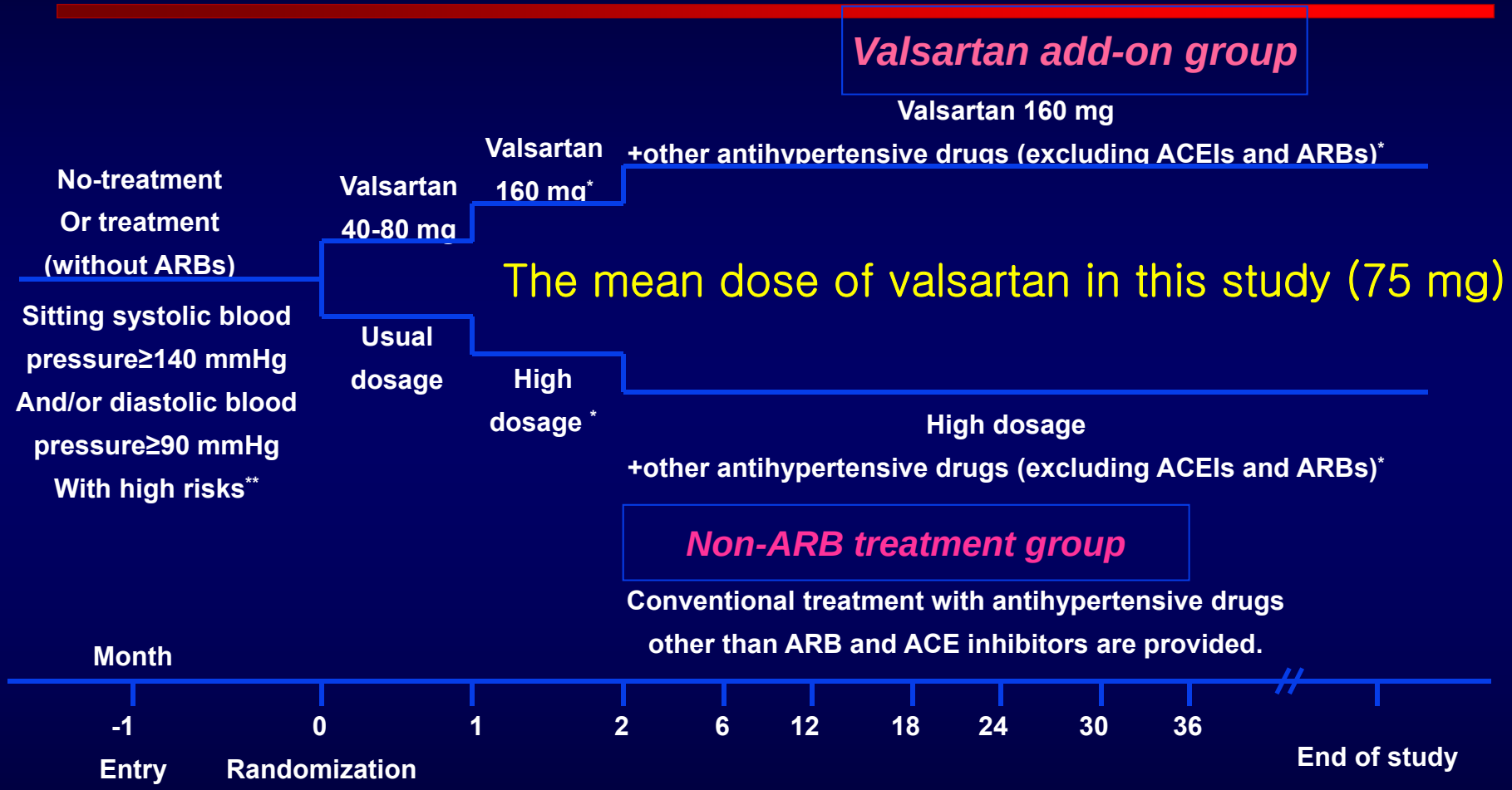
JIKEI HEART Study



TIA = transient ischemic attack
*With DIOVAN-based therapy compared with non-ARB therapy; †primary endpoint

Lancet 2007;369:1431–9

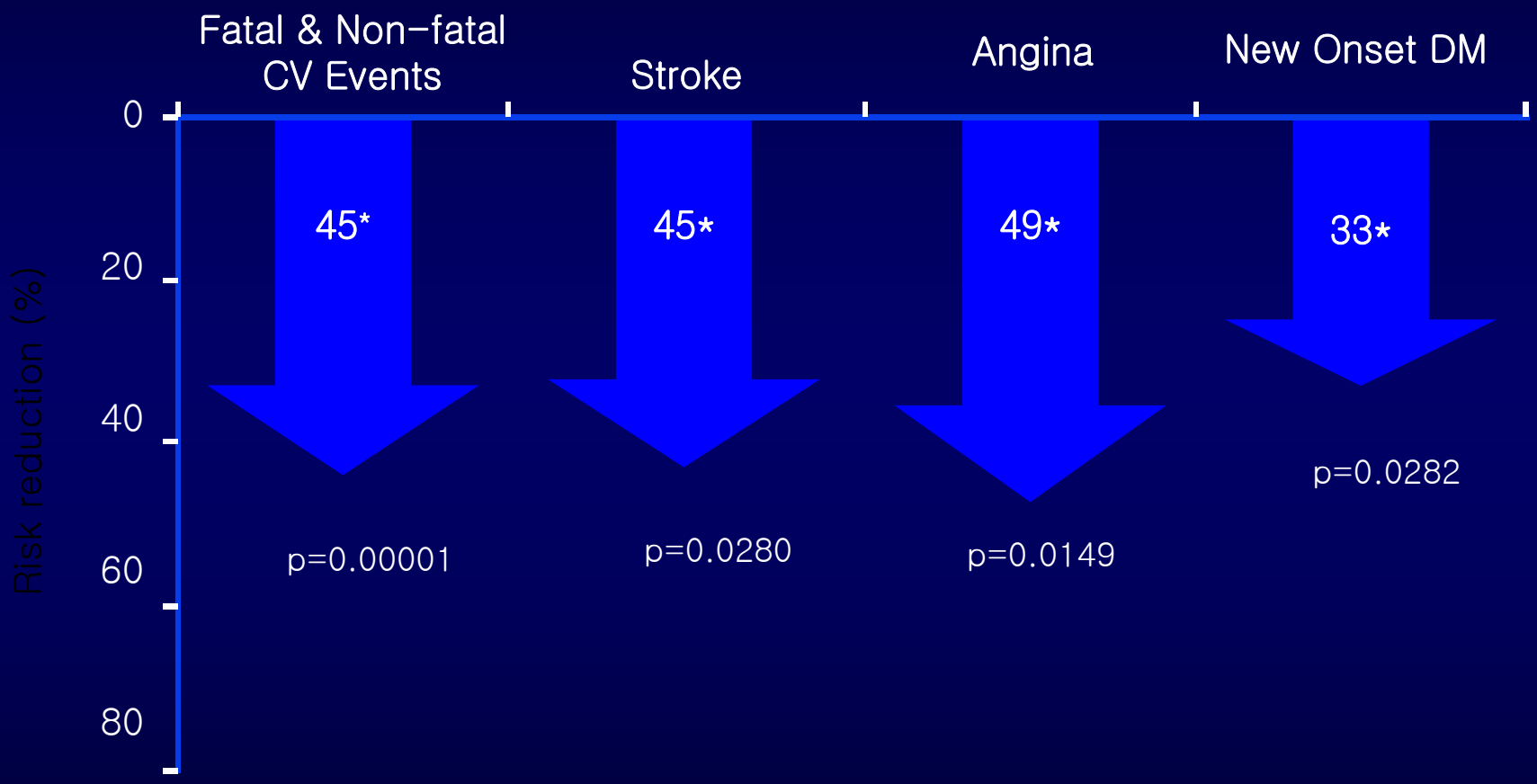
KYOTO Heart Study : uncontrolled hypertensive patients with high risk of cardiovascular events



*Titration upward if blood pressure does not reach the common goal of blood pressure control.

**High risks are defined as having at least one of a history of cardiovascular events, diabetes, smoking habit, dyslipidemia, obesity, and left ventricular hypertrophy.

KYOTO Heart Study



*With valsartan-based therapy compared with non-ARB therapy †Primary endpoint

European Heart Journal Advance Access published Aug. 2009

ARB Dose in Oriental study

JIKEI HEART Study

The mean dose of valsartan in this study (75 mg)

Kyoto study;

The mean dose of valsartan in this study (88 mg)

might seem low, but studies in Japanese people have shown that 80 mg of valsartan produced similar antihypertensive effects to those of nifedipine (20 mg) and amlodipine(5 mg).

The mean BMI in japanese study was low (24, compared with the VALUE trial, for which mean BMI was 28.

Valsartan AMI TTE Study; Korean

low mean dose- 74 mg

High mean dose- 176 mg

VARIANT ; Western

Discontinuation of valsartan; 34%

Valsartan AMI TTE Study:

Discontinuation of valsartan; 68 %

The ARB dose may vary according to race and personal preferences.

SUMMARY

- Post-MI: ARB is as effective as a proven dose of ACE-I in reducing the risk of: Death,CV death or nonfatal MI or heart failure admission

  from VARIANT,OPTIMAAL

- High dose ARB : incremental inhibition of the renin-angiotensin system, within the range explored in HF trials to date, achieves a progressively favorable impact on clinical outcomes from HEAAL.

- High dose valsartan is more effective than low-dose valsartan in improving segmental wall motion in acute myocardial infarction treated by primary PCI

- High dose was associated with higher rates of hypotension, hyperkalemia, and renal impairment, although the overall rates of clinically relevant adverse events were small.

Thank You for Careful Listening