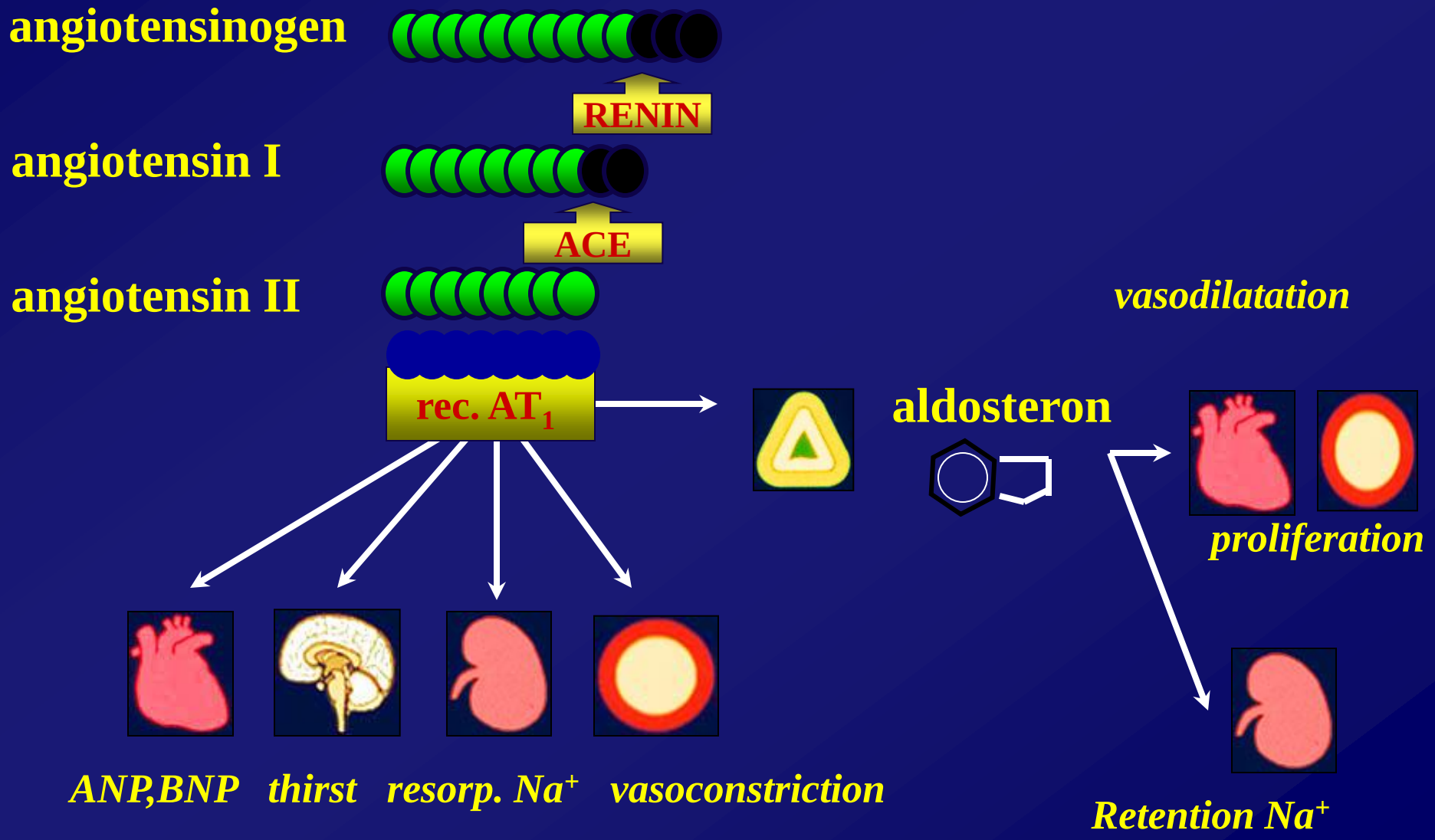
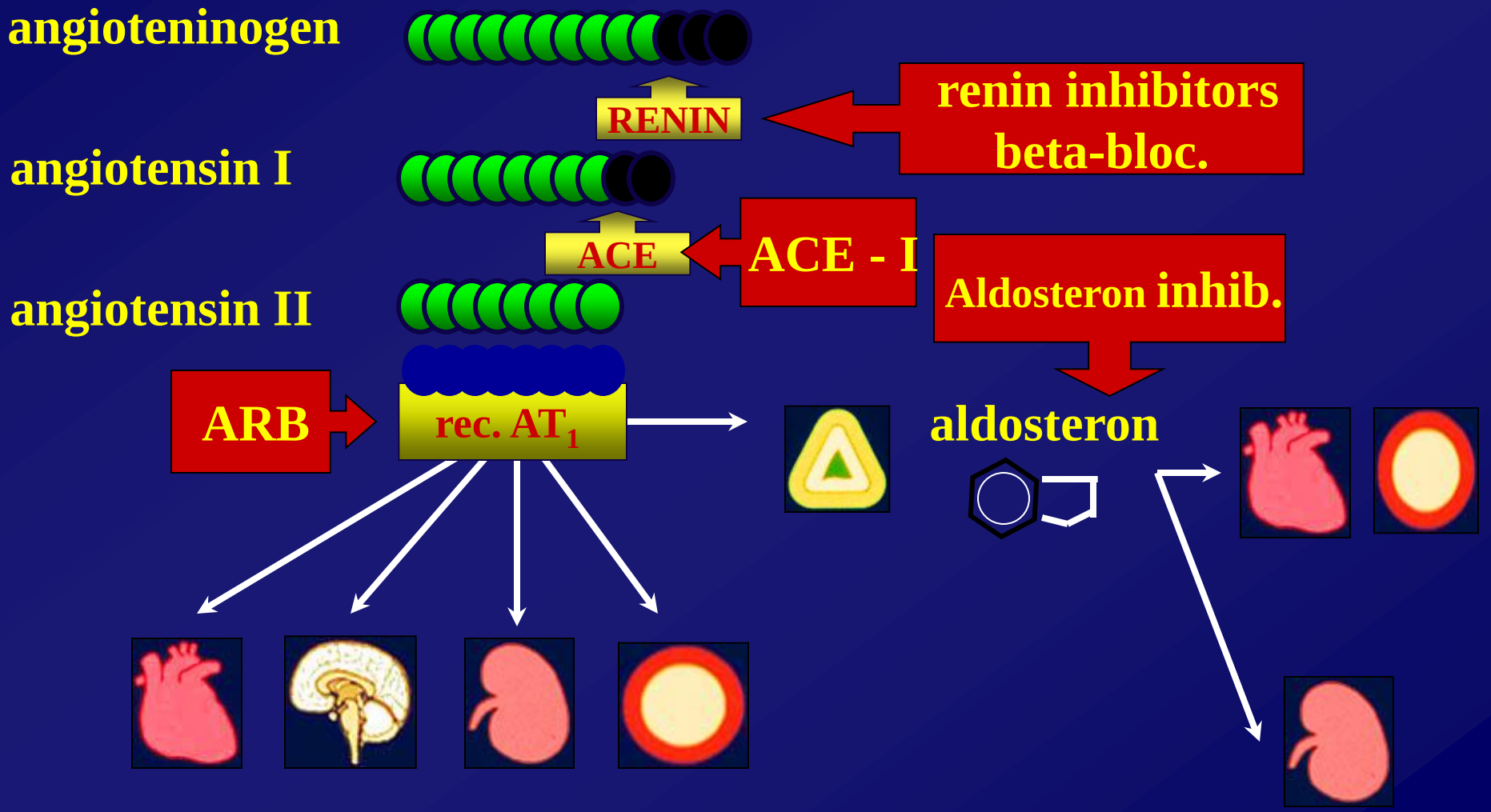
Update on Valsartan

Špinar J.

System renin-angiotensin-aldosteron



System renin-angiotensin-aldosteron



Indications for AT_1 receptor blocade - EBM

HYPERTENSION

LIFE

CORD

VALUE

MYOCARDIAL INFARCTION

OPTIMAAL

VALIANT

Brno remodeling trial

Brno first dose hypotension trial

HEART FAILURE

Exercise trials

ELITE

ELITE II

Val HeFT

RENAL FALIURE

RENAAL

MARVAL

Indications for AT_1 receptor blocade - EBM

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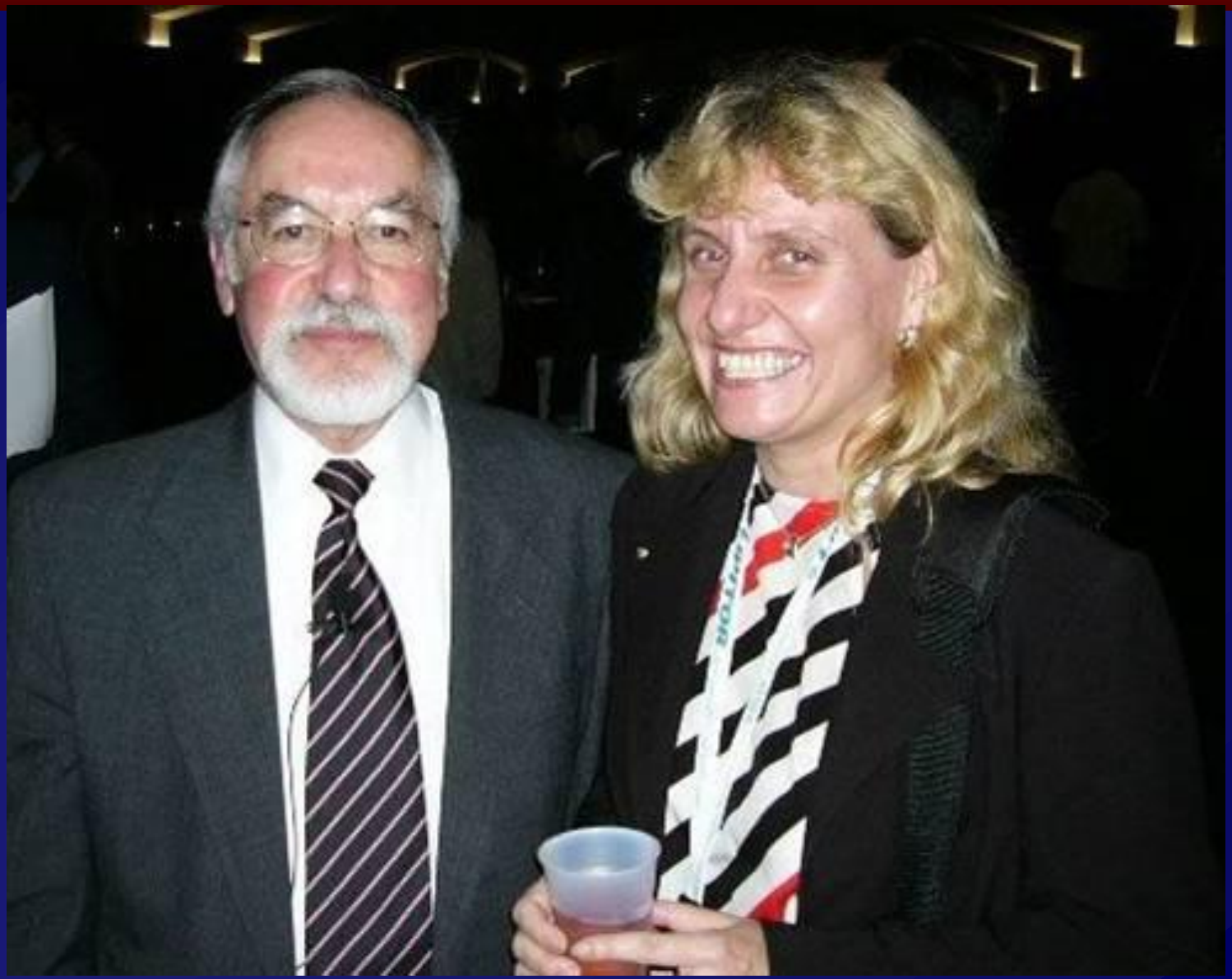
Val-HeFT



Val-HeFT

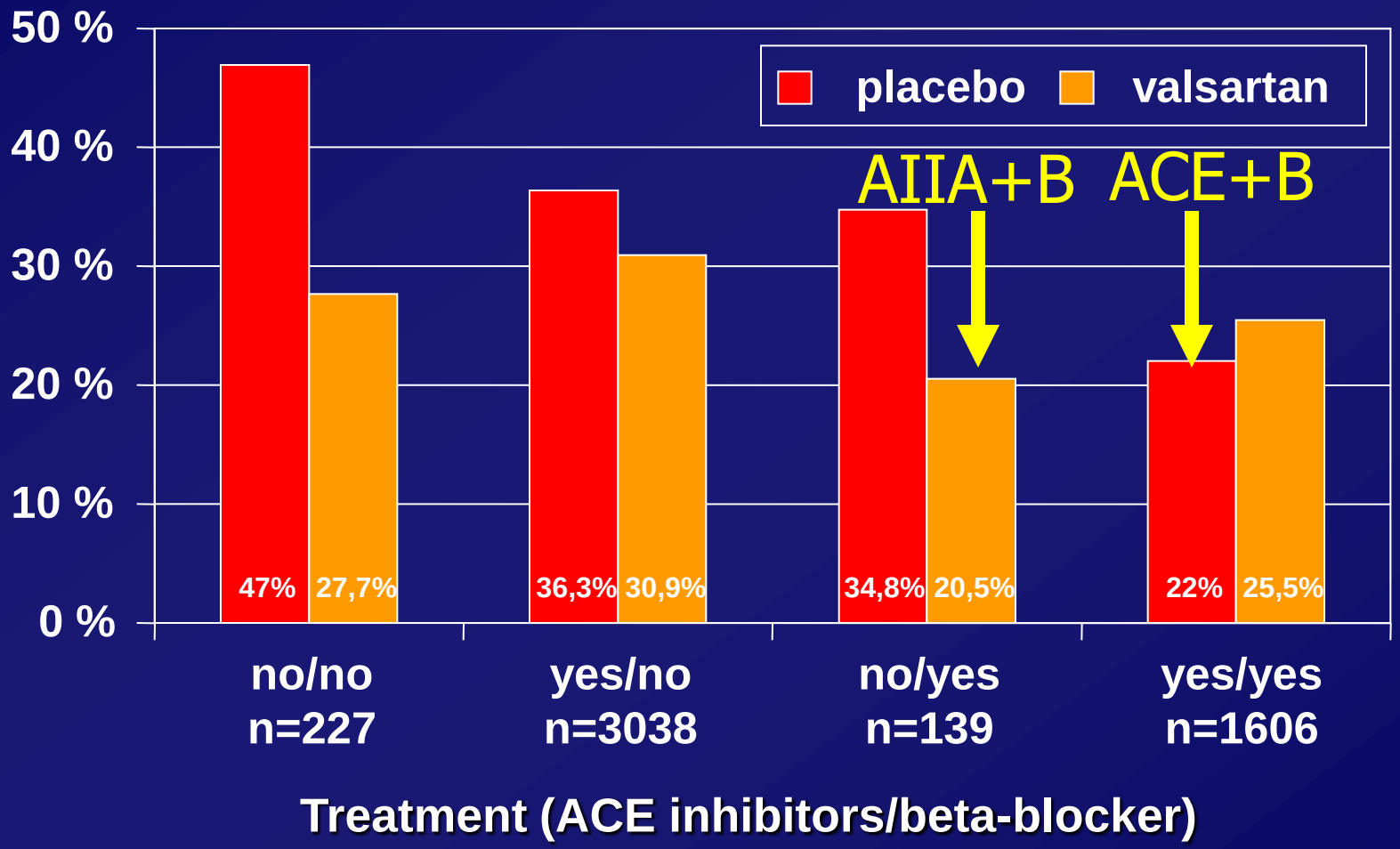
valsartan+ACE-I vs placebo+ACE-I

5010 patients

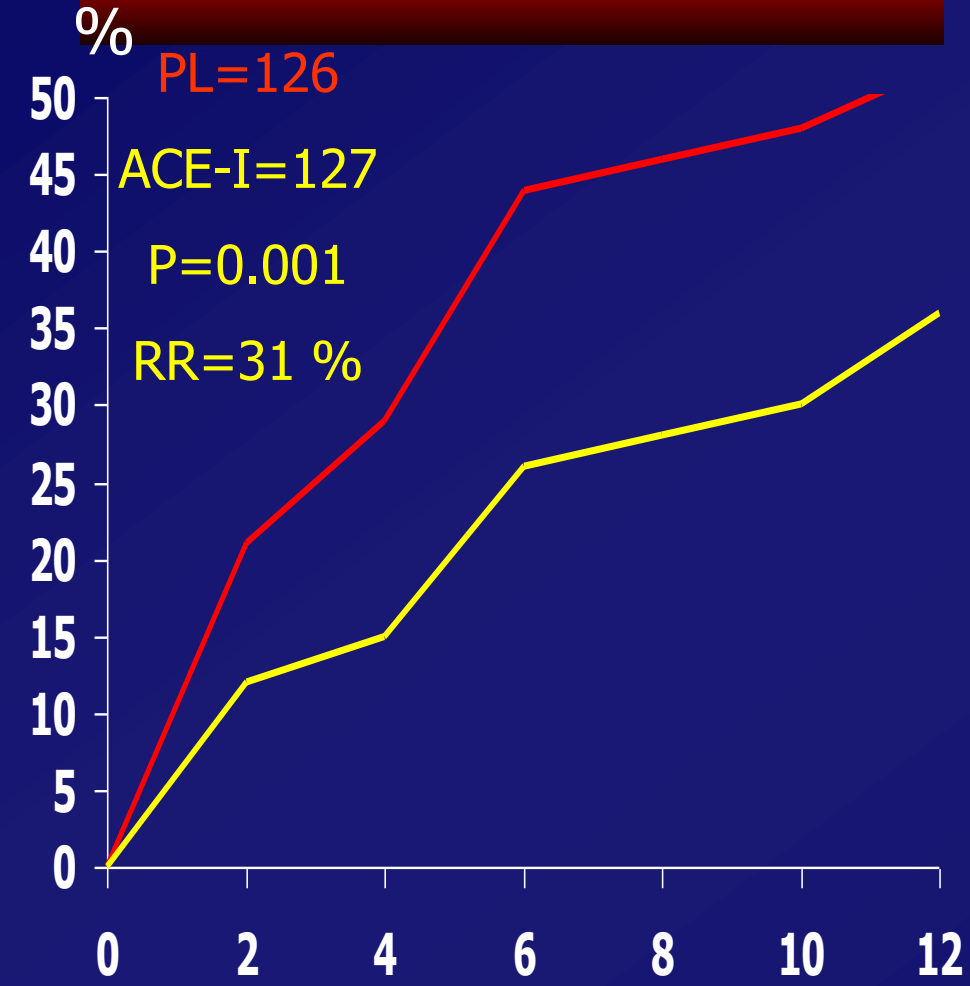
EF < 40% , ICHS 57 %

NYHA II	**62%**
NYHA III	**36%**
NYHA IV	**2%**

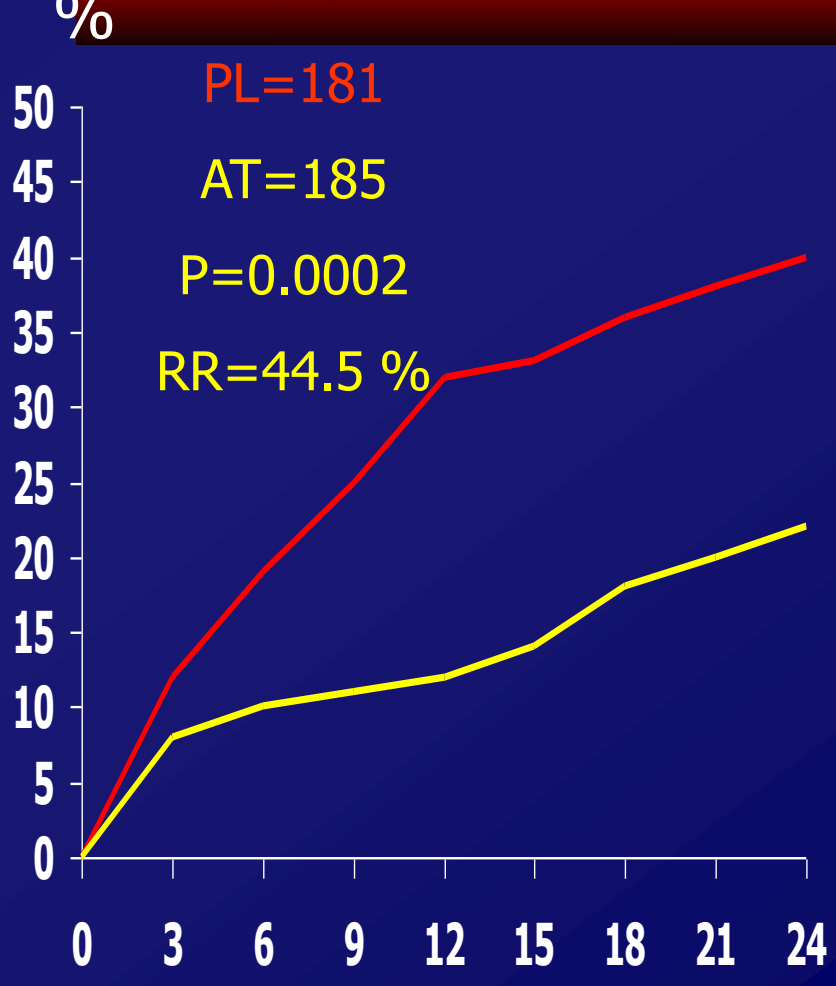
Mortality and morbidity (ACE inhibitor/beta-blocker subgroups)



CONSENSUS I MORTALITY



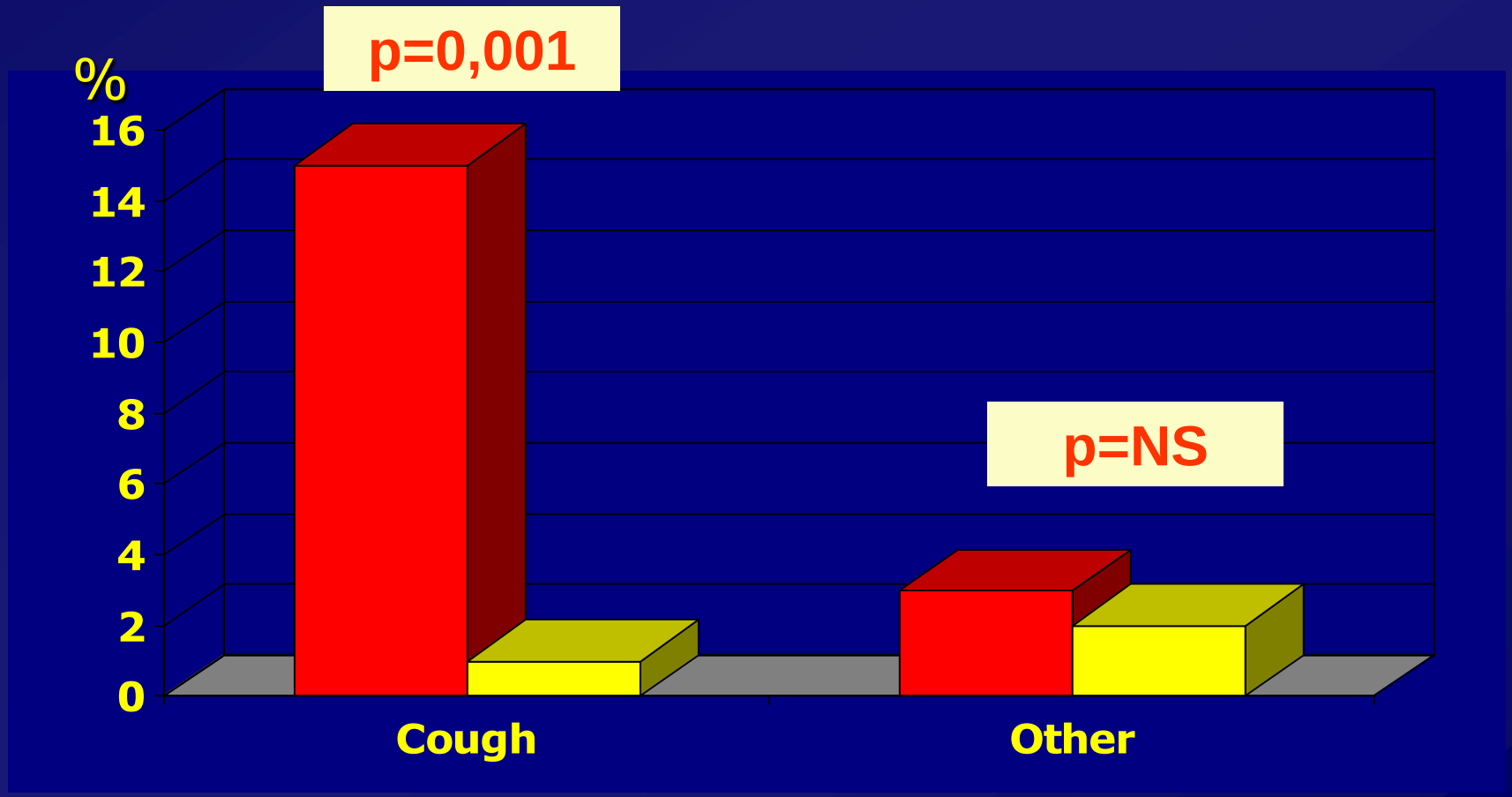
Val HeFT (ACE-I NAIVE) MORTALITY



MONTHS

Adverse events

Mortality studies in Heart Failure with ACE-I + ELITE II + Val HeFT (without placebo)



Indications for AT_1 receptor blocade - EBM

MYOCARDIAL INFARCTION

OPTIMAAL

VALIANT

Brno remodeling trial

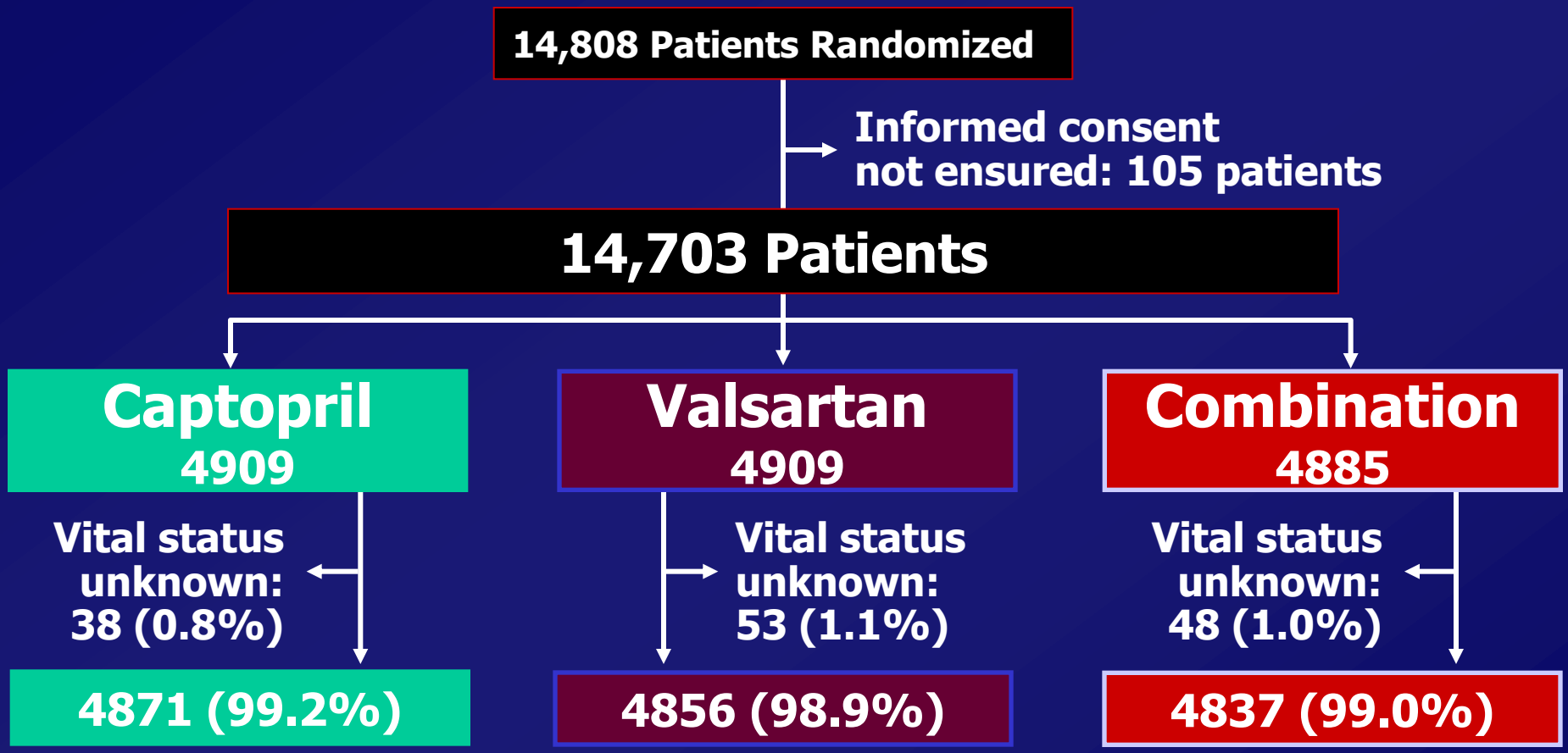
Brno first dose hypotension trial

Enrollment

24 Countries. 931 Sites. 14,703 Patients.


VALIANT
Top 10

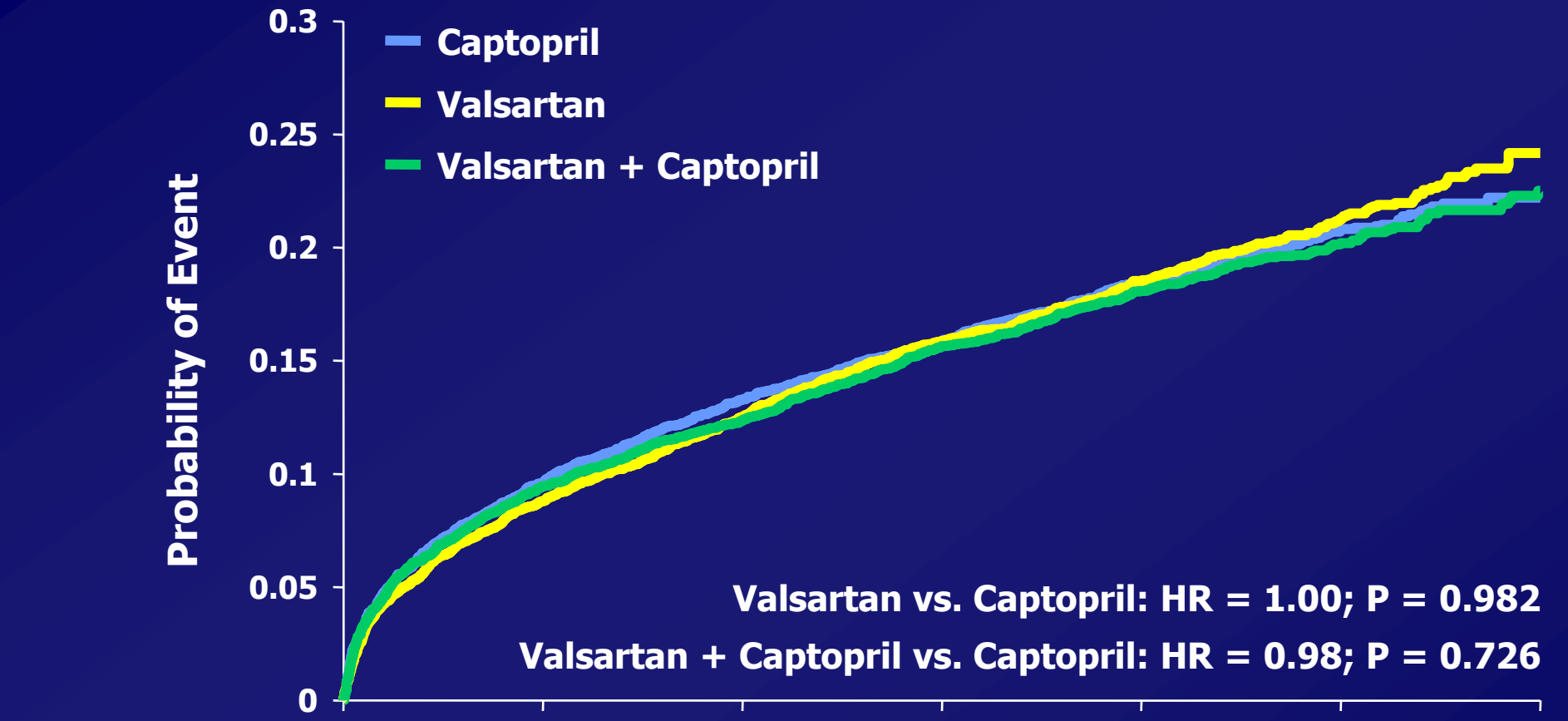
Enrollment and Follow-up



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%)

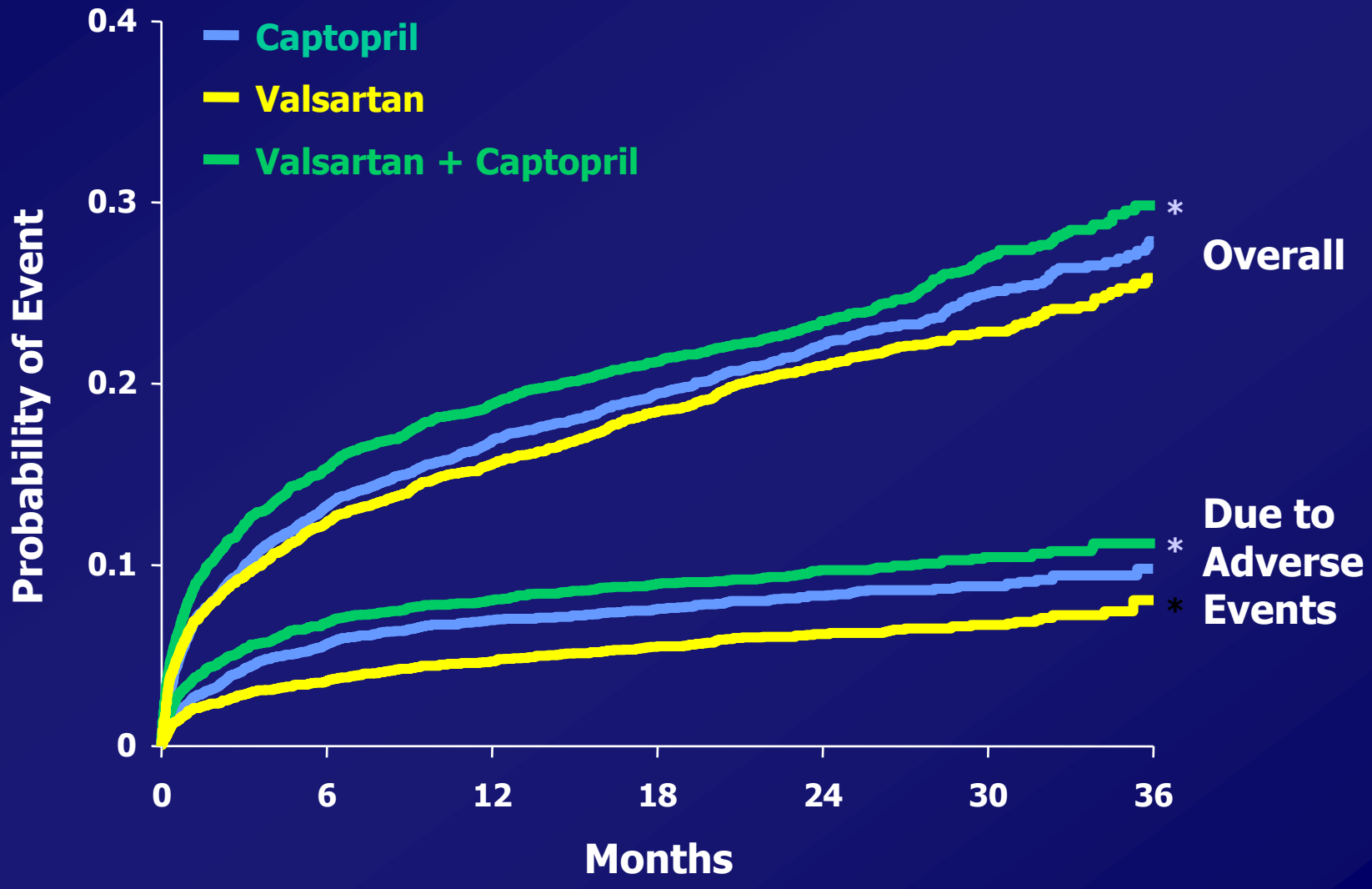
VALIANT - MORTALITY



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

Study Drug discontinuation



*P < 0.05 vs Captopril

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.

Indications for AT_1 receptor blocade - EBM

HYPERTENSION

LIFE

CORD

VALUE

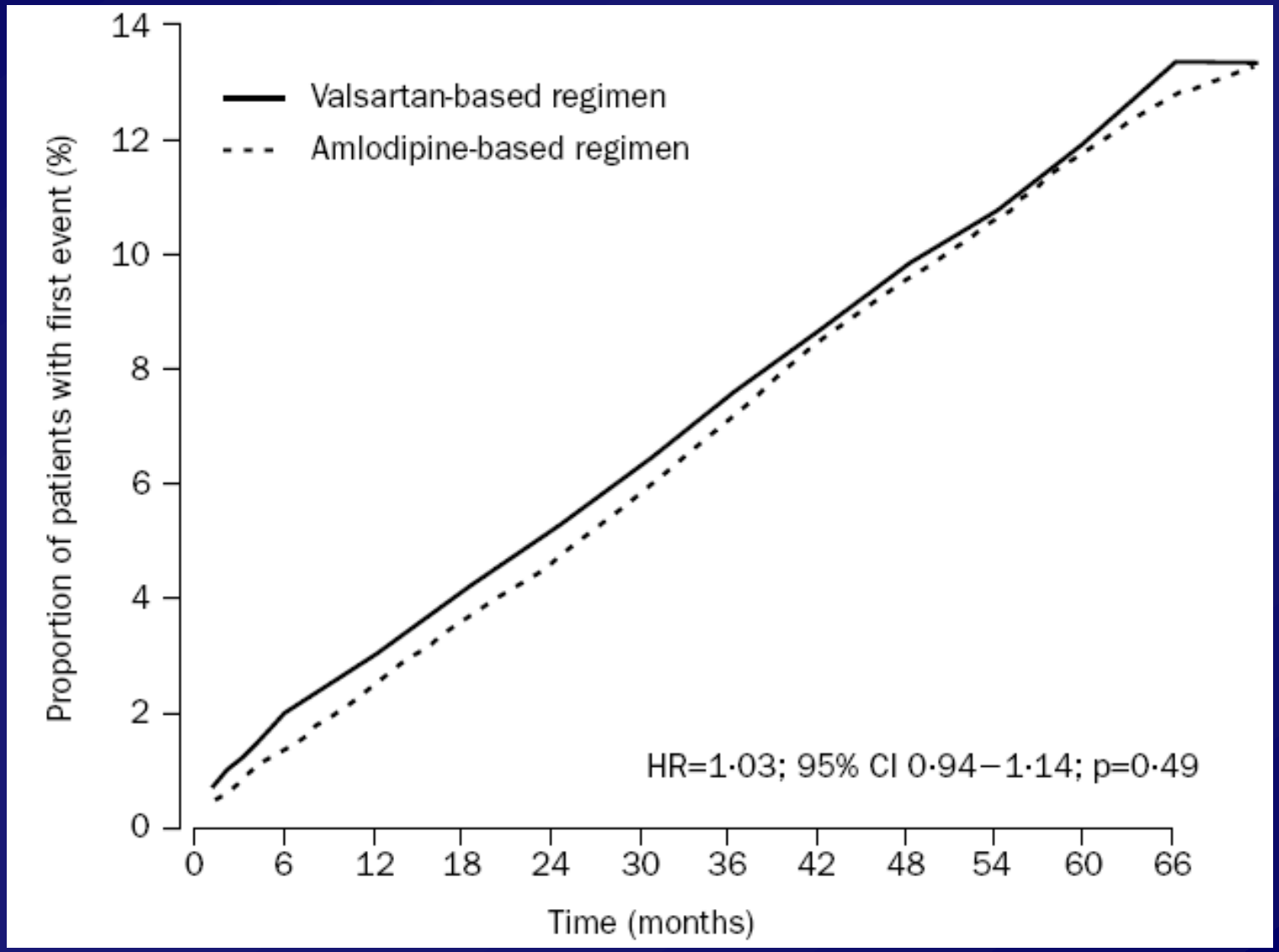
VALUE TRIAL -methods

- Would valsartan reduce cardiac morbidity and mortality more than amlodipine in hypertensive patiens at high cardiovascular risk?
- Multicenter, multinational, double-blind randomized study
- 15 245 patients ≥50years
- treated or untreated hypertension at high risk for CV events
- **Primary endpoint** – First event : a composite of cardiac morbidity and mortality
- Valsartan 80mg or amlodipine 5mg initially - titrated up to BP<140/90 was achieved

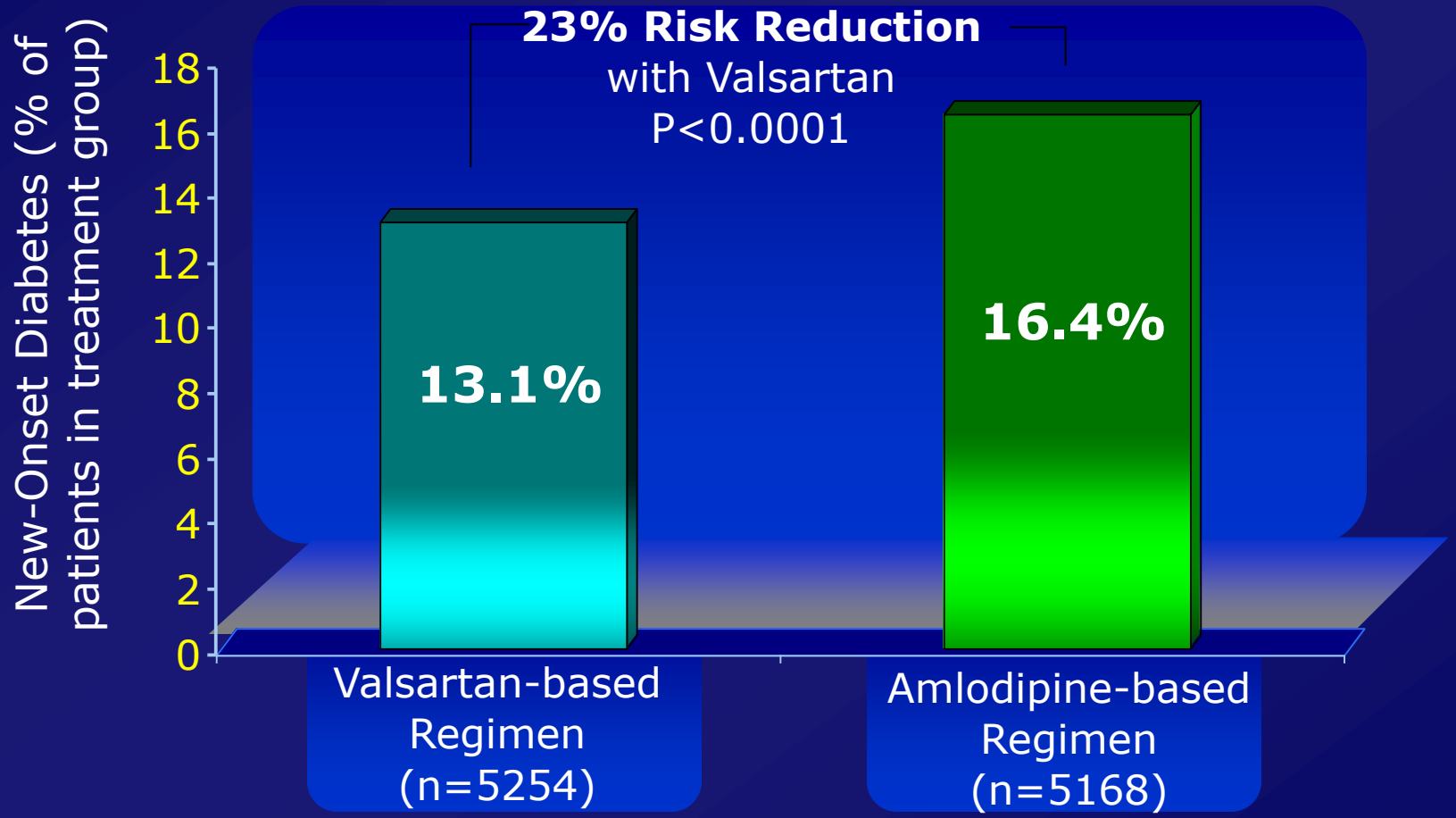
Julius et al. *Lancet* 2004;363:2022-2031

VALUE: primary endpoint

CV morbidity a mortality



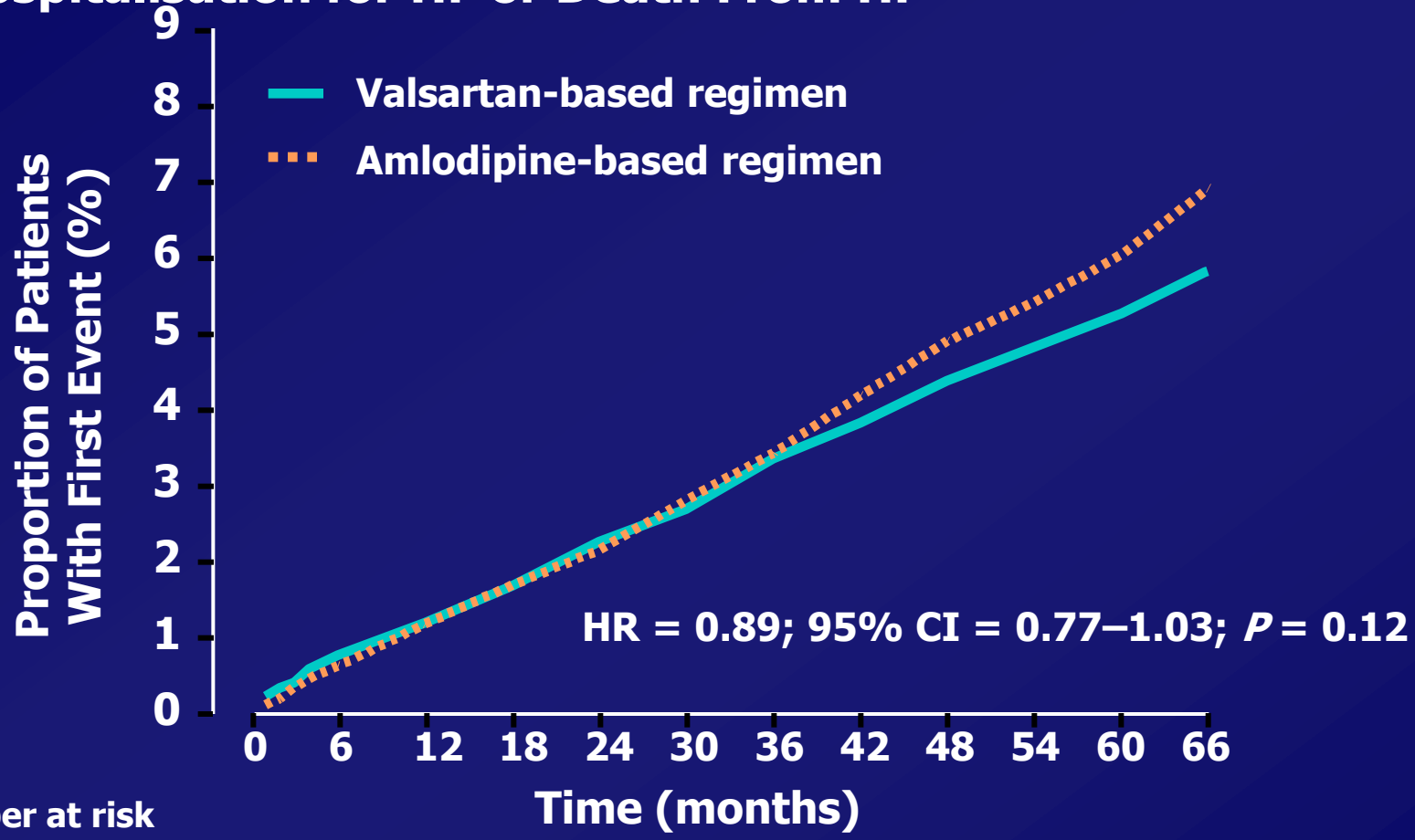
VALUE TRIAL : Valsartan-based Regimen is Associated with Less Incidence of New-onset Diabetes



Julius et al. *Lancet* 2004;363:2022-2031.

VALUE: Heart Failure

Hospitalisation for HF or Death From HF



Number at risk												
Valsartan	7649	7485	7444	7312	7169	7012	6852	6671	6498	6072	3860	1513
Amlodipine	7596	7486	7444	7312	7176	7033	6874	6702	6534	6100	3823	1511

Julius S et al. *Lancet*. June 2004;363.

VALUE: Tolerability

	Valsartan (%)	Amlodipine (%)	*P* Value
Discontinuations due to AE	13.4	14.5	0.045
Prespecified adverse evets			
Peripheral Oedema	14.9	32.9	<0.0001
Dizziness	16.5	14.3	
Headache	15.2	12.9	<0.0001
Additional common adverse events			
Diarrhoea*	8.8	6.8	<0.0001
Angina Pectoris*	9.3	6.4	<0.0001
Angina Pectoris†	4.4	3.1	<0.0001
Oedema Other*	3.2	6.1	<0.0001
Hypokalaemia*	3.5	6.2	<0.0001
Atrial Fibrillation†	2.4	2.0	0.1197
Syncope†	1.7	1.0	<0.0001

*With an incidence >3% and a difference between treatment groups >1%.
†Reported as serious.

Data on file. Novartis Pharmaceuticals.

VALUE: Main Results

- **The primary composite cardiac endpoint was not different between the treatment groups**
- **There was a positive trend in favour of valsartan for less heart failure but this did not reach significance**
- **VALUE is the first trial to show a highly significant lower rate of new-onset diabetes when an ARB (valsartan) was compared to a CCB (amlodipine)**

Julius S et al. *Lancet*. June 2004;363.

Indications for AT_1 receptor blocade - EBM

RENAL FALIURE

RENAAL

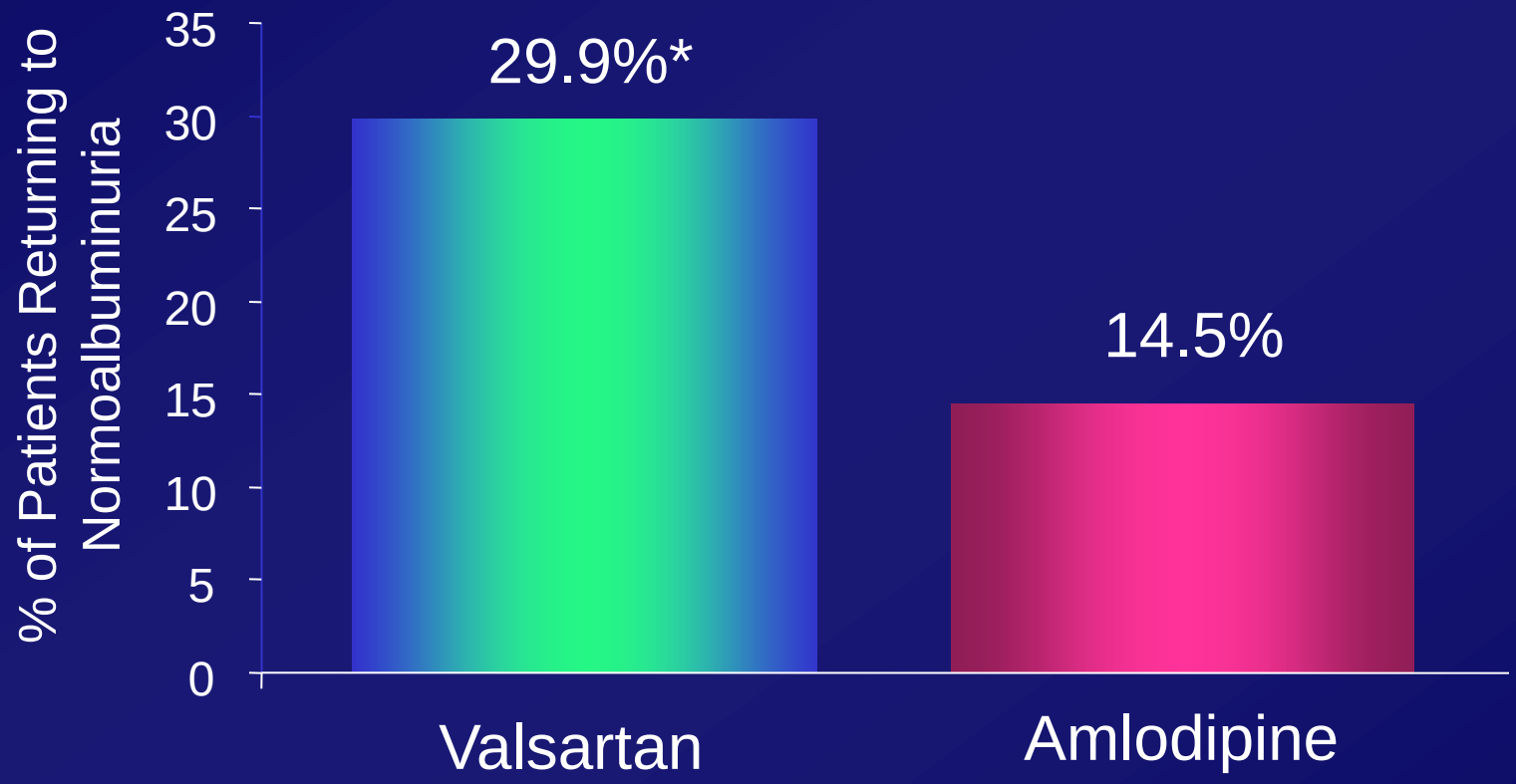
MARVAL

MARVAL TRIAL

- **M**icro**A**lbuminuria **R**eduction With **VAL**sartan
- 332 patients with DM2 and microalbuminuria
- With or without hypertension
- 80mg/d valsartan or 5mg/d amlodipine
- 24 weeks
- The primary end point was the percent change in UAER from baseline to 24 weeks.
- UAER – elevated urine albumine excretion

Viberti G et al. Circulation 2002;106(6):672-8

VALSARTAN CORRECTS MICROALBUMINURIA IN TYPE 2 DM



Normoalbuminuria = UAER < 20 μg/min; *P = 0.001 vs. amlodipine

Viberti G. *Circulation.* 2002;106:672-678.

MARVAL TRIAL RESULTS

- The UAER at 24 weeks was
  - **56% of baseline with valsartan**
  - 92% of baseline with amlodipine,
  - a highly significant between-group effect (*P*0.001)
- **More patients reversed to normoalbuminuria with valsartan** **29.9%** versus 14.5% (*P*0.001)
- BP reductions were similar between the two treatments

Viberti, Circulation 2002, 106;672-678

Indications for AT_1 receptor blocade - EBM

UPDATE 2010

HEAL

KYOTO

NAVIGATOR

KYOTO HEART Study

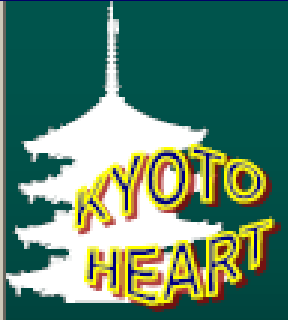
Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high risk of cardiovascular events

H.Matsubara[1], T.Sawada[1], T.Takahashi[1], H.Yamada[1], B.Dahröf[2]

[1] *Department of Cardiology, Kyoto Prefectural University of Medicine, Kyoto, Japan*
[2] *Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden*

Study design

- 3,042 Japanese pts with high risk hypertension
- Prospective, randomized, open-label, blinded endpoint (PROBE)
- Randomization using the minimization method
  - Factors: age, gender, hyperlipidemia, diabetes, smoking, obesity, history of IHD and CVA
- Valsartan vs Non-ARB-based optimal therapy to achieve BP target
- Investigator initiated and conducted



Assessed for eligibility 3042 pts

withdrew Informed consent 4pts
Incompatible object 7pts

Random allocation 3031 pts

Valsartan treatment group 1517 pts

Non-ARB treatment group 1514 pts

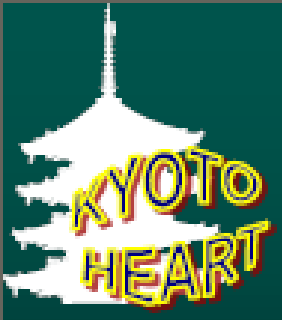
withdrew consent 11pts
Loss of follow-up 7pts

withdrew consent 6pts
loss of follow-up 10pts

available for intention-to-treat analysis 1517 pts

available for intention-to-treat analysis 1514 pts

Scheme of study protocol



ARB add-on group

No-treatment or treatment (without ARBs)

Sitting systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg with high risks**

Valsartan 40—80 mg

Usual dosage

Valsartan 160 mg*

High dosage*

Valsartan 160 mg
+other antihypertensive drugs (excluding ACEIs and ARBs)*

High dosage
+ other antihypertensive drugs (excluding ACEIs and ARBs)*

Non- ARB treatment group

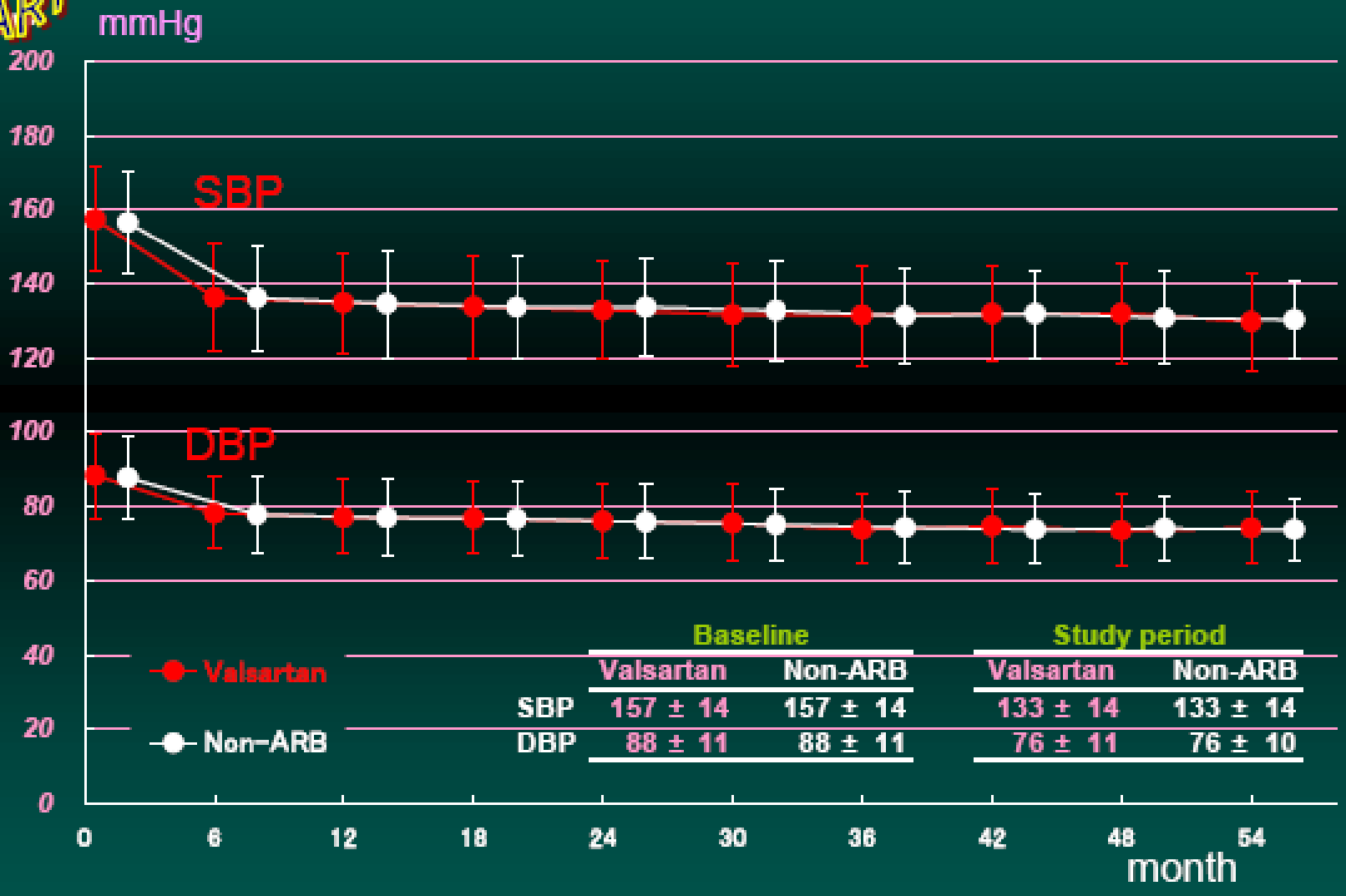
Conventional treatment with antihypertensive drugs other than ARB and ACE inhibitors are provided.

Month

-1 (Entry) 0 (Randomization) 1 2 6 12 18 24 30 36 // (End of study)

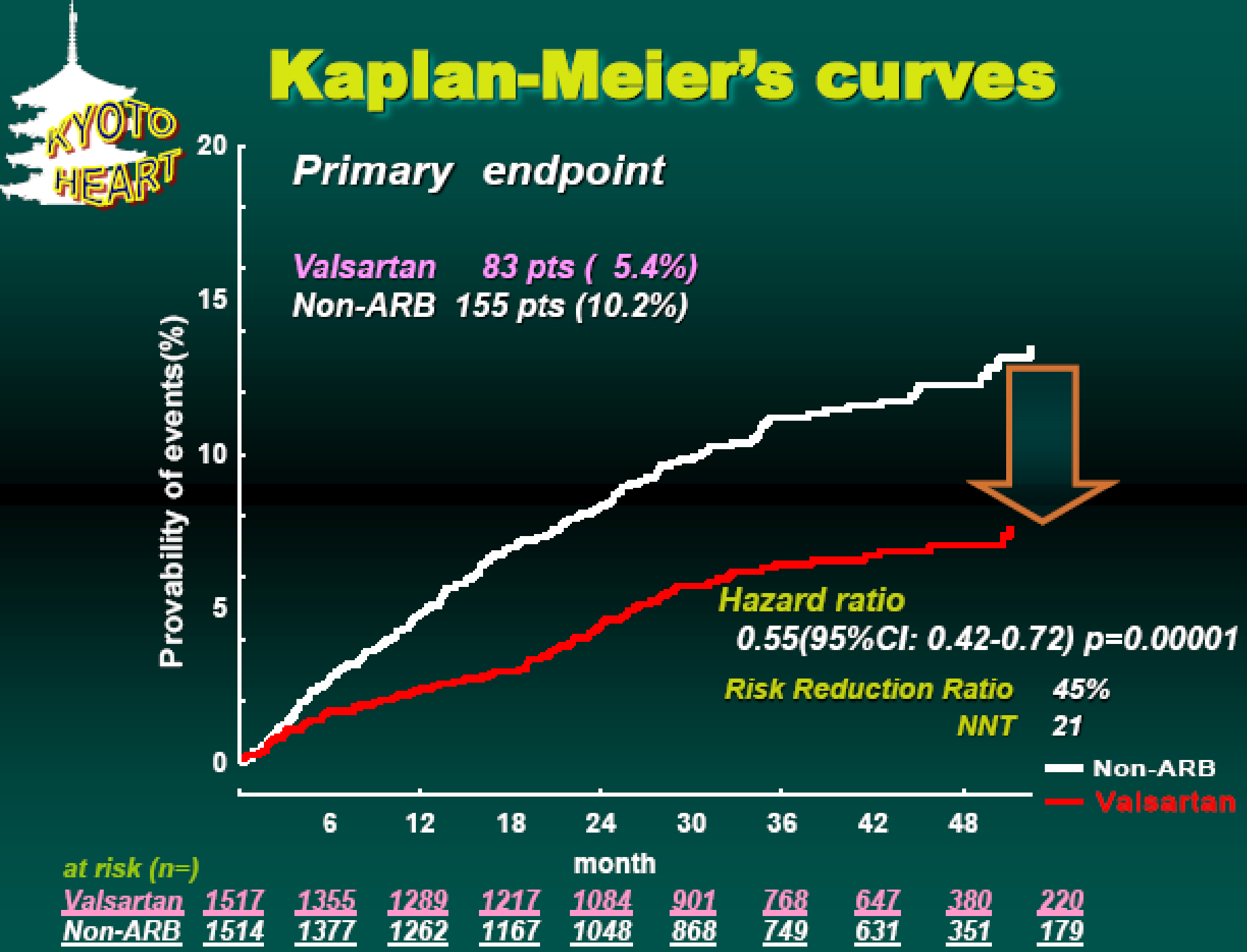
*Titration upward if blood pressure does not reach the common goal of blood pressure control.
**High risks are defined as having at least one of a history of cardiovascular events, diabetes, smoking habit, dyslipidemia, obesity, and left ventricular hypertrophy.

Changes of blood pressure

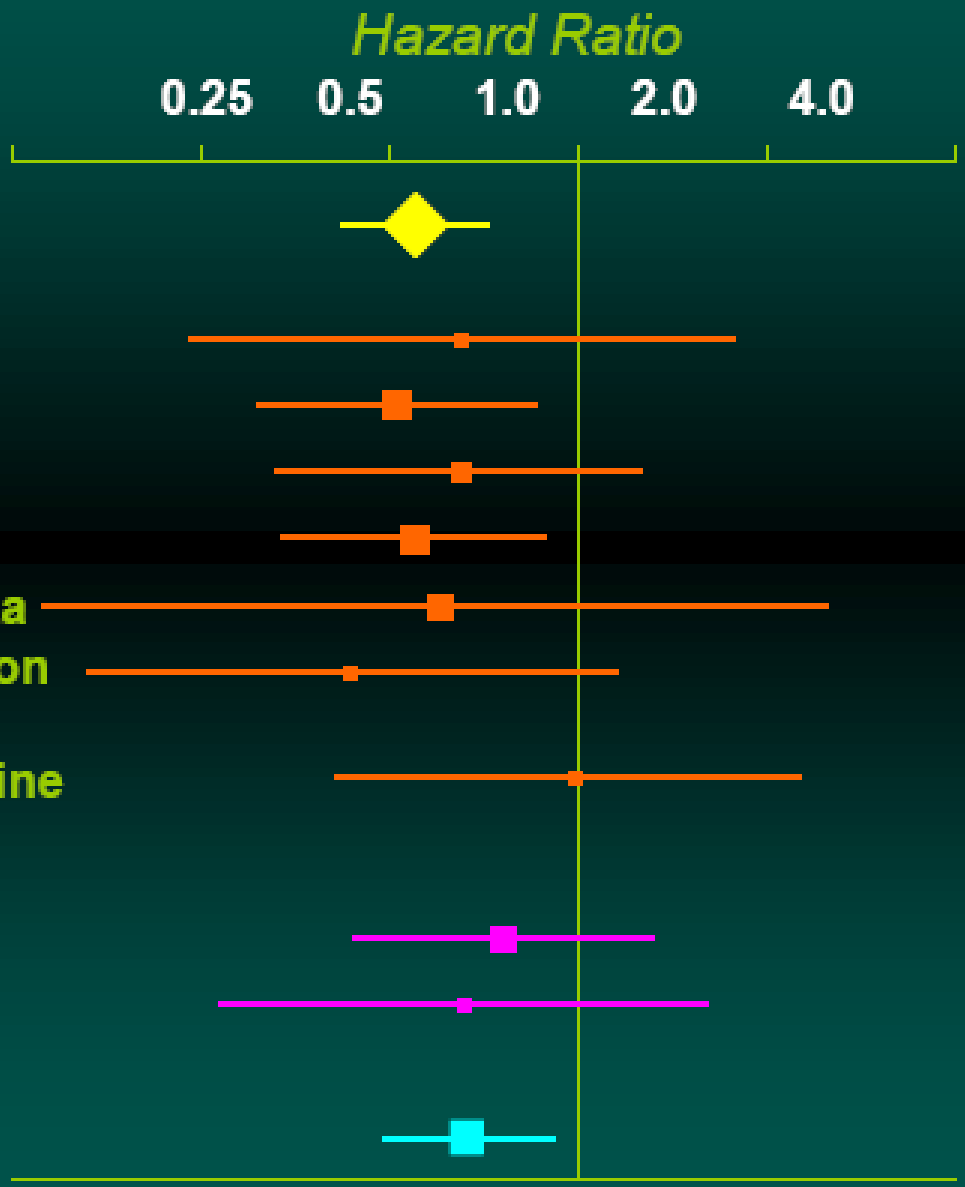


	Baseline		Study period	
	Valsartan	Non-ARB	Valsartan	Non-ARB
SBP	157 ± 14	157 ± 14	133 ± 14	133 ± 14
DBP	88 ± 11	88 ± 11	76 ± 11	76 ± 10

Kaplan-Meier's curves



Hazard ratio and 95% confidence intervals

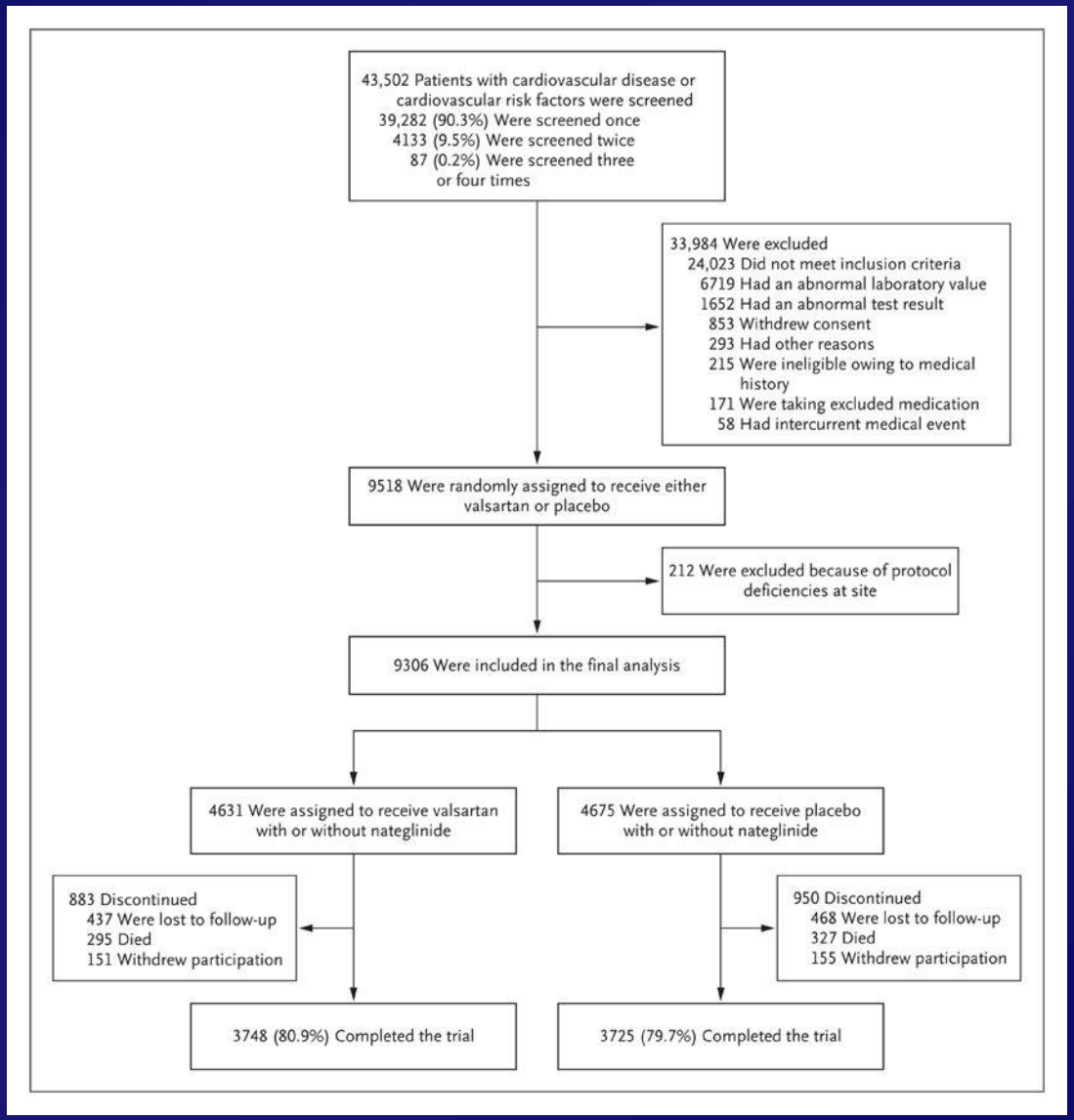


	P-value
Primary endpoint	0.00001
Acute Myocardial Infarction	0.39466
Angina Pectris	0.01058
Heart Failure	0.20857
Stroke	0.01488
Dissecting Aneurysm of Aorta	0.69987
Lower limb arterial obstruction	0.98106
Transition to dialysis or doubling of serum creatinine levels	0.34666
All cause mortality	0.32851
Cardiovascular death	0.37121
New onset Diabetes	0.02817

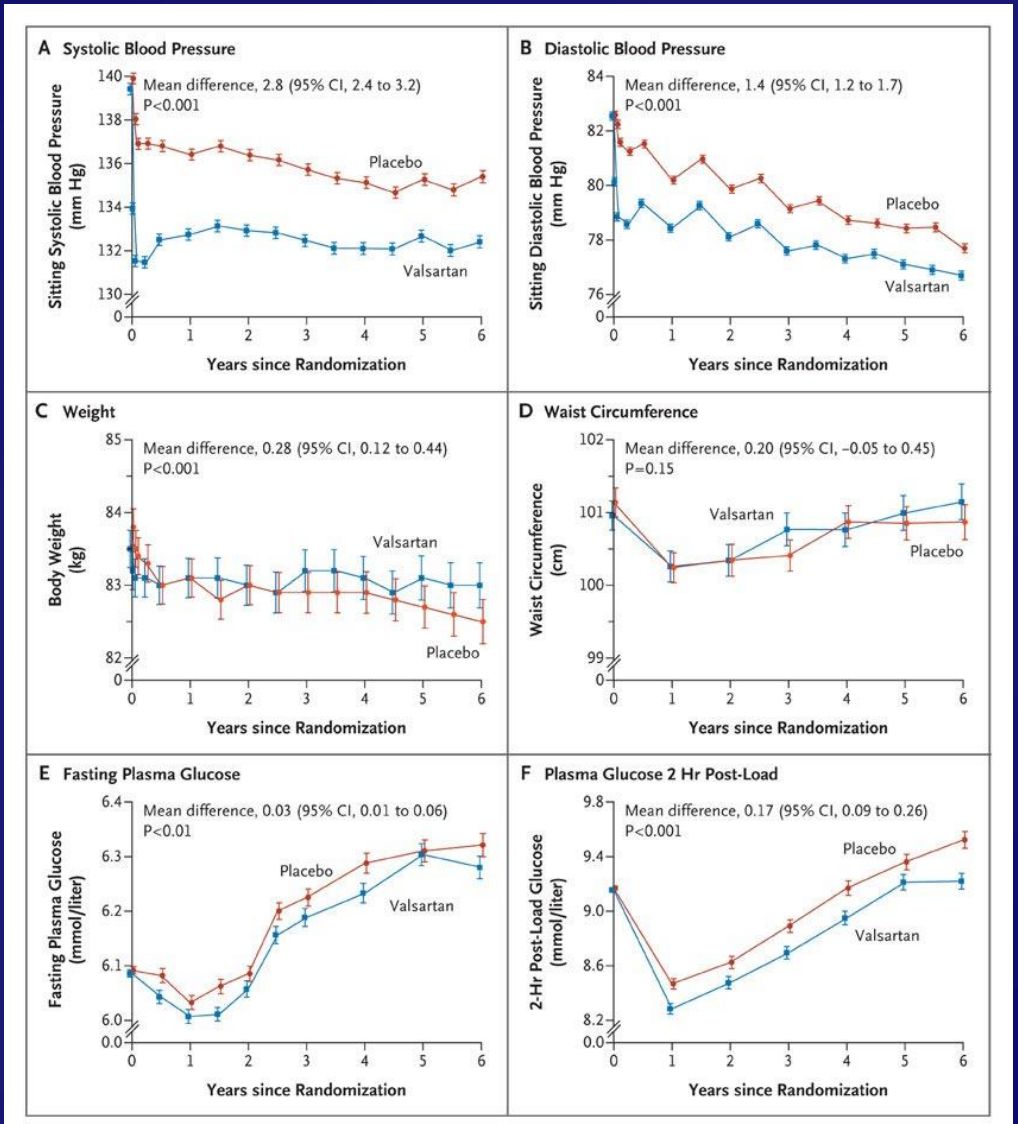
Clinical relevance

- ✓ *KYOTO HEART Study confirms that the ARB valsartan exerts an overall cardiovascular protective effect in high risk Japanese hypertensive patients and in particular exerts anti-stroke and anti-angina actions.*
- ✓ *Valsartan provide an useful information about Asian populations that have similar genetic predisposition and lifestyles as the Japanese population.*

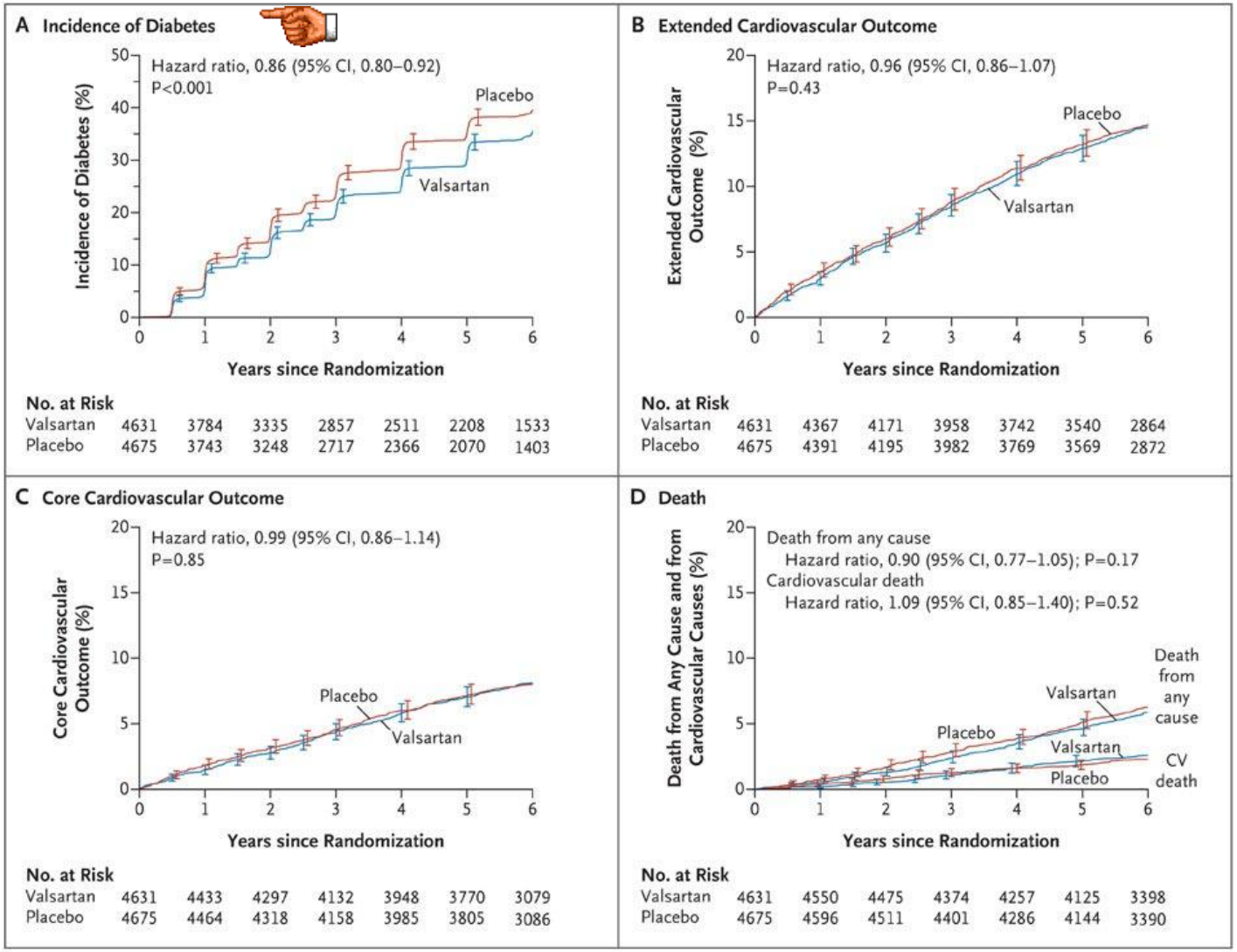
NAVIGATOR


43,502 Patients with cardiovascular disease or cardiovascular risk factors were screened
39,282 (90.3%) Were screened once
4133 (9.5%) Were screened twice
87 (0.2%) Were screened three or four times
33,984 Were excluded
24,023 Did not meet inclusion criteria
6719 Had an abnormal laboratory value
1652 Had an abnormal test result
853 Withdrew consent
293 Had other reasons
215 Were ineligible owing to medical history
171 Were taking excluded medication
58 Had intercurrent medical event
9518 Were randomly assigned to receive either valsartan or placebo
212 Were excluded because of protocol deficiencies at site
9306 Were included in the final analysis
4631 Were assigned to receive valsartan with or without nateglinide
4675 Were assigned to receive placebo with or without nateglinide
883 Discontinued
437 Were lost to follow-up
295 Died
151 Withdrew participation
950 Discontinued
468 Were lost to follow-up
327 Died
155 Withdrew participation
3748 (80.9%) Completed the trial
3725 (79.7%) Completed the trial

NAVIGATOR


A Systolic Blood Pressure
Sitting Systolic Blood Pressure (mm Hg)
Mean difference, 2.8 (95% CI, 2.4 to 3.2)
P<0.001
Placebo
Valsartan
Years since Randomization
B Diastolic Blood Pressure
Sitting Diastolic Blood Pressure (mm Hg)
Mean difference, 1.4 (95% CI, 1.2 to 1.7)
P<0.001
Placebo
Valsartan
Years since Randomization
C Weight
Body Weight (kg)
Mean difference, 0.28 (95% CI, 0.12 to 0.44)
P<0.001
Valsartan
Placebo
Years since Randomization
D Waist Circumference
Waist Circumference (cm)
Mean difference, 0.20 (95% CI, −0.05 to 0.45)
P=0.15
Valsartan
Placebo
Years since Randomization
E Fasting Plasma Glucose
Fasting Plasma Glucose (mmol/liter)
Mean difference, 0.03 (95% CI, 0.01 to 0.06)
P<0.01
Placebo
Valsartan
Years since Randomization
F Plasma Glucose 2 Hr Post-Load
2-Hr Post-Load Glucose (mmol/liter)
Mean difference, 0.17 (95% CI, 0.09 to 0.26)
P<0.001
Placebo
Valsartan
Years since Randomization

NAVIGATOR


A Incidence of Diabetes
Hazard ratio, 0.86 (95% CI, 0.80–0.92)
P<0.001
Placebo
Valsartan
Incidence of Diabetes (%)
Years since Randomization
No. at Risk
Valsartan 4631 3784 3335 2857 2511 2208 1533
Placebo 4675 3743 3248 2717 2366 2070 1403
B Extended Cardiovascular Outcome
Hazard ratio, 0.96 (95% CI, 0.86–1.07)
P=0.43
Placebo
Valsartan
Extended Cardiovascular Outcome (%)
Years since Randomization
No. at Risk
Valsartan 4631 4367 4171 3958 3742 3540 2864
Placebo 4675 4391 4195 3982 3769 3569 2872
C Core Cardiovascular Outcome
Hazard ratio, 0.99 (95% CI, 0.86–1.14)
P=0.85
Placebo
Valsartan
Core Cardiovascular Outcome (%)
Years since Randomization
No. at Risk
Valsartan 4631 4433 4297 4132 3948 3770 3079
Placebo 4675 4464 4318 4158 3985 3805 3086
D Death
Death from any cause
Hazard ratio, 0.90 (95% CI, 0.77–1.05); P=0.17
Cardiovascular death
Hazard ratio, 1.09 (95% CI, 0.85–1.40); P=0.52
Valsartan
Placebo
Death from any cause
Valsartan
Placebo
CV death
Death from Any Cause and from Cardiovascular Causes (%)
Years since Randomization
No. at Risk
Valsartan 4631 4550 4475 4374 4257 4125 3398
Placebo 4675 4596 4511 4401 4286 4144 3390

NAVIGATOR

Valsartan had no effect on CV disease but moderately reduced progression to diabetes.

Thank you for your atention