2011. 4. 27-29 angioplasty summit

Improving Effect of ARB to Asian Hypertension Patients

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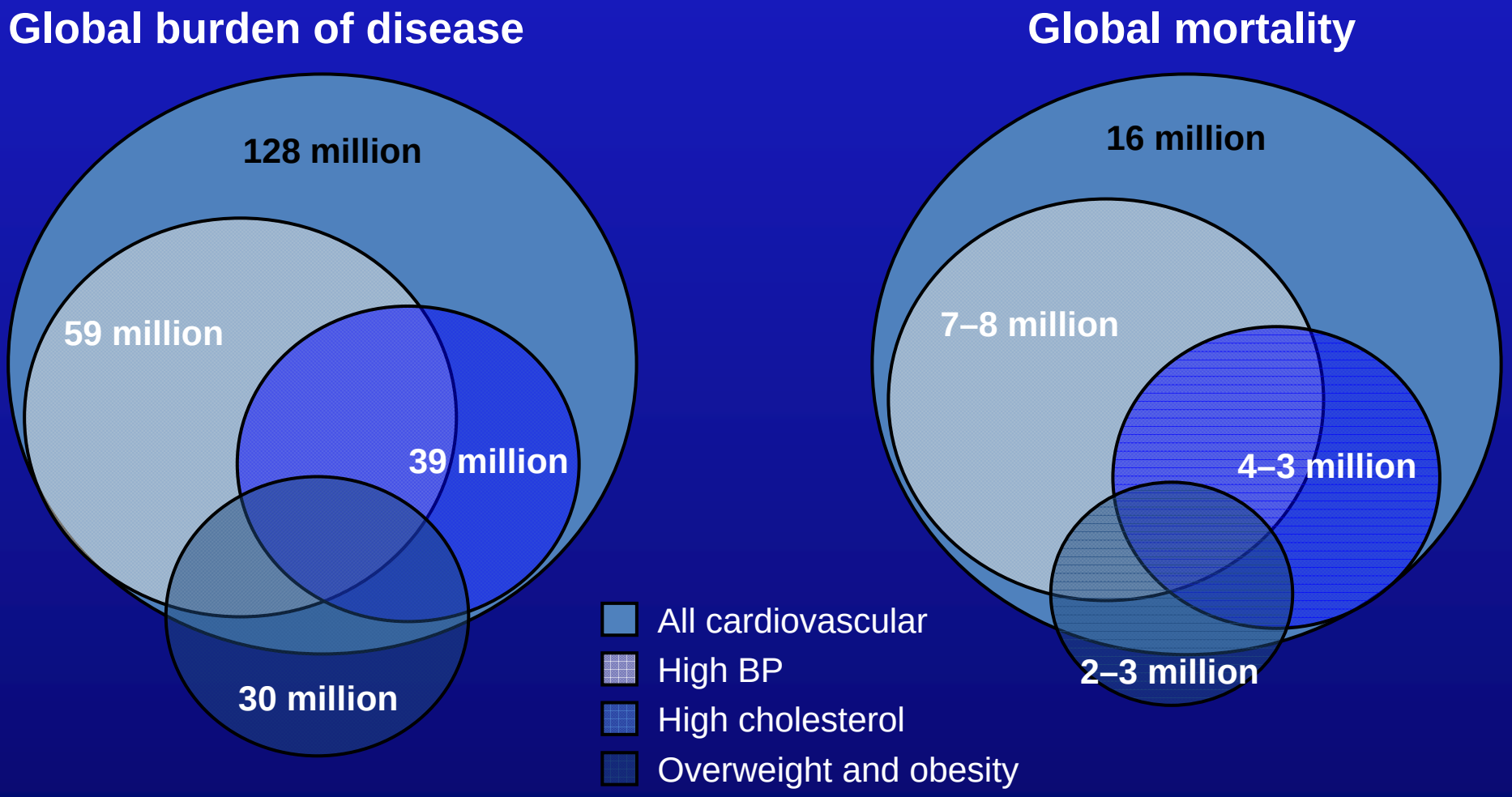
Hypertension is the most powerful risk factor for cardiovascular morbidity and mortality



Ezzati et al. PloS Med 2005;2:e133

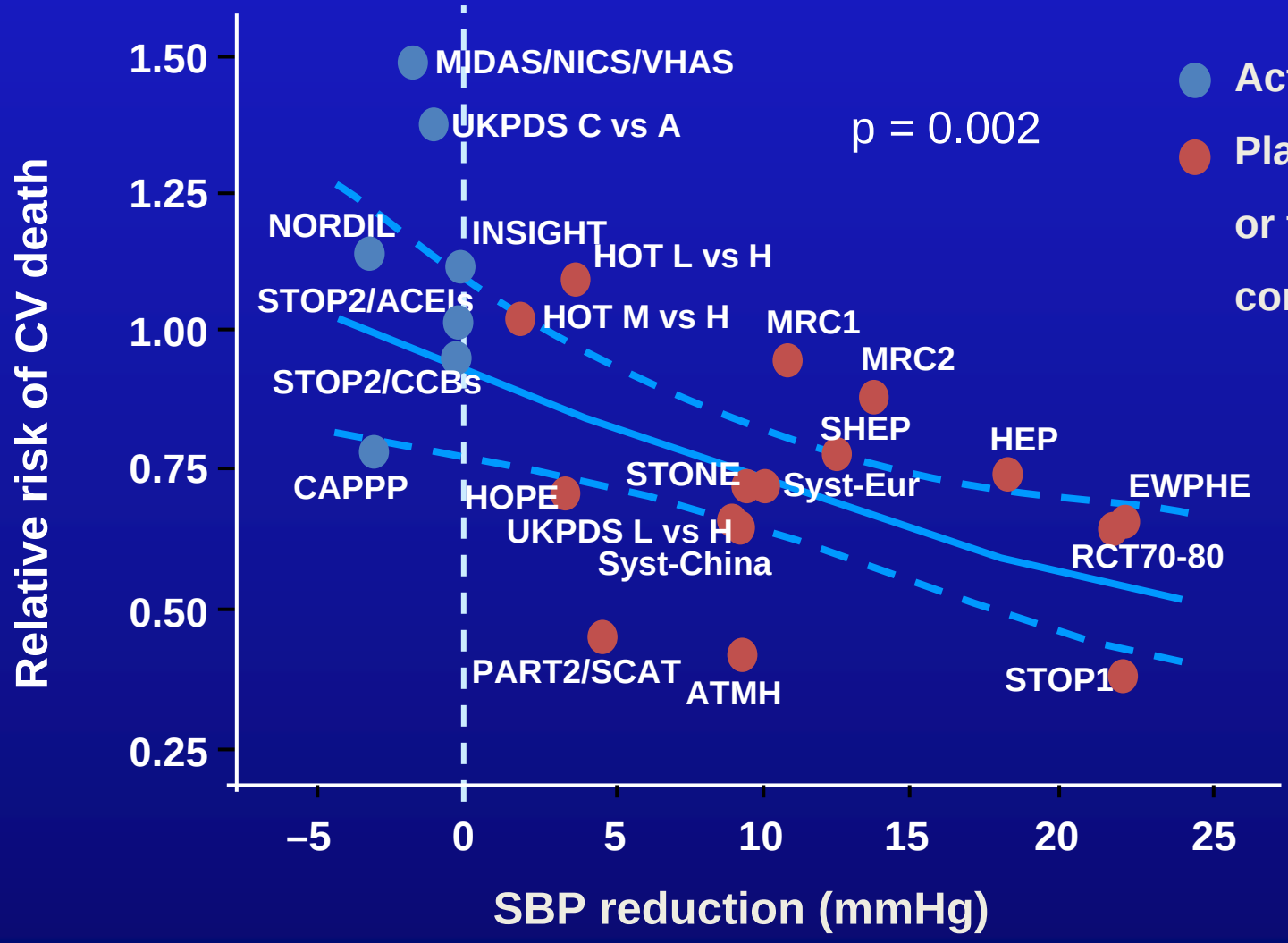
How about hypertension in Asia

Region	Death	Disability*
East Asia & Pacific	**13.6%**	**6.5%**
Europe & Central Asia	35.0%	19.6%
Latin America & The Caribbean	13.0%	5.1%
Middle East & North Africa	16.5%	6.1%
South Asia	9.6%	4.3%
Sub-Saharan Africa	4.0%	1.7%
Low-/ middle-income economies	12.9%	5.6%
High-income economies	17.6%	9.3%
World	**13.5%**	**6.0%**

* Disability-adjusted life years

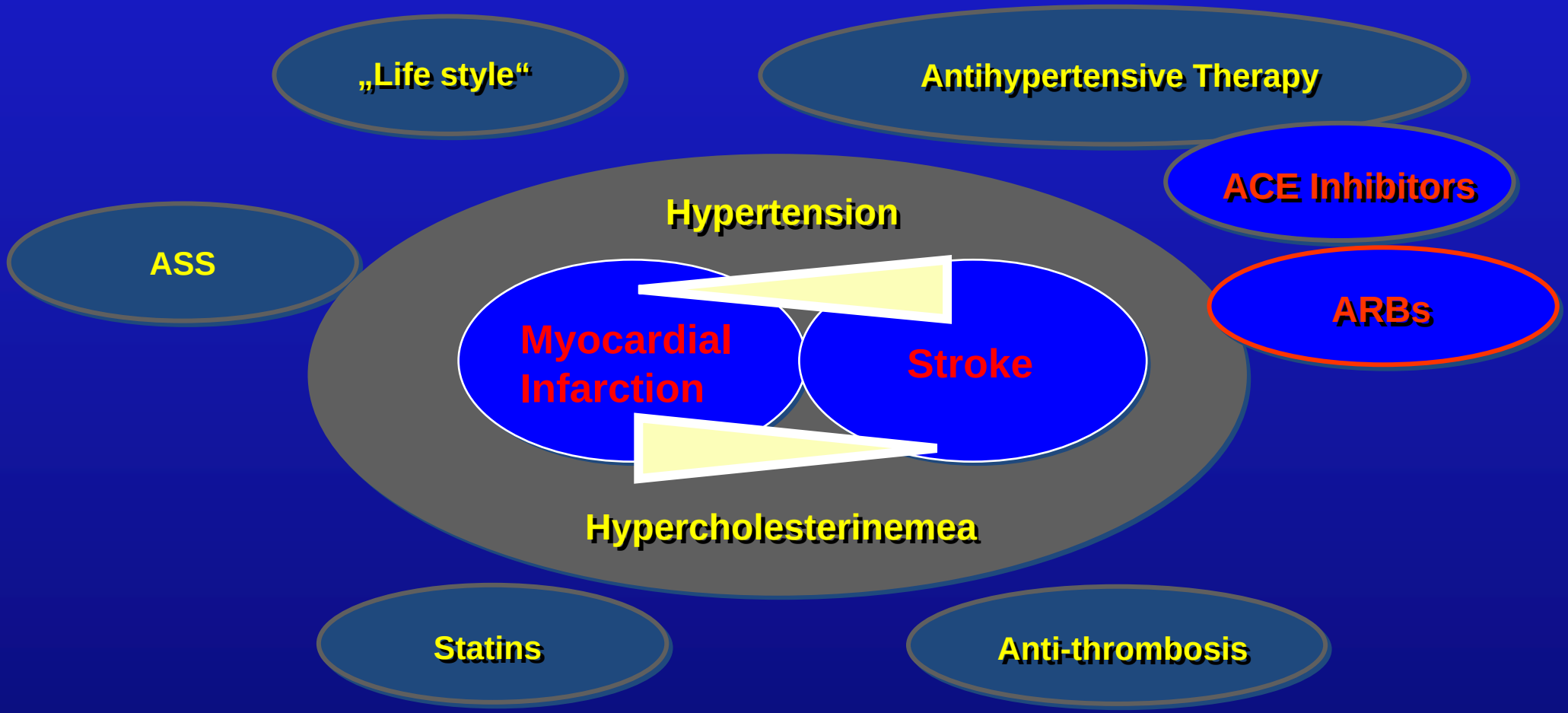
Lawes et al. Lancet 2008;371:1513–8

BP reduction reduces CV risk



Staessen et al. Hypertens Res. 2005;28:385-407.

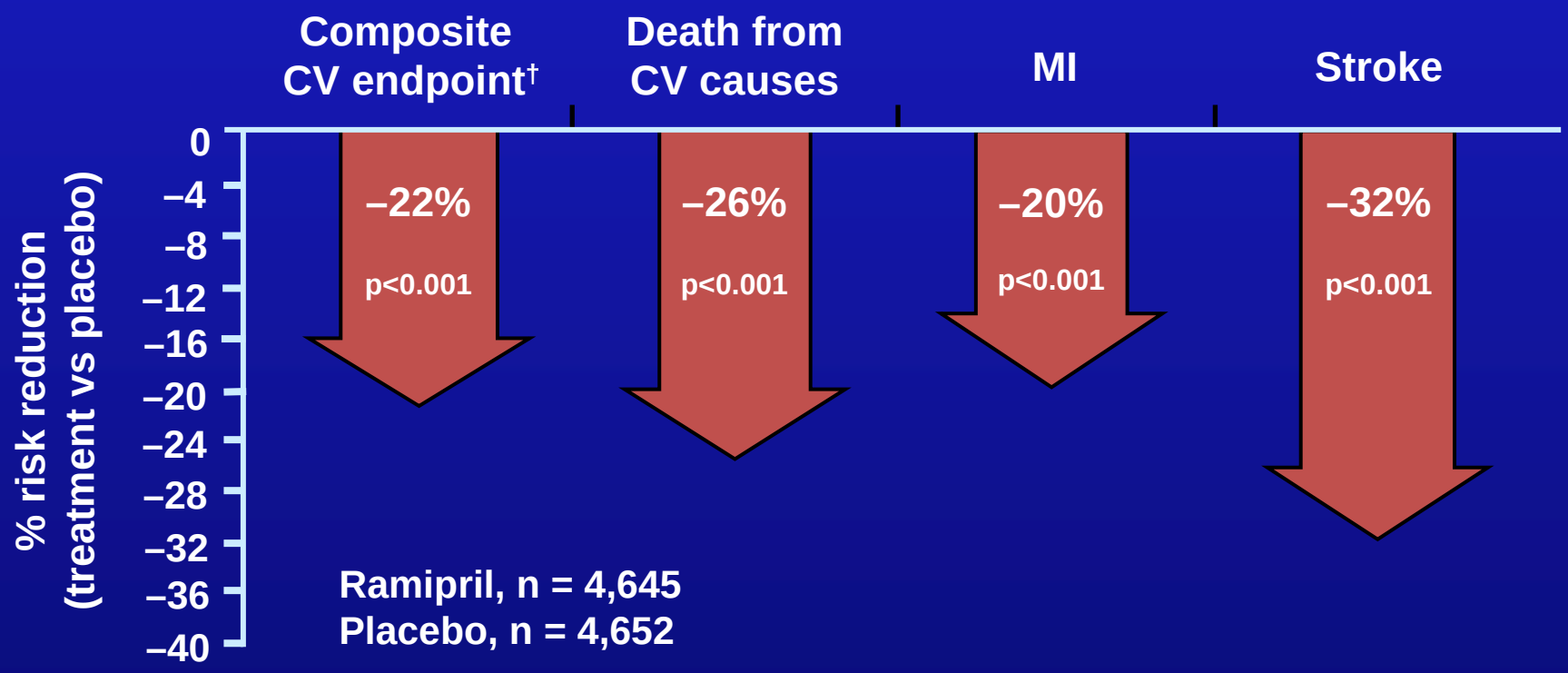
Interaction between Risk and Therapy



RAS-Inhibition – CV Global Protection?

The ACEi ramipril reduces CV mortality and morbidity in CV high-risk patients

HOPE: **CV high-risk patients; mean baseline SBP/DBP 139/79 mmHg**



Ramipril, n = 4,645
Placebo, n = 4,652

† Composite CV endpoint = death from CV causes + MI + stroke
HOPE = Heart Outcomes Prevention Evaluation

Yusuf et al. N Engl J Med 2000;342:145

Concerns about Angiotensin receptor blockers (ARB)

- **ARBs 'may increase myocardial infarction' : ARB-MI Paradox**

  Verma and Strauss. BMJ 2004;329:1248

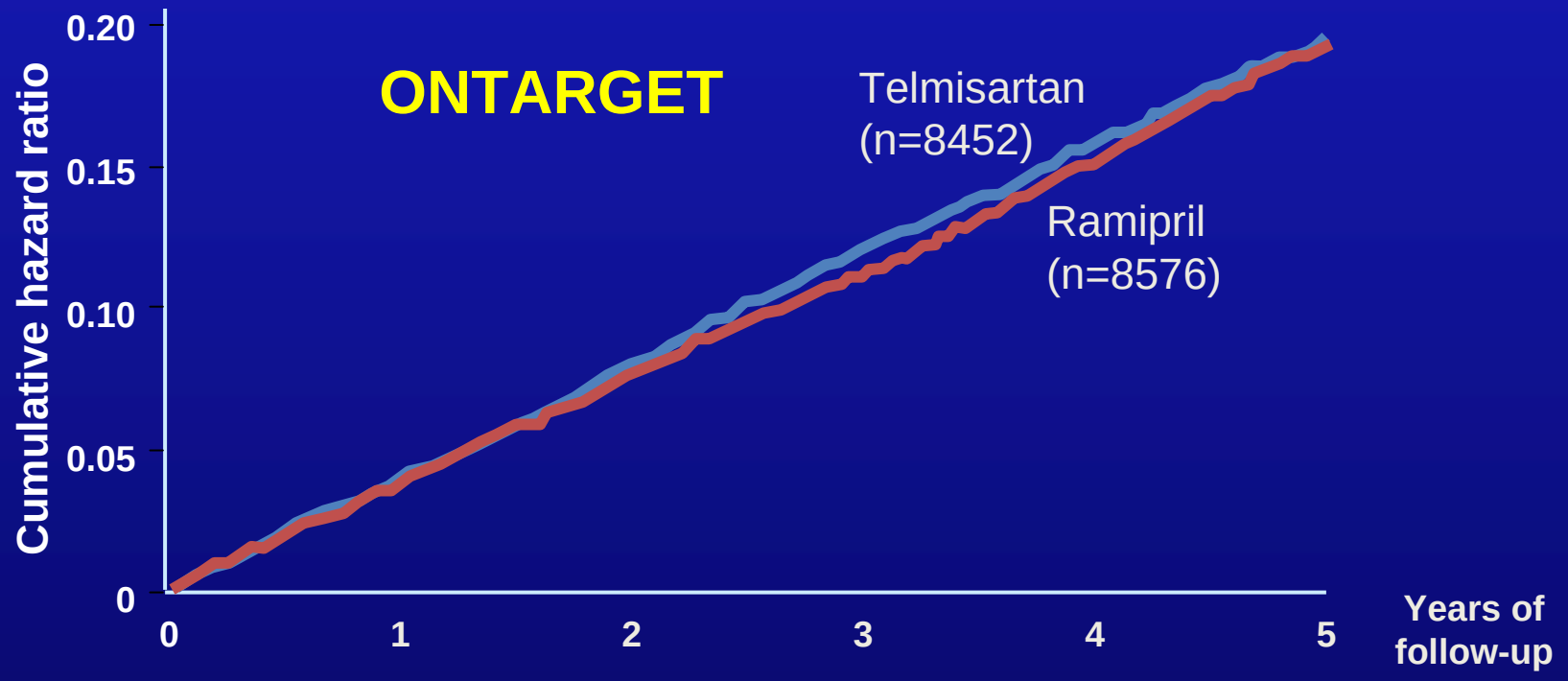
- **There were similar BP-dependent effects of ACE inhibitors and ARBs for the risk of stroke, coronary artery disease, & heart failure. And only for ACE inhibitors but not for ARBs, was there evidence of a BP-independent effect on the risk of major coronary disease events.**

  BP lowering treatment trialists collaboration, J Hypertens 2007;25:951

The ARB telmisartan is similarly effective to ACE inhibitor ramipril in preventing CV events in CV high-risk patients

Reduction in composite CV risk

(Primary endpoint: CV mortality, non-fatal MI, hospitalisation for CHF, non-fatal stroke)



The ONTARGET Investigators. N Engl J Med 2008;358:1547-1559.

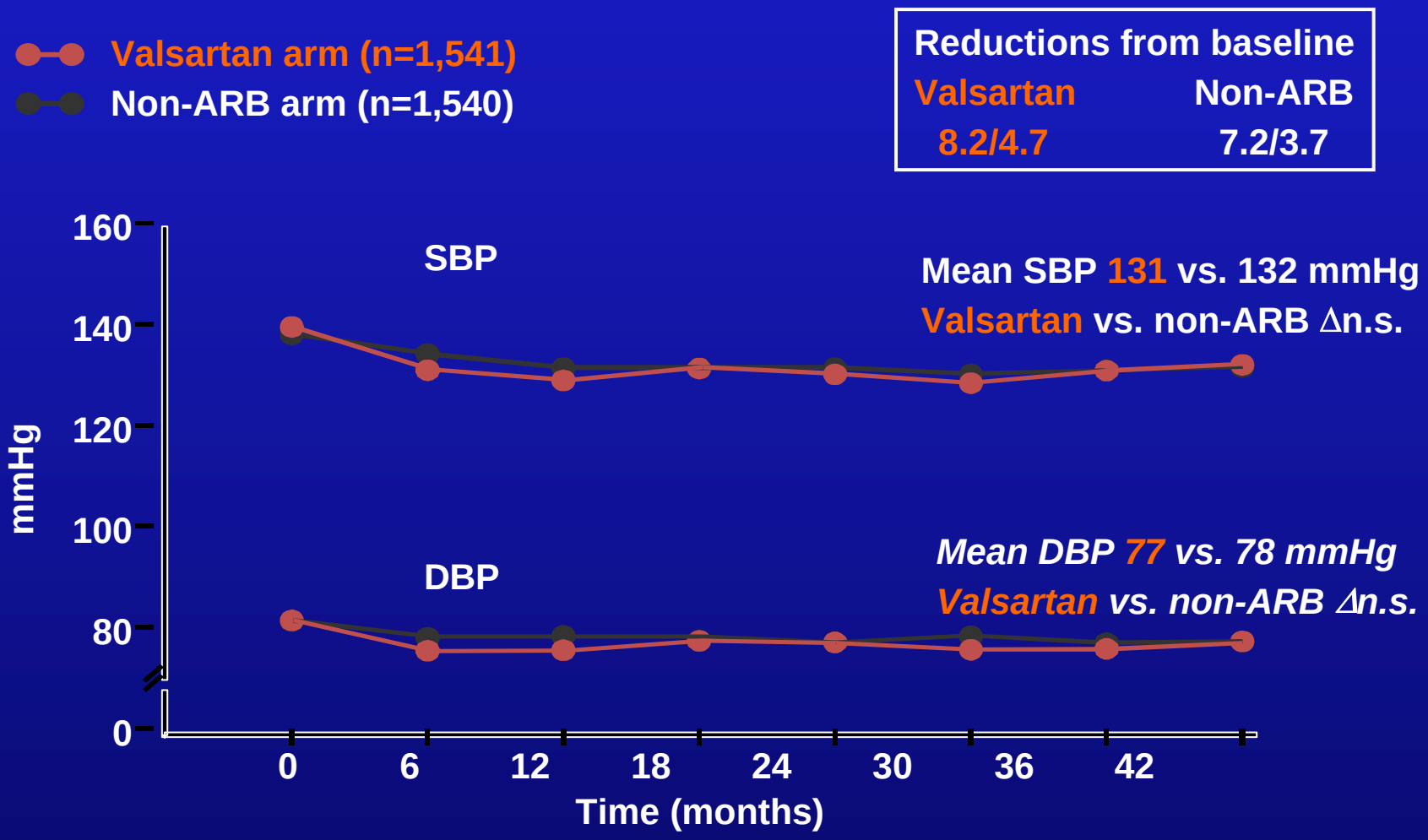
Valsartan in a Japanese population with HT and other CVD (Jikei Heart Study):

a randomised, open-label, blinded endpoint morbidity-mortality study

*Seibu Mochizuki, Bjorn Dahlof, Mitsuyuki Shimizu, Katsunori Ikewaki, Makoto Yoshikawa, Ikuo Taniguchi, Makoto Ohta, Taku Yamada, Kazuhiko Ogawa, Kiyoshi Kanae, Makoto Kawai, Shingo Seki, Fumiko Okazaki, Masayuki Taniguchi, Satoru Yoshida, Naoko Tajima, for the Jikei Heart Study group**

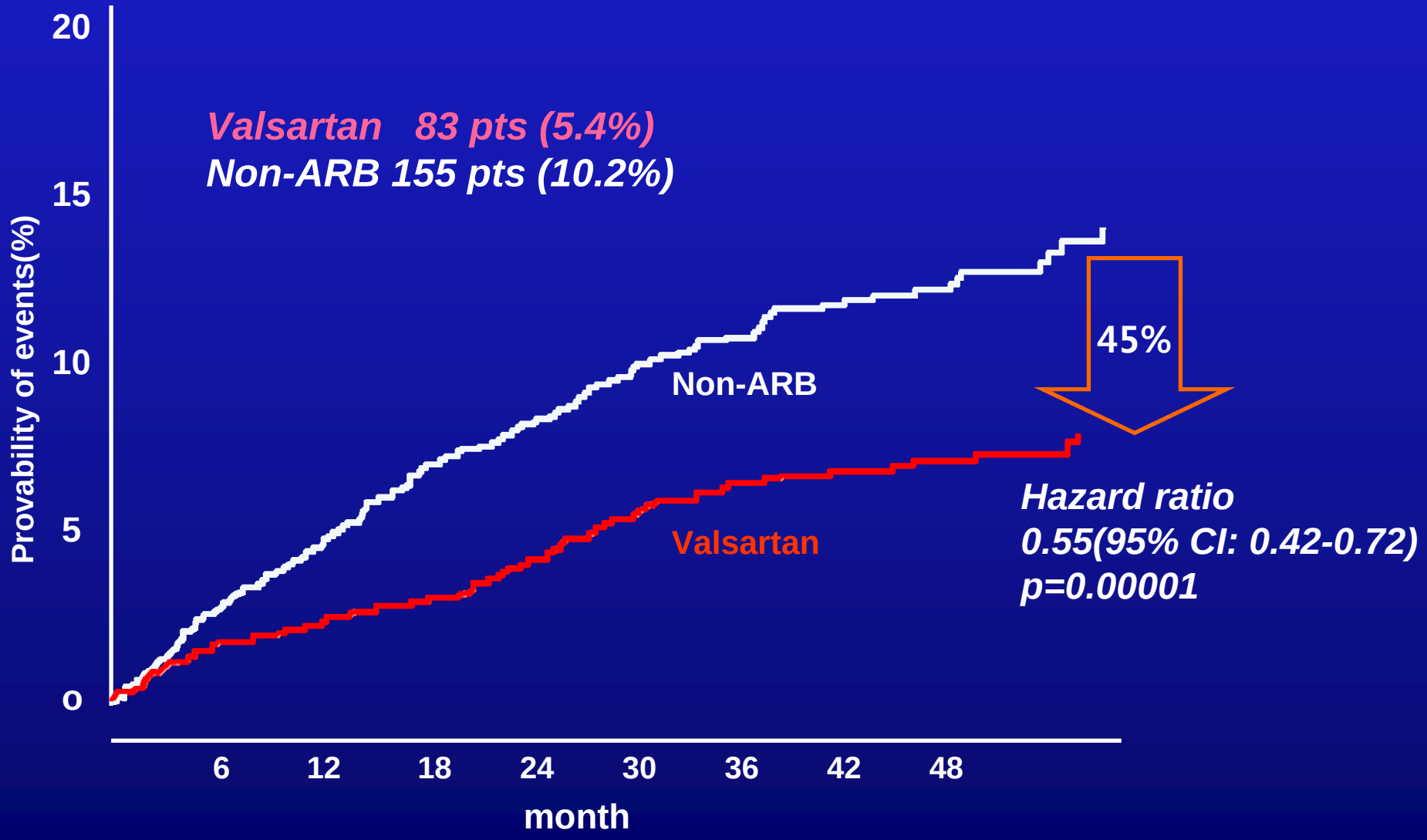
Lancet 2007;369:1431-1439

Blood Pressure Results



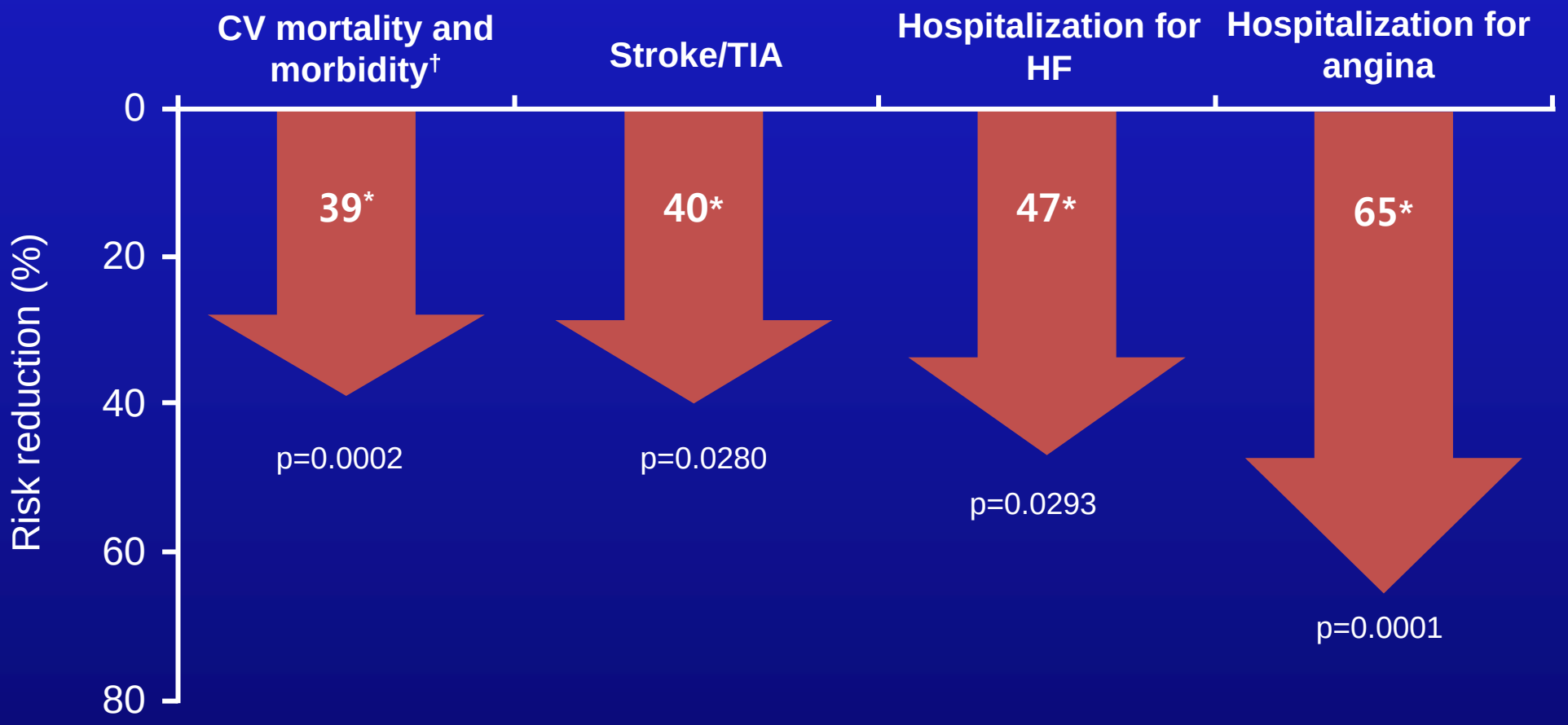
Primary endpoint

Fatal & non-fatal cardiovascular events



ARB Effects on Asian Hypertension

JIKEI Heart study



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

TIA = transient ischemic attack

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

Effect of valsartan in Japanese hypertensive patients with coronary artery disease:

Results from the Jikei Heart Study

Sub-analysis

Mitsuyuki Shimizu1, Hiroshi Yoshida, 2, Katsunori Ikewaki 3, Ikuo Taniguchi 1, Michihiro Yoshimura 1, Björn Dahlöf 4, Seibu Mochizuki 1, for the Jikei Heart Study group

1 Division of Cardiology
2 Department of Laboratory Medicine, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.
3 Division of Anti-Aging, Department of Internal Medicine, National Defense Medical College, Saitama, Japan.
4 Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

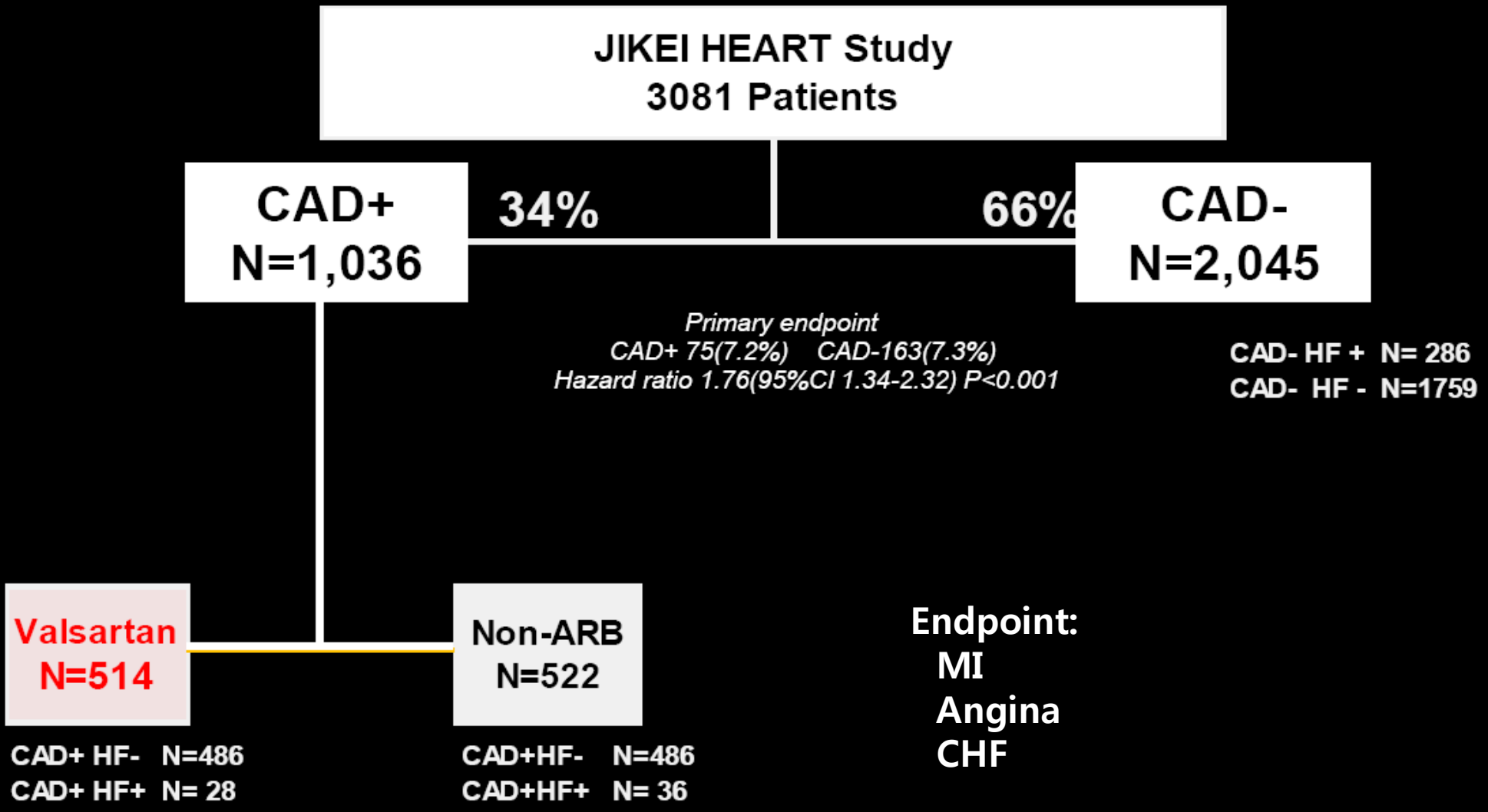
JIKEI

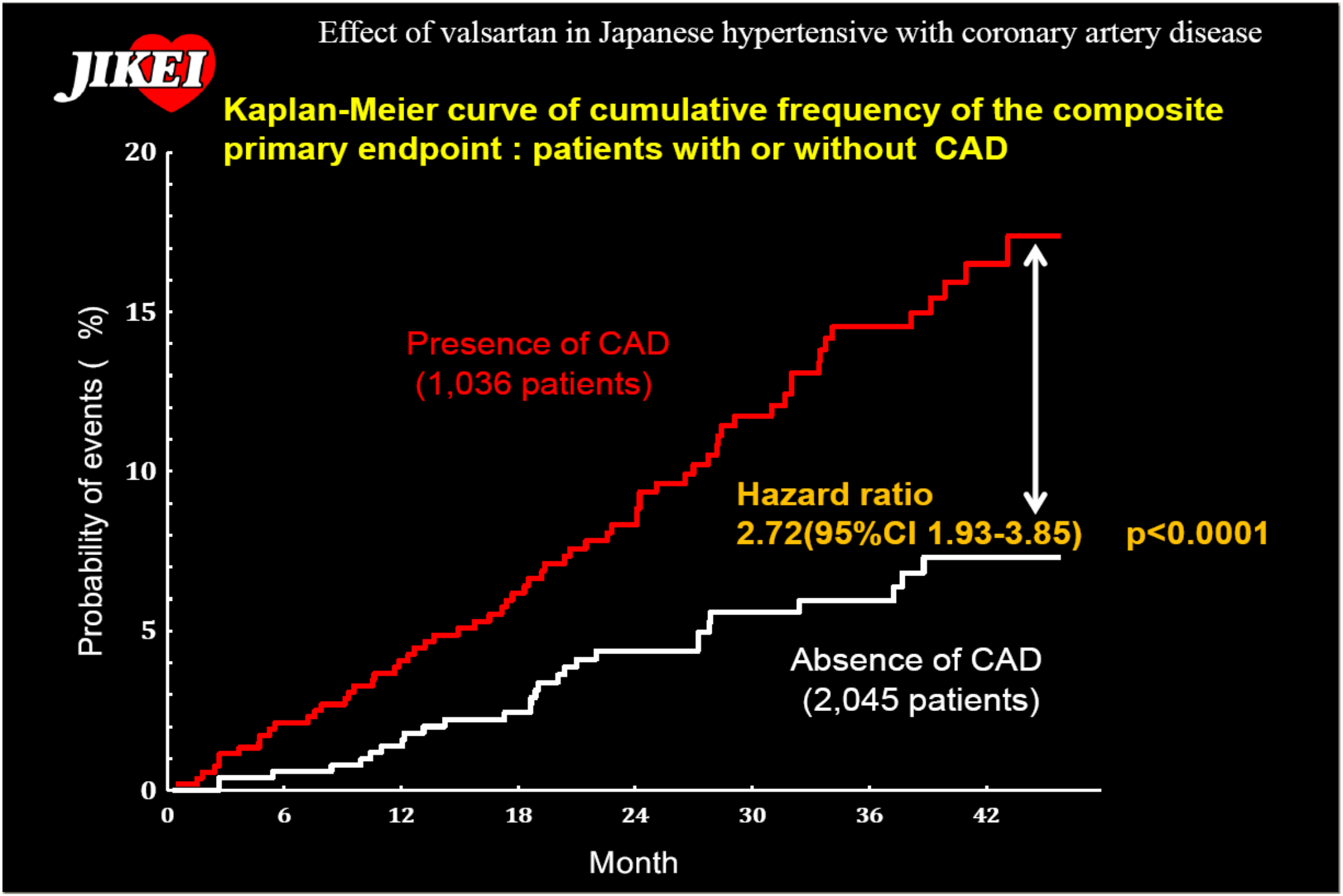
AIM

The risk of cardiac events in hypertensive patients with coronary artery disease (CAD) was higher than in those without CAD. We here report the result of a sub-analysis of a large-scale trial [JIKEI HEART Study (JHS)] which demonstrated that the addition of the angiotensin II receptor blocker (ARB) valsartan to standard cardiovascular treatments significantly reduced the primary composite endpoint of cardiovascular complications as compared with conventional treatments without ARB in Japanese patients.

Effect of valsartan in Japanese hypertensive with coronary artery disease

Trial profile

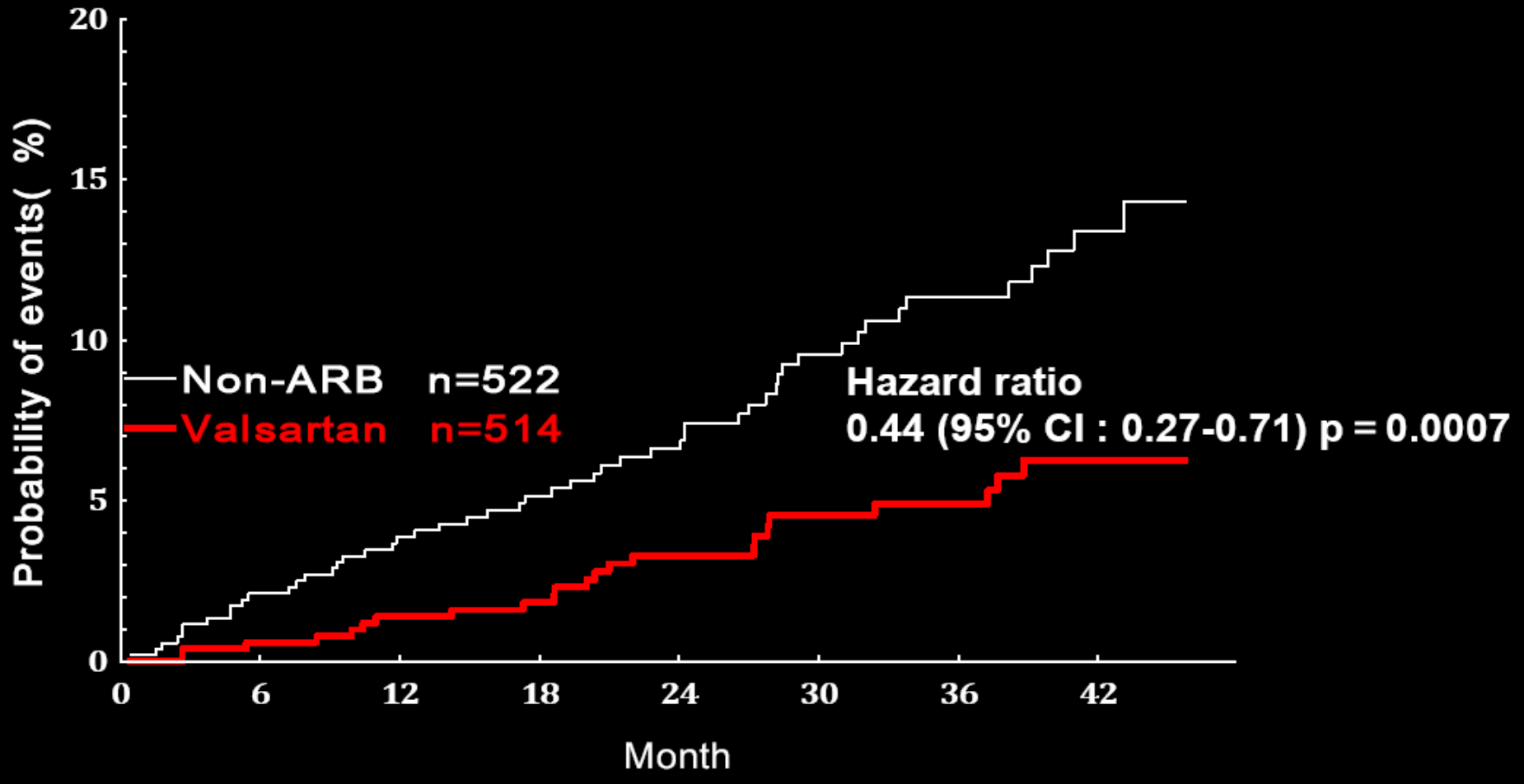



JIKEI
Effect of valsartan in Japanese hypertensive with coronary artery disease
Kaplan-Meier curve of cumulative frequency of the composite primary endpoint : patients with or without CAD
Probability of events (%)
20
15
10
5
0
Presence of CAD
(1,036 patients)
Hazard ratio
2.72(95%CI 1.93-3.85)
p<0.0001
Absence of CAD
(2,045 patients)
0
6
12
18
24
30
36
42
Month

Effect of valsartan in Japanese hypertensive patients with coronary artery disease

JIKEI

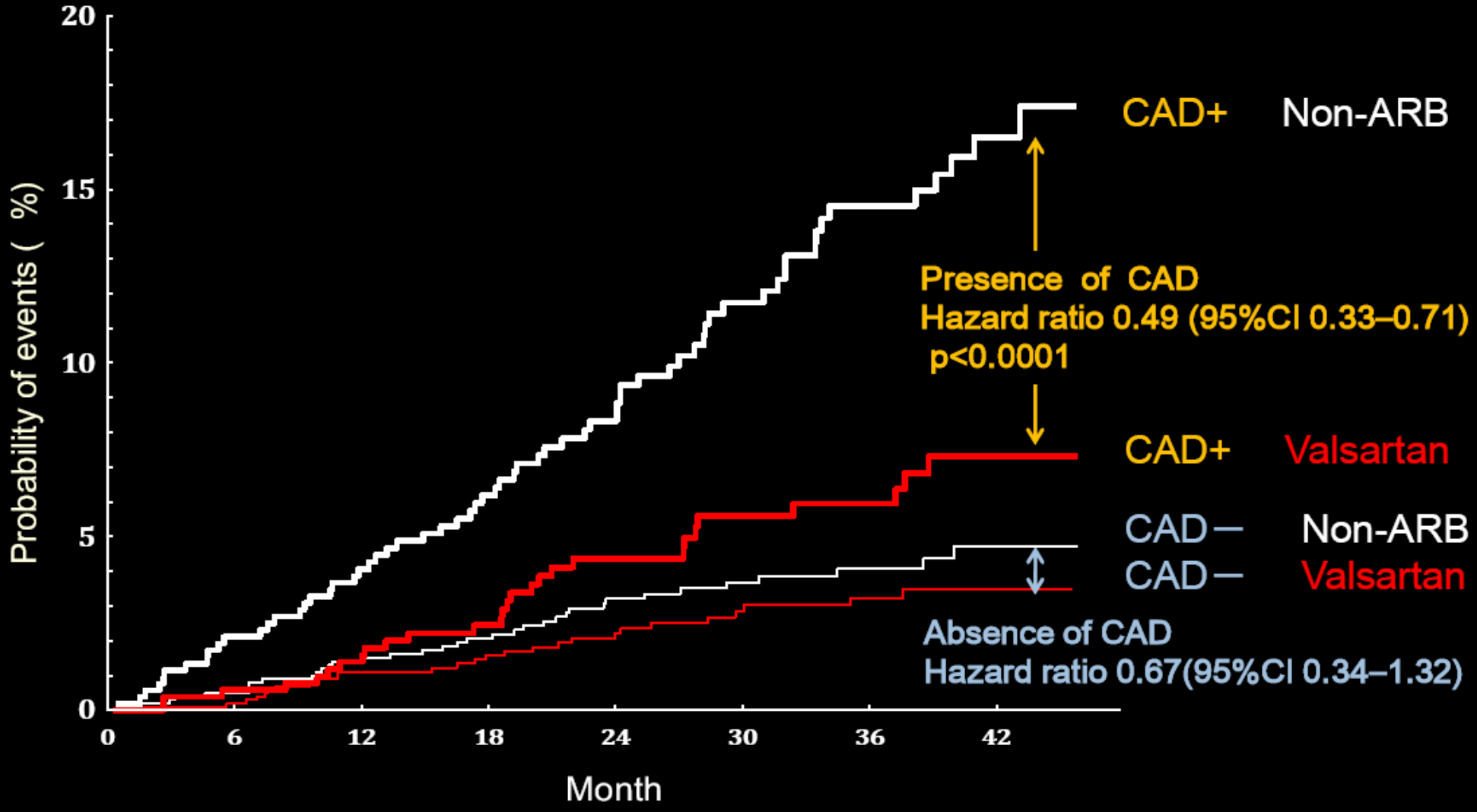
Kaplan-Meier curve of cumulative frequency of the fatal and non-fatal coronary events : patients with CAD



Effect of valsartan in Japanese hypertensive patients with coronary artery disease

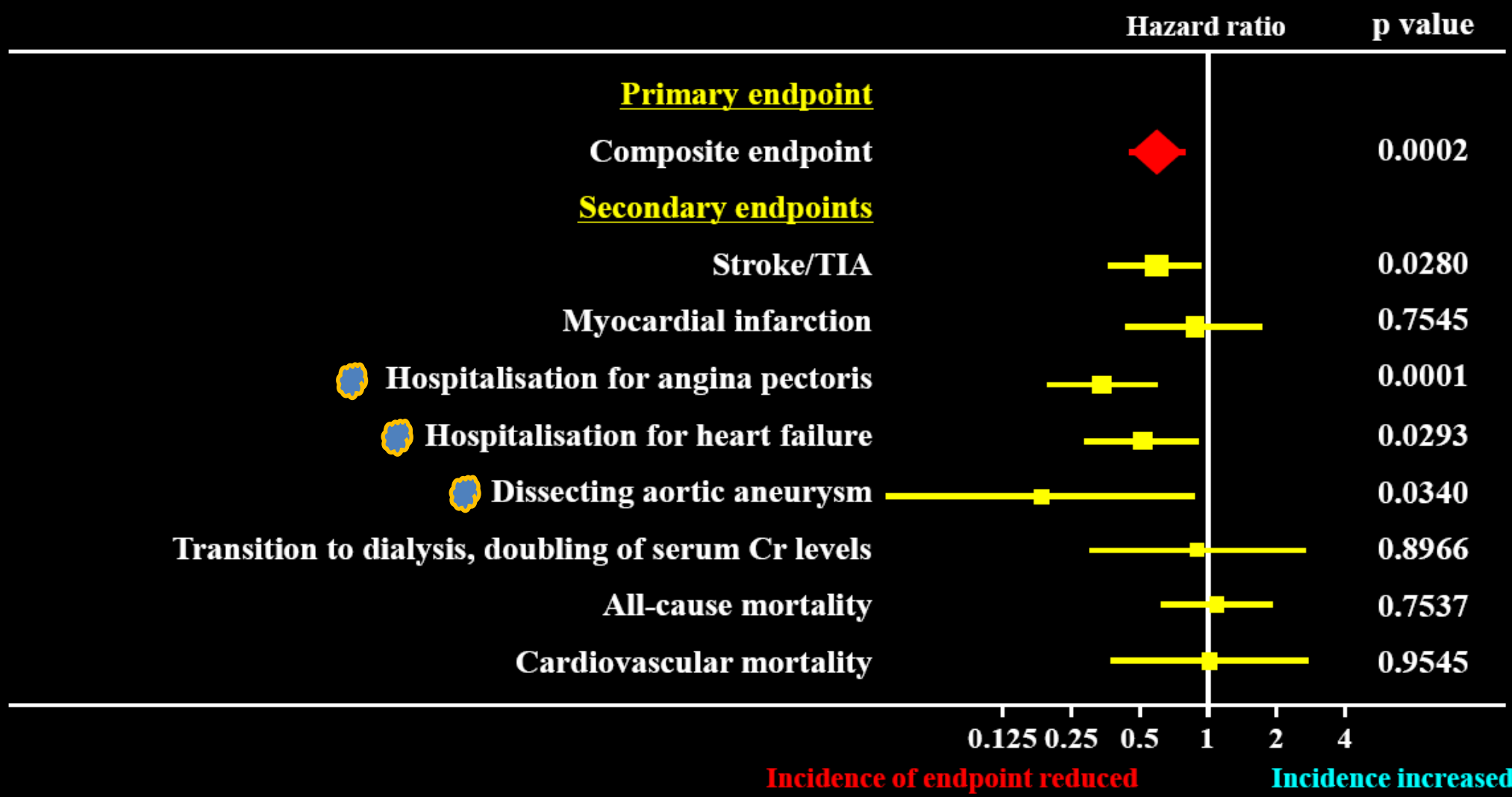
JIKEI

Kaplan-Meier curve of cumulative frequency of the cardiac events: patients with or without CAD



JIKEI HEART Study

Effect of treatment on endpoints

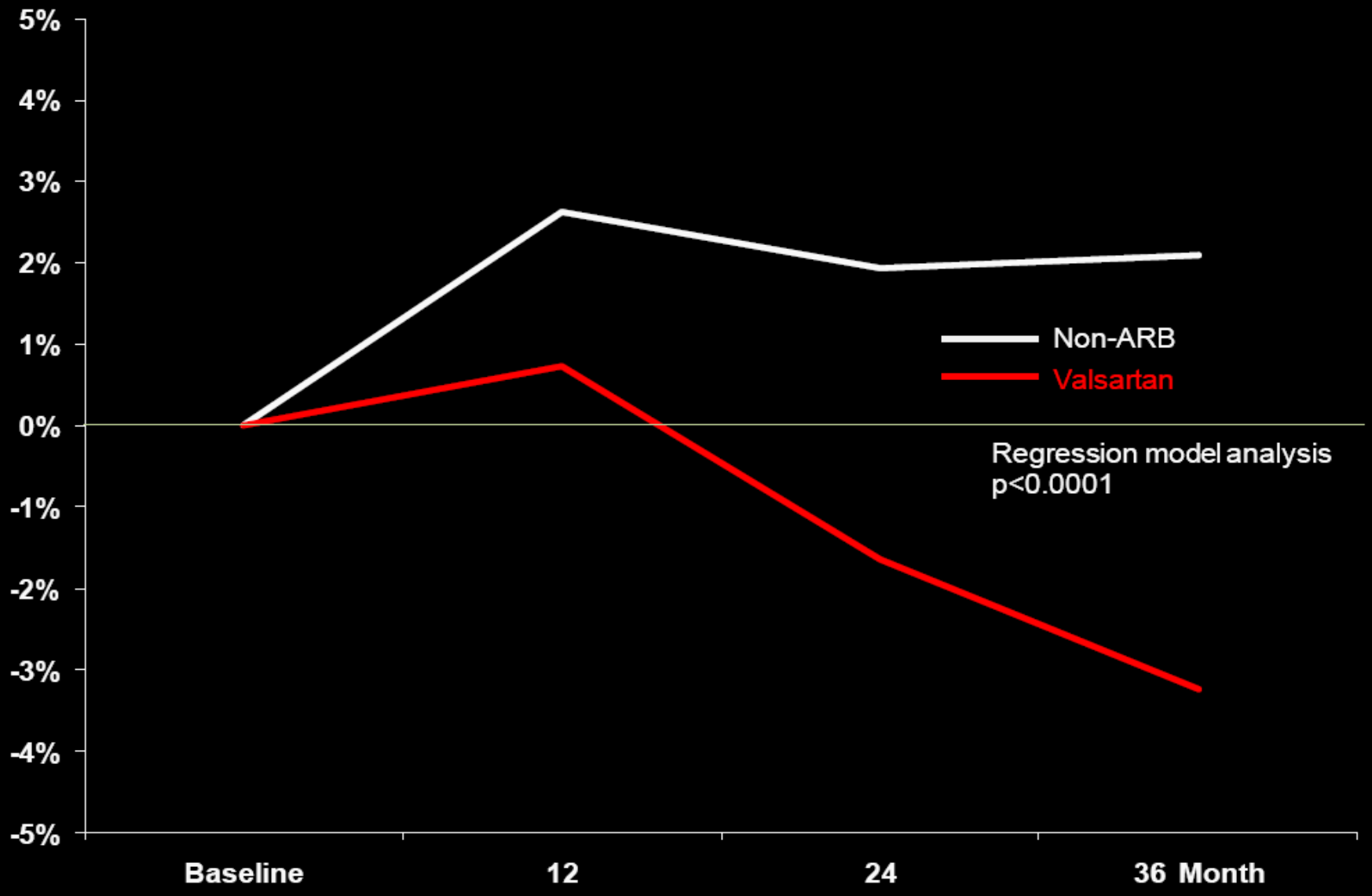


Mochizuki S et al, for the Jikei heart study group: Lancet 2007 ; 369 1431-9

Effect of valsartan in Japanese hypertensive patients with coronary artery disease

JIKEI

Percent changes in LVMI : patients with CAD



KYOTO HEART Study: Effect of Valsartan on cardiovascular outcomes in patients with high-risk hypertension: updated ancillary analyses

H.Matsubara, T.Sawada, H. Yamada, S. Kimura, J. Shiraishi

Kyoto Prefectural University of Medicine, Kyoto, Japan

Study background and hypothesis

- **Although many reports show that ACEi and ARB are superior for prevention of CV events, data are not enough for the patients with high risk hypertension.**
- **In Japan, there were only a few large-scale trials for CVD prevention, and it has not been clarified whether the evident in Western countries could be unqualifiedly applied to Japanese patients.**
- ***Valsartan will improve the CV morbidity and mortality when added to the conventional anti-hypertensive treatment in high-risk Japanese patients with uncontrolled hypertension.***

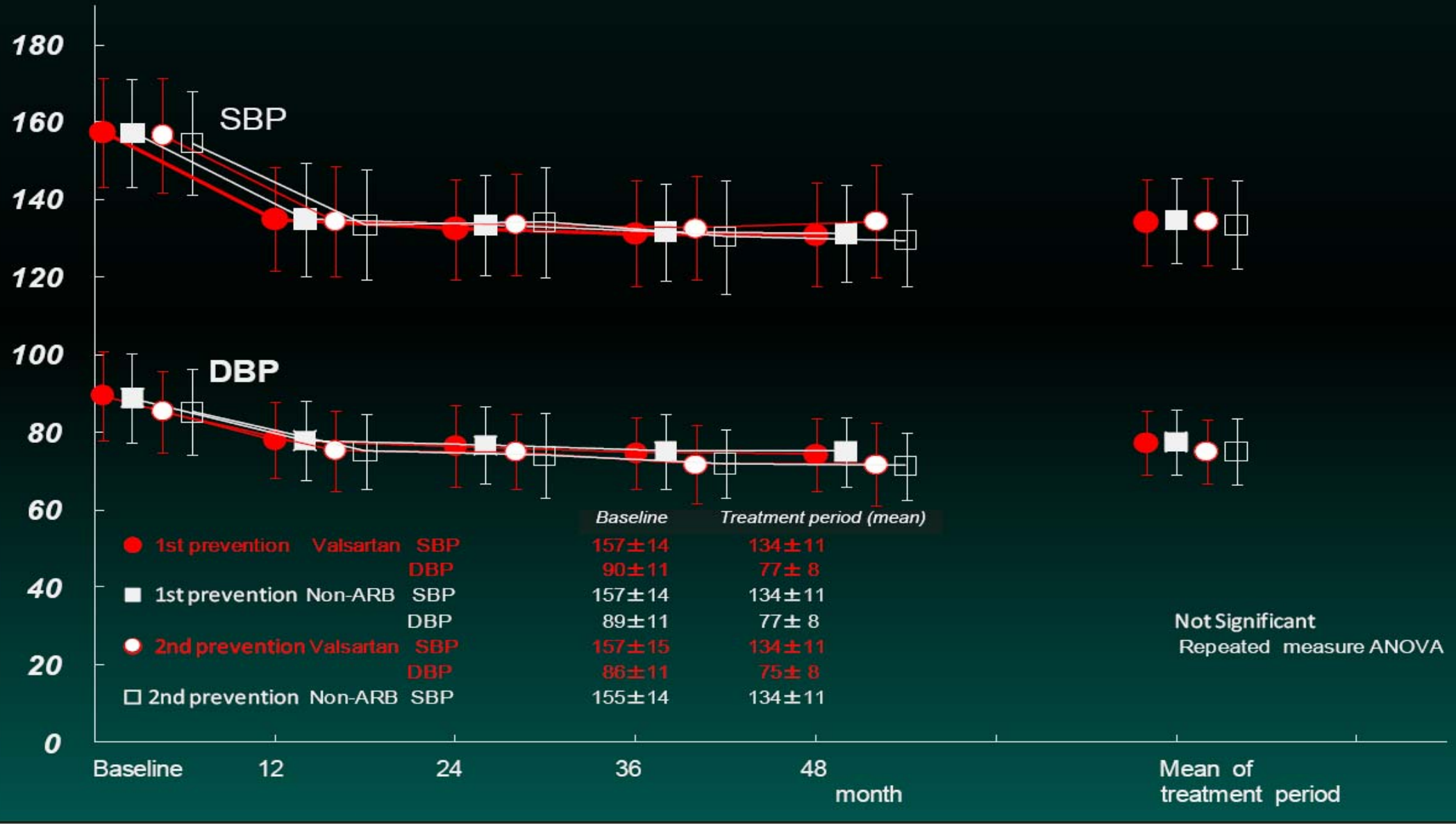
Study purpose

As the ancillary analysis of the KYOTO HEART study, we investigated:

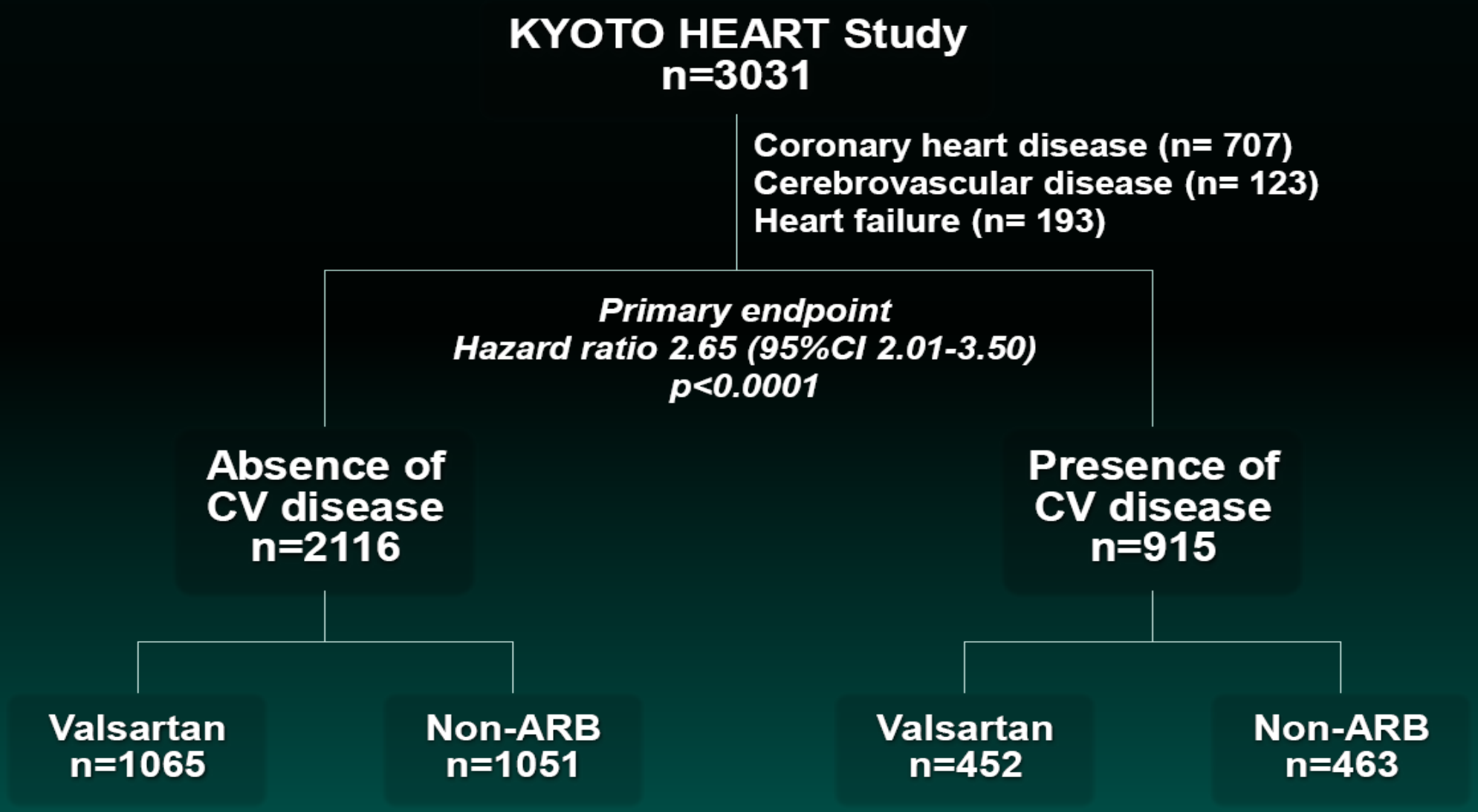
1) Effects of valsartan on primary and secondary prevention
2) Combination therapy with calcium channel blockers (CCB)
3) Additional analysis of angina & stroke events

KYOTO HEART study

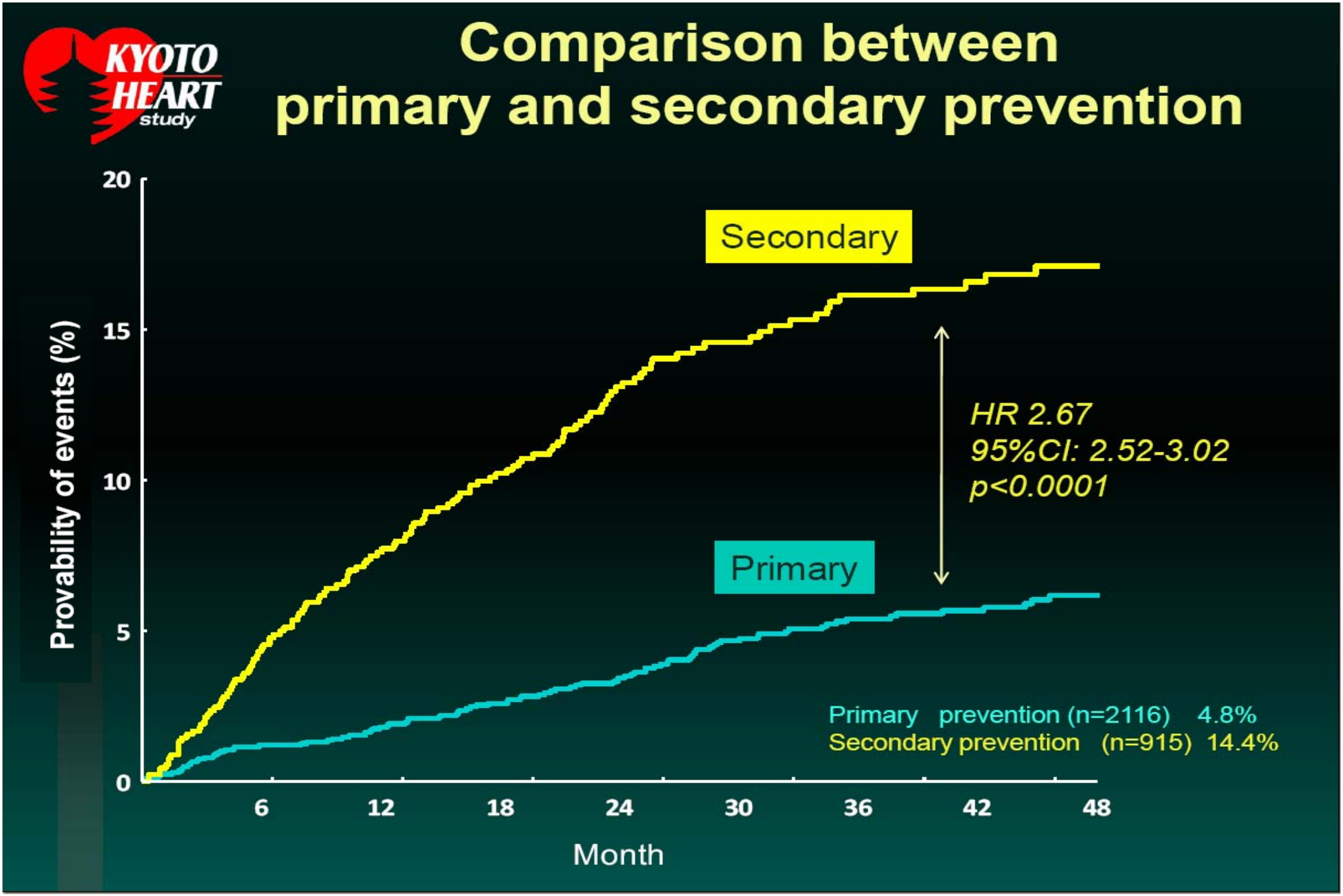
Changes of Blood pressure



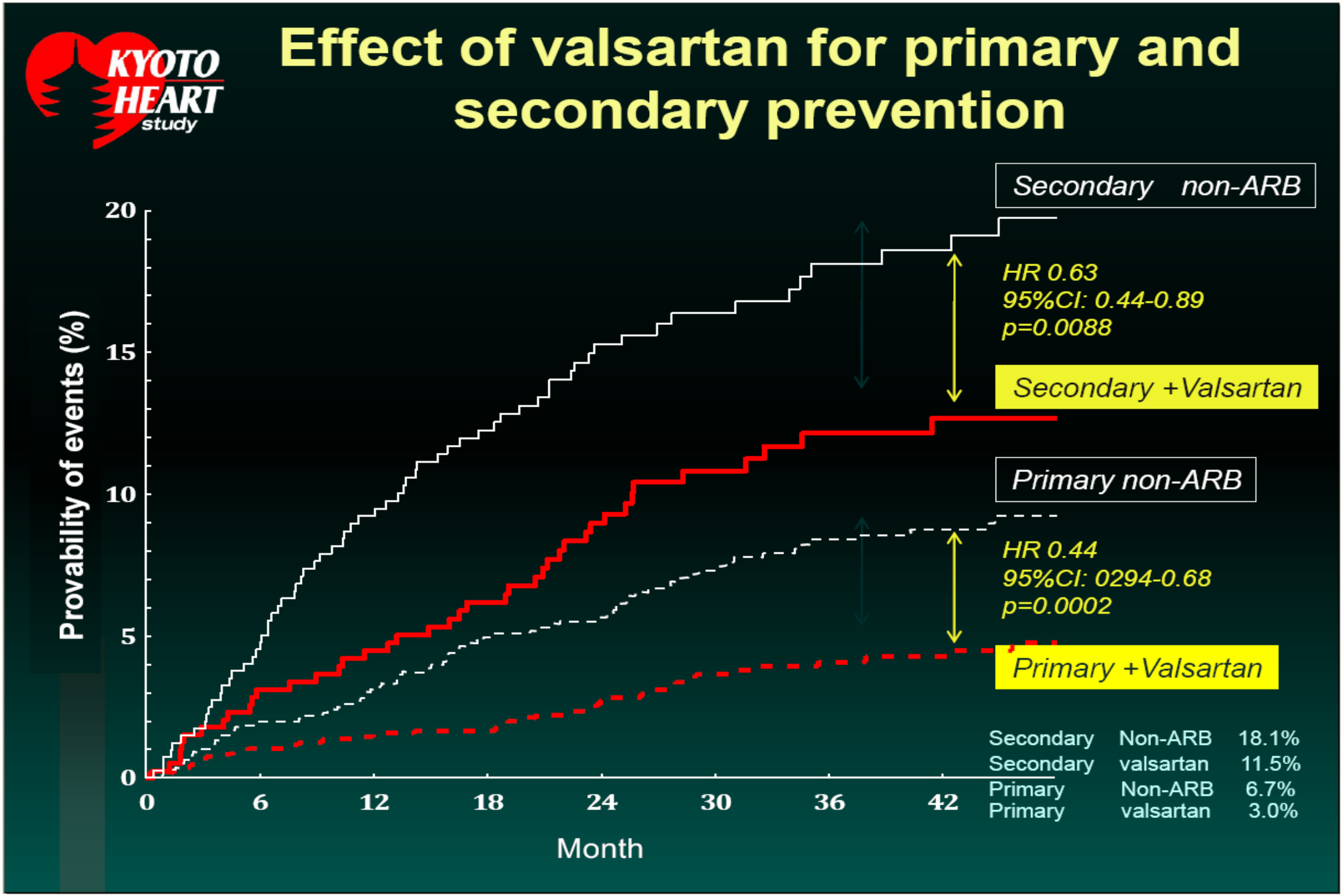
Primary & secondary prevention



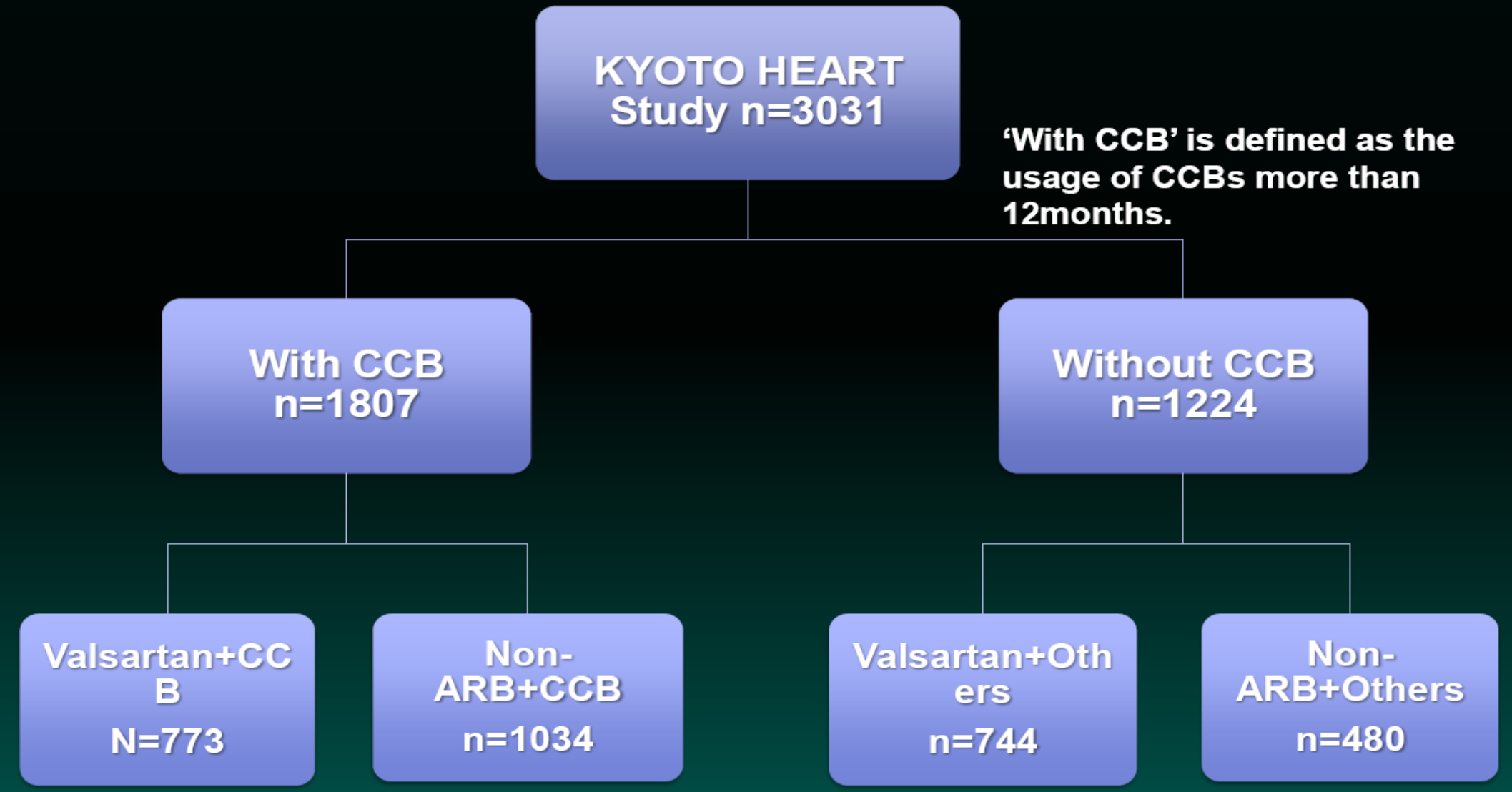
Comparison between primary and secondary prevention



Effect of valsartan for primary and secondary prevention

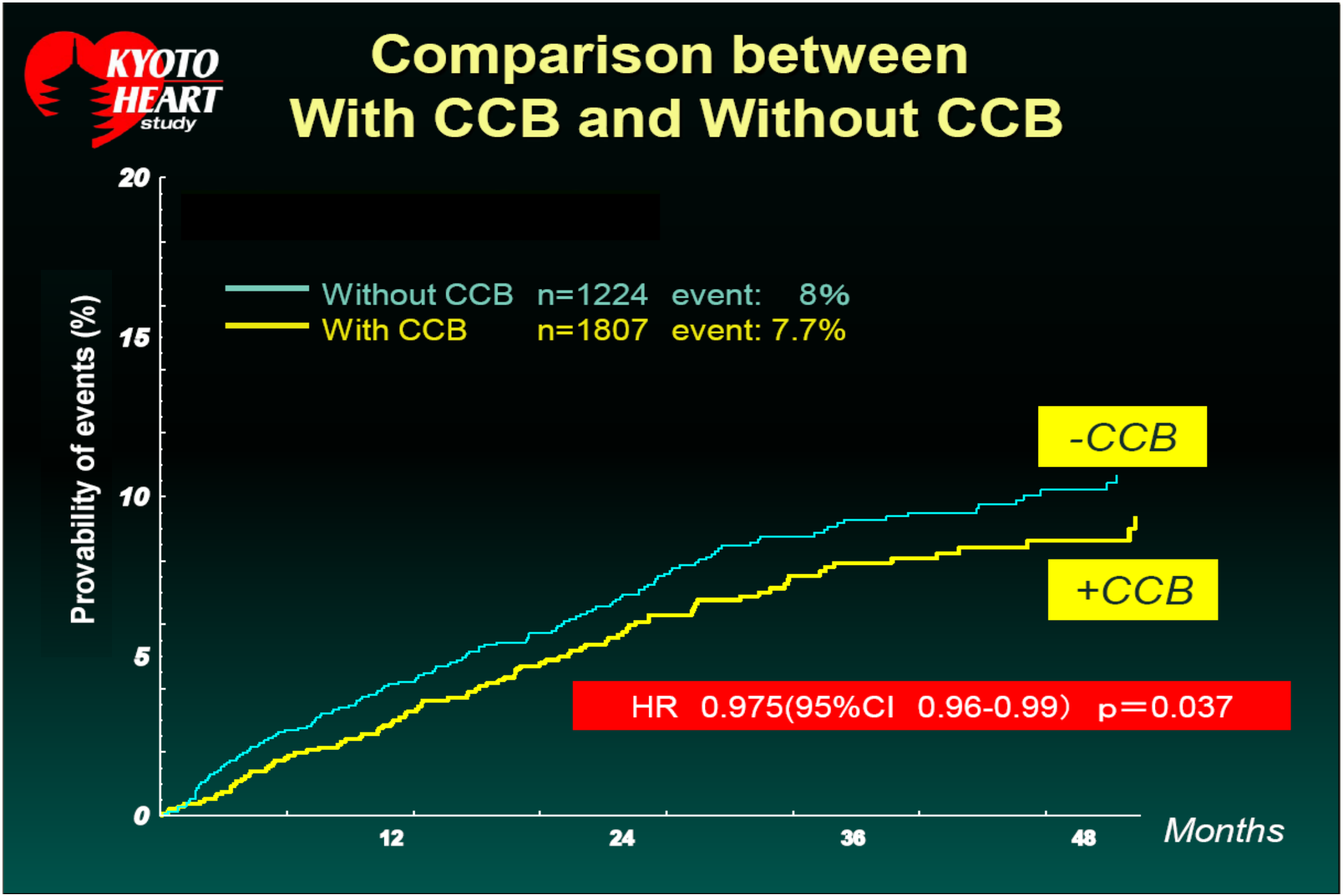


Combination therapy with CCB

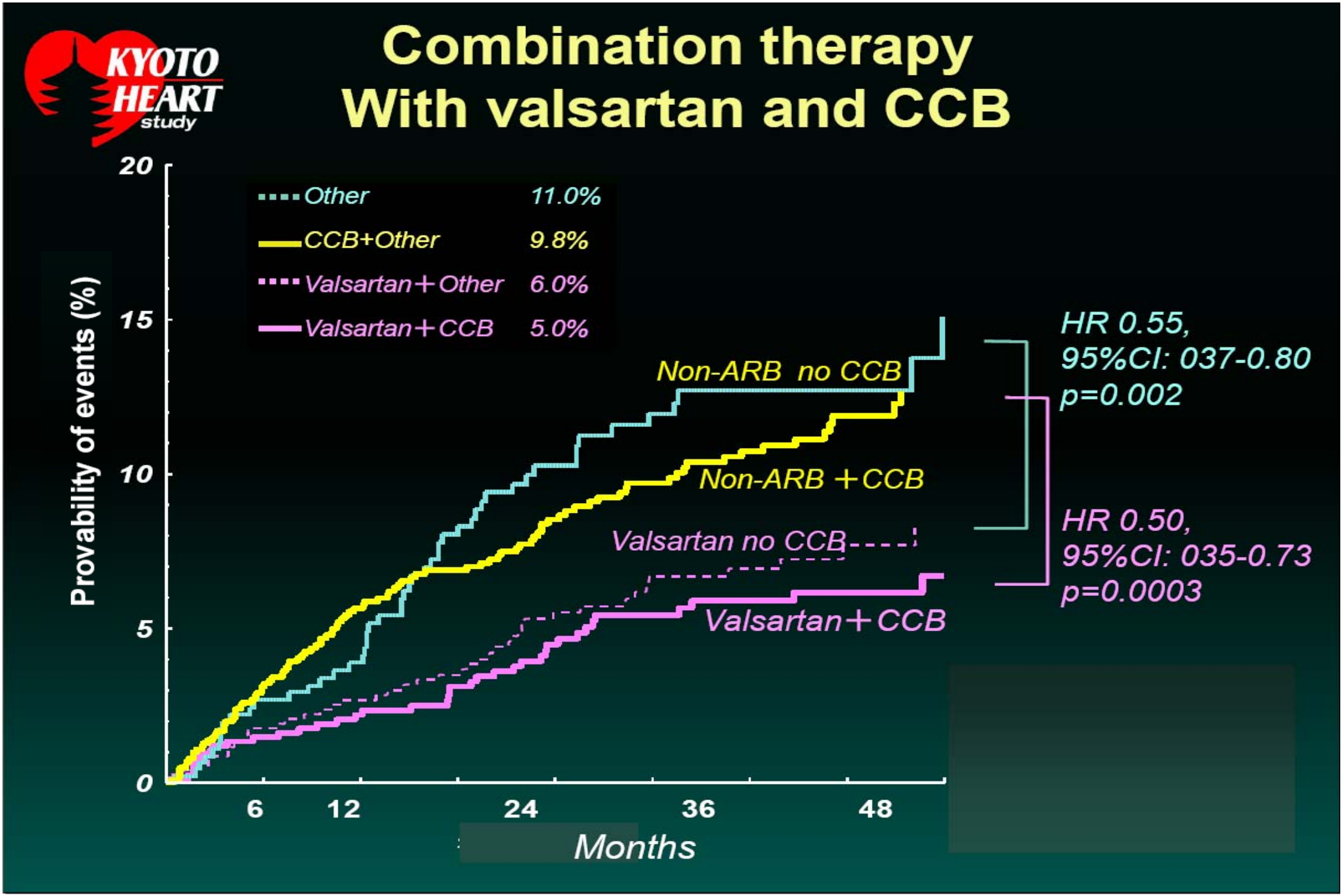


KYOTO HEART study

Comparison between With CCB and Without CCB



Combination therapy With valsartan and CCB

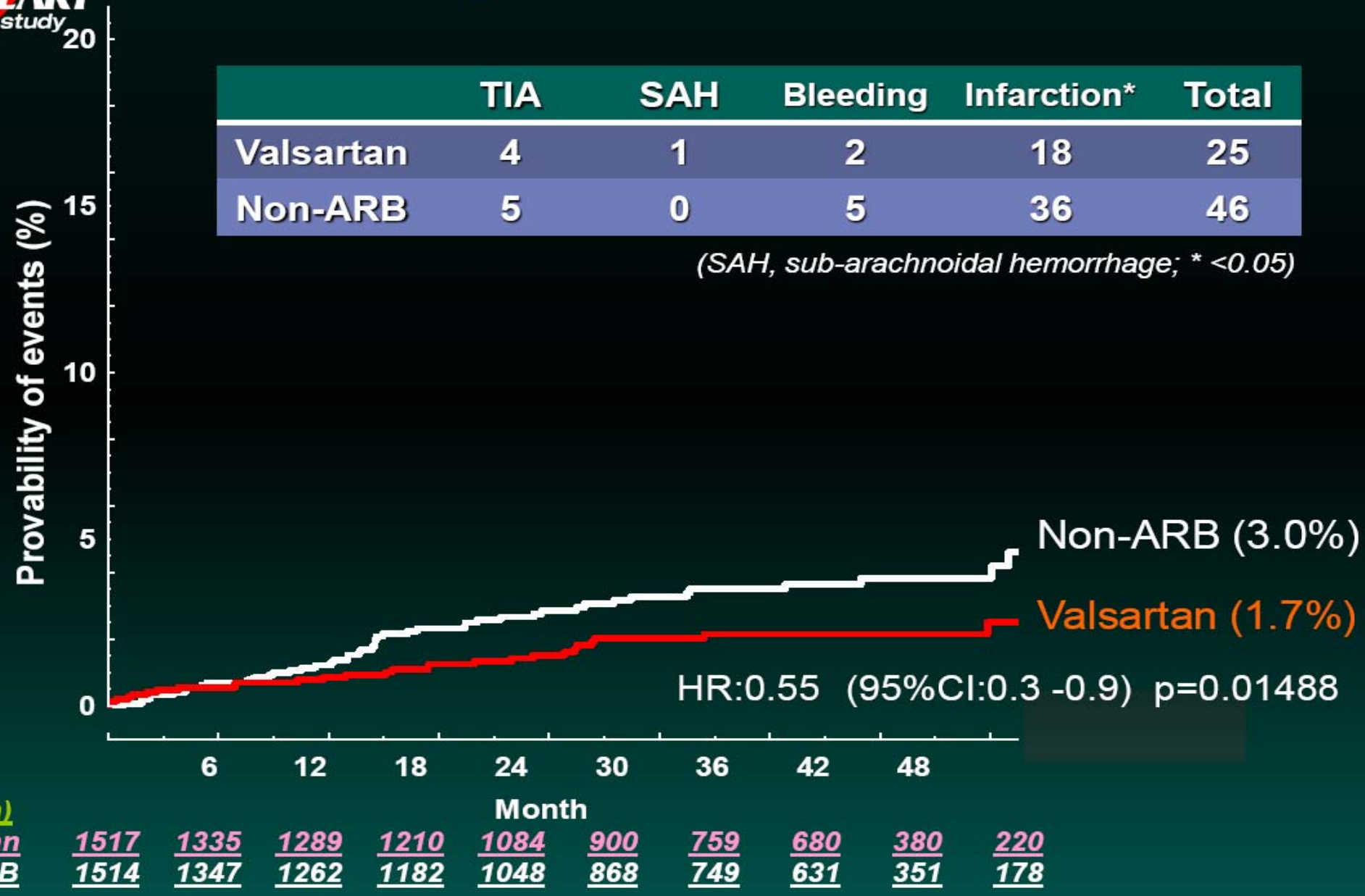


KYOTO HEART study

analysis of stroke events

	TIA	SAH	Bleeding	Infarction*	Total
Valsartan	4	1	2	18	25
Non-ARB	5	0	5	36	46

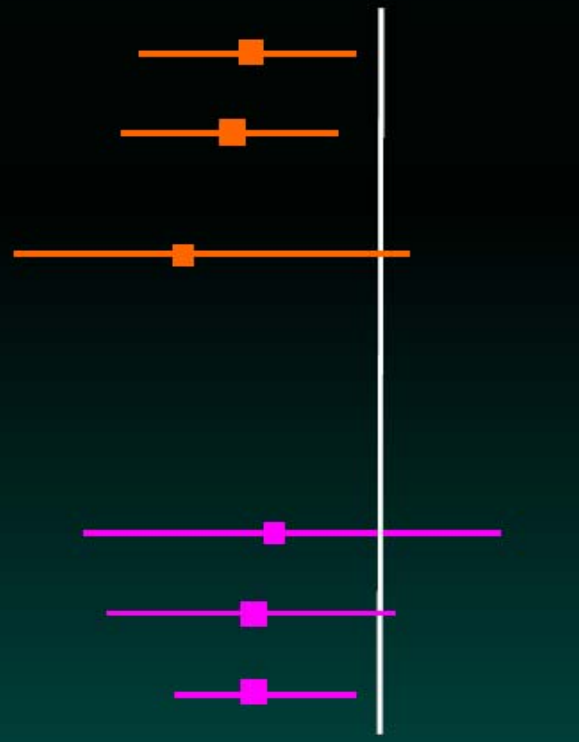
*(SAH, sub-arachnoidal hemorrhage; * <0.05)*



at risk(n)									
Valsartan	1517	1335	1289	1210	1084	900	759	680	380	220
Non-ARB	1514	1347	1262	1182	1048	868	749	631	351	178

Hazard ratio and 95% confidence intervals

Event	Valsartan 1517		Non-ARB 1514		HR	95%CI	p
Angina	22	1.45%	44	2.91%	0.51	0.30 - 0.90	0.0106
Effort	16	1.05%	34	2.25%	0.47	0.26 - 0.86	0.0134
Unstable	3	0.20%	9	0.59%	0.33	0.09 - 1.22	0.0974
Unknown	3	0.20%	1	0.06%			
AMI	7	0.46%	11	0.73%	0.65	0.20 - 1.80	0.6500
ACS	10	0.66%	20	1.32%	0.53	0.24 - 1.14	0.1019
Coronary	29	1.91%	55	3.63%	0.54	0.35 - 0.85	0.0082



AMI, acute myocardial infarction; ACS, acute coronary syndrome, AMI+unstable angina;
Coronary, all events

Summary

- In JIKEY HEART Sub-Study done in 3081 Japanese patients with hypertension, coronary heart disease, and/or heart failure, valsartan adding to conventional therapy resulted in significant 51% reduction in the risk of CV events in CAD patients.
- In the KYOTO HEART subanalysis stratified among primary- and secondary-prevention patients,
  - the benefit of treatment was largest among primary-prevention patients, 56%, and 37% among secondary-prevention patients, which, while smaller, was still statistically significant.
  - patients treated with the valsartan-CCB combination had lower event rates compared with patients in the non-ARB/CCB arm (5.0% vs 9.8%).

Conclusion:
ARB in Japanese Hypertensives

- **ARB is, at least, as effective in Japanese hypertensives as shown in Western patients. This is probably true in other eastern Asians.**

- **“ARBs might not be inferior to ACEis with respect to prevention of MI and CV death”. Therefore, there exits BP-independent effect of ARB in hypertension with high CV risk.**

KYOTO HEART study

Summary

- Valsartan was more effective for both primary prevention (3.0% vs 6.7%) and secondary prevention (11.5% vs 18.1%), in which primary stroke and secondary AP events are significantly inhibited, respectively.
- Combination with Valsartan+CCB showed lower primary events than non-ARB+CCB (5.0% vs 9.8%)
- Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs 36) but not bleeding.
- Valsartan was significantly effective for prevention of effort angina (1.1% vs 2.3%), but not for unstable angina (0.20% vs 0.59%, p=0.10).