

KYOTO HEART Study

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



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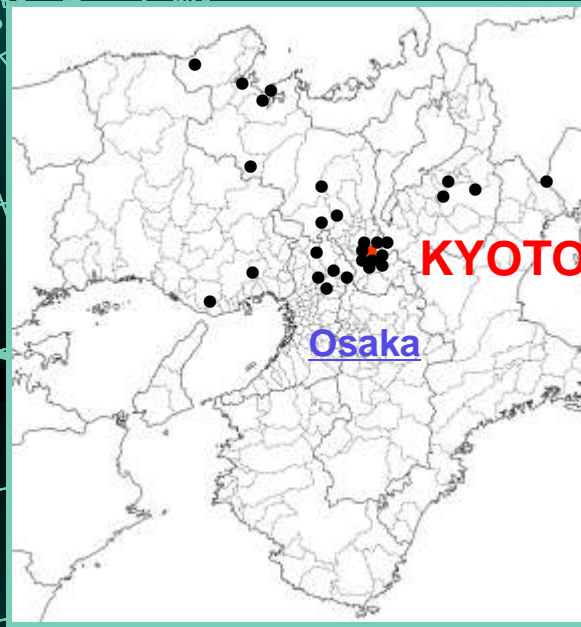
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Conflict of Interest

- ✓ *The study was funded by Kyoto Prefectural University School of Medicine.*
- ✓ *The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The executive committee had full access to all the data at the end of the study, and has final responsibility for the decision to submit for publication.*

KYOTO HEART Study



Hospital's site that participates in KYOTO HEART Study.
This Study was investigated in the Kinki region of Japan. It is comparatively cold climate with the snowfall in winter and the southern part is warm climate. The population concentrates on the ancient city and the large city, and the regional city is scattered radially. Therefore, The Kinki region is like the downsized Japan. Each plot shows the site of the participation hospitals.



Study background

- ✓ *Although many reports show that ACE inhibitors and ARB are superior for prevention of cardiovascular events, previous data are not enough for the patients with high risk hypertension.*
- ✓ *In Japan, there were only a few large-scale trials for cardiovascular disease prevention, and it has not been clarified whether the evidence in Western countries could be unqualifiedly applied to Japanese patients as a long term strategy.*



Study hypothesis

Valsartan will improve the cardiovascular morbidity and mortality when added to the conventional anti-hypertensive treatment in high-risk Japanese patients with uncontrolled hypertension.



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*



Inclusion criteria

- ✓ Clinical diagnosis of hypertension
 - ✓ Mean sitting SBP \geq 140 and /or DBP \geq 90mmHg
- ✓ Clinical diagnosis of one or more risk factors
 - ✓ Diabetes
 - ✓ Smoking habit
 - ✓ Lipid metabolism abnormality
 - ✓ History of ischemic heart disease or cerebrovascular disease >6 months before the screening
 - ✓ Obesity (BMI \geq 25)
 - ✓ Left ventricular hypertrophy (LVH) in ECG



Exclusion criteria

- ✓ *Patients who have already been administered ARB*
- ✓ *Patients with IHD within 6 months after PCI, and who are stable but are going to implement PCI or CABG*
- ✓ *Severe / malignant / secondary hypertensive patients*
- ✓ *Pregnant women and women of childbearing potential*
- ✓ *History of acute heart failure, unstable angina, MI, PCI, or CABG within the preceding 6 months*
- ✓ *Arrhythmia needed to be treated or accompanied with symptoms, second or third degree AV block*
- ✓ *Severe renal impairment (Serum creatinine >3.0 mg/dl)*
- ✓ *Severe hepatic impairment (Hepatic failure, Cirrhosis)*



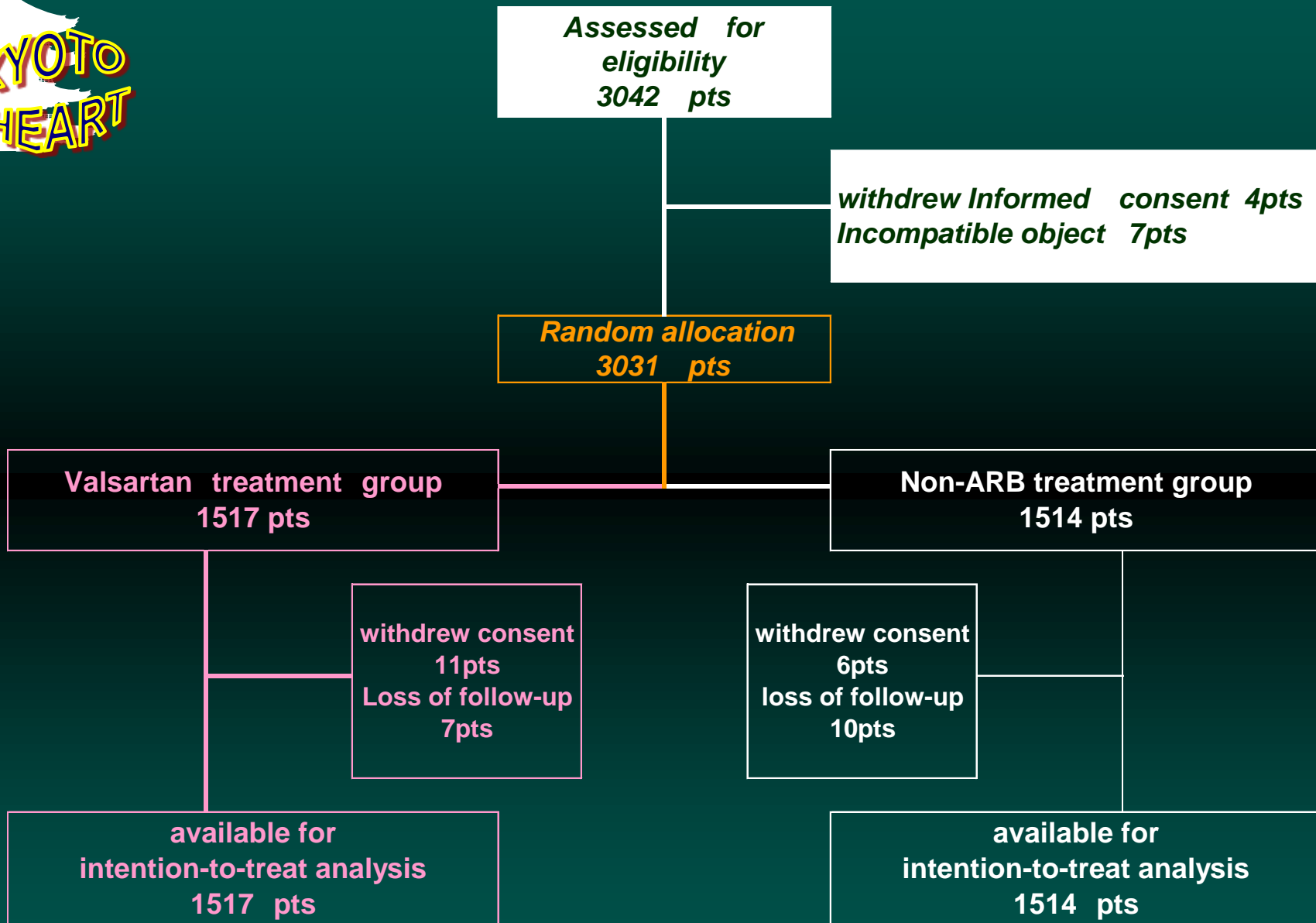
Primary endpoint

- ✓ *Fatal & non-fatal cardiovascular events
(Composite Endpoints)*
 - ✓ *New onset or recurrence of stroke*
 - ✓ *New onset or recurrence of transient ischemic attack*
 - ✓ *New onset or recurrence of acute MI*
 - ✓ *Hospitalization due to heart failure*
 - ✓ *Hospitalization due to angina pectoris*
 - ✓ *Operation of PCI or CABG*
 - ✓ *New onset of aortic dissection*
 - ✓ *New onset, recurrence or worsening of ASO*
 - ✓ *Transition to dialysis, doubling of plasma Cr levels*



Secondary endpoint

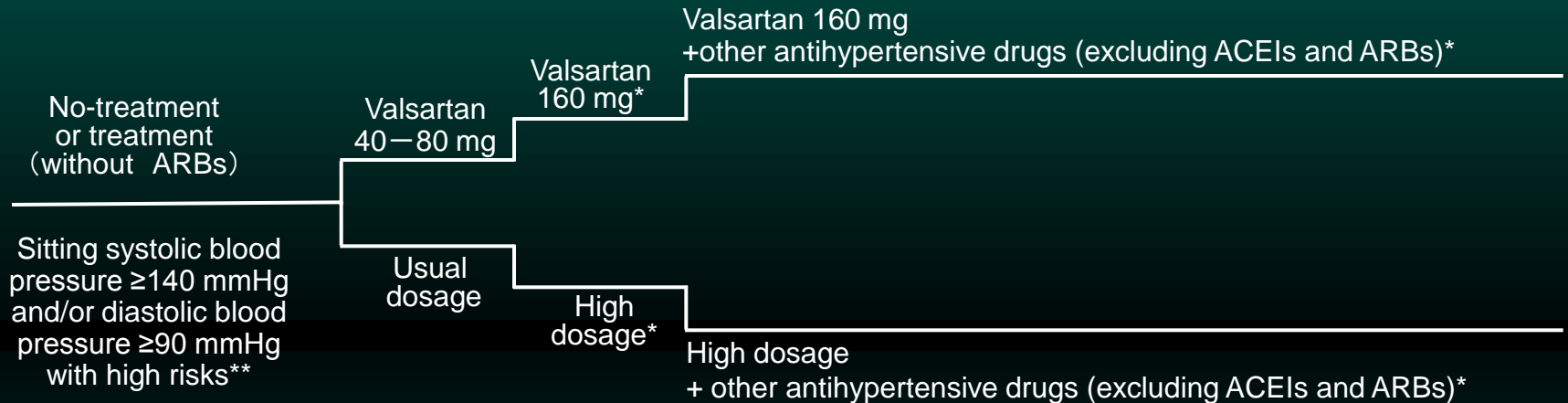
- ✓ *All cause mortality*
- ✓ *Worsening of cardiac function*
- ✓ *New onset or worsening of arrhythmias*
- ✓ *New onset or worsening of diabetes mellitus or IGT*
- ✓ *Uncontrolled blood pressure, etc.*





Scheme of study protocol

ARB add-on group



Non- ARB treatment group

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

Month

-1

0

1

2

6

12

18

24

30

36



Entry

Randomization

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.



Baseline characteristics

	Valsartan N=1517		Non-ARB N=1514	
Age	66	(11)	66	(11)
men/women	861/656	(57/43 %)	867/647	(57/43 %)
current smoker	341	(22%)	332	(22%)
Obesity BMI≥25	593	(39%)	584	(39%)
Coronary artery disease	355	(23%)	352	(23%)
Cerebrovascular disease	58	(4%)	65	(4%)
Heart failure	84	(6%)	109	(7%)
Diabetes	401	(26%)	406	(27%)
Dyslipidemia	1065	(70%)	1079	(71%)
LVH by electrocardiogram	122	(8%)	129	(9%)



Biochemical data at baseline

	Valsartan N=1517		Non-ARB N=1514	
Systolic blood pressure (mmHg)	157	(14)	157	(14)
Diastolic blood pressure (mmHg)	88	(11)	88	(11)
Heart rate (bpm)	70	(18)	70	(16)
EF (%)	63	(10)	63	(9)
HDL cholesterol (mg/dL)	55	(15)	55	(15)
LDL cholesterol (mg/dL)	121	(31)	123	(31)
Triglyceride (mg/dL)	147	(83)	150	(84)
Fasting plasma glucose (mg/dL)	121	(43)	121	(43)
HbA1c (%)	6.1	(2.3)	6.0	(1.3)
Serum creatinine (mg/dL)	0.87	(0.35)	0.84	(0.38)
Sodium (mEq/L)	142	(2.7)	142	(2.5)
Potassium (mEq/L)	4.5	(2.2)	4.3	(2.2)
Mean(SD)				



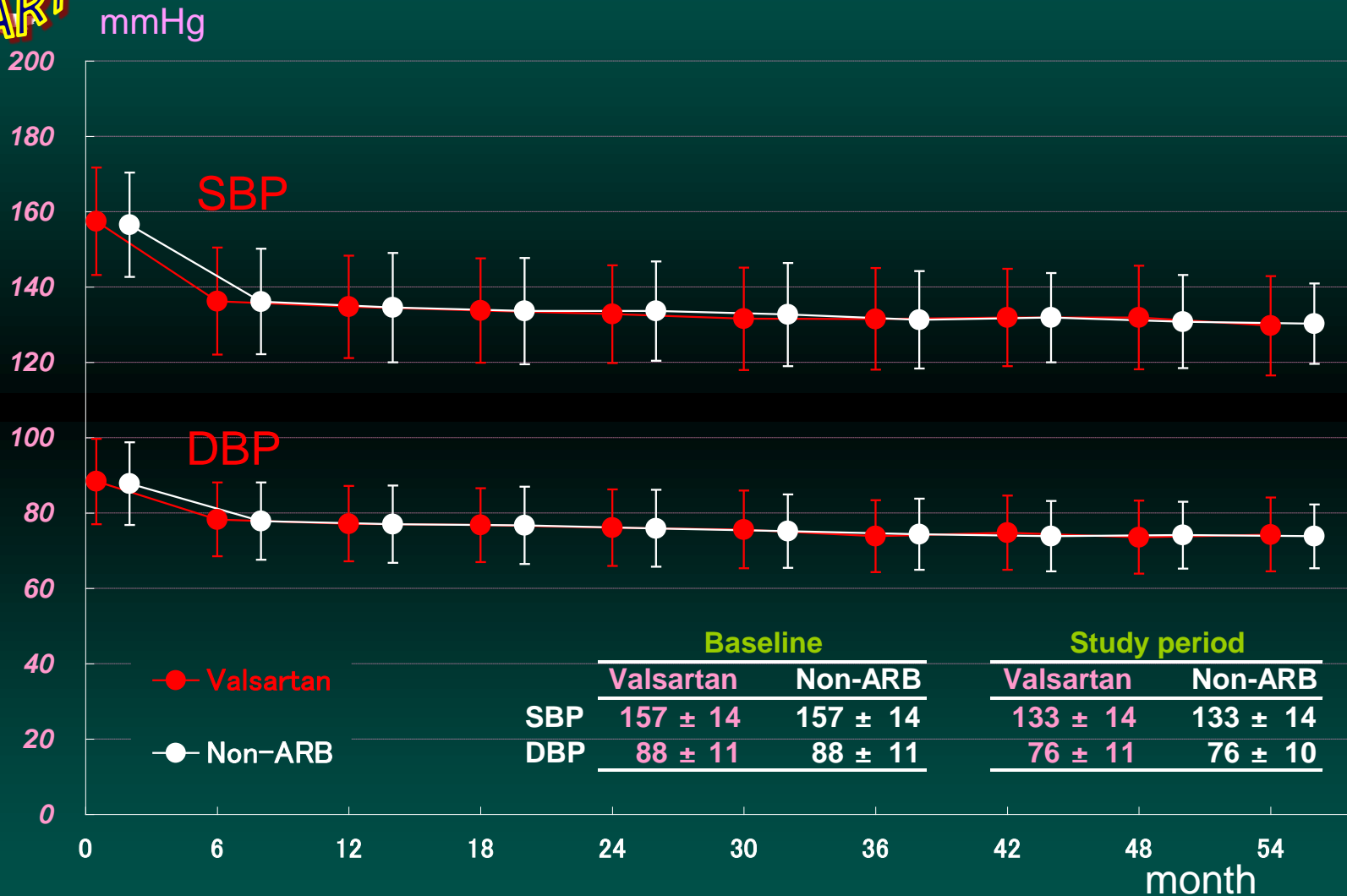
Medications at baseline

	Valsartan N=1517		Non-ARB N=1514	
Angiotensin converting enzyme inhibitor	289	(19%)	305	(20%)
Calcium-channel blocker	825	(54%)	832	(55%)
α blocker	45	(3%)	51	(3%)
β blocker	264	(17%)	277	(18%)
Anti-aldosterone agents	31	(2%)	26	(2%)
Thiazide	52	(3%)	45	(3%)
Other diuretics	76	(5%)	86	(6%)
Statin	491	(32%)	503	(33%)
Fibrate	35	(2%)	30	(2%)
Oral hypoglycemic agents	219	(14%)	202	(13%)
Anti-coagulation agents	89	(6%)	106	(7%)
Anti-platelet agents	402	(26%)	427	(28%)

Data are number (%).



Changes of blood pressure



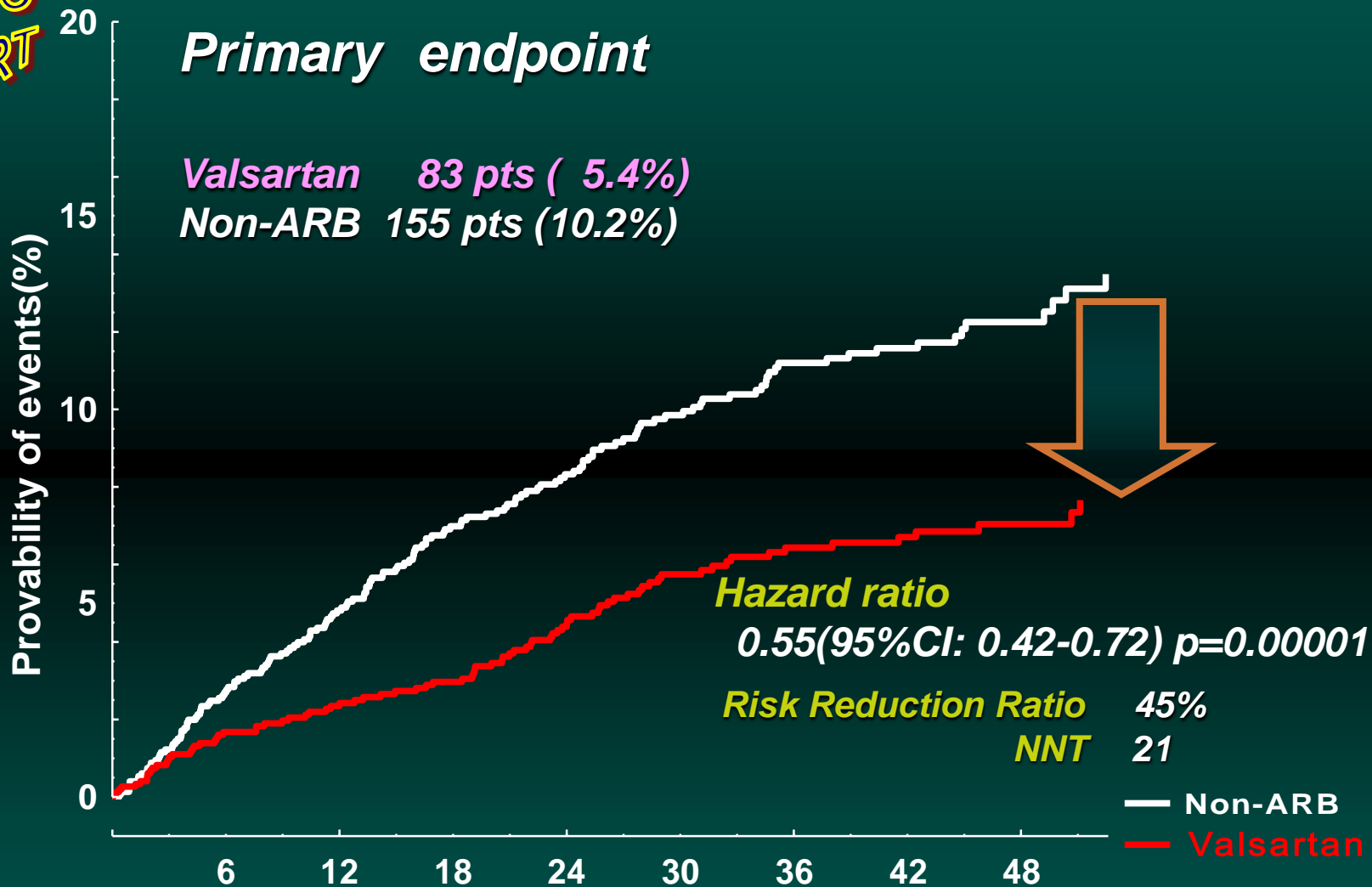


Kaplan-Meier's curves

Primary endpoint

Valsartan 83 pts (5.4%)

Non-ARB 155 pts (10.2%)



at risk (n=)

month

Valsartan	1517	1355	1289	1217	1084	901	768	647	380	220
Non-ARB	1514	1377	1262	1167	1048	868	749	631	351	179

Hazard ratio and 95% confidence intervals



**KYOTO
HEART**

Primary endpoint

Acute Myocardial Infarction

Angina Pectris

Heart Failure

Stroke

Dissecting Aneurysm of Aorta

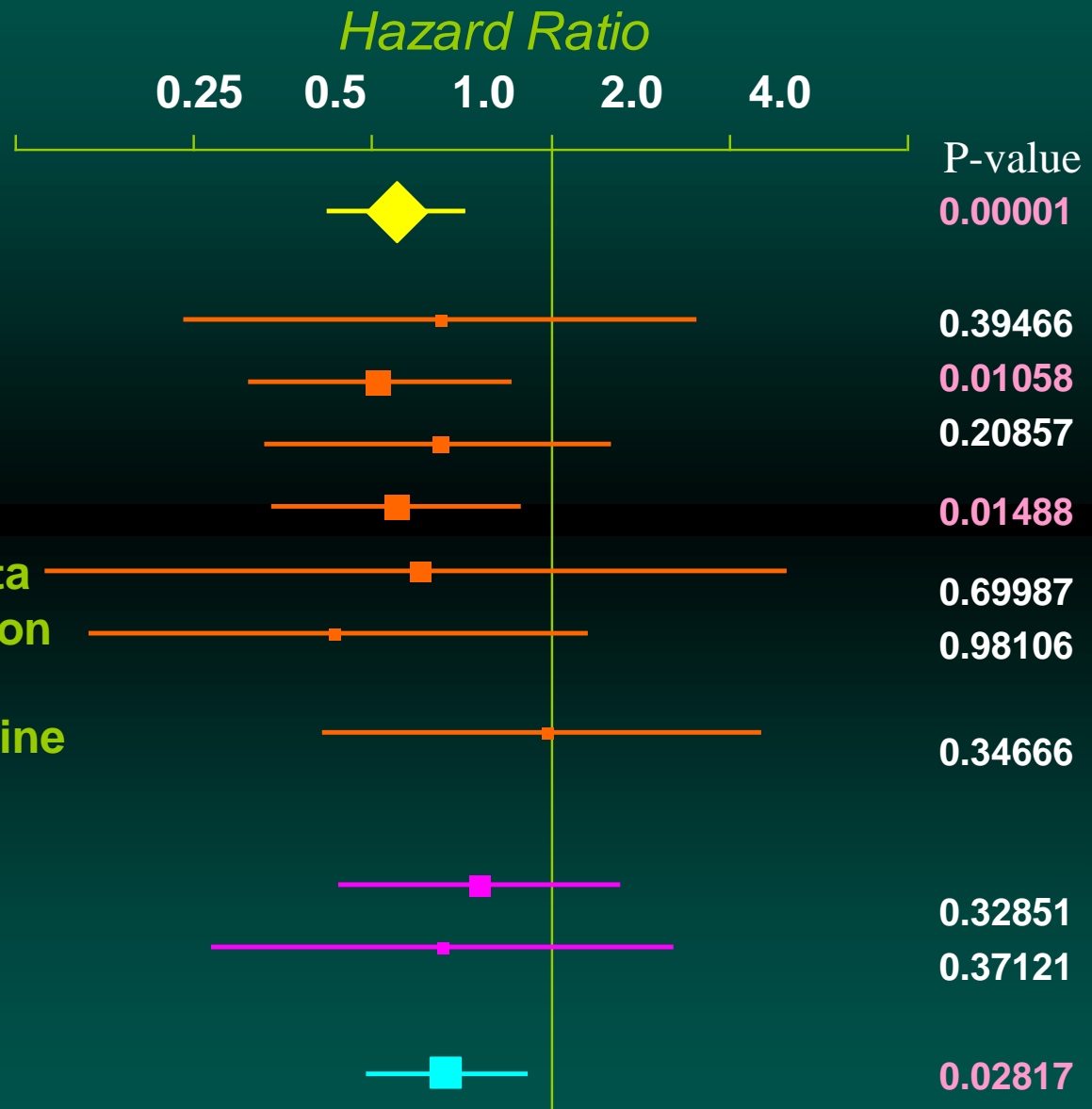
Lower limb arterial obstruction

**Transition to dialysis
or doubling of serum creatinine
levels**

All cause mortality

Cardiovascular death

New onset Diabetes



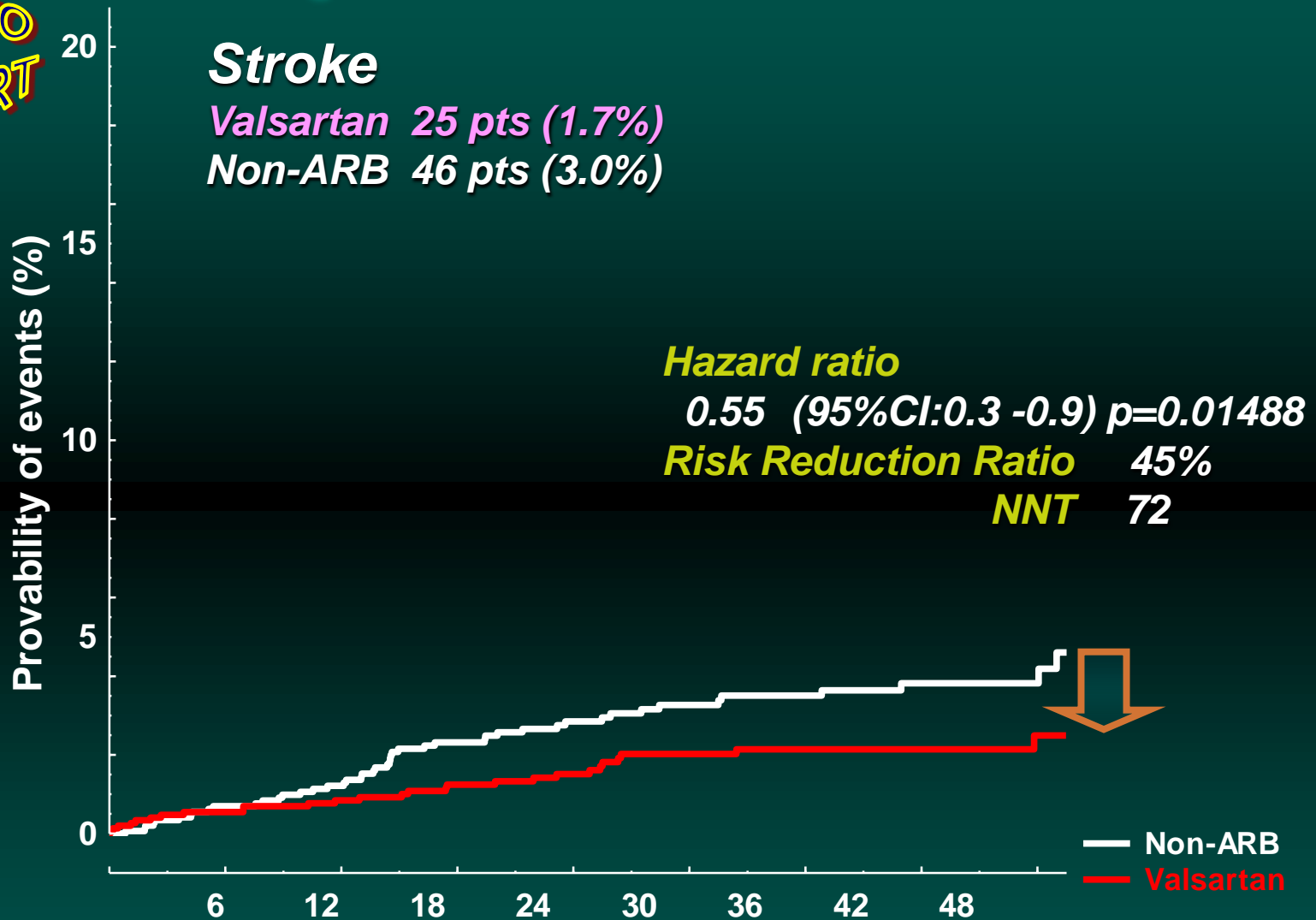


Kaplan-Meier's curves

Stroke

Valsartan 25 pts (1.7%)

Non-ARB 46 pts (3.0%)



at risk(n)

	0	6	12	18	24	30	36	42	48	
<u>Valsartan</u>	<u>1517</u>	<u>1335</u>	<u>1289</u>	<u>1210</u>	<u>1084</u>	<u>900</u>	<u>759</u>	<u>680</u>	<u>380</u>	<u>220</u>
<u>Non-ARB</u>	<u>1514</u>	<u>1347</u>	<u>1262</u>	<u>1182</u>	<u>1048</u>	<u>868</u>	<u>749</u>	<u>631</u>	<u>351</u>	<u>178</u>



Kaplan-Meier's curves

Angina

Valsartan 22 pts (1.5%)

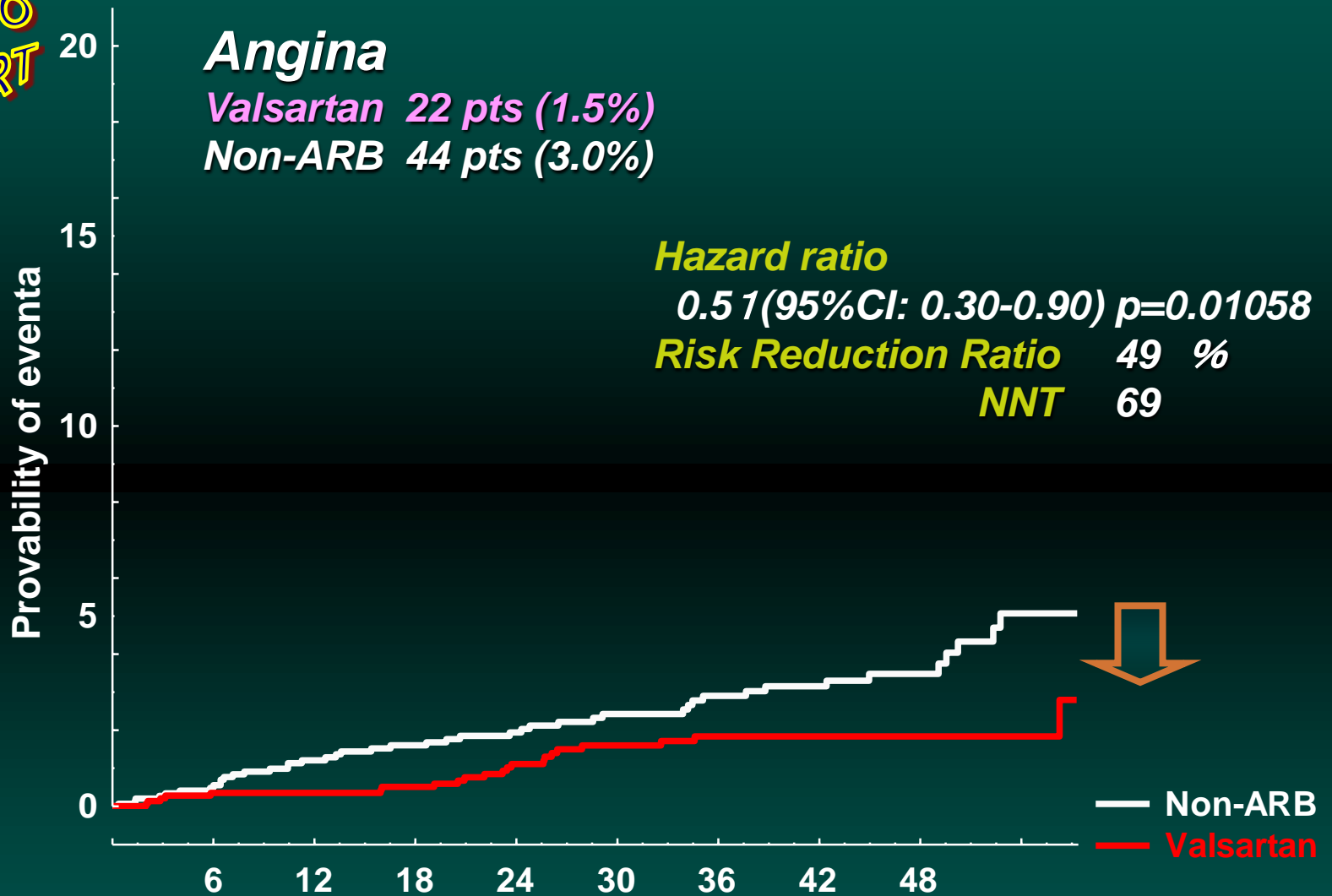
Non-ARB 44 pts (3.0%)

Hazard ratio

0.51 (95%CI: 0.30-0.90) $p=0.01058$

Risk Reduction Ratio 49 %

NNT 69



at risk(n)

	0	6	12	18	24	30	36	42	48	
<u>Valsartan</u>	<u>1517</u>	<u>1352</u>	<u>1289</u>	<u>1214</u>	<u>1084</u>	<u>899</u>	<u>766</u>	<u>647</u>	<u>377</u>	<u>220</u>
<u>Non-ARB</u>	<u>1514</u>	<u>1374</u>	<u>1262</u>	<u>1177</u>	<u>1048</u>	<u>868</u>	<u>749</u>	<u>631</u>	<u>351</u>	<u>177</u>



Biochemical markers during the study period

	Valsartan				Non-ARB			
	Baseline		mean of study period		Baseline		mean of study period	
S V1 wave and R V5/V6 wave, EF(%)	3.1	(2.9)	3.0	(0.9)	3.0	(2.1)	3.1	(1.3)
FS(%)	63	(10)	62	(7)	63	(9)	62	(9)
HDL cholesterol (mg/DL)	38	(8)	38	(6)	38	(7)	38	(7)
LDL cholesterol (mg/DL)	55	(15)	55	(15)	55	(15)	53	(12)
Triglyceride (mg/DL)	121	(31)	103	(25)	123	(31)	108	(21)
Fasting plasma glucose (mg/DL)	147	(83)	156	(86)	150	(84)	149	(84)
HbA1c (%)	121	(43)	125	(41)	121	(43)	128	(43)
Serum creatinine (mg/DL)	6.1	(2.3)	6.0	(0.9)	6.0	(1.3)	6.0	(1.1)
Sodium (mg/DL)	0.9	(0.4)	0.9	(0.3)	0.8	(0.4)	0.9	(0.3)
Potassium (mEq)	142	(3)	142	(2)	142	(3)	142	(2)
BUN(mg/DL)	4.5	(2.2)	4.3	(0.3)	4.3	(2.2)	4.2	(0.4)
Uric acid(mg/DL)	16	(5)	18	(5)	16	(6)	16	(5)
	5.7	(2.4)	6.0	(5.6)	5.8	(3.2)	5.7	(6.8)



Adverse events during the study

Adverse events (n≥2)	Valsartan		Non-ARB	
Cancer or metastasis	12	(0.8%)	14	(0.9%)
Stomach discomfort	9	(0.6%)	11	(0.7%)
Dizziness	8	(0.5%)	9	(0.6%)
Haemoptysis	5	(0.3%)	7	(0.5%)
Rashes	4	(0.3%)	6	(0.4%)
Headache	2	(0.1%)	6	(0.4%)
Gastrointestinal bleeding	3	(0.2%)	4	(0.3%)
Liver dysfunction	3	(0.2%)	4	(0.3%)
Dry cough	2	(0.1%)	4	(0.3%)
Elevated serum potassium	4	(0.3%)	2	(0.1%)
Cellulitis	1	(0.1%)	3	(0.2%)
Palpitations	2	(0.1%)	2	(0.1%)
Fracture	1	(0.1%)	3	(0.2%)
Other adverse event	41	(2.7%)	39	(2.6%)
	97	3.2%	114	3.8%



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.*



Study organization

Executive committee

Hiroaki Matsubara (Chair), Kyoto Prefectural University of Medicine
Björn Dahlöf, Sahlgrenska University Hospital/ Östra, Göteborg, Sweden

Steering committee

Takahisa Sawada (Main Steering Committee), Tomosaburo Takahashi,
Hiroyuki Yamada, Kyoto Prefectural University of Medicine

Endpoint committee

Jitsuo Higaki, Ehime University Graduate School of Medicine; Shohei Kim-
Mitsuyama, Kumamoto University School of Medicine; Toshihiro Ichiki,
Kyushu University School of Medicine

Safety committee

Masafumi Kitakaze, National Cardiovascular Center; Tetsuro Sugiura, Kochi
University School of Medicine; Hiromi Rakugi, Osaka University School of
Medicine

Data and safety monitoring board

Katsumi Yagi, Louis Pasteur Center for Medical Research; Keiichi Kanda,
Chouhei Sakakura, Kyoto Prefectural University of Medicine

Statistical analysis organization

Katsumi Yagi, Louis Pasteur Center for Medical Research

Data monitoring board

Marika Miki, Sachiko Toyoda, Kyoto Prefectural University School of Medicine