Cardiovascular protective effects of valsartan in high-risk hypertensive patients with chronic kidney disease: updated analysis of KYOTO HEART Study

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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.

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FASTTRACK
ESC HOT LINE

Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study

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See page 2427 for the commentary on this article (doi:10.1093/eurheartj/ehp364)

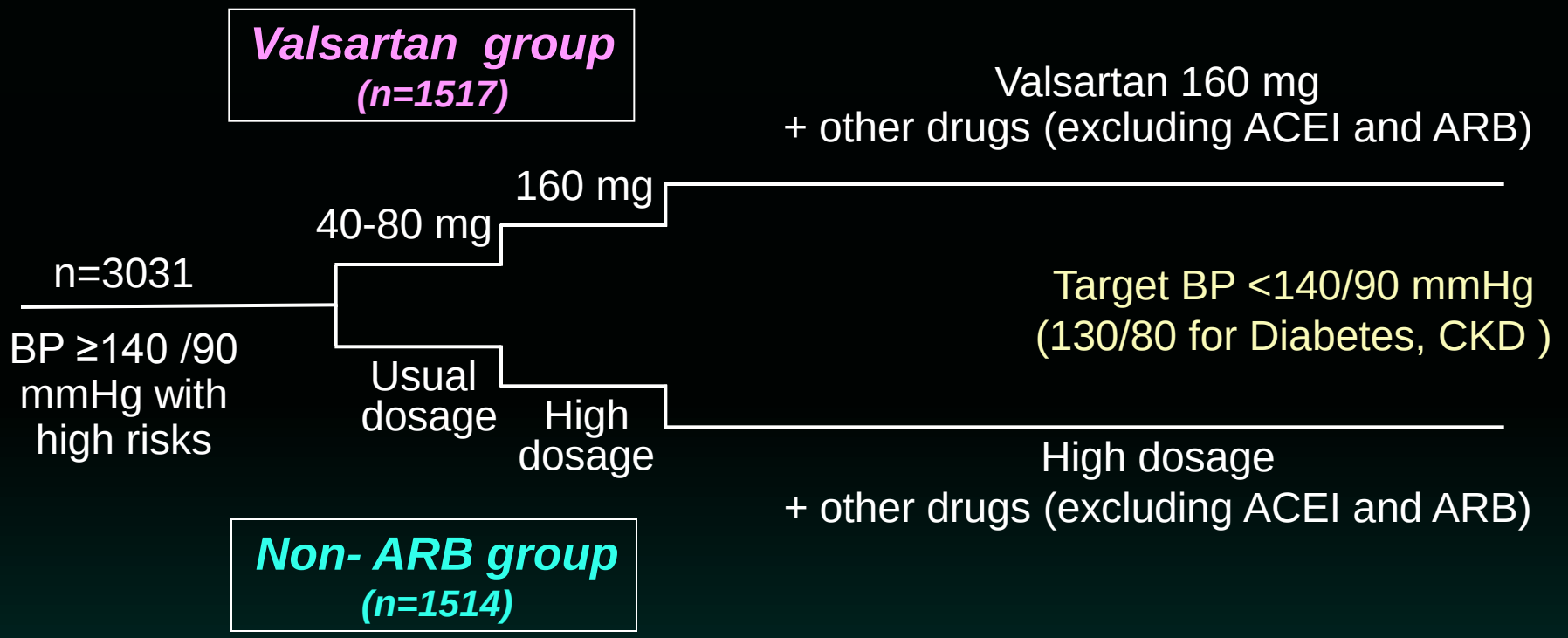
Aims The objective was to assess the add-on effect of valsartan on top of the conventional treatment for high-risk hypertension in terms of the morbidity and mortality.

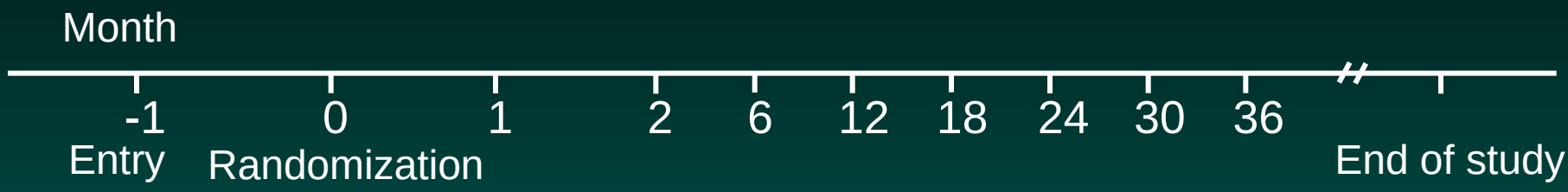
Methods and results The KYOTO HEART Study was of a multicentre, Prospective Randomised Open Blinded Endpoint (PROBE) design, and the primary endpoint was a composite of fatal and non-fatal cardiovascular events (clintrials.gov NCT00149227). A total of 3031 Japanese patients (43% female, mean 66 years) with uncontrolled hypertension were randomized to either valsartan add-on or non-ARB treatment. Median follow-up period was 3.27 years. In both groups, blood pressure at baseline was 157/88 and 133/76 mmHg at the end of study. Compared with non-ARB arm, valsartan add-on arm had fewer primary endpoints (83 vs. 155; HR 0.55, 95% CI 0.42–0.72, $P = 0.00001$).

Conclusion Valsartan add-on treatment to improve blood pressure control prevented more cardiovascular events than conventional non-ARB treatment in high-risk hypertensive patients in Japan. These benefits cannot be entirely explained by a difference in blood pressure control.

Keywords High-risk hypertension • Angiotensin receptor blockers • Cardiovascular mortality–morbidity • Valsartan

Scheme of study protocol





Multi-center, PROBE design, two-arm parallel treatment group comparison study with a response-dependent dose titration scheme

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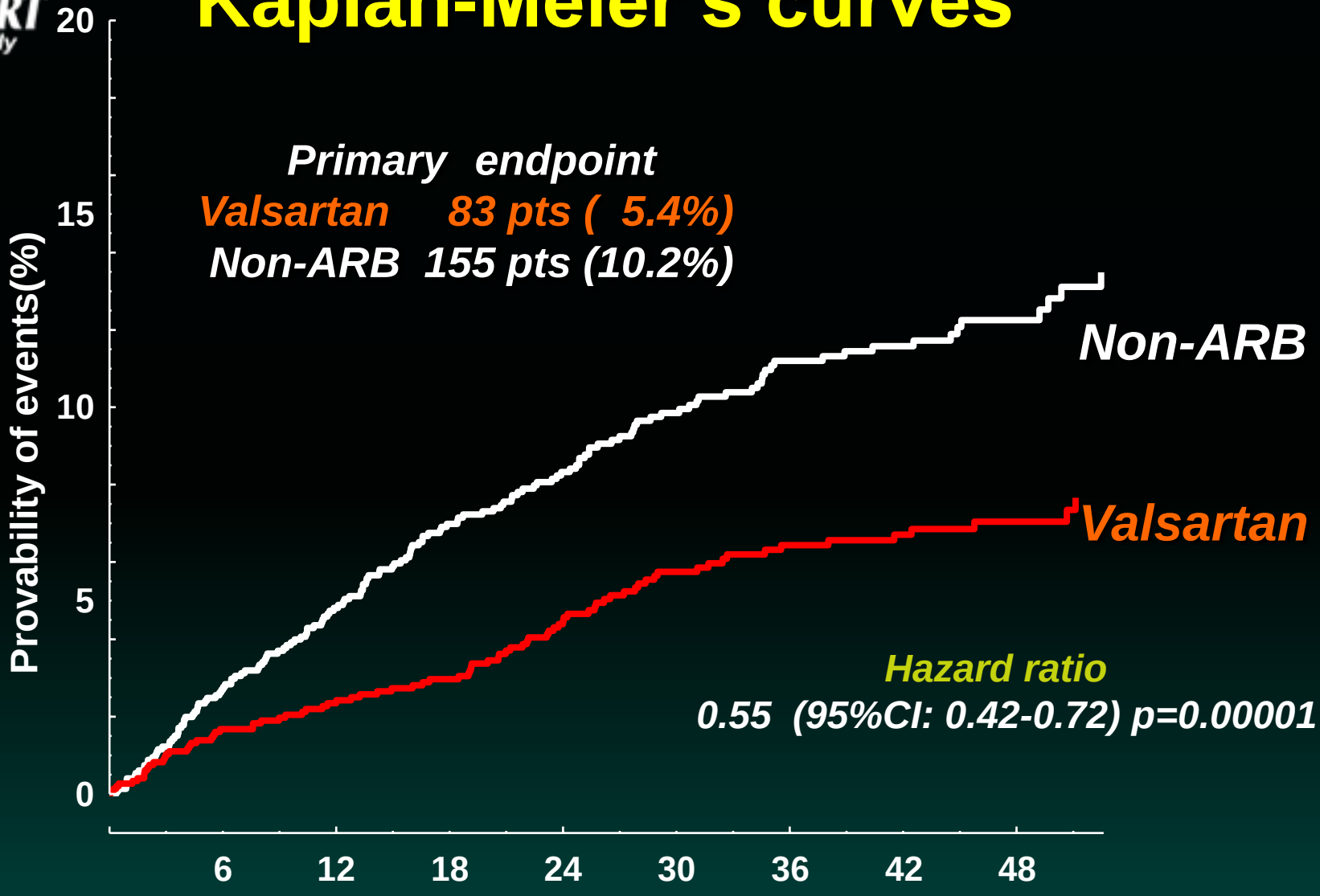
Kaplan-Meier's curves



at risk (n=)									
Valsartan	1517	1355	1289	1217	1084	901	768	647	380
Non-ARB	1514	1377	1262	1167	1048	868	749	631	351

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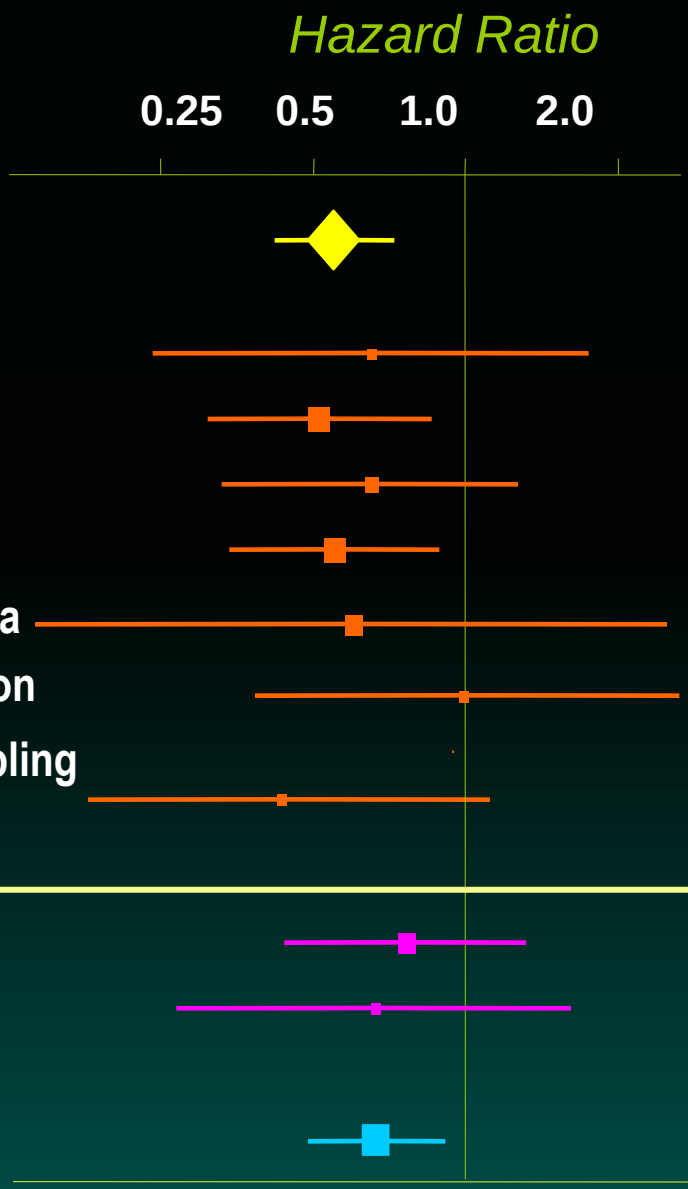
Hazard ratio and 95% confidence intervals



	Patients (n)		HR	*P*-value
	Valsartan	Non-ARB		
Primary endpoint	83	155	0.55	0.00001
Acute Myocardial Infarction	7	11	0.65	0.39466
Angina Pectoris	22	44	0.51	0.01058
Heart Failure	12	26	0.65	0.20857
Stroke	25	46	0.55	0.01488
Dissecting Aneurysm of Aorta	3	5	0.60	0.69987
Lower limb arterial obstruction	11	12	0.99	0.98106
Transition to dialysis or doubling of serum creatinine level	6	14	0.43	0.34666
All cause mortality	22	32	0.76	0.32851
Cardiovascular death	8	13	0.66	0.37121
New onset Diabetes	58	86	0.67	0.02817

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Background

- Chronic renal dysfunction is an independent risk factor for cardiovascular disease (CVD).

(Circulation 2003;108:2154, J Am Soc Nephrol 2003;14:3233.)

- Chronic kidney disease (CKD) is associated with increased CVD-related and all-cause mortality rates.

(Am J Kidney Dis 2003;42:677.)

- Dysfunction of the heart can develop the kidney dysfunction in various clinical settings.

(Am Heart J 2005;149:209, J Card Fail 2007;13:422-430.)

- Bidirectional interaction between CKD and CVD is defined as cardiorenal syndrome.

(Circulation 2010;121:2592-2600.)

Study purpose

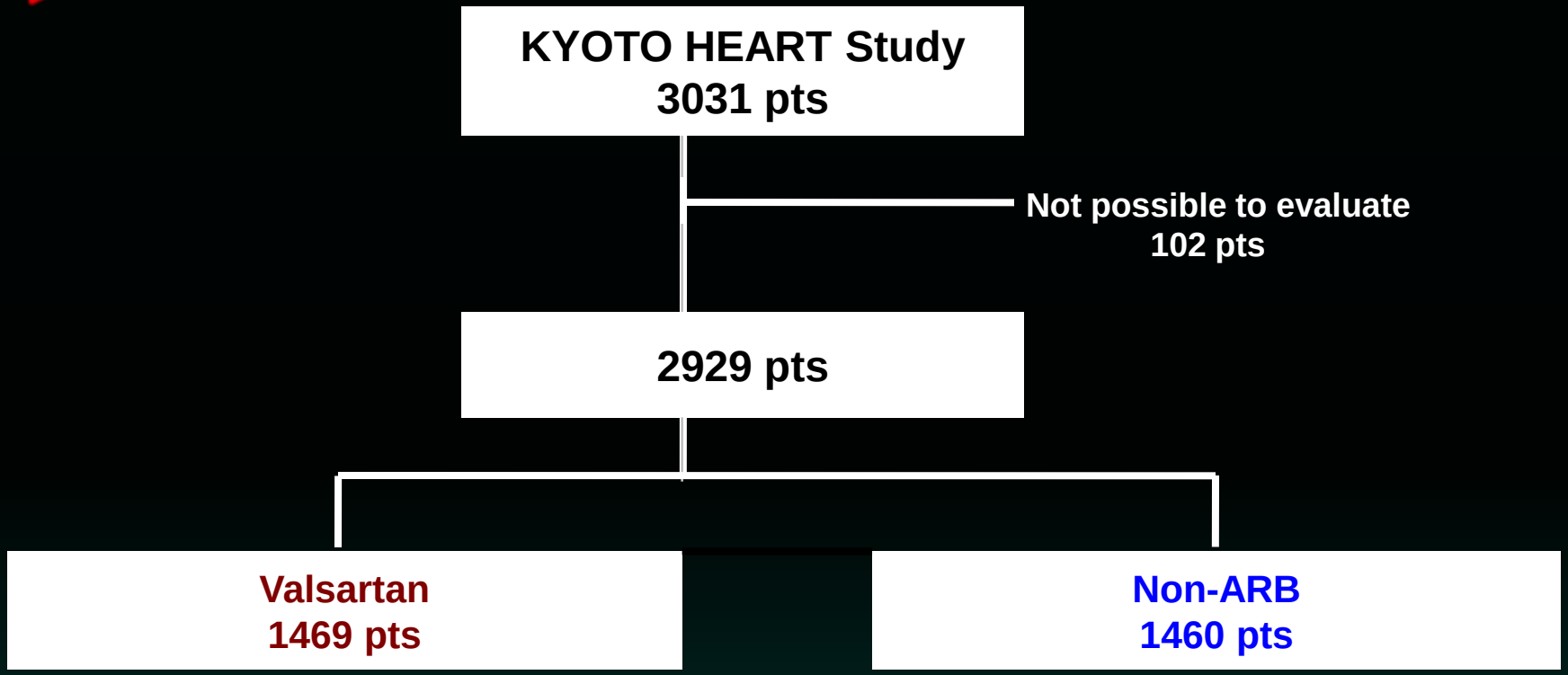
As the ancillary analysis of the KYOTO HEART study, we investigated the cardiovascular protective effects of valsartan in high-risk hypertensive patients with chronic kidney disease.

Method

- Estimated glomerular filtration rate (eGFR) at study entry
  - eGFR (mL/min/1.73 m^2) = 194 x Serum $Cr^{(-1.094)}$ x $Age^{(-0.287)}$ x 0.739 (if female)

    (Revised equations for eGFR from sCr in Japan. Am J Kidney Dis 2009; 53:982.)
- Comparison between With-CKD and Without-CKD groups
  - CKD was defined by eGFR of less than 60 (mL/min per 1.73 m^2)
  - The primary endpoint was the same as in the main study: Composite of defined cardio- or cerebro-vascular events such as stroke/TIA, MI, worsening heart failure, angina pectoris, dissecting aortic aneurysm, lower limb arterial obstruction, transition to dialysis or doubling of serum creatinine levels.
- Relationship between CKD severity and CV events
  - The study population were staged into five categories
  - CKD-1 (eGFR>=90 mL/min/1.73m^2), CKD-2 (60-89), CKD-3 (30-59), CKD-4 (15-29) and CKD-5 (<15) according to the K/DOQI clinical practice guidelines for CKD. (Am J Kidney Dis 2002; 39(2 Suppl 1):S1.)

Flow chart of the study population



CKD Stage	N		CKD
1	175	12%	Without CKD 67%
2	814	55%	
3	456	31%	With-CKD 33%
4	20	1.4%	
5	4	0.3%	

CKD Stage	N		CKD
1	183	13%	Without-CKD 66%
2	776	53%	
3	474	32%	With-CKD 34%
4	20	1.4%	
5	7	0.5%	

Baseline characteristics

	With-CKD			Without-CKD		
	Valsartan	Non-ARB	ALL	Valsartan	Non-ARB	ALL
	480	501	981	989	959	1948
Age (years)*	70 ± 10	70 ± 10	70 ± 10	63.9 ± 11.1	63.8 ± 11	63.8 ± 11
Gender (men/women)	273 / 207	276 / 225	549 / 432	563 / 426	561 / 398	1124 / 824
Blood pressure (mmHg)						
Systole	158 ± 15	158 ± 15	158 ± 15	157 ± 14	156 ± 13	156 ± 14
Diastole	88 ± 12	87 ± 12	87 ± 12	89 ± 11	88 ± 11	89 ± 11
Heart rate (beats/min)	71 ± 19	72 ± 15	71 ± 17	70 ± 17	70 ± 17	70 ± 17
Body-mass index (kg/m^2)	25 ± 3.5	24 ± 3.9	24 ± 3.7	24.5 ± 3.7	24.7 ± 3.8	24.6 ± 3.8
LDL-cholesterol (mg/dL)	123 ± 32	123 ± 31	123 ± 31	122 ± 53	123 ± 31	122 ± 43
HDL-cholesterol (mg/dL)	54 ± 15	54 ± 16	54 ± 16	56 ± 15	55 ± 15	55 ± 15
Triglyceride (mg/dL)	151 ± 82	152 ± 86	152 ± 84	149 ± 102	154 ± 97	151 ± 99
HbA1c(%)	6.3 ± 3.7	6.1 ± 1.3	6.2 ± 2.7	6.0 ± 1.4	6.0 ± 1.2	6.0 ± 1.3
Fasting plasma glucose (mg/dL)	124 ± 49	122 ± 44	123 ± 47	121 ± 45	122 ± 46	121 ± 46
Serum creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
eGFR ($mL/min/1.73m^2$)**	48 ± 9	48 ± 10	48 ± 9	78 ± 15	79 ± 16	78 ± 16
Sodium (mEq/L)	144 ± 16	142 ± 14	143 ± 14	141 ± 6	146 ± 11	144 ± 8
Potassium (mEq/L)	4.3 ± 0.4	4.3 ± 1.0	4.3 ± 0.8	4.6 ± 1.0	4.3 ± 2.5	4.5 ± 0.8
Risk factor						
Obesity	189 (39%)	179 (36%)	368 (38%)	382 (39%)	384 (40%)	766 (39%)
Dyslipidemia	349 (73%)	378 (75%)	727 (74%)	687 (69%)	669 (70%)	1356 (70%)
Diabetes	124 (26%)	148 (30%)	272 (28%)	260 (26%)	241 (25%)	501 (26%)
Current smoker	87 (18%)	87 (17%)	174 (18%)	244 (25%)	232 (24%)	476 (24%)
Ischemic heart disease**	143 (30%)	152 (30%)	295 (30%)	200 (20%)	182 (19%)	382 (20%)
Cerebrovascular disease	19 (4%)	26 (5%)	45 (5%)	39 (4%)	37 (4%)	76 (4%)
LVH on ECG	129 (27%)	141 (28%)	270 (28%)	266 (27%)	259 (27%)	525 (27%)
Congestive heart failure**	35 (7%)	67 (13%)	102 (10%)	45 (5%)	36 (4%)	81 (4%)

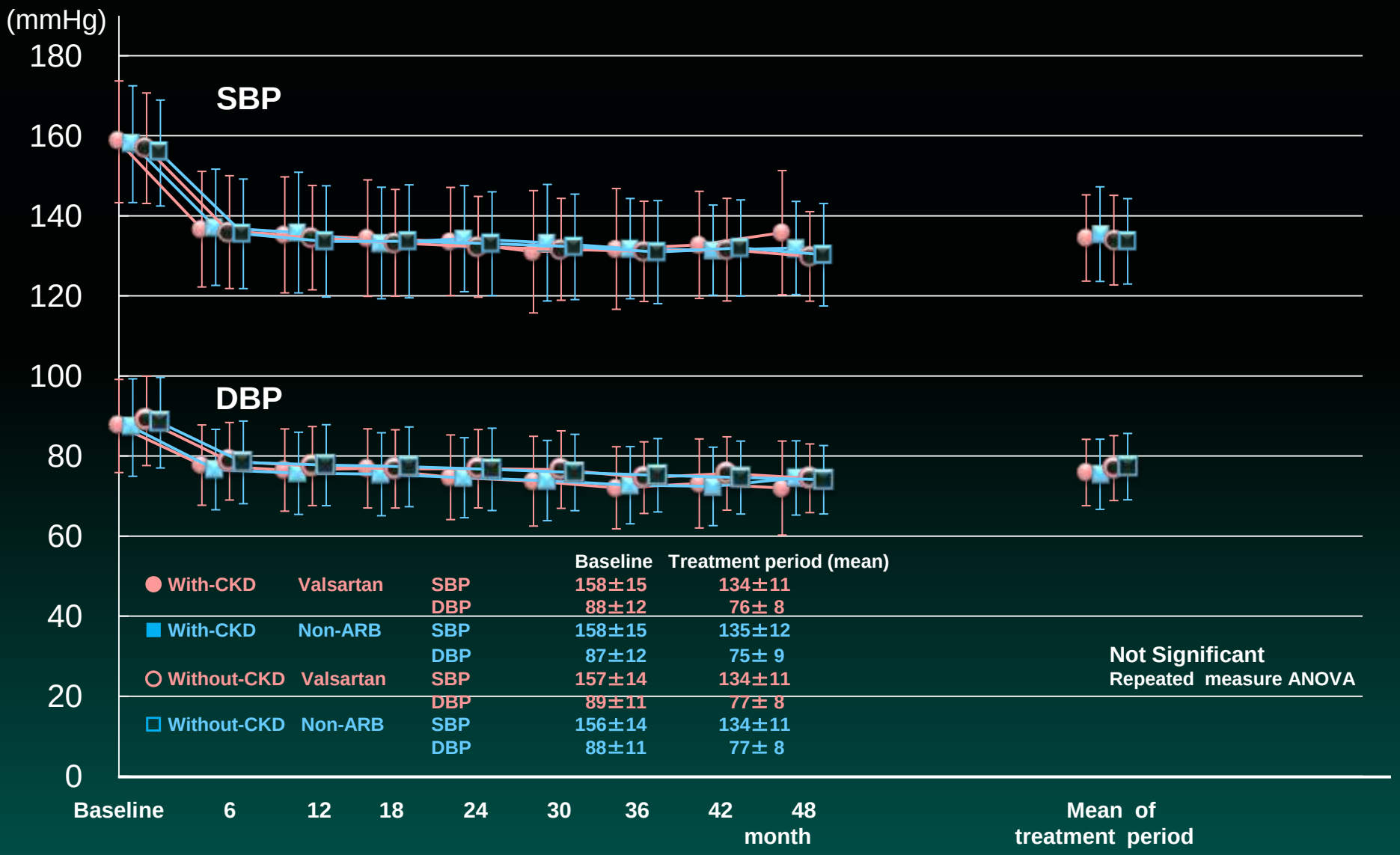
Data are mean±SD or number(%), $p^*<0.05$ and $p^{**}<0.01$ compared between With-CKD vs Without-CKD.

Baseline medications at the entry

	With-CKD			Without-CKD		
	Valsartan 480	Non-ARB 501	ALL 981	Valsartan 989	Non-ARB 959	ALL 1948
Calcium-channel blocker	265 (55%)	297 (59%)	562 (57%)	542 (55%)	503 (52%)	1045 (54%)
ACE inhibitor**	100 (21%)	123 (25%)	223 (23%)	177 (18%)	171 (18%)	348 (18%)
β-blocker**	99 (21%)	106 (21%)	205 (21%)	157 (16%)	161 (17%)	318 (16%)
α-blocker	19 (4%)	19 (4%)	38 (4%)	25 (3%)	28 (3%)	53 (3%)
Thiazide	14 (3%)	19 (4%)	33 (3%)	38 (4%)	25 (3%)	63 (3%)
Other diuretics	38 (8%)	53 (11%)	91 (9%)	33 (3%)	28 (3%)	61 (3%)
Anti-aldosterone agent	15 (3%)	15 (3%)	30 (3%)	15 (2%)	10 (1%)	25 (1%)
Antiarrhythmic drugs	15 (3%)	29 (6%)	44 (4%)	31 (3%)	26 (3%)	57 (3%)
Nicorandil	31 (6%)	20 (4%)	51 (5%)	33 (3%)	31 (3%)	64 (3%)
Anti-coagulating agent	35 (7%)	45 (9%)	80 (8%)	51 (5%)	57 (6%)	108 (6%)
Anti-platelet agent**	149 (31%)	161 (32%)	310 (32%)	238 (24%)	245 (26%)	483 (25%)
Nitroglycerine or ISDN	53 (11%)	58 (12%)	111 (11%)	76 (8%)	65 (7%)	141 (7%)
Digoxin	11 (2%)	20 (4%)	31 (3%)	20 (2%)	21 (2%)	41 (2%)
Statin	150 (31%)	182 (36%)	332 (34%)	324 (33%)	303 (32%)	627 (32%)
Fibrarte	14 (3%)	14 (3%)	28 (3%)	21 (2%)	16 (2%)	37 (2%)
Other lipid modulating drugs	18 (4%)	12 (2%)	30 (3%)	25 (3%)	17 (2%)	42 (2%)
Oral hypoglycemic agent (SU)	44 (9%)	55 (11%)	99 (10%)	122 (12%)	113 (12%)	235 (12%)
Other hypoglycemic agent	46 (10%)	50 (10%)	96 (10%)	92 (9%)	89 (9%)	181 (9%)
Insulin	13 (3%)	24 (5%)	37 (4%)	25 (3%)	15 (2%)	40 (2%)

Data are number (%), p**<0.01 compared between With-CKD vs Without-CKD.

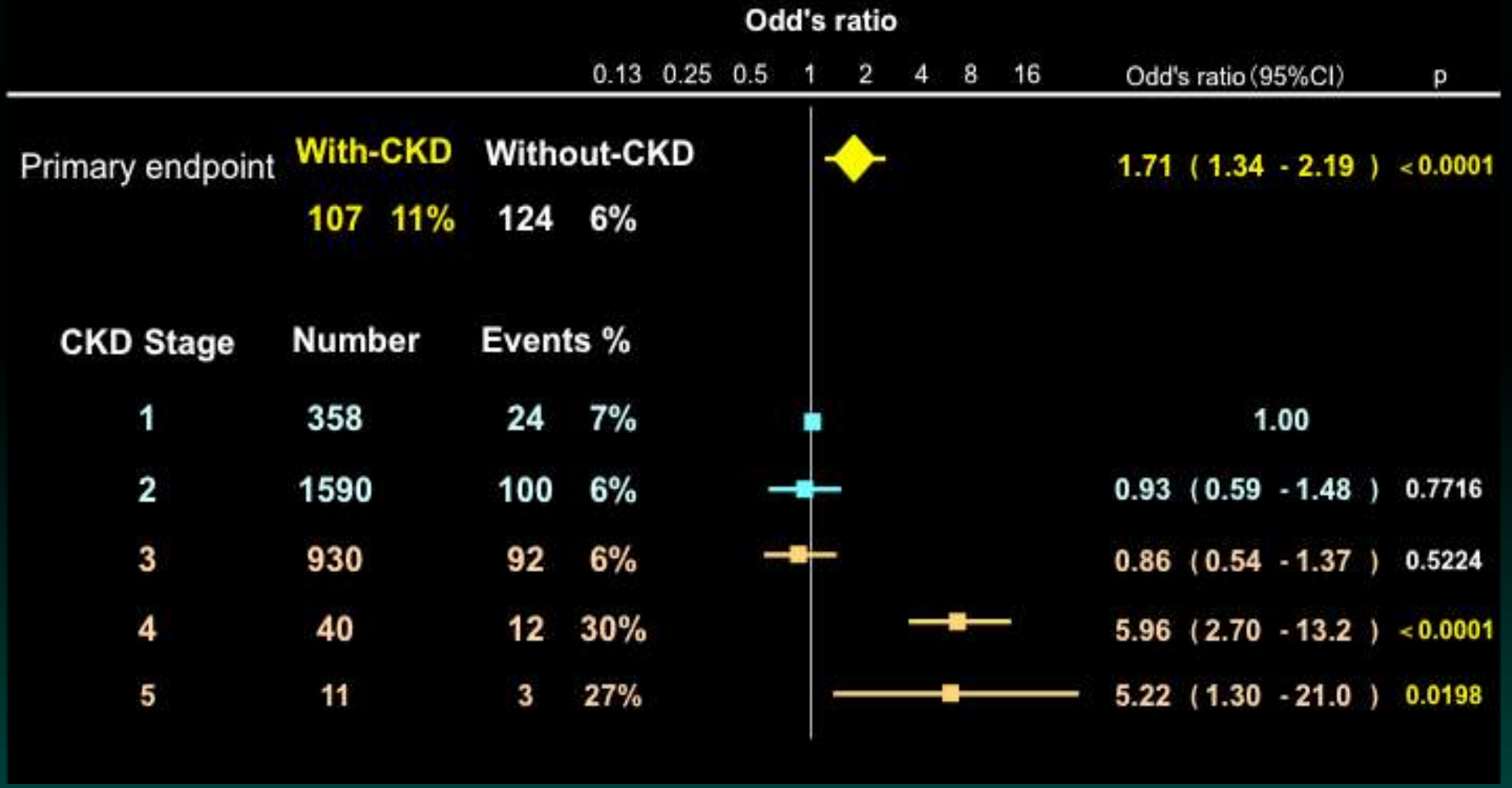
BP changes during the study period



			Baseline	Treatment period (mean)
● With-CKD	Valsartan	SBP	158±15	134±11
		DBP	88±12	76± 8
■ With-CKD	Non-ARB	SBP	158±15	135±12
		DBP	87±12	75± 9
○ Without-CKD	Valsartan	SBP	157±14	134±11
		DBP	89±11	77± 8
□ Without-CKD	Non-ARB	SBP	156±14	134±11
		DBP	88±11	77± 8

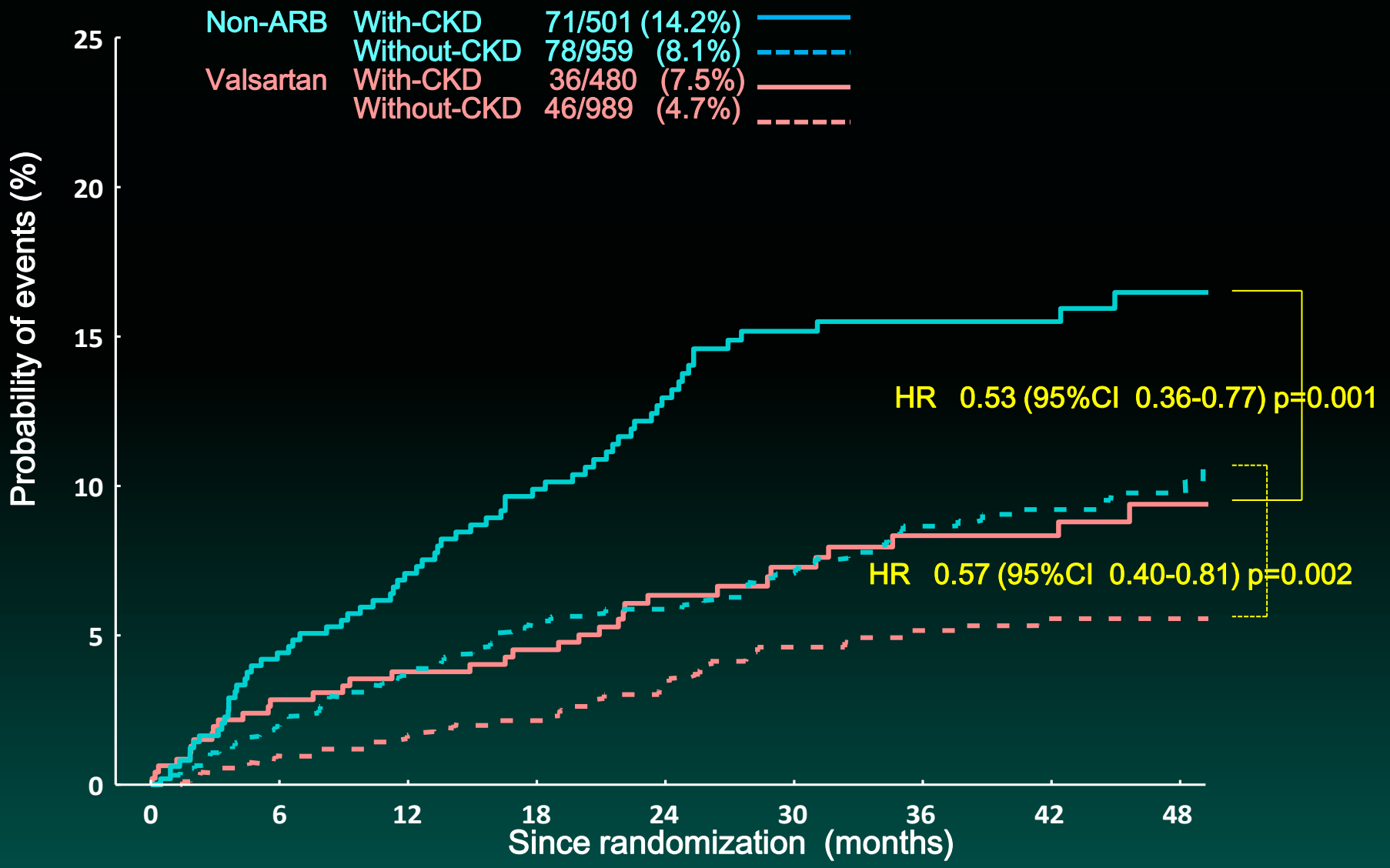
Not Significant
Repeated measure ANOVA

Odd's ratio & 95% CIs for primary endpoint

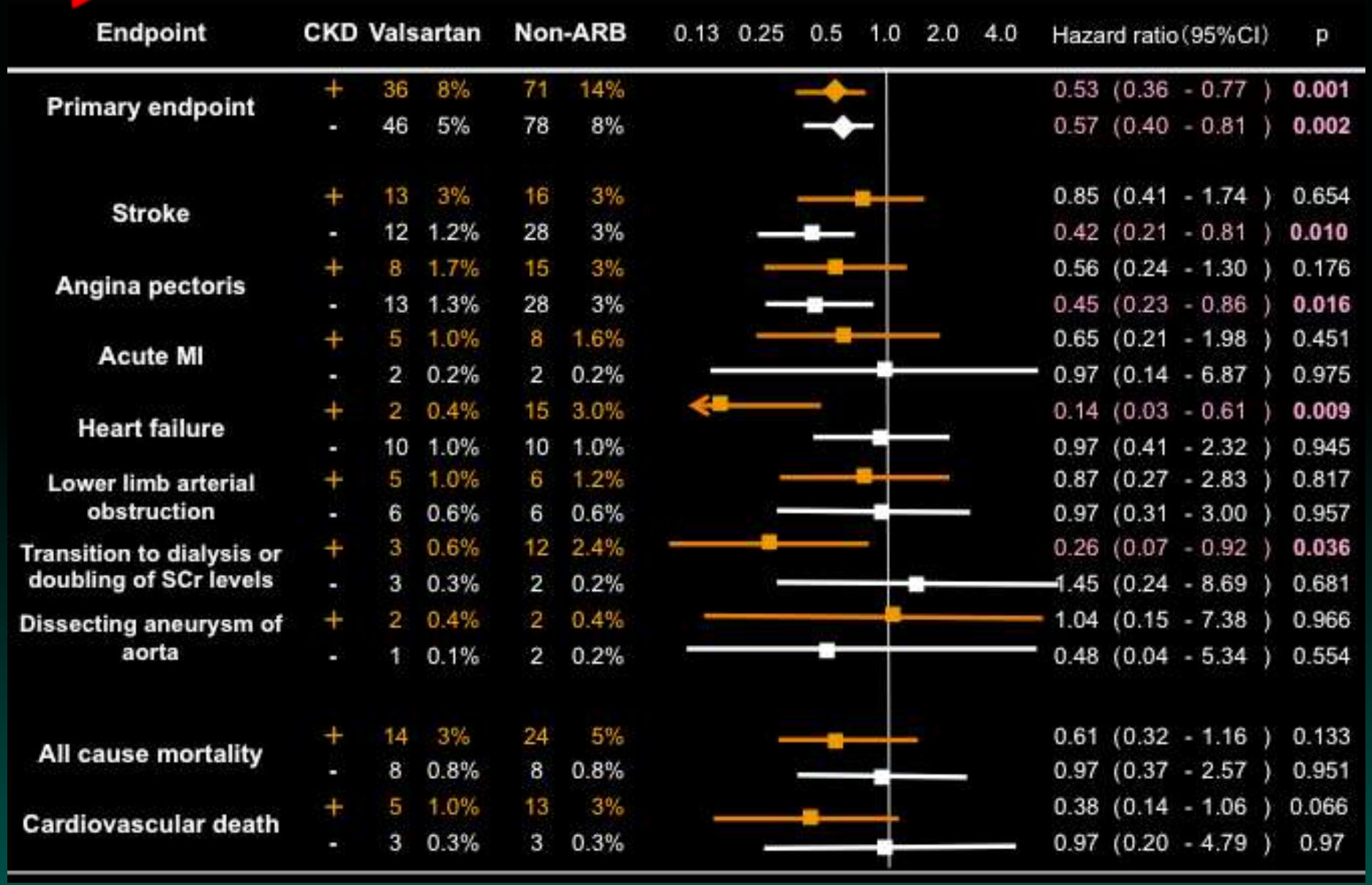


Upper part indicates the comparison between With-CKD and Without-CKD, and lower part indicates Odd's ratios of each CKD stages compared to CKD-1.

Kaplan-Meier curves in With/Without-CKD between valsartan and Non-ARB groups



Hazard ratio and 95% CIs for effects of valsartan on primary endpoints and components



Summary

- Hypertensive patients with CKD had significantly higher CV events than patients without CKD.
- Severity of CKD stage is closely related to the CV event incidence in patients with high-risk hypertension.
- Valsartan add-on treatment is more efficient than non-ARB treatment in high-risk hypertensive patients irrespective of CKD, although there was no significant difference in BP reduction levels among these regimens.
- Valsartan add-on regimen provides beneficial effects, especially in the prevention of heart failure and renovascular events in With-CKD and stroke and angina pectoris in Without-CKD.

Limitations

- The study is a *post-hoc* analysis. The differences of patient characteristics in the groups cannot be completely excluded, and lower sample volume in each sub-groups might undersize the statistical power.
- Patient numbers in CKD stages are not equally distributed in the study. *Most of CKD-5 were excluded* because valsartan is a contra-indication in patients with Cr > 3.0mg/dL.
- 102 patients who could not provide Cr data at the entry were excluded from the ancillary analysis.
- Since the main study was performed in the *PROBE design*, we could not exclude possible bias in event reporting, particularly for softer endpoints such as angina and TIA.

Conclusion

- The ancillary analysis from the KYOTO HEART Study showed that CKD was significantly associated with CV events in high-risk hypertension, and the event rate stepped up according to CKD stages.
- Valsartan add-on regimen for high-risk hypertension is more efficient for CV event prevention not only for the patients with CKD but also without CKD.