APSN CME at Yokohama, Japan

July 02, 2014

UDON noodle (5.6 g NaCl)

Hypertension and renin-angiotensin system (RAS)

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Disclosure: APSN CME

Presenter: Akira Nishiyama

- Consulting or lecture fees: Daiichi-Sankyo, Takeda, Novartis, Pfizer, Boehringer-Ingelheim, Taisyo-Toyama
- Grant supports for collaborative studies: Daiichi-Sankyo, Chugai, Novartis, Boehringer-Ingelheim, Taisyo-Toyama
- Drug supply for basic studies: Daiichi-Sankyo, Novartis, Boehringer-Ingelheim, Taisyo-Toyama

These are not related to this presentation.

Attainment targets

- ✓ To understand the role of systemic vs. intrarenal renin-angiotensin system (RAS) in the pathogenesis of hypertension
- ✓ To understand the Japanese guideline for hypertensive patients with CKD (treated with RAS inhibitors)

Attainment targets

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- ✓ To understand the Japanese guideline for hypertensive patients with CKD (treated with RAS inhibitors)

RAS–dependent hypertension

- ✓ **Reno-vascular hypertension**

  (systemic RAS-dependent)

- ✓ **Salt-dependent hypertension**

  (kidney RAS-dependent)

RAS–dependent hypertension

- ✓ **Reno-vascular hypertension and renioma**

  (systemic RAS-dependent)

- ✓ **Salt-dependent hypertension**

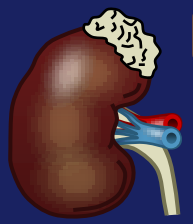
  (kidney RAS-dependent)

Classical pathway of circulating renin-angiotensin system (RAS) in anesthetized rats

Angiotensinogen (AGT)

300-600 nM

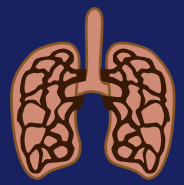
renin



Ang I

50-150 pM

ACE



aldosterone

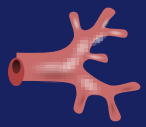
Ang II

50-150 pM

Negative feedback loop

AT_1 receptor

Na^+/H_2O reabsorption



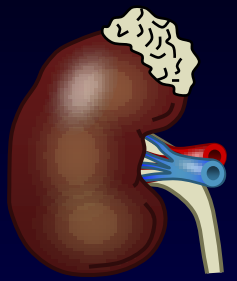
Vasoconstriction

Hypertension

Gibbons GH. *Am J Hypertens 1998; 11: 177S*

Circulating RAS

AGT (1000)



Renin from JG cells

Kobori H et al. Pharmacol Rev. 2007.

Ang I (1)

Ang II (0.5)

- ✓ Changes in AGT synthesis occur slowly and thus are less responsible for the regulation of plasma Ang I and Ang II than renin

Patients profile (1)

- Aneurysm of thoracic aorta was diagnosed in December 2008 (74-year-old woman).
- Aortitis was also identified when ascending aorta replacement was carried out.
- Steroid therapy was started (prednisolone 20 mg/day) for controlling aortitis.
- In 2010, BP increased and antihypertensive drug was started (with prednisolone 10 mg/day).

Patients profile (2)

- In June 2012, BP was increased up to 190/90 mmHg during treatment with CCB and diuretic.
- The levels for plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were 55.4 ng/ml/hr and 252 pg/mL, respectively.
- This patient was admitted in September 2012.

Physical examination on admission

Height, 144cm; weight, 52.1kg; prednisolone at 10mg/day

Blood pressure 180/74 mmHg; heart rate 70 beats/min, regular.

Conjunctiva: not anemic, not icteric

Oral and neck regions: normal, no lymphadenopathy

Heart sounds: normal, no murmur; Lung sounds: normal, no rale

Abdomen: soft and distension, no palpitations, bruits

Upper and lower extremities: palpable artery

Neurological findings: nothing of note

Results of laboratory investigations on admission

Urinalysis		
Gravity	1.006	
pH	7.5	
Protein	-	
Occult blood	-	

CBC		
WBC	10,760	/μl
RBC	366×10^4	/μl
Hb	11.2	g/dl
Ht	34.4	%
PLT	23.1×10^4	/μl

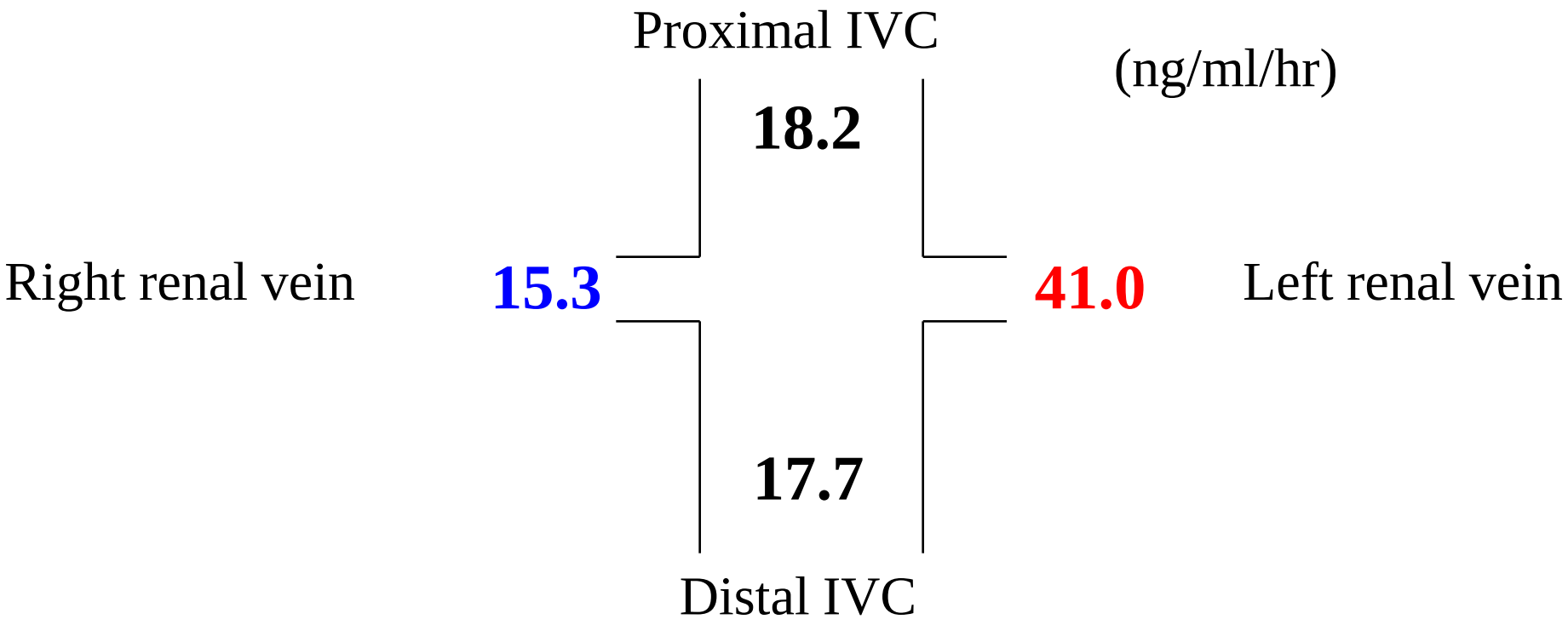
Biochemistry		
AST	17	IU/l
ALT	16	IU/l
ALP	190	IU/l
LDH	172	IU/l
T-Bil	0.4	mg/dl
TP	5.1	g/dl
Alb	2.8	g/dl
BUN	15.0	mg/dl
Cre	0.81	mg/dl
UA	6.3	mg/dl
Na	141	mEq/l
K	3.9	mEq/l
Cl	104	mEq/l
Ca	8.4	mg/dl
P	3.7	mg/dl
HDL-Cho	50	mg/dl
LDL-Cho	146	mg/dl
TG	137	mg/dl
BS	98	mg/dl
HbA1c	5.2	%
CRP	0.29	mg/dl
IgG	418	mg/dl
PRA	20.5	ng/ml/h
PAC	139	pg/ml


2010.10.05
120kV/153mAs
0.50s/0.5mm
CT
40mm
30mm
20mm
10mm
0mm
R
IOPAMIRON 370/70ml
Aquilion
LAO: 12.0
CRA: 0.0
A
75Y/F
FC13
SID 34205
IM:22 SE:1001
OSAKA CITY GENERAL HOSPITAL CT1

Captopril test

	Before test	After test
PRA (ng/ml/hr)	13.7	158.2
PAC (pg/ml)	73	47

Selective renal venous sampling



RAS–dependent hypertension

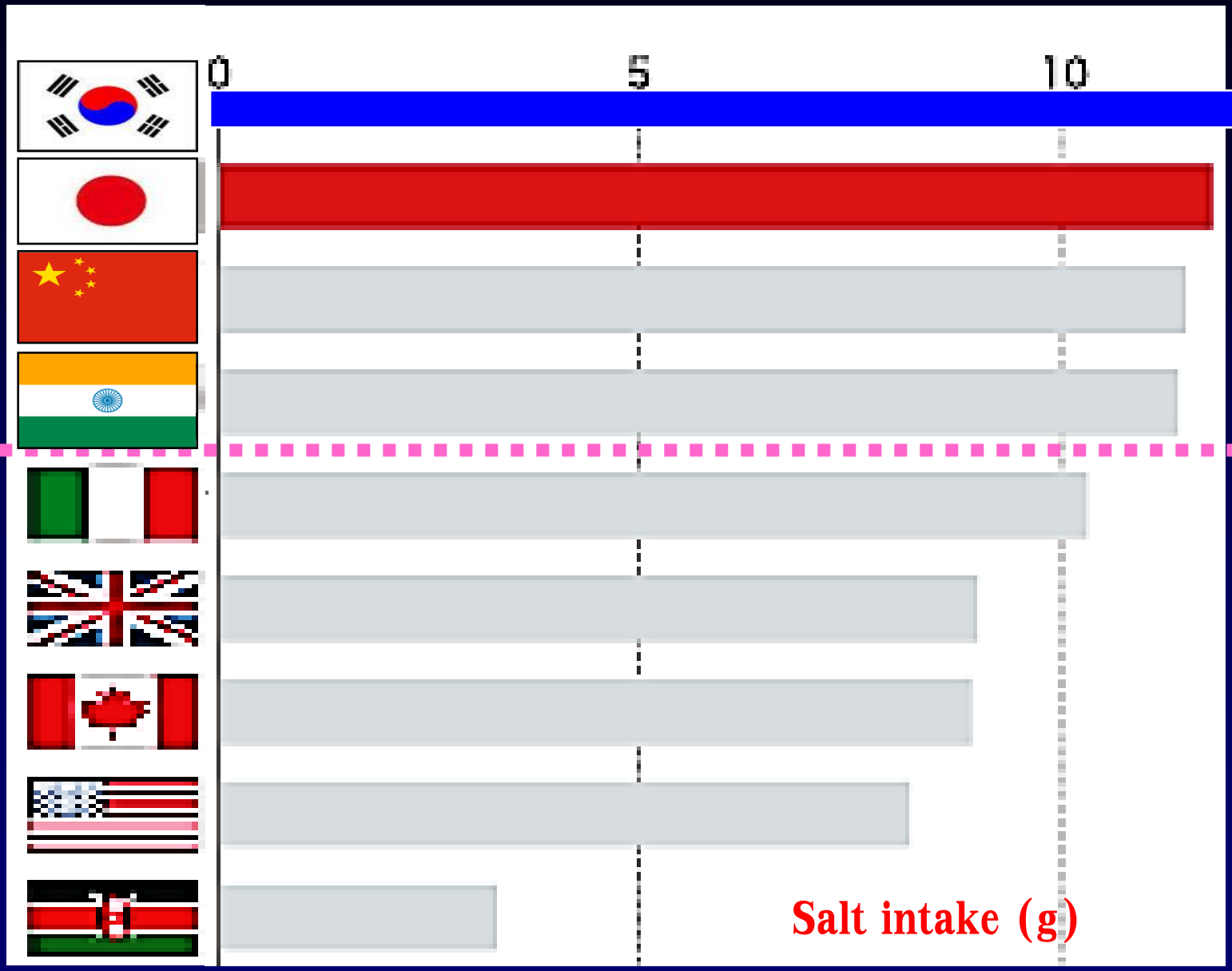
- ✓ **Reno-vascular hypertension**

  (systemic RAS-dependent)

- ✓ **Salt-dependent hypertension**

  (kidney RAS-dependent)

Asians love salt !



miso soup

2.0 g NaCl

ramen noodle

6.3 g NaCl

Paella

1.1 g NaCl

UDON noodle

5.6 g NaCl

Omelet

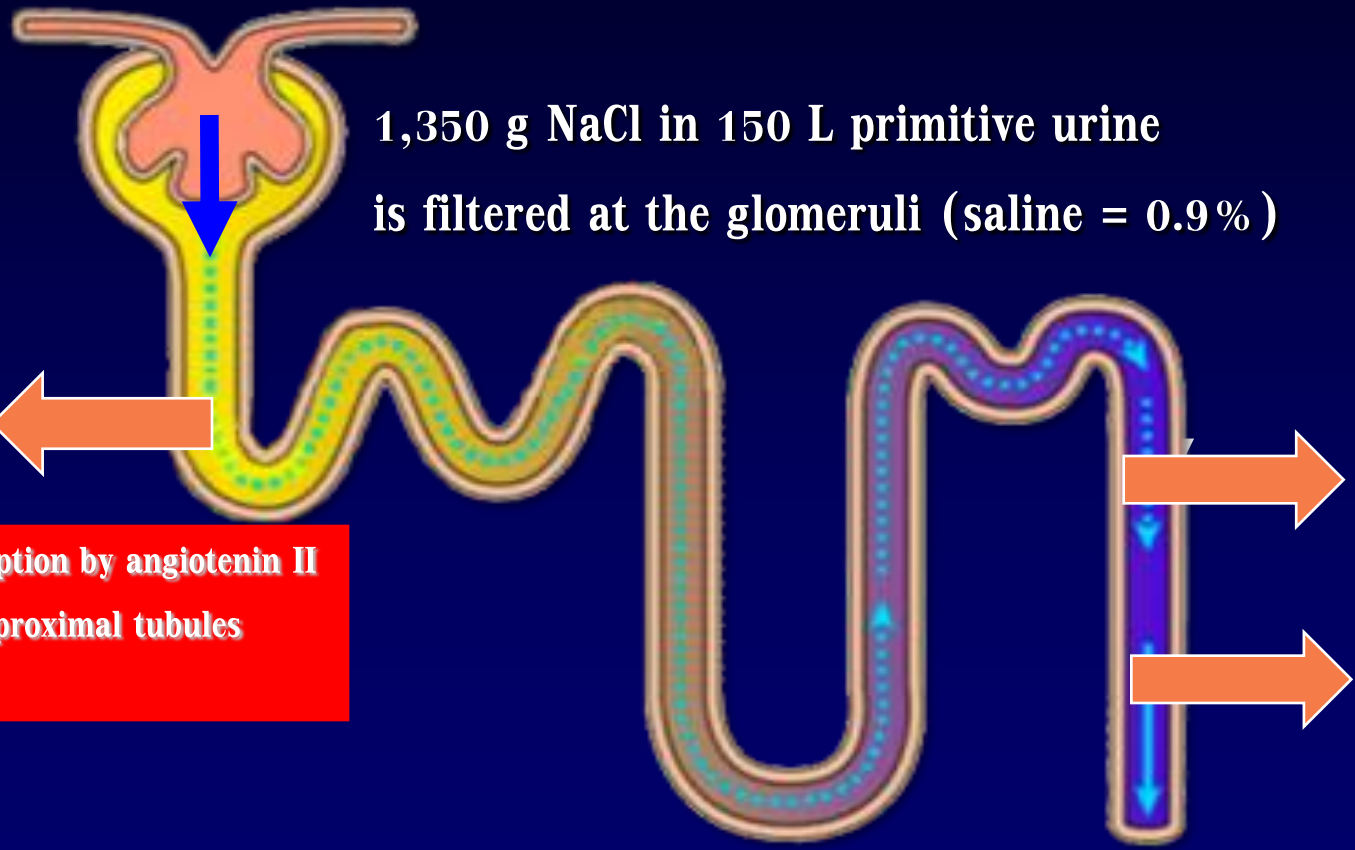
1.1 g NaCl

Carpaccio

0.6 g NaCl

NaCl dynamics in Asians

Renal blood flow = approx. 1,500 L / day



1,350 g NaCl in 150 L primitive urine

is filtered at the glomeruli (saline = 0.9%)

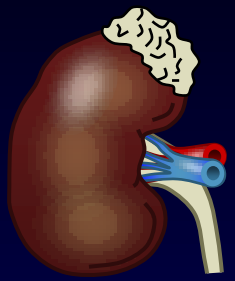
Reabsorption by angiotenin II at proximal tubules

Reabsorption by angiotenin II and aldosterone at distal tubules

Less than 10 g/day in the urine

Circulating RAS

AGT (1000)



Renin from JG cells

Kobori H et al. Pharmacol Rev. 2007.

Ang I (1)

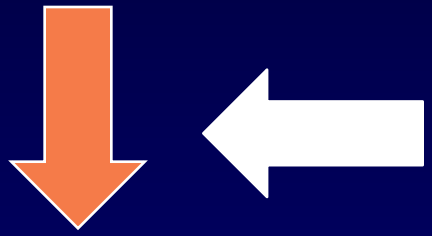
Ang II (0.5)

- ✓ The concentrations of plasma AGT are close to the Michaelis-Menten constant of the proteolytic activity of renin.
- ✓ Therefore, changes in AGT concentrations can also influence the Ang I generation rate.
- ✓ However, changes in AGT synthesis occur slowly and thus are less responsible for the regulation of plasma Ang I and Ang II than renin

In the kidney

Because of its molecular size, it seems unlikely that much of the plasma AGT filters across the glomerular membrane

AGT (plasma >> kidney)



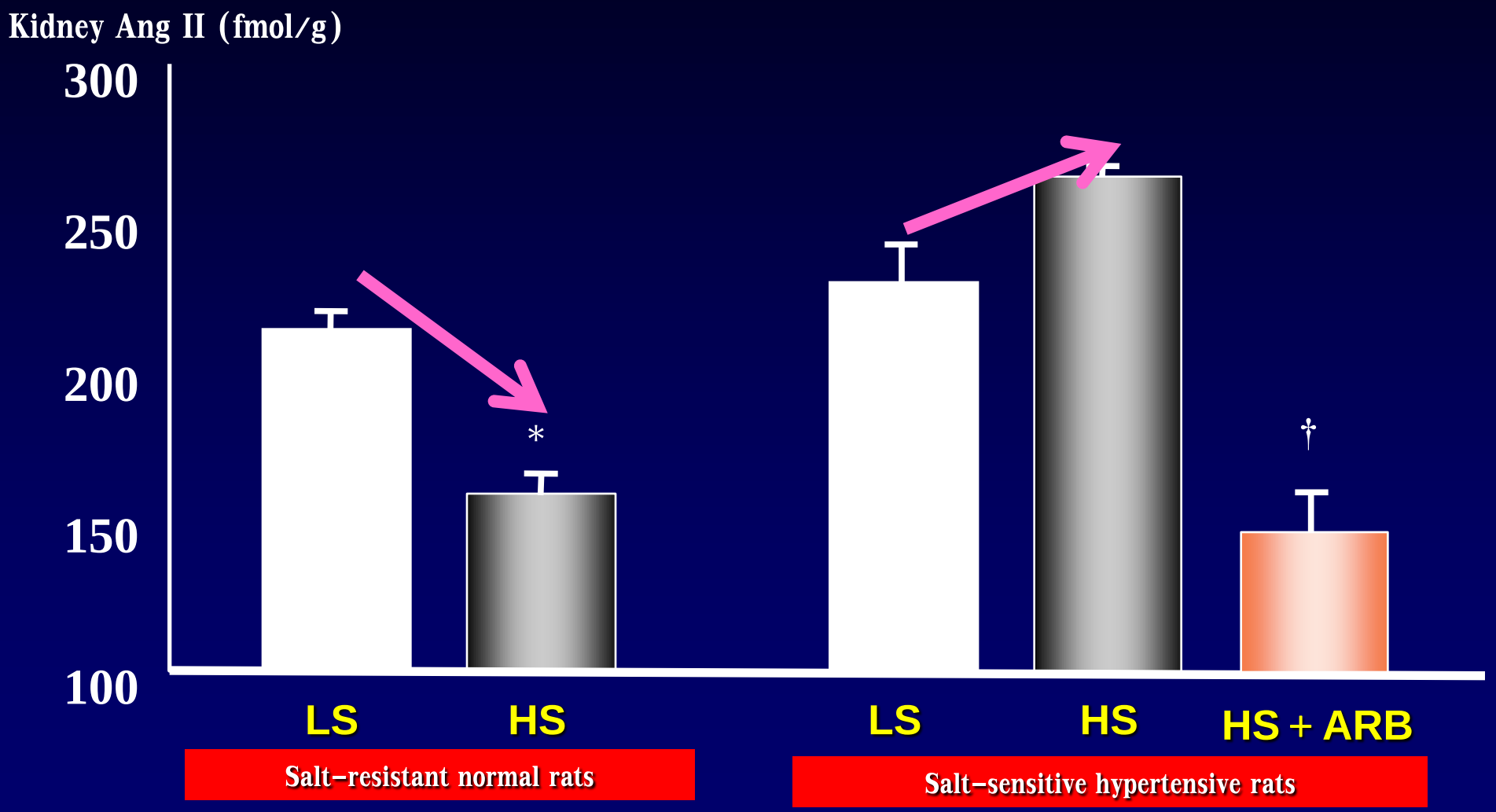
Ang I

Kidney renin activity is 1,000-fold higher than plasma (plasma << kidney)

Ang II

Kidney Ang II levels are much higher than plasma (plasma < kidney)

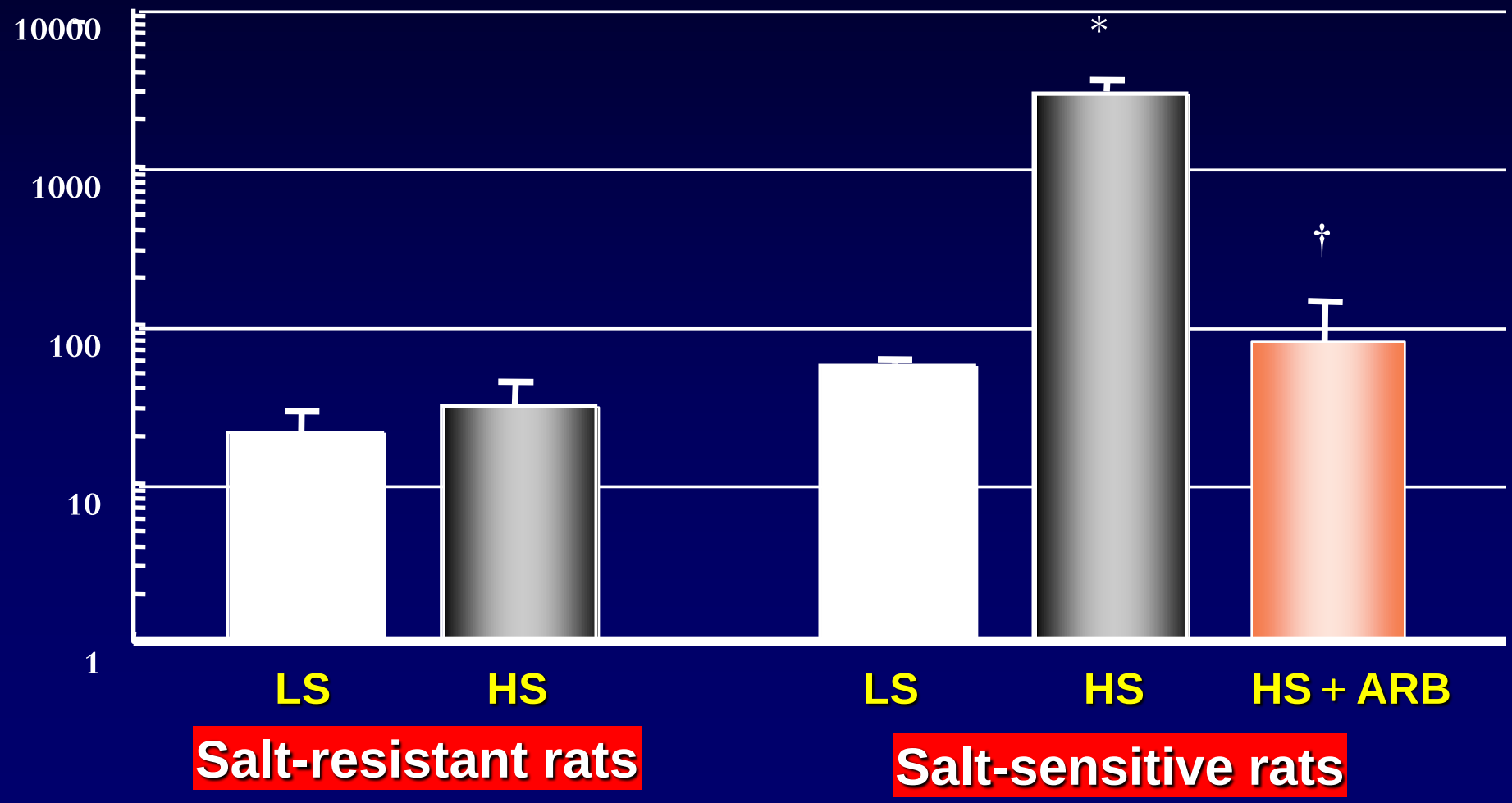
High salt (HS) diet does NOT reduce intrarenal Ang II levels in Dahl salt-sensitive rats



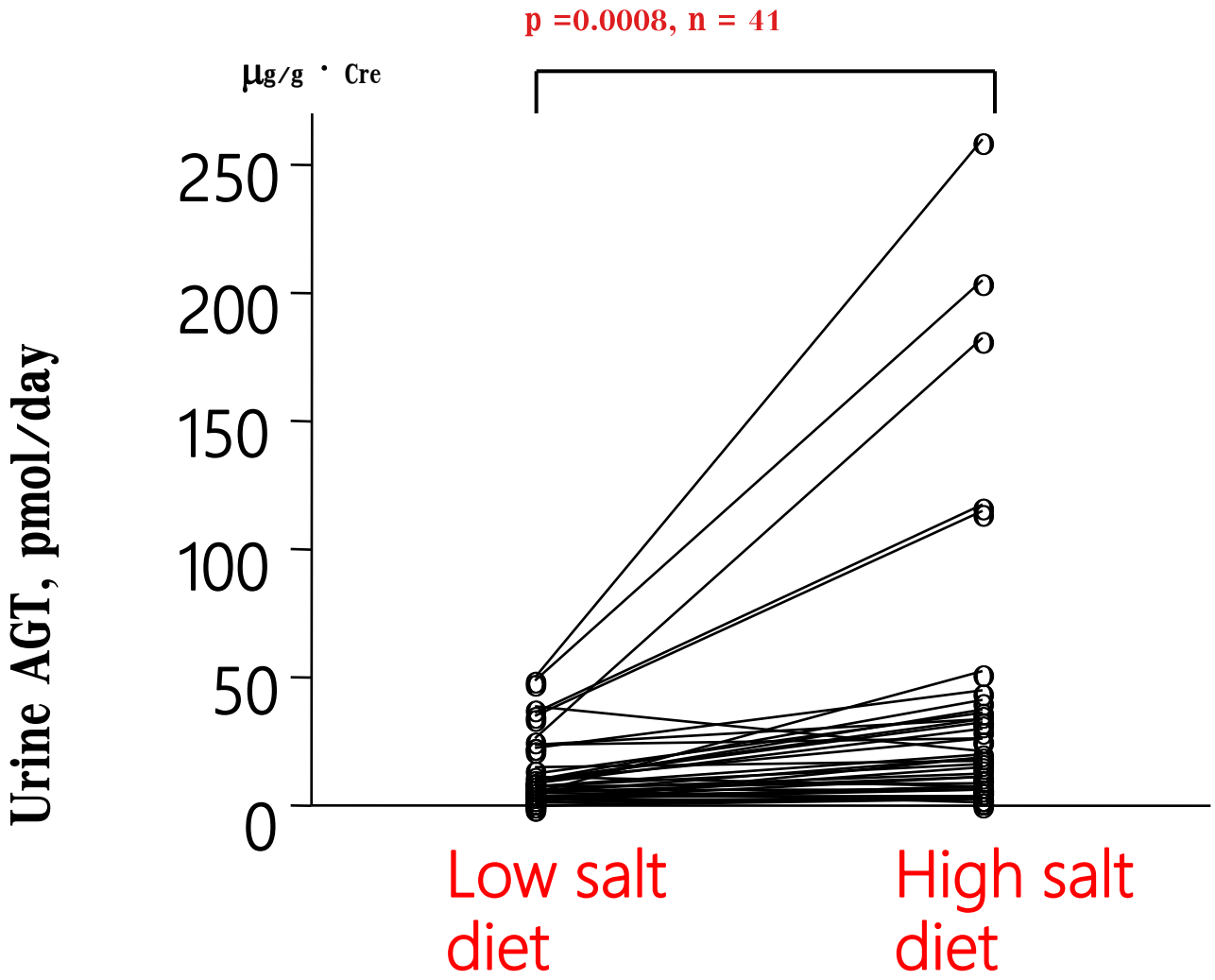
Nishiyama and Kobori. KI, 2005.

Maintenance of intrarenal AngII is associated with 100-fod increases in urinary AGT in DSS rats

Kobori and Nishiyama. Hypertension, 2003.

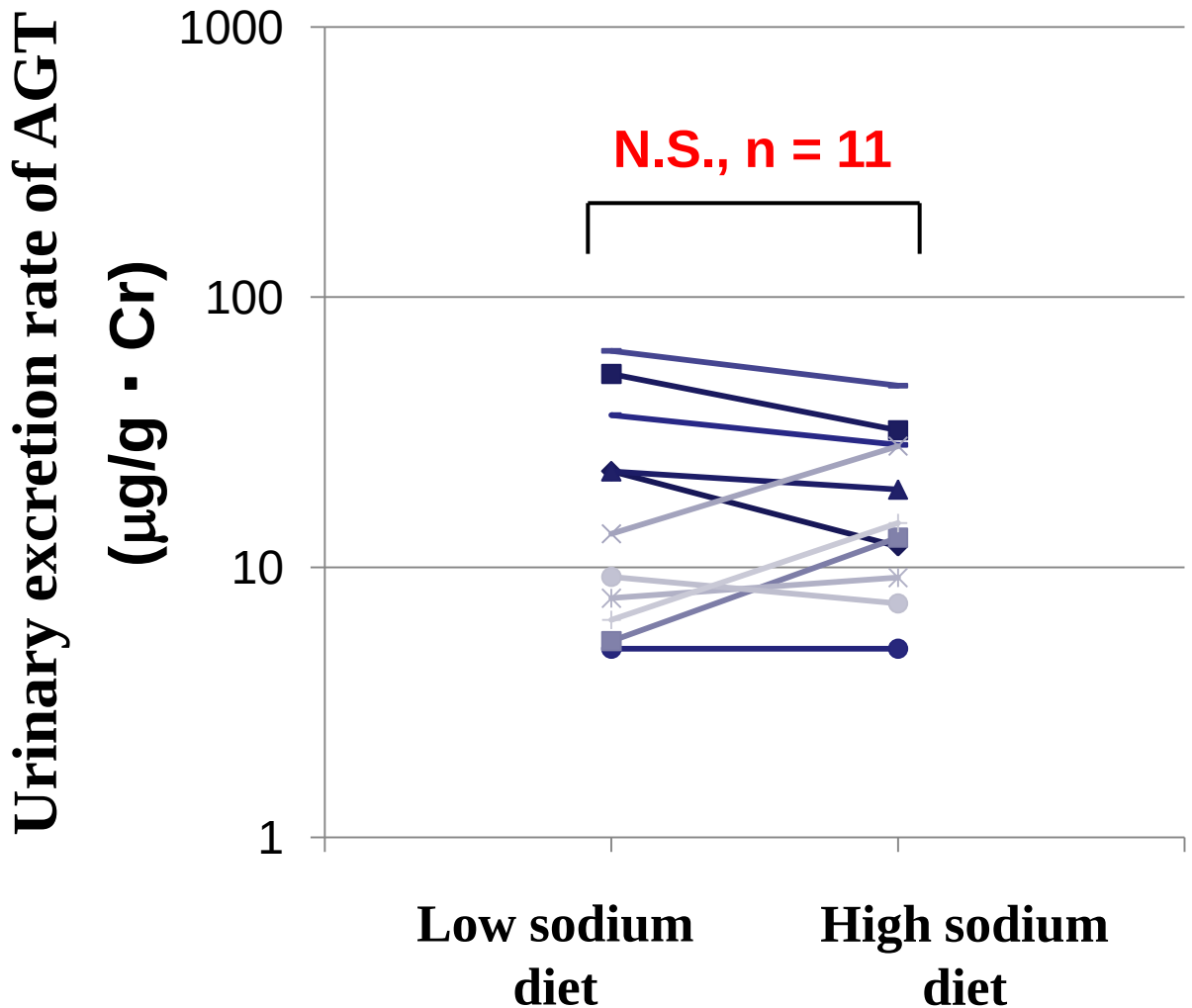


High salt diet increases urinary AGT in patients with IgA nephropathy

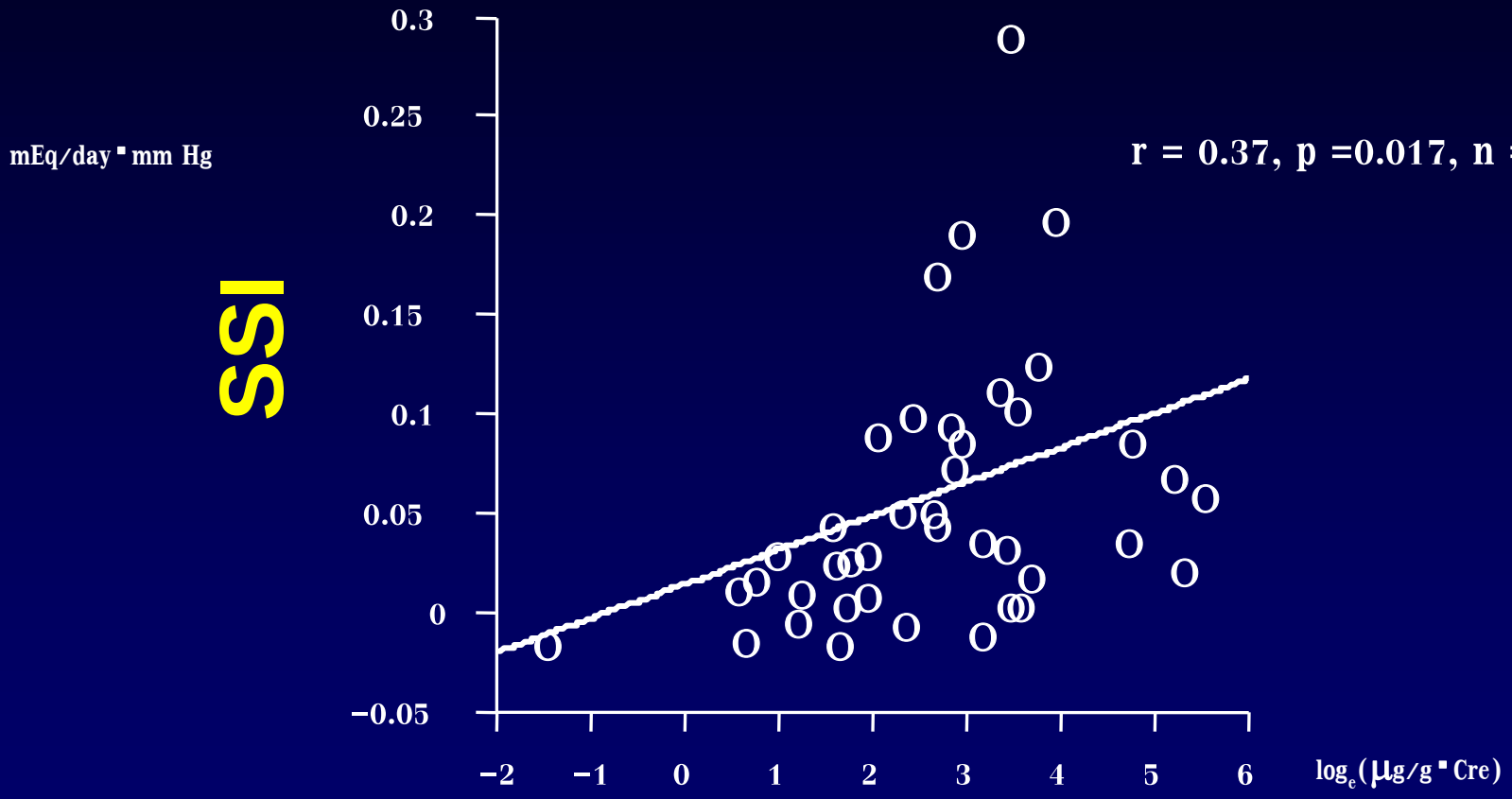


Konishi et al. Hypertension, 2011.

High salt diet does NOT change urinary AGT in subjects with normal kidney function



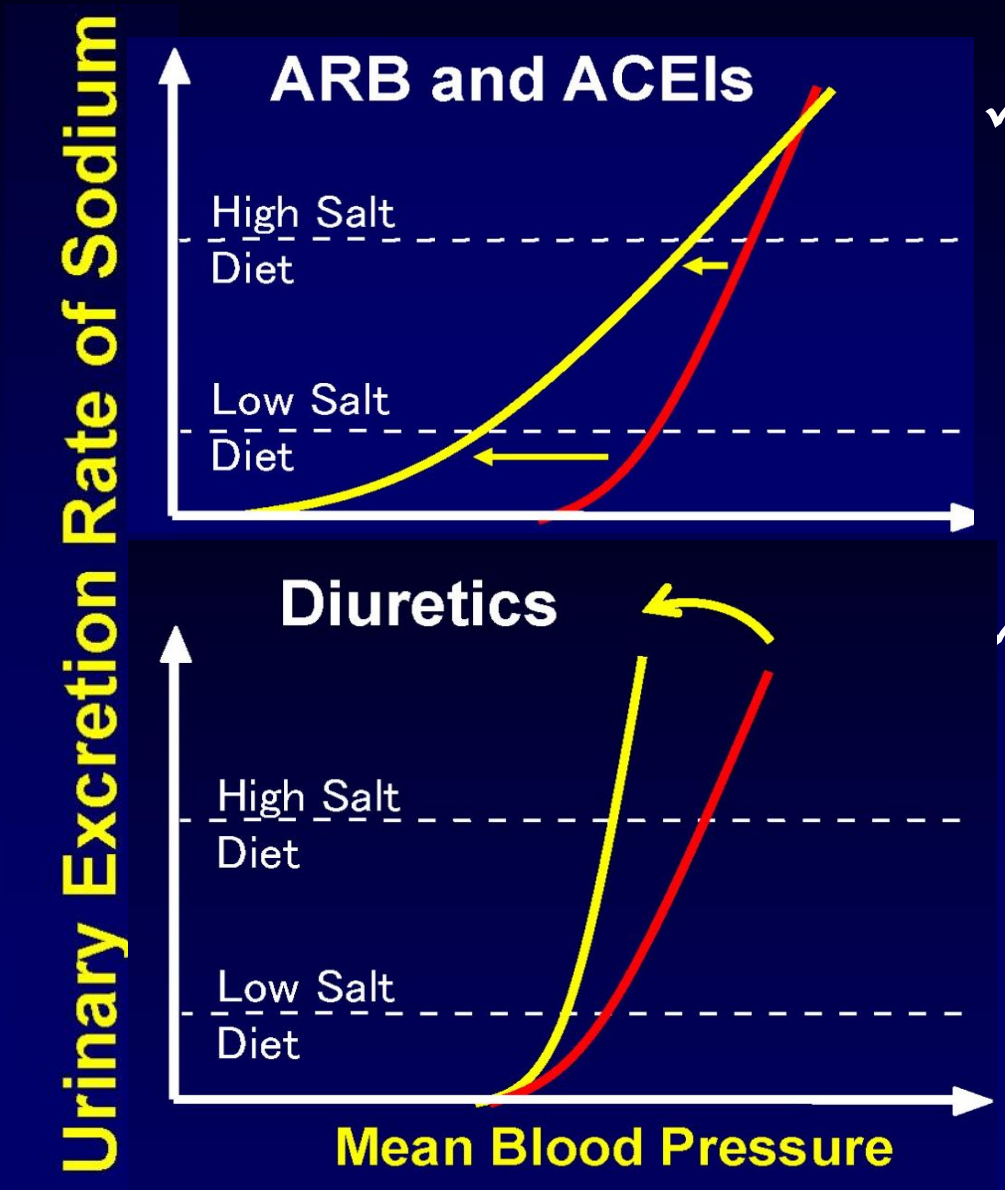
Relationship between sodium-sensitivity index (SSI) and urinary ATG excretion



Changes in urinary AGT

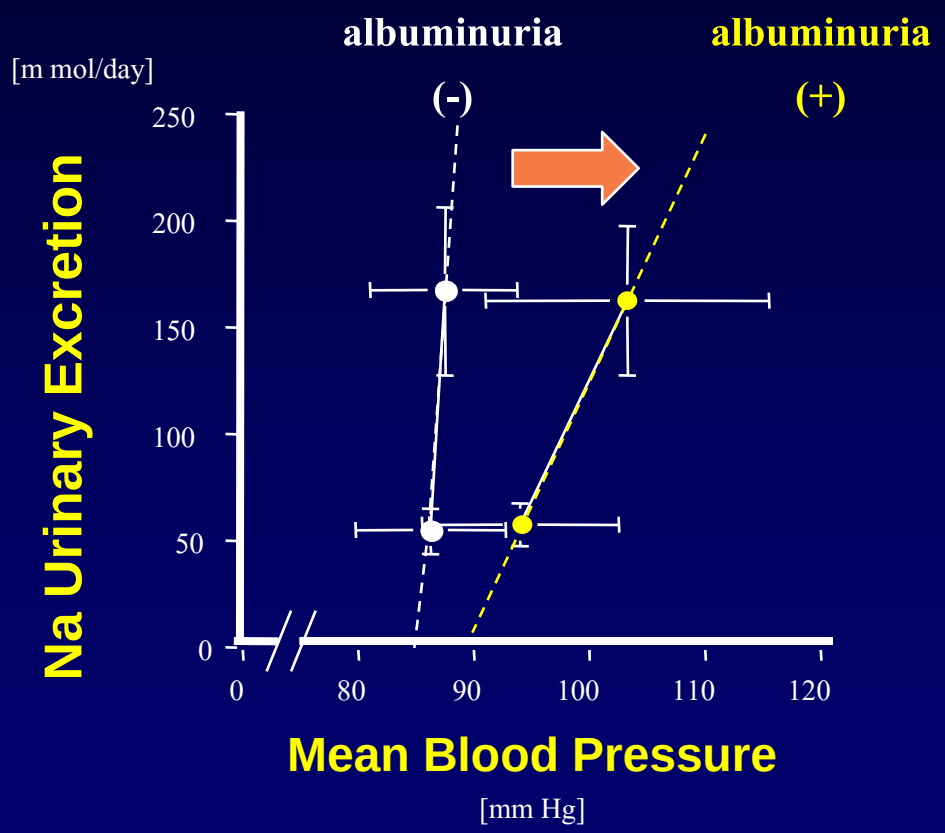
Konishi et al. Hypertension, 2011.

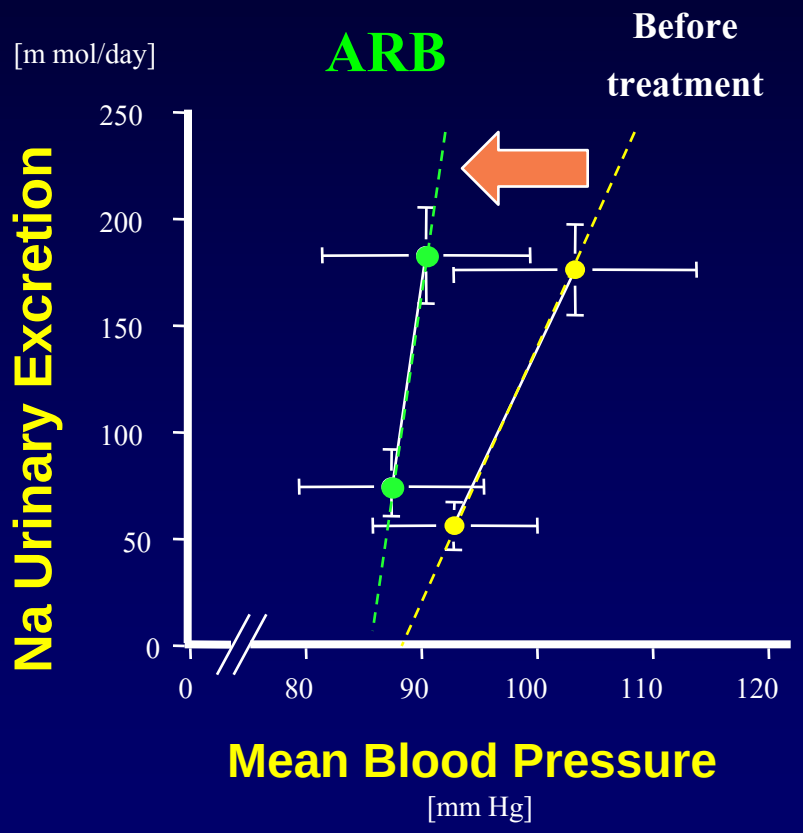
ARBs worsen Sodium Sensitivity of Blood Pressure in subjects with Normal Kidney Function



- ✓ Pressure natriuresis is defined as the relationship between sodium excretion and mean blood pressure.
- ✓ Increase in slope indicates an improvement of sodium-sensitivity of blood pressure, whereas reduction in slope indicates a change for the worse

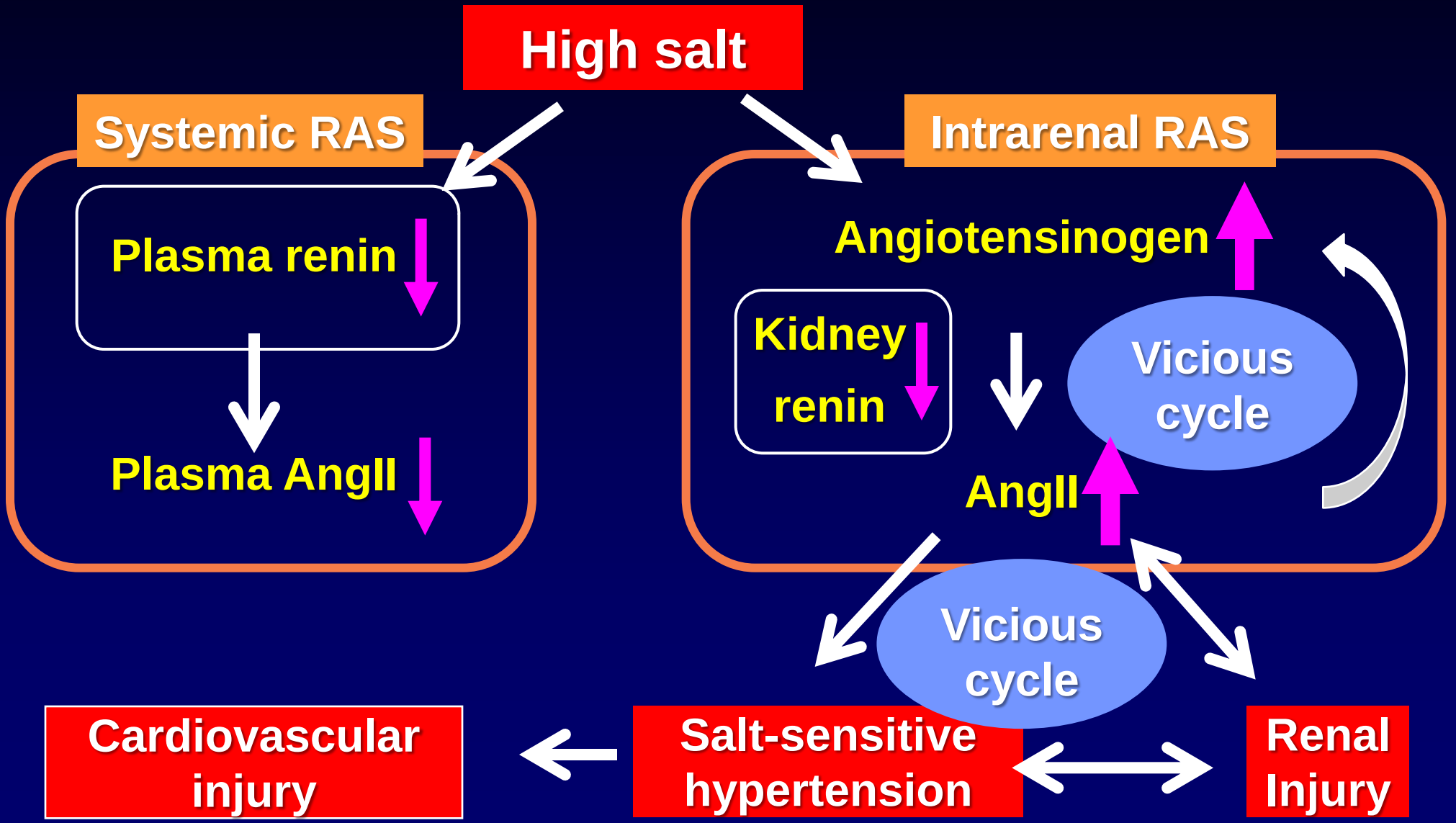
Treatment with an ARB improves sodium sensitivity of blood pressure in Japanese type 2 diabetic patients with microalbuminuria





Imanishi et al. JAAS, 2013.

Systemic vs. Intrarenal RAS in salt-dependent hypertension



Specific aim

- ✓ To understand the role of systemic vs. intrarenal renin-angiotensin system (RAS) in the pathogenesis of hypertension
- ✓ To understand the Japanese guideline for hypertensive patients with CKD (treated with RAS inhibitors)

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014)

Kazuaki SHIMAMOTO, Katsuyuki ANDO, Toshiro FUJITA, Naoyuki HASEBE, Jitsuo HIGAKI, Masatsugu HORIUCHI, Yutaka IMAI, Tsutomu IMAIZUMI, Toshihiko ISHIMITSU, Masaaki ITO, Sadayoshi ITO, Hiroshi ITOH, Hiroshi IWAO, Hisashi KAI, Kazuomi KARIO, Naoki KASHIHARA, Yuhei KAWANO, Shokei KIM-MITSUYAMA, Genjiro KIMURA, Katsuhiko KOHARA, Issei KOMURO, Hiroo KUMAGAI, Hideo MATSUURA, Katsuyuki MIURA, Ryuichi MORISHITA, Mitsuhide NARUSE, Koichi NODE, Yusuke OHYA, Hiromi RAKUGI, Ikuo SAITO, Shigeyuki SAITOH, Kazuyuki SHIMADA, Tatsuo SHIMOSAWA, Hiromichi SUZUKI, Kouichi TAMURA, Norio TANAHASHI, Takuya TSUCHIHASHI, Makoto UCHIYAMA, Shinichiro UEDA, Satoshi UMEMURA, on behalf of The Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension

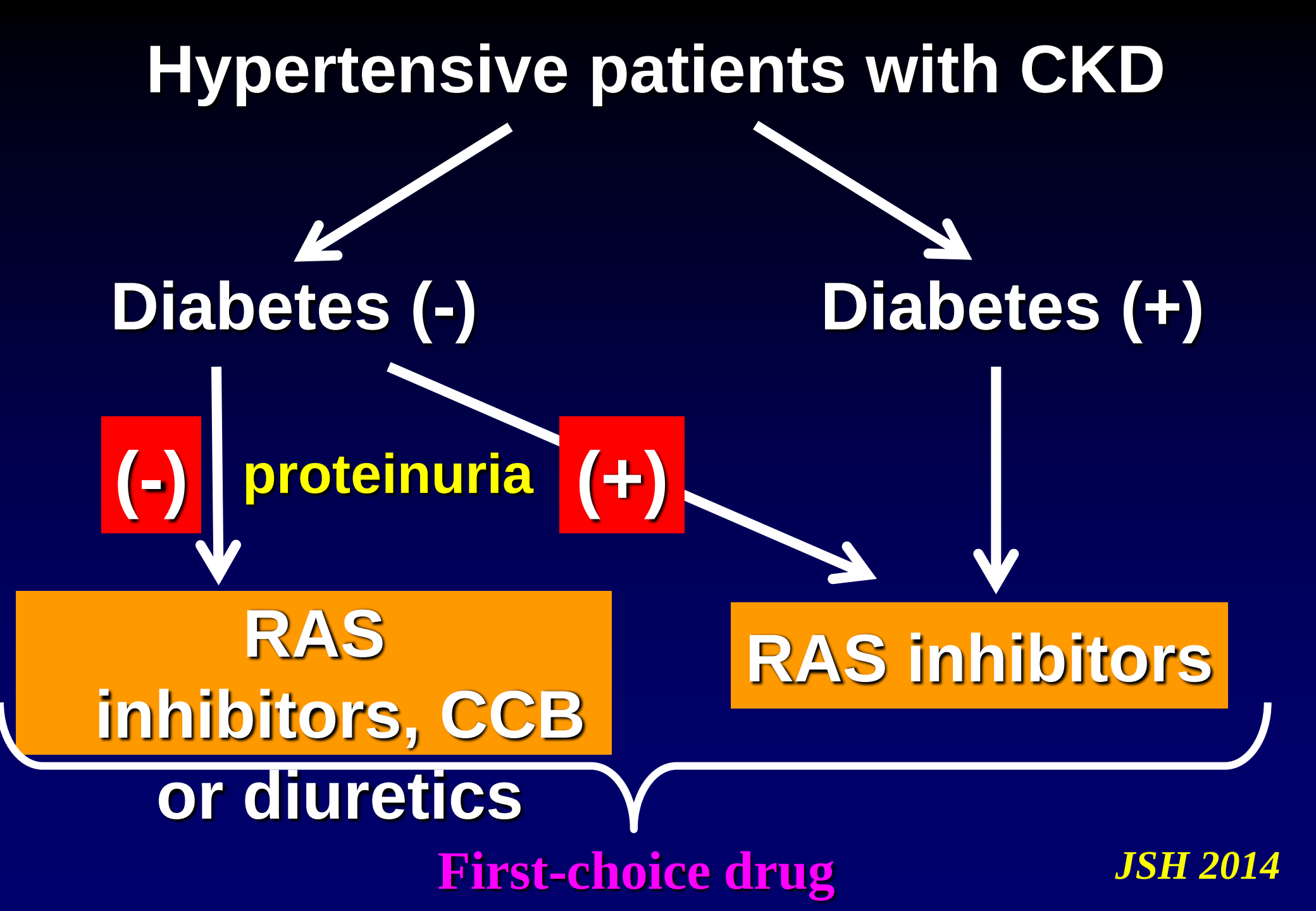
Hypertension Research 2014, Apr; 37(4): 253-387.

Target blood pressure for hypertensive patients with CKD

Table 6-3 Target of blood pressure control and first-choice drugs in patients with chronic kidney disease

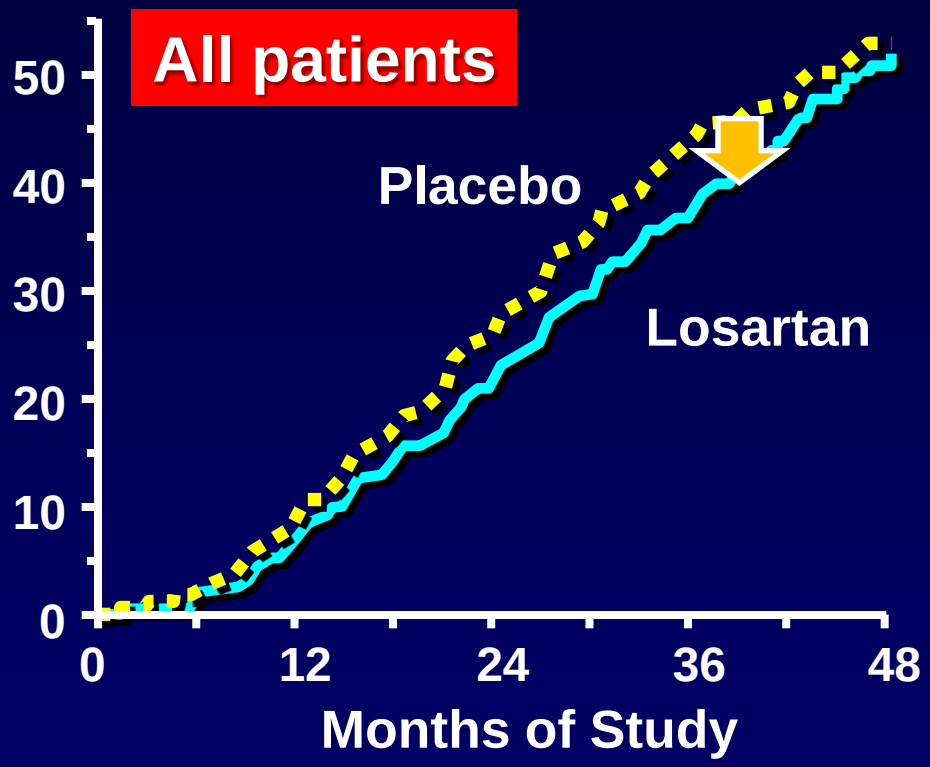
			Target of blood pressure control
Diabetes mellitus (+)			<130/80 mm Hg
Diabetes mellitus (–)	Urinary protein	Absent	<140/90 mm Hg
	Urinary protein	Present	<130/80 mm Hg

JSH 2014

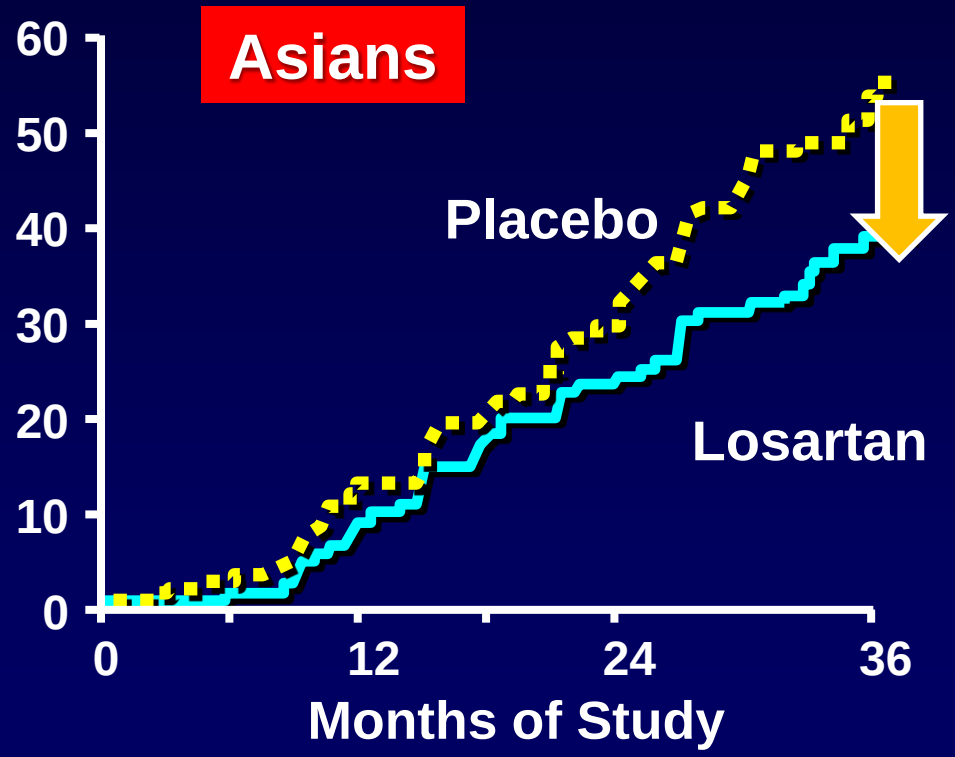

Hypertensive patients with CKD
Diabetes (-)
Diabetes (+)
(-)
proteinuria
(+)
RAS inhibitors, CCB or diuretics
RAS inhibitors
First-choice drug
JSH 2014

RENAAL study and its sub-analysis

Renal events (%)



Brenner et al: N Engl J Med 2001



Chan et al: Diabetes Care 2004

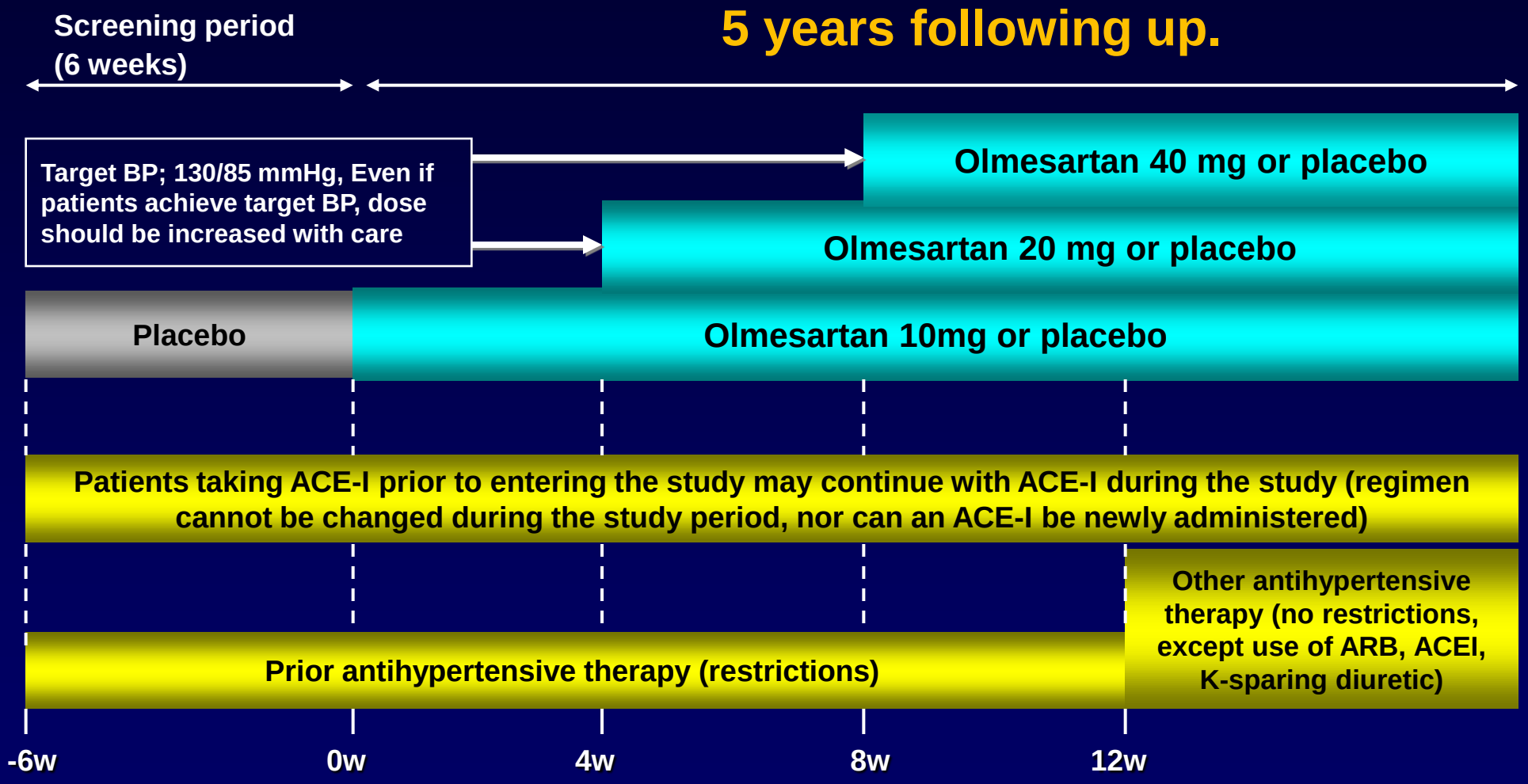
ORIENT study; RCT studies with an ARB in Asian type 2 diabetic nephropathy

To evaluate renal protective effects of an ARB, olmesartan medoxomil, in **Asian type 2 diabetic patients with overt proteinuria**, as defined by time to the first occurrence of the renal composite outcomes including **a doubling of serum creatinine, ESRD* or death**.

***ESRD: End-Stage Renal Disease**

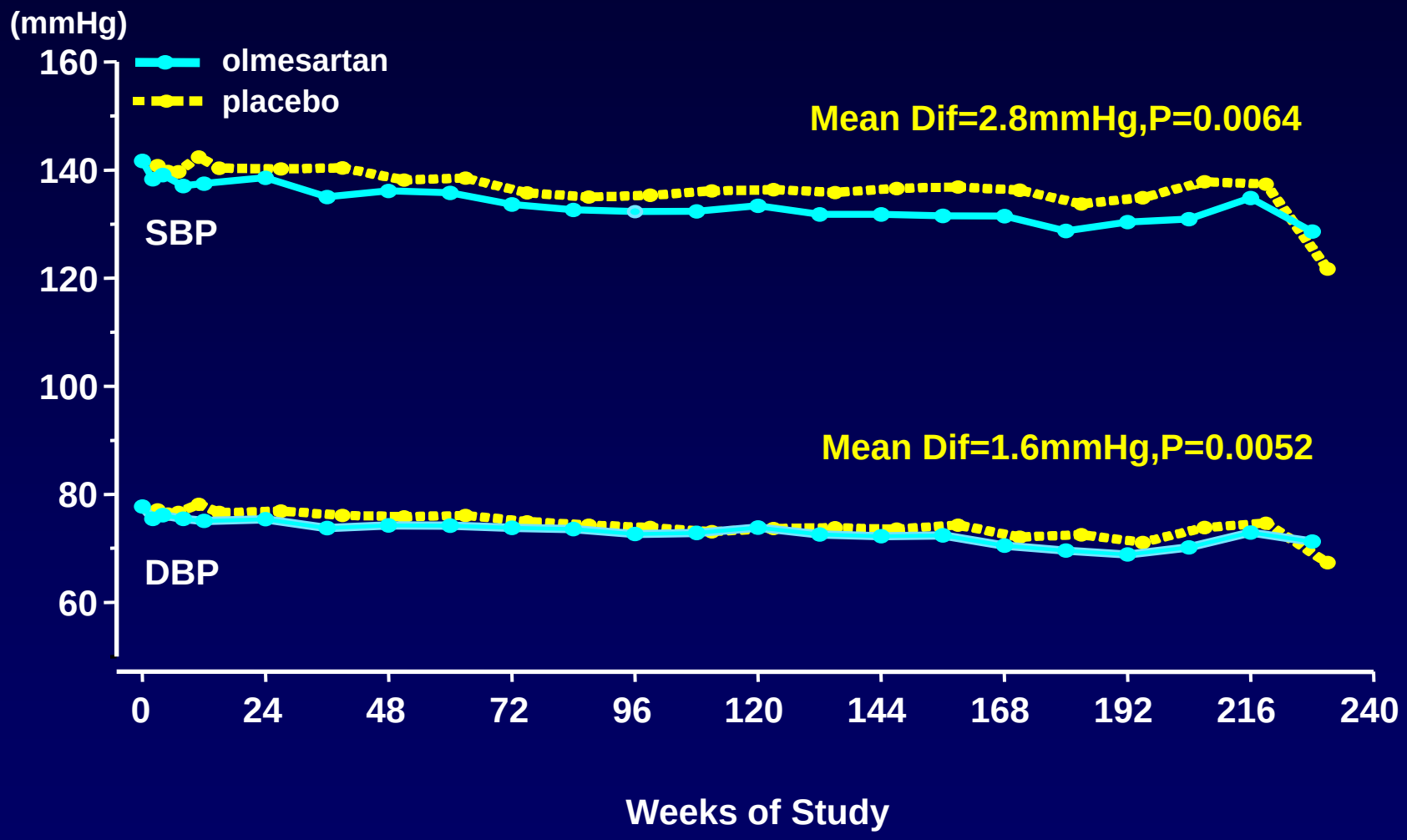
(serum creatinine ≥ 5 mg/dL, chronic dialysis or renal transplantation)

Study Design



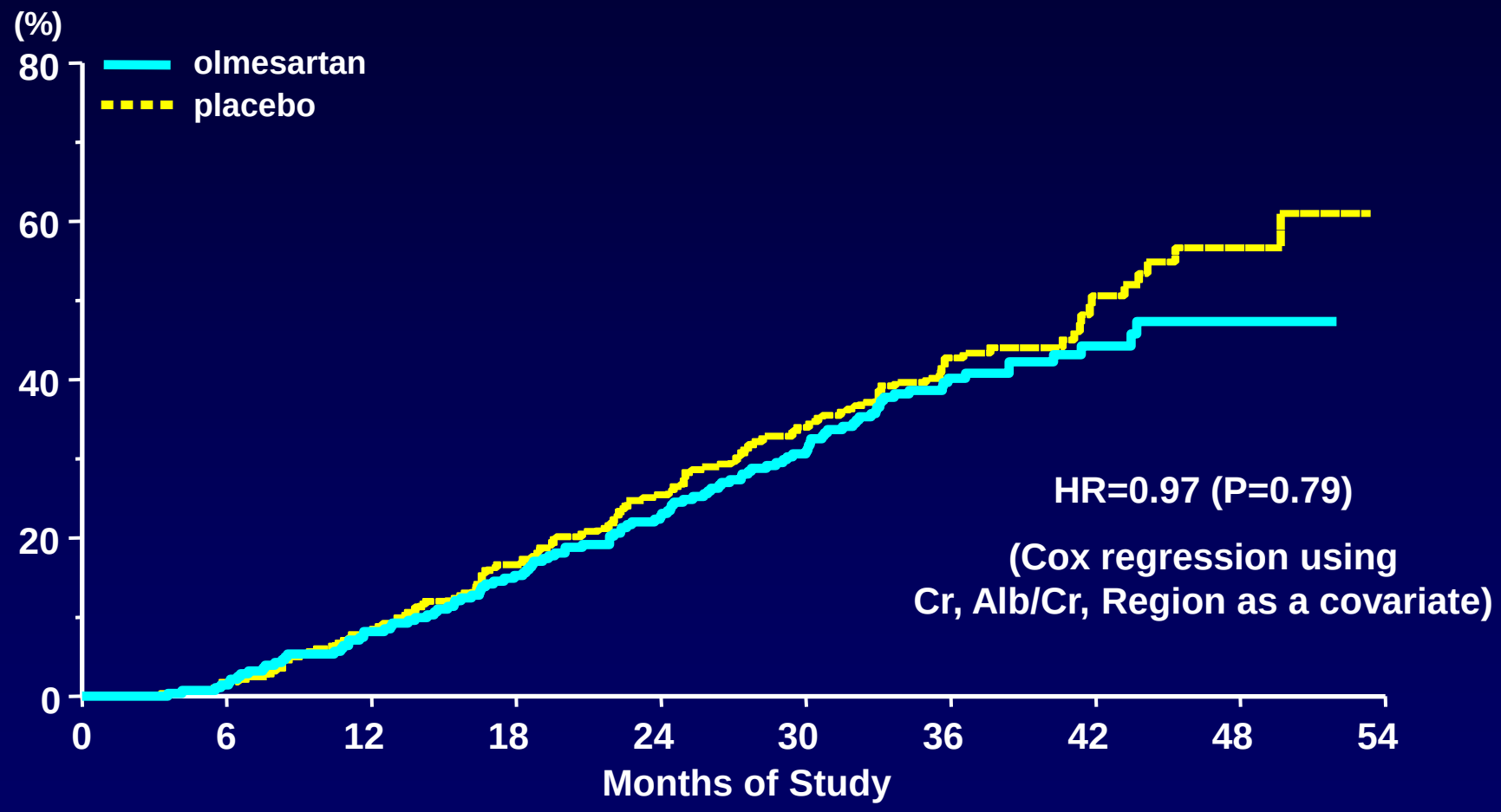
Study design paper in Imai E, et al. *Hypertens Res* ; Vol. 29, No.9 (2006)

Time Course Change in Blood Pressure



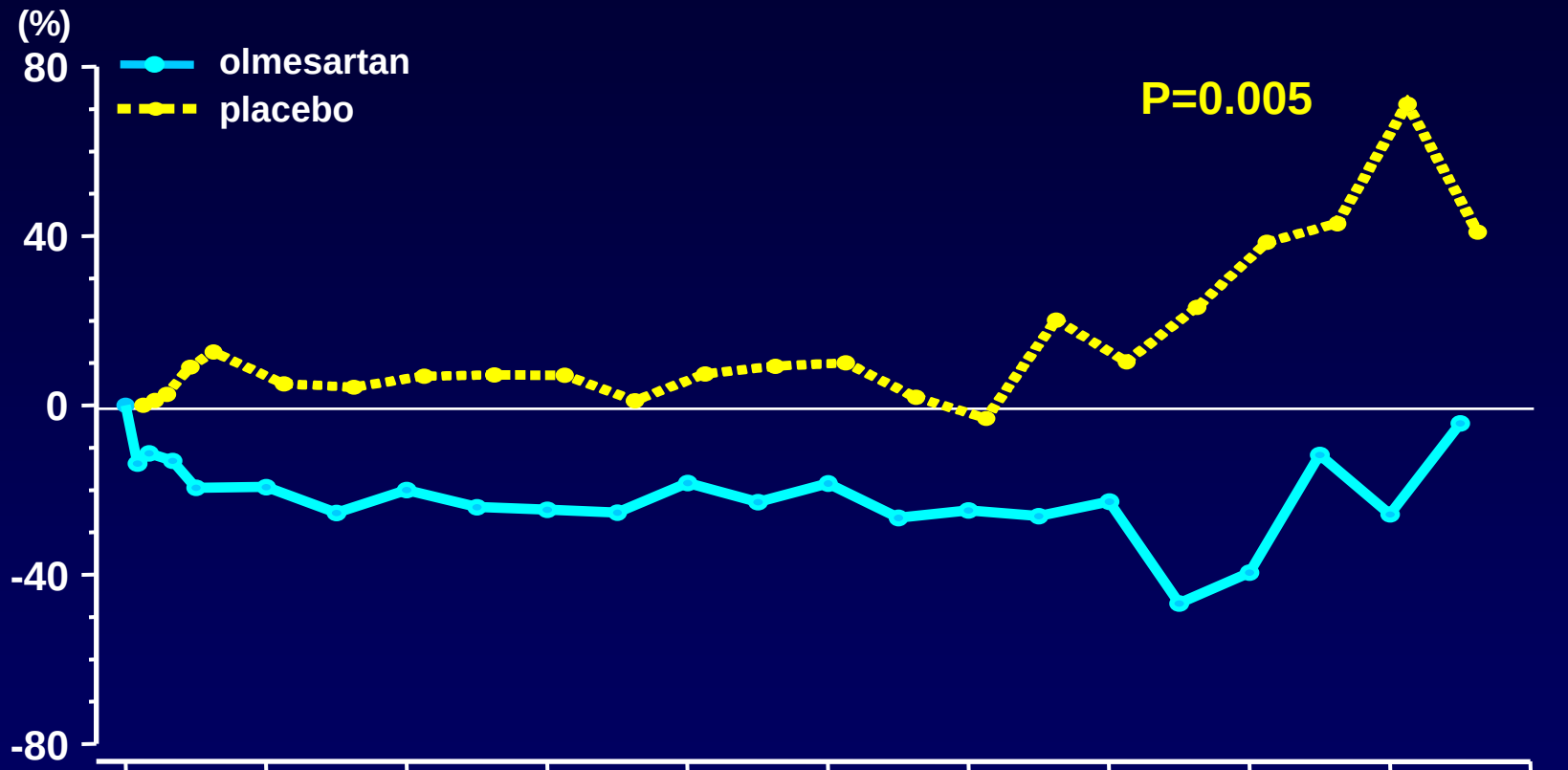
Diabetologia. 2011 Dec;54(12):2978-86.

Primary Composite Renal Outcome



Diabetologia. 2011 Dec;54(12):2978-86.

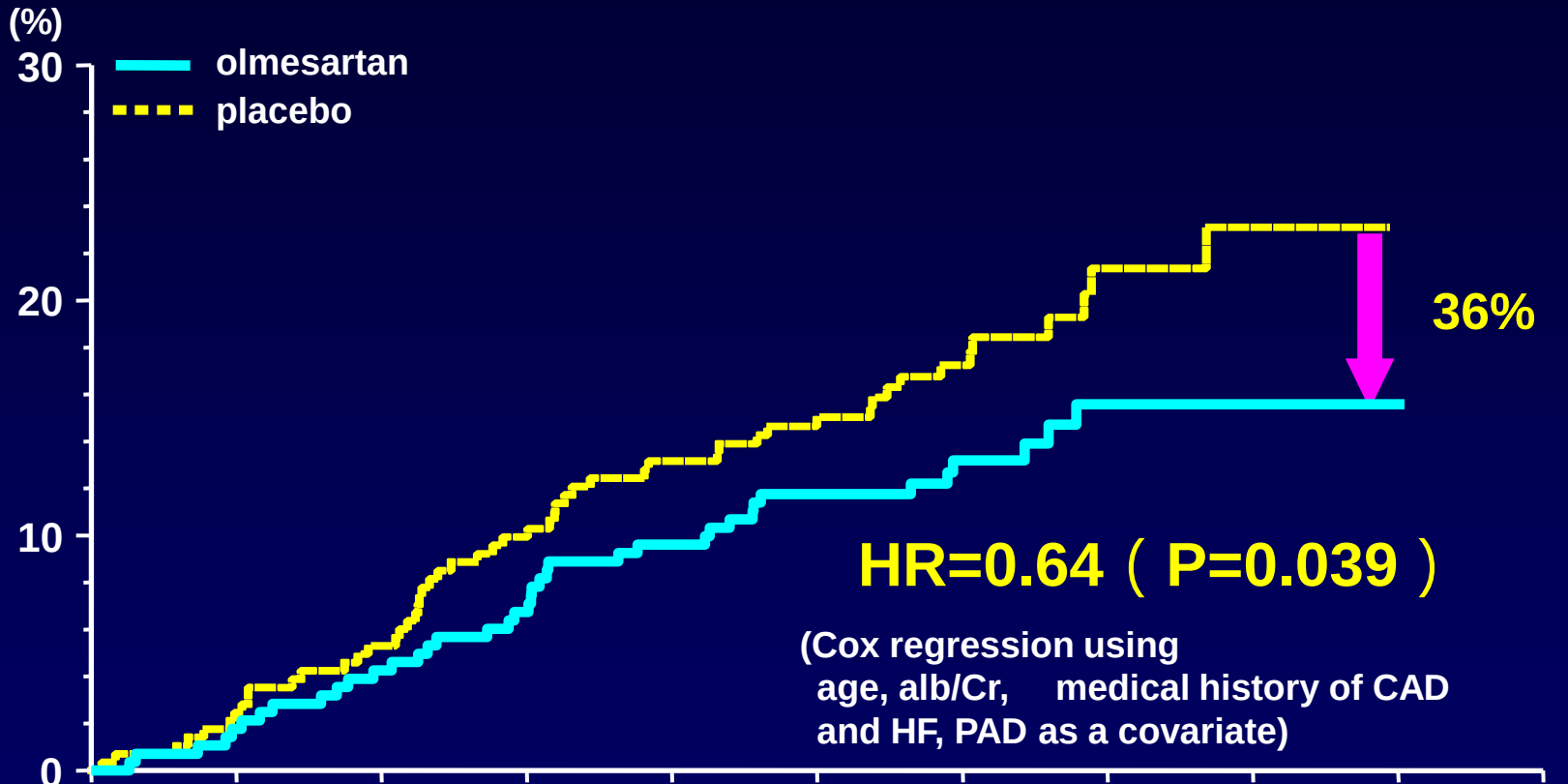
Urinary Protein to Creatinine Ratio (mg/g.CRE)



olmesartan	282	265	245	228	205	183	138	78	38	15
placebo	284	274	246	220	192	170	129	75	33	15

Diabetologia. 2011 Dec;54(12):2978-86.

Cardiovascular Outcomes



NO. AT RISK

olmesartan	282	277	270	261	252	230	160	77	31	1
placebo	284	277	266	253	240	218	149	65	32	0

Diabetologia. 2011 Dec;54(12):2978-86.

Take home message

- ✓ Intrarenal renin-angiotensin system (RAS) plays a role in the pathogenesis of salt-dependent hypertension
- ✓ Japanese guideline suggests the potential utility and benefit of RAS inhibitors for Asian hypertensive patients with CKD

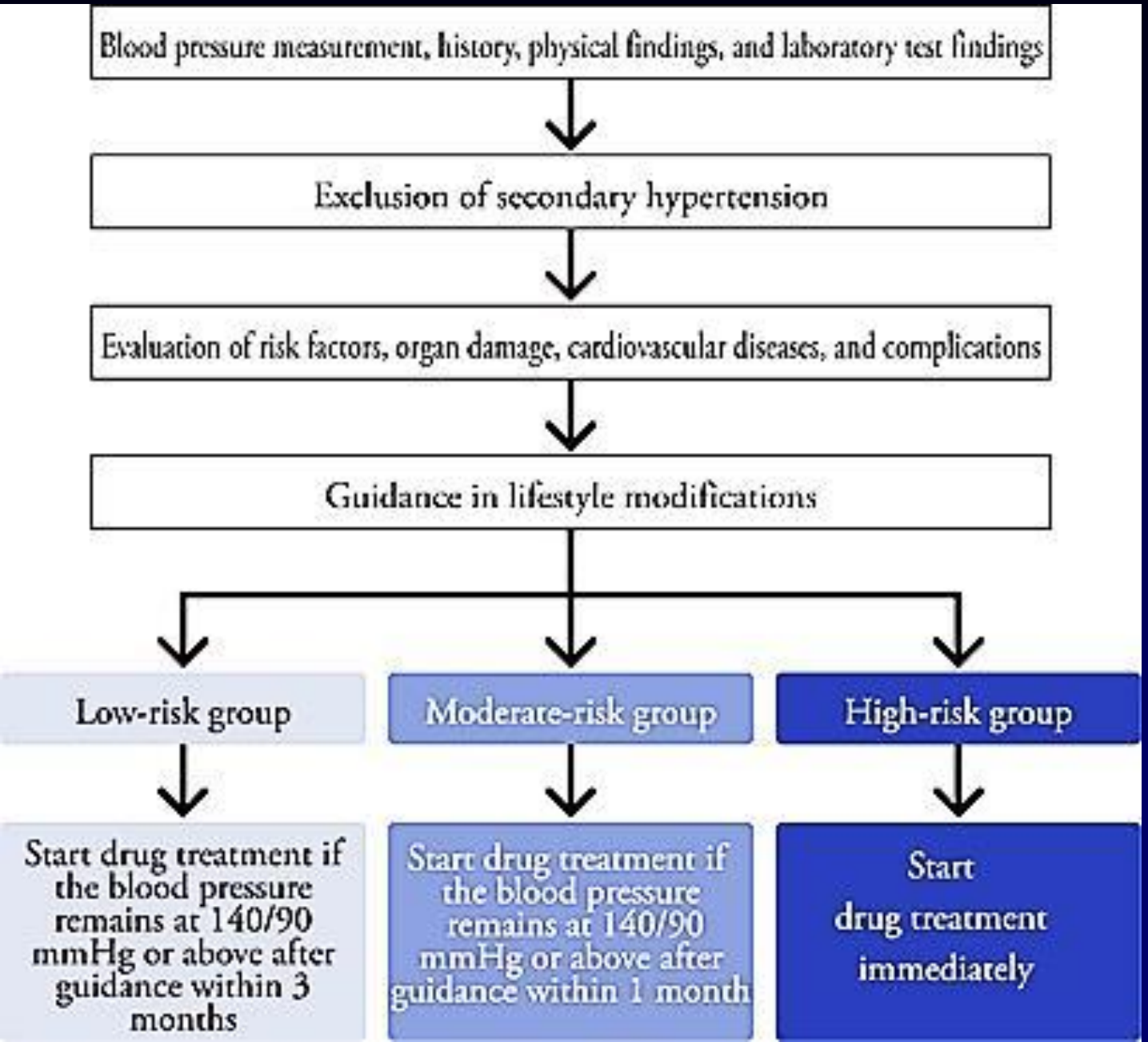

Blood pressure measurement, history, physical findings, and laboratory test findings
Exclusion of secondary hypertension
Evaluation of risk factors, organ damage, cardiovascular diseases, and complications
Guidance in lifestyle modifications
Low-risk group
Moderate-risk group
High-risk group
Start drug treatment if the blood pressure remains at 140/90 mmHg or above after guidance within 3 months
Start drug treatment if the blood pressure remains at 140/90 mmHg or above after guidance within 1 month
Start drug treatment immediately

Table 3-3 Target levels of blood pressure control

	Clinic blood pressure	*Home blood pressure*
Young, middle-aged and early-phase elderly patients	<140/90 mm Hg	<135/85 mm Hg
Late-phase elderly patients	<150/90 mm Hg (<140/90 mm Hg if tolerant)	<145/85 mm Hg (<135/85 mm Hg if tolerant)
Diabetic patients	<130/80 mm Hg	<125/75 mm Hg
Patients with CKD (with proteinuria)	<130/80 mm Hg	<125/75 mm Hg (criterion)
Patients with cerebrovascular diseases	<140/90 mm Hg	<135/85 mm Hg (criterion)
Patients with coronary artery disease		

Abbreviation: CKD, chronic kidney disease.
Note: As diagnostic criteria for hypertension include a clinic blood pressure of 140/90 mm Hg and a home blood pressure of 135/85 mm Hg, the difference between the two values was applied to the difference between the target levels of clinic and home blood pressures.

Table 3-2 Stratification of the risk of cardiovascular disease based on clinic blood pressure

Classification of blood pressure / Risk category (prognostic factors other than blood pressure)	Grade I hypertension 140-159/90-99 mmHg	Grade II hypertension 160-179/100-109 mmHg	Grade III hypertension ≥180/≥110 mmHg
Risk I (no prognostic factor)	Low risk	Moderate risk	High risk
Risk II (either 1 to 2 risk factors other than diabetes mellitus or MetS meeting 3 items is present)	Moderate risk	High risk	High risk
Risk III (one of the following factors is present: diabetes mellitus, CKD, organ damage/cardiovascular disease, MetS meeting 4 items, or 3 or more risk factors)	High risk	High risk	High risk

Abbreviations: CKD, chronic kidney disease; MetS, metabolic syndrome.

Table 4-1 Points of lifestyle modifications

1. Salt reduction	<6 g per day
2a. Vegetables/fruit	Increased intake of vegetables/fruits[a]
2b. Lipids	Reduced intake of cholesterol and saturated fatty acids, increased intake of fish (fish oil)
3. Weight loss	BMI ([body weight (kg)] ÷ [height (m)]^2): $<25\,kg\,m^{-2}$
4. Exercise	In hypertensive patients with no cardiovascular disease, exercise, primarily aerobic exercise, should be performed periodically (for $\geqslant$30 min daily, if possible).
5. Reduction of alcohol intake	$\leqslant$20–30 ml per day in men and $\leqslant$10–20 ml per day in women as ethanol
6. Smoking cessation	including the prevention of passive smoking

Combined lifestyle modifications are more effective.

[a]An increased intake of vegetables/fruits is not recommended for patients with severe renal dysfunction because of the risk of hyperkalemia. An excessive intake of fruit with a high fructose content is not recommended in patients who need to restrict their energy intake, such as obese and diabetic patients.

Table 5-1 Conditions for which major antihypertensive drugs are indicated

	Ca channel blockers	*ARBs/ACE inhibitors*	*Thiazide diuretics*	*β-Blockers*
Left ventricular hypertrophy	●	●		
Heart failure		●[a]	●	●[a]
Tachycardia	● (Non-dihydropyridines)			●
Angina pectoris	●			●[b]
Post myocardial infarction		●		●
CKD				
Proteinuria (–)	●	●	●	
Proteinuria (+)		●		
Chronic phase of cerebrovascular disorders	●	●	●	
Diabetes mellitus/MetS[c]		●		
Osteoporosis			●	
Aspiration pneumonia		● (ACE inhibitors)		

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; MetS, metabolic syndrome.

[a]Administration should be started at a low dose, and the dose should be gradually increased carefully.

[b]Caution is needed in patients with coronary spastic angina pectoris.

[c]Metabolic syndrome.

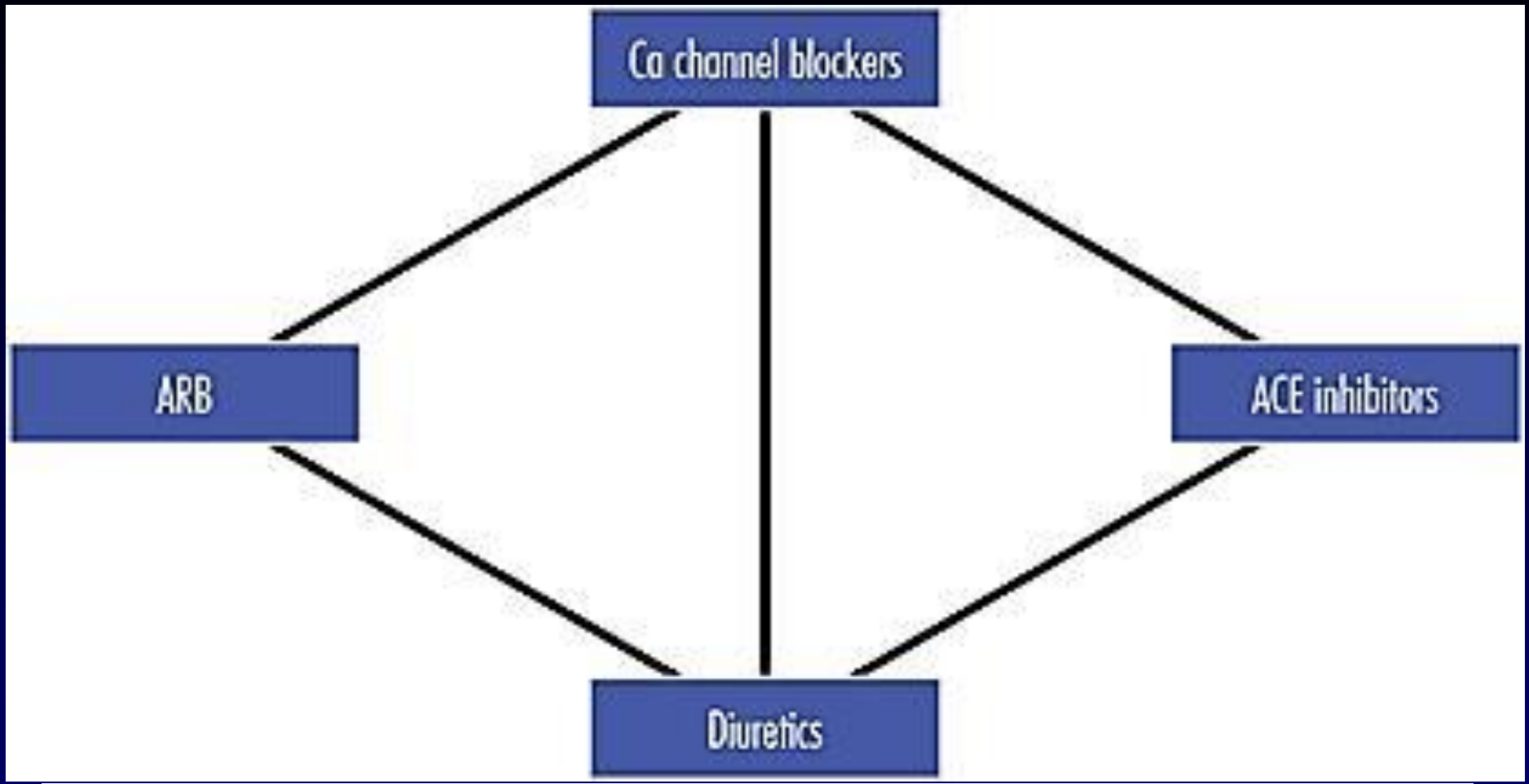
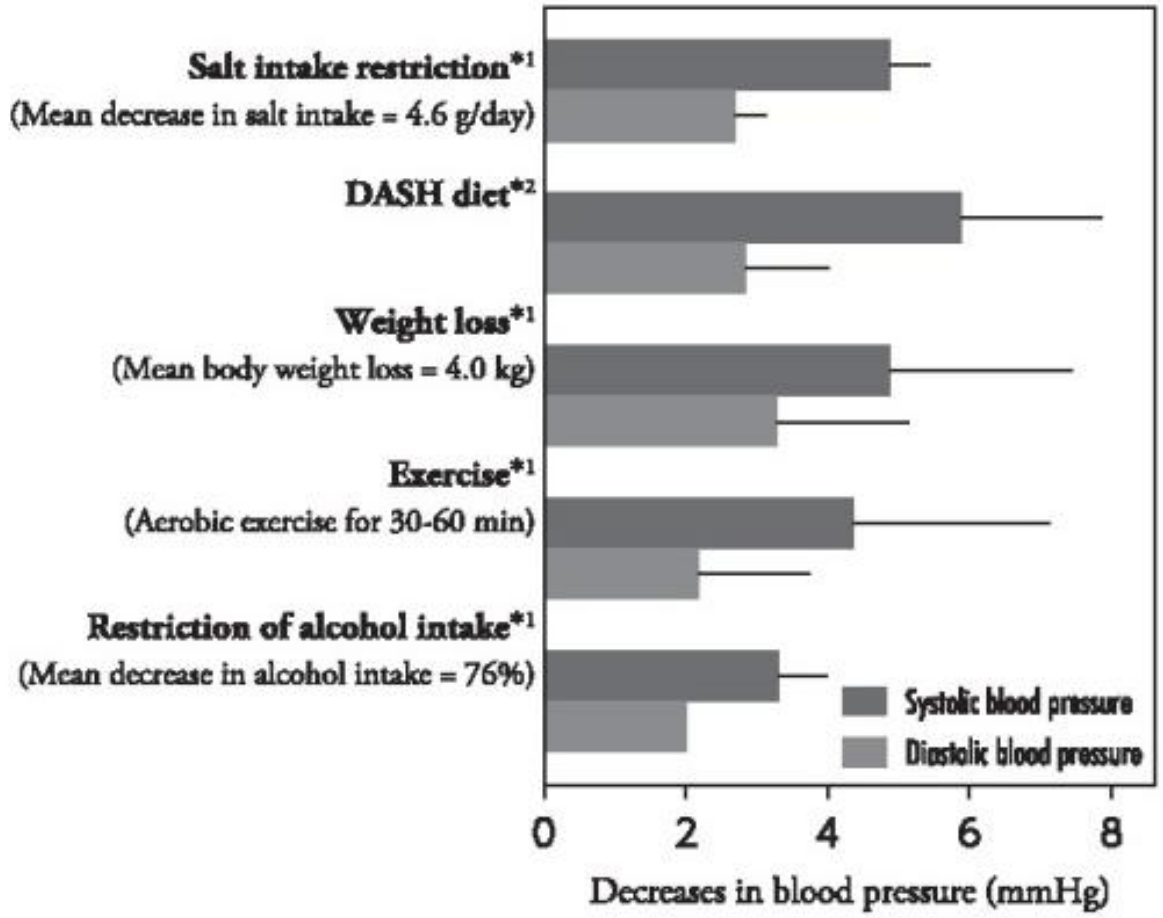


Figure 5-3 Combination of two drugs. *Combination therapy with an ARB and an ACE inhibitor is not commonly used. If the two drugs are concomitantly used to protect the kidney, they must be carefully administered while monitoring kidney function and considering the risk of hyperkalemia. A full color version of this figure is available at the *Hypertension Research* journal online.



*1. metaanalysis, *2. randomized intervention study
Salt intake restriction [341], DASH diet [339], weight loss [374], exercise [342], restriction of alcohol intake [382]

Figure 4-1 Decreases in blood pressure levels through lifestyle modifications. *1. meta-analysis, *2. randomized intervention study. Salt intake restriction,[341] DASH diet,[339] weight loss,[374] exercise,[342] restriction of alcohol intake.[382]

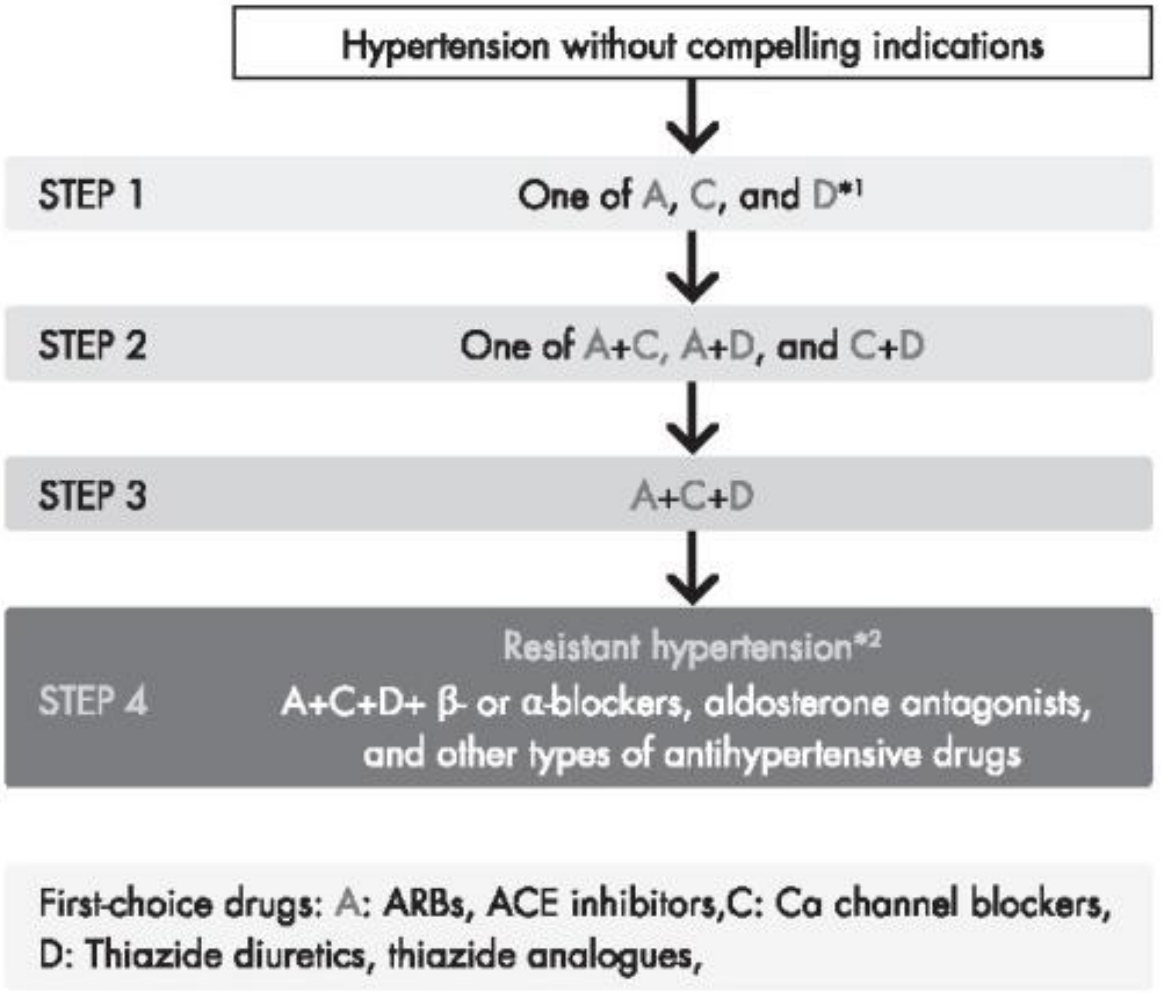


Figure 5-2 Procedures of hypertension treatment in the absence of compelling indications. *1In elderly patients, administration should be started at 1/2 of the standard dose, and the dose should be increased at 1–3-month intervals. *2See the section 5 'Strategies for resistant or poorly controlled hypertension'. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 5-2 Contraindications for major antihypertensive drugs and conditions requiring careful administration

	Contraindications	*Conditions that require careful use*
Ca channel blockers	Bradycardia (non-dihydropyridines)	Heart failure
ARB	Pregnancy Hyperkalemia	Renal artery stenosis[a]
ACE inhibitors	Pregnancy Angioneurotic edema Hyperkalemia	Renal artery stenosis[a]
Diuretics (thiazide)	Hypokalemia	Gout Pregnancy Impaired glucose tolerance
β-Blockers	Asthma Marked bradycardia	Impaired glucose tolerance Obstructive pulmonary disease Peripheral artery disease

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers.
[a]As a rule, ARBs/ACE inhibitors are contraindicated for patients with bilateral renal artery stenosis.

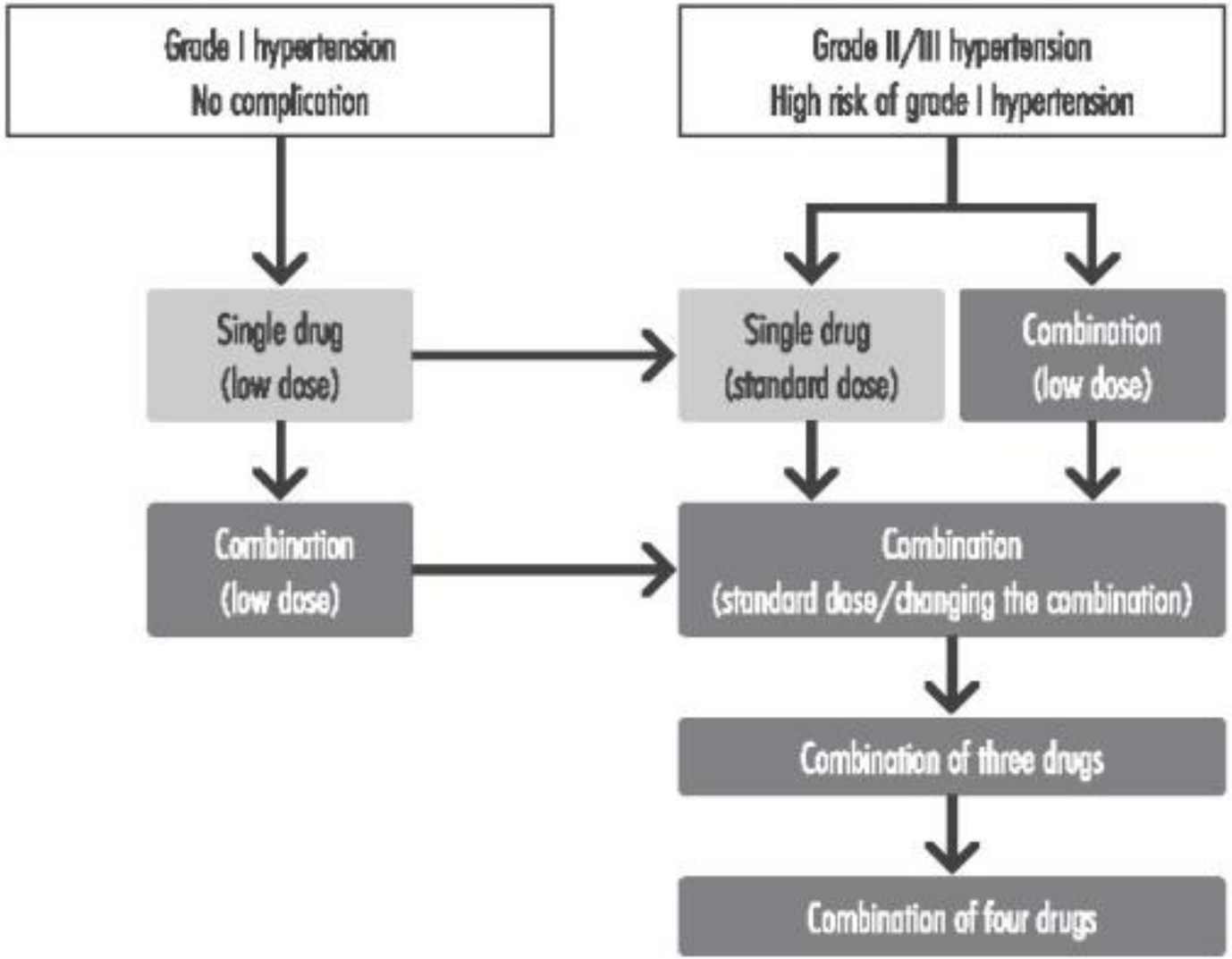


Figure 5-1 Use of antihypertensive drugs to achieve the target level of blood pressure control. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 6-1 Treatment for hypertension complicated by cerebrovascular diseases

			Conditions to treat	*Target BP level*	*Antihypertensive drugs*
Hyperacute phase (within 24 h after onset)	Cerebral infarction	Within 4.5 h after onset	Patients awaiting thrombolytic therapy[a]	During thrombolytic therapy and 24 h after thrombolytic therapy	i.v. instillation of nicardipine, diltiazem, nitroglycerin or nitroprusside
			SBP >185 mm Hg or DBP >110 mm Hg	<180/105 mm Hg	
		Within 24 h after onset	Patients in whom thrombolytic therapy is not performed SBP >220 mm Hg or DBP >120 mm Hg	85–90% of the pretreatment value	
	Cerebral hemorrhage		SBP >180 mm Hg or MBP >130 mm Hg	80% of the pretreatment value[b]	
			SBP 150–180 mm Hg	SBP: ~140 mm Hg	
	Subarachnoid hemorrhage (from the onset of ruptured cerebral aneurysm until the treatment of cerebral aneurysm)		SBP >160 mm Hg	80% of the pretreatment value[c]	
Acute phase (within 2 weeks after onset)	Cerebral infarction		SBP >220 mm Hg or DBP >120 mm Hg	85–90% of the pretreatment value	i.v. instillation of nicardipine, diltiazem, nitroglycerin, or nitroprusside, or oral drugs (Ca channel blockers, ACE inhibitors, ARBs or diuretics)
	Cerebral hemorrhage		SBP >180 mm Hg or MBP >130 mm Hg	80% of the pretreatment value[b]	
			SBP 150–180 mm Hg	SBP: ~140 mm Hg	
Subacute phase (3–4 weeks after onset)	Cerebral infarction		SBP >220 mm Hg or DBP >120 mm Hg	85–90% of the pretreatment value	Oral drugs (Ca channel blockers, ACE inhibitors, ARBs or diuretics)
			Patients with an SBP of 180–220 mm Hg in whom there is no 50% or greater stenosis of the carotid artery or a main trunk of the cerebral arteries	85–90% of the pretreatment value	
	Cerebral hemorrhage		SBP >180 mm Hg MBP >130 mm Hg	80% of the pretreatment value	
			SBP 150–180 mm Hg	SBP: ~140 mm Hg	
Chronic phase (1 month or more after onset)	Cerebral infarction		SBP ⩾140 mm Hg	<140/90 mm Hg[d]	
	Cerebral hemorrhage Subarachnoid hemorrhage		SBP ⩾140 mm Hg	<140 mm Hg[e]	

Abbreviations: DBP, diastolic blood pressure; MBP, mean arterial blood pressure; SBP, systolic blood pressure.
[a]In patients in whom endovascular therapy is scheduled, it should be performed in accordance with thrombolytic therapy.
[b]In patients in whom increased intracranial pressure is expected due to a severe condition, cerebral perfusion pressure may reduce with blood pressure, deteriorating symptoms or inducing acute renal dysfunction; therefore, antihypertensive treatment should be performed carefully.
[c]In patients in whom increased intracranial pressure is expected due to a severe condition or those with acute cerebral infarction or cerebrovascular spasm, cerebral perfusion pressure may reduce with blood pressure, deteriorating symptoms; therefore, antihypertensive treatment should be performed carefully.
[d]Blood pressure should be reduced slowly. In patients with marked bilateral carotid artery stenosis or those with occlusion of a main trunk of the cerebral arteries, an excessive decrease in blood pressure should be particularly avoided. In patients with lacunar infarction or those concomitantly taking antithrombotic drugs, a lower level, <130/80 mm Hg, should be targeted.
[e]If possible, the target blood pressure should be <130/80 mm Hg.

Table 6-2 Treatment for hypertension complicated by heart disease

Angina pectoris	Organic coronary stenosis[a]: β-blockers, long-acting Ca channel blockers
	Coronary vasospasm: long-acting Ca channel blockers
	If a decrease in blood pressure is insufficient, an RA system inhibitor (ACE inhibitor, ARB) is added.
Old myocardial infarction	RA system inhibitors or β-blockers are the first choice.
	If a decrease in blood pressure is insufficient, a long-acting Ca channel blocker or diuretic is added.
	Patients with systolic dysfunction: an aldosterone antagonist is added[b].
Heart failure	Heart failure with reduced ejection fraction
	Standard treatment: RA system inhibitor[c] + β-blocker[c] + diuretic
	Severe heart failure patients: an aldosterone antagonist is added.
	If a decrease in blood pressure is insufficient, a long-acting Ca channel blocker is added.
	Heart failure with preserved ejection fraction
	A sustained and sufficient decrease in blood pressure is important.
Cardiac hypertrophy	A sustained and sufficient decrease in blood pressure is necessary.
	RA system inhibitors or long-acting Ca channel blockers are the first choice.

Abbreviation: RA, renin–angiotensin.
[a]Coronary revascularization is performed in patients with significant organic coronary stenosis.
[b]Be aware of hyperkalemia.
[c]Administration should be started at a low dose, and the dose should be titrated carefully and slowly.

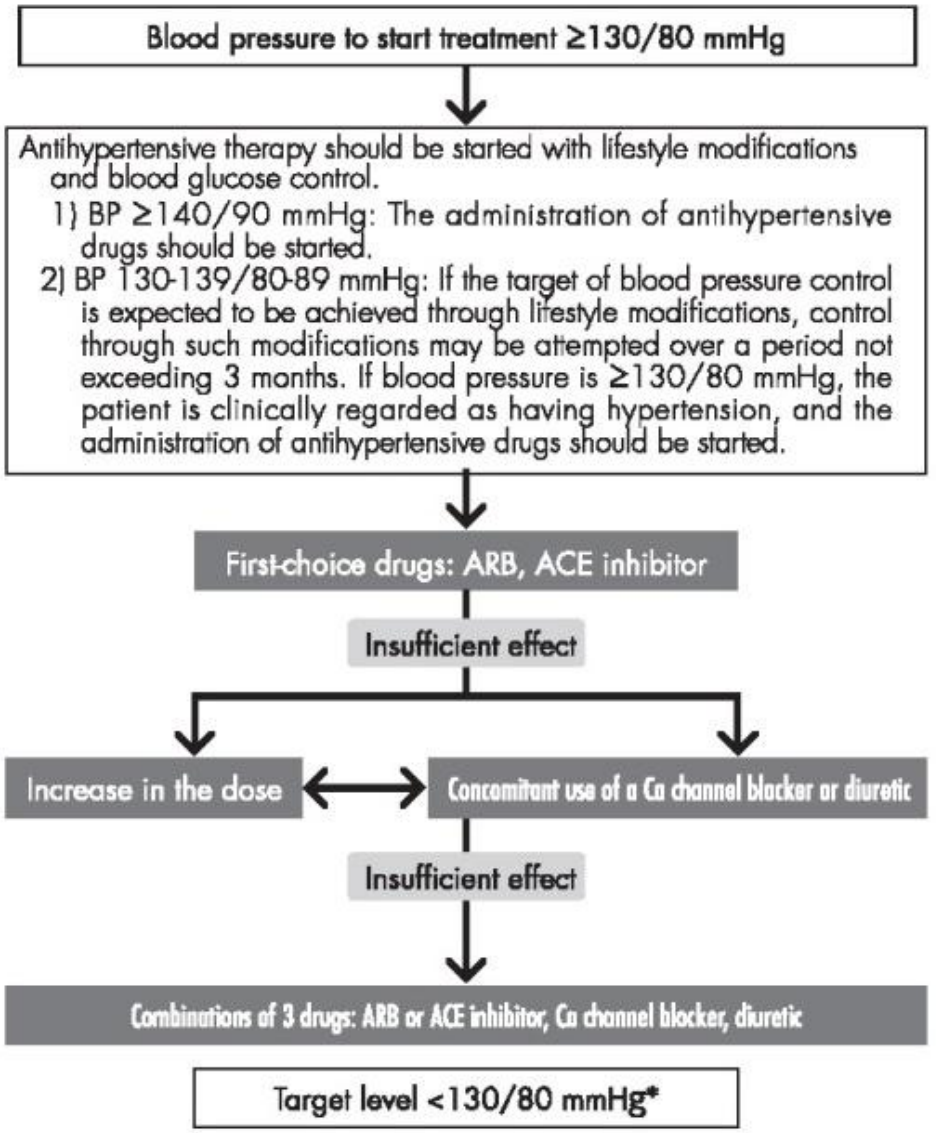


Figure 7-1 Treatment plan for hypertension complicated by diabetes mellitus. *However, a reduction in organ perfusion related to a decrease in blood pressure must be considered in patients with atherosclerotic coronary artery disease or peripheral arterial disease and elderly patients. A full color version of this figure is available at the *Hypertension Research* journal online.