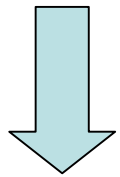
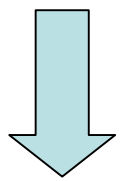
Hypertensive Patient with Renal Damage

가톨릭의대 강남성모병원
신장내과 양 철우

Renal Damage?



Structural or functional abnormalities in kidney



- >3 months
- GFR< 60

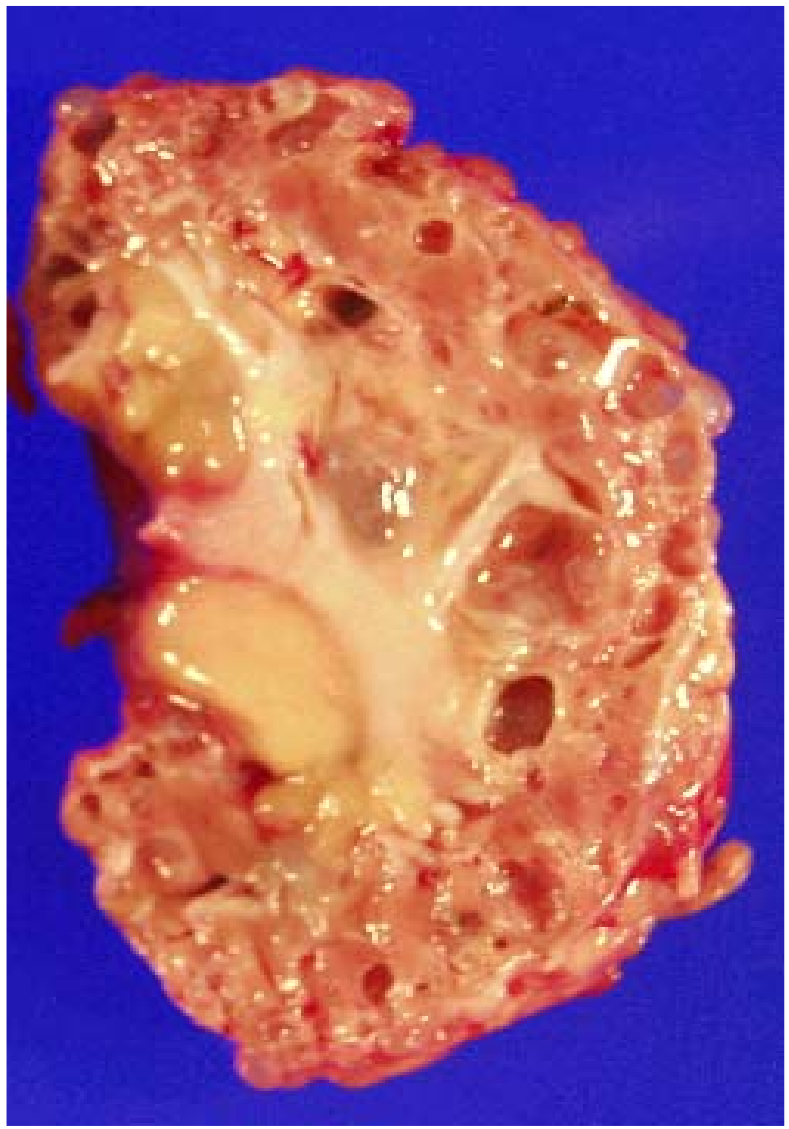
Chronic Kidney Disease (CKD)

Stages of Chronic Kidney Disease

Stage	GFR	%
1	$\geq$ 90	64.3
2	60-89	31.2
3	30-59	4.3
4	15-29	0.2
5	< 15	0.2

Data from NHANES III (1988-1994) and USRDS (1998)

Stage I

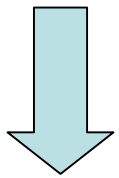


Stage 5: ESRD

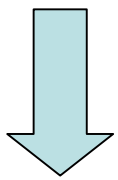
Clinical Plan of Action for Stages of Chronic Kidney Disease

Stage	Clinical Plan of Action
1	Diagnose and treat Slow progression Reduce risk of cardiovascular disease
2	Estimate rate of progression
3	Evaluate and treat complications
4	Prepare for dialysis and kidney TXPL
5	Dialysis and kidney TXPL

A marker of kidney damage?



An early and sensitive marker



Microalbuminuria

Microalbuminuria and Essential Hypertension-I

Viazzi F et al. J Am Soc Nephrol 16:S89, 2005

- **BP load and Dyslipidemia**
- **Endothelial dysfunction**
- **Salt sensitivity**
- **Activation of RAS**

An integrated marker of cardiovascular risk

Microalbuminuria and Essential Hypertension-II

Viazzi F et al. J Am Soc Nephrol 16:S89, 2005

- **Left ventricular hypertrophy**
- **Carotid wall thickness**

20-fold increase!!!

<u>A marker of subclinical organ damage</u>

Definition of microalbuminuria

Method	Microalbuminuria
24hr urine excretion	30-300 mg/day
Spot urine* Alb to Cr ratio (ACR)	17-250 mg/g (men) 25-355 mg/g (women)

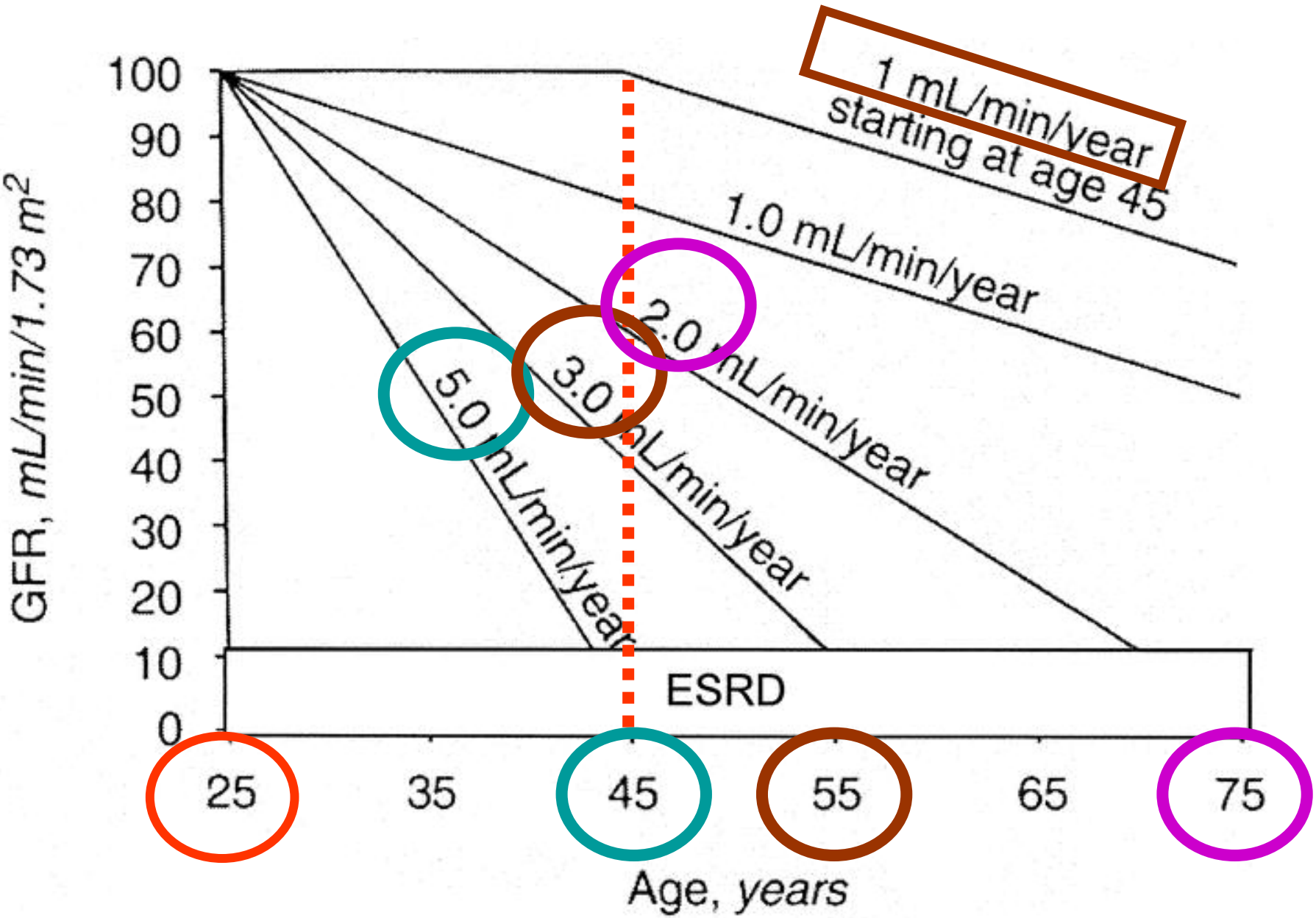
* Preferred method

Overt Proteinuria

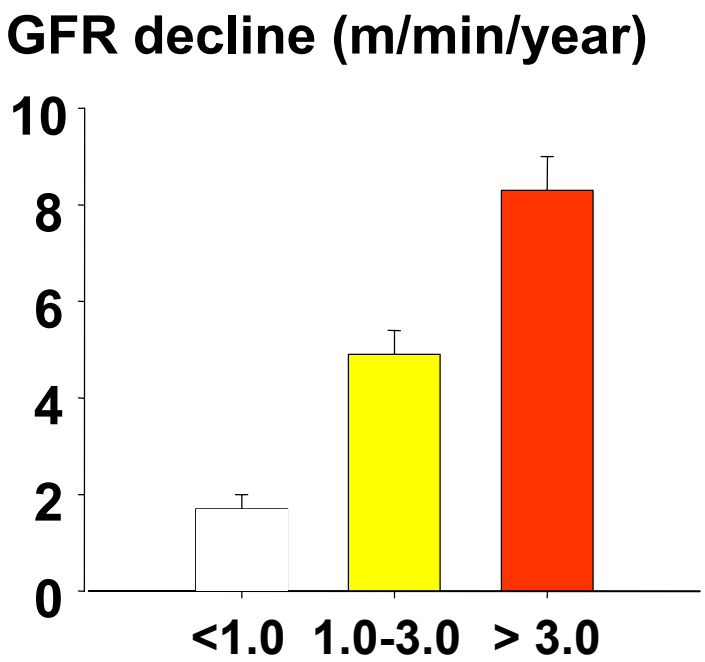
Toxic/inflammatory systems

- **Complement**
- **Inflammatory lipoproteins**
- **Iron species**

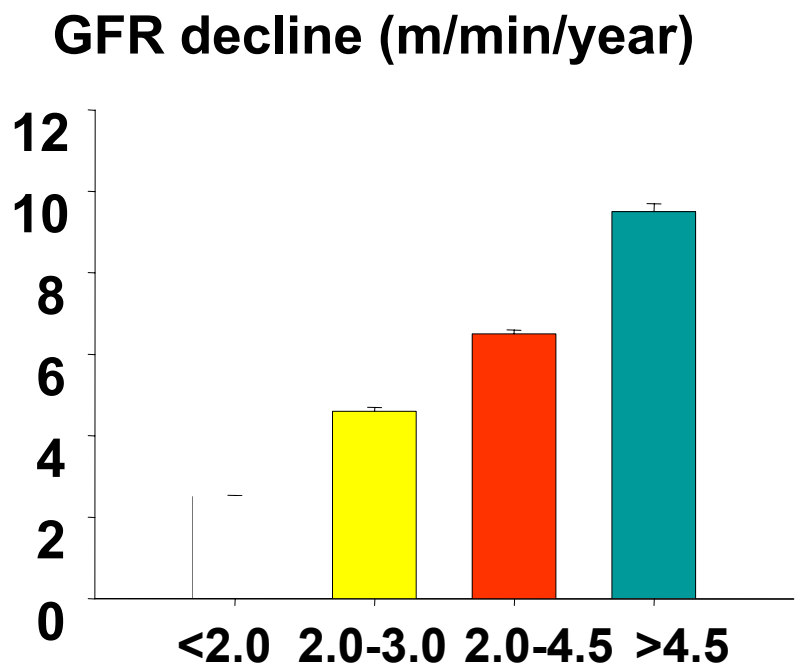
Proteinuria is Nephrotoxic


GFR, mL/min/1.73 m2
100
90
80
70
60
50
40
30
20
10
0
25
35
45
55
65
75
Age, years
1 mL/min/year starting at age 45
1.0 mL/min/year
2.0 mL/min/year
3.0 mL/min/year
5.0 mL/min/year
ESRD

GFR decline according to baseline proteinuria

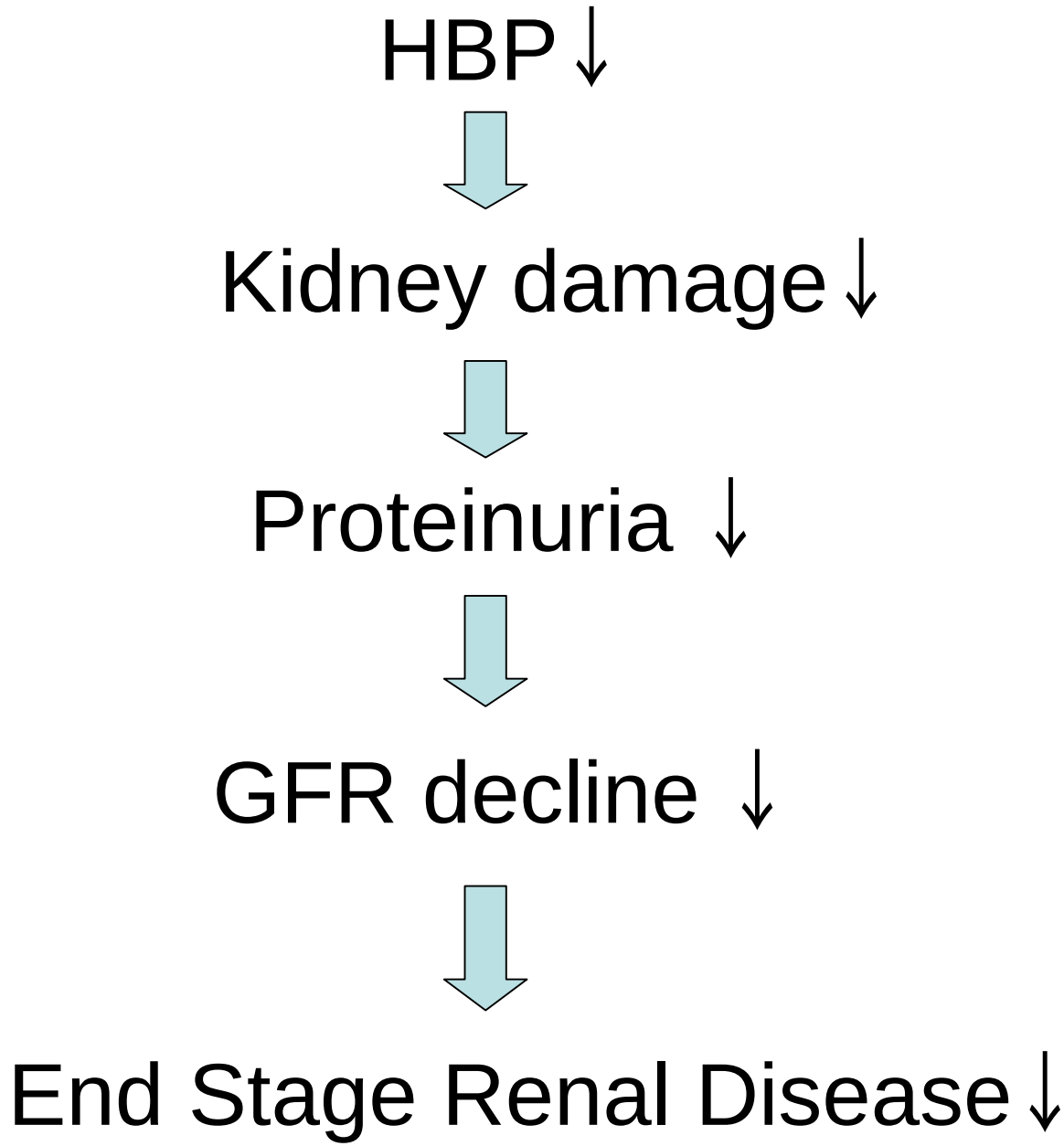


MDRD study (n=585)

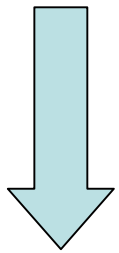


REIN study (n=585)

Urine protein (g/day)


HBP↓
Kidney damage↓
Proteinuria ↓
GFR decline ↓
End Stage Renal Disease↓

Choice of anti-HBP Medication in Patients with Proteinuria



Anti-HBP Drugs which Decrease Proteinuria

Pharmacologic approach

ACEI or ARB	Choice
CCB	NDH > DH
Others	• β-blocker • Aldosterone antagonist • Statin

Anti-Proteinuric Strategy

Target of BP	SBP<125 mmHg DBP< 75 mmHg
Goal of Proteinuria	<0.5 gram/day

Algorithm

Wilmer WA et al. J Am Soc Nephrol 14:3217, 2003

ACEI or ARB

↓

ACEI or ARB+ diuretics

↓

ACEI or ARB+ diuretics+ 3rd drug

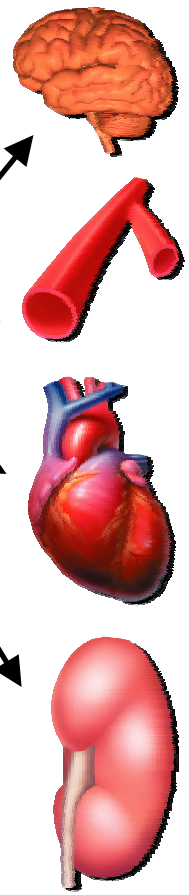
3rd drug: β-blocker, CCB (NDH> DH), α-blocker

↓

RAS inhibitor+ diuretics+ combination of 3rd drug

Why ARB?

Angiotensin II



Stroke

Hypertension

Peripheral vascular disease

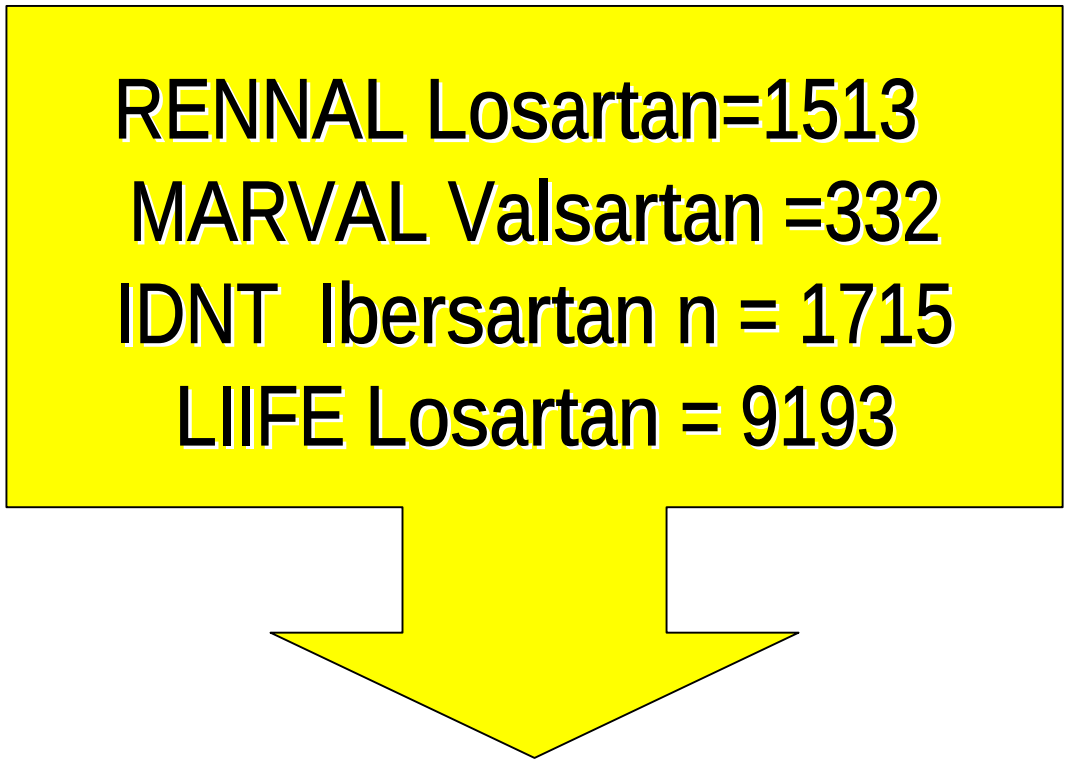
Ischemic heart disease

Heart failure

Renal failure

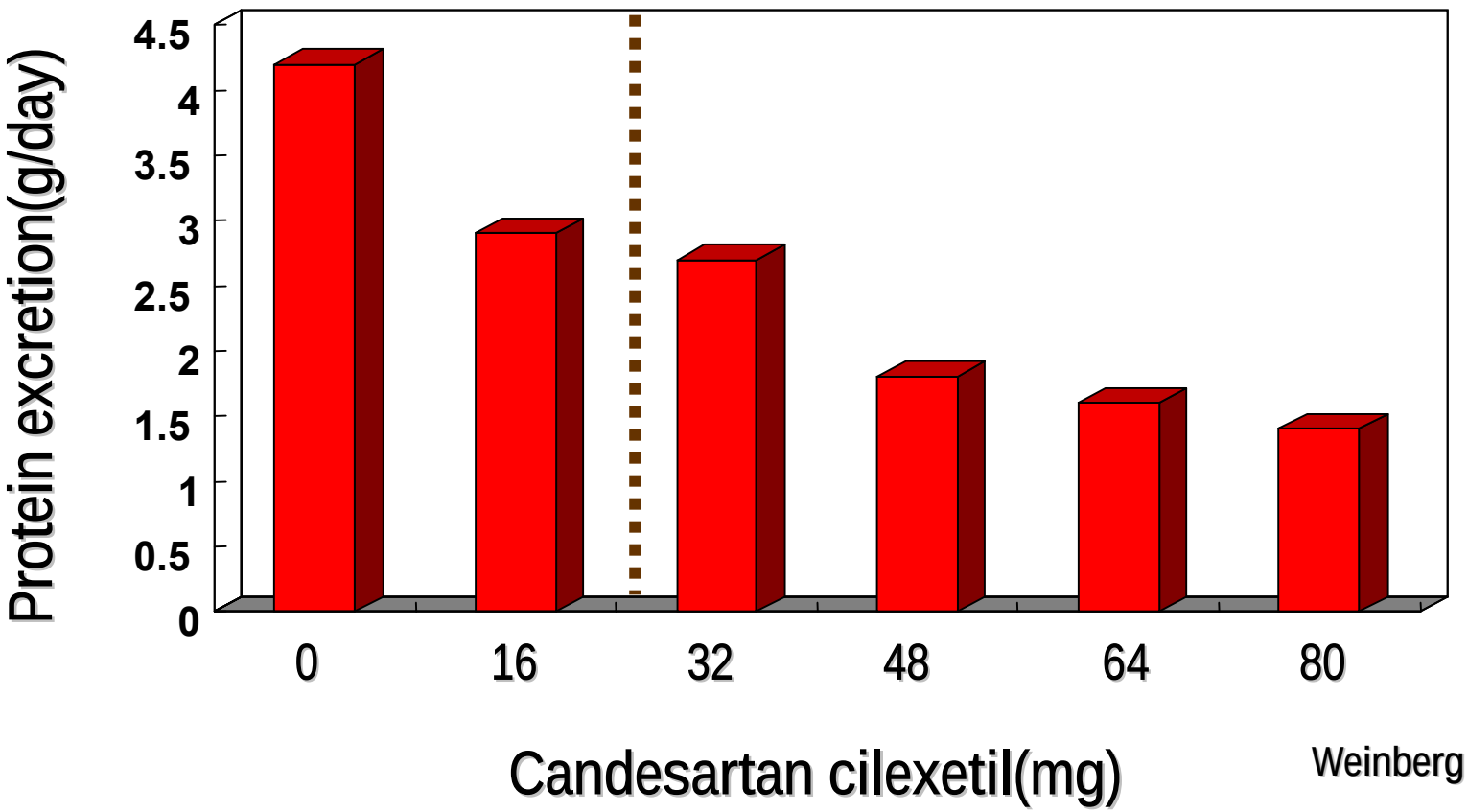
DEATH

Large Scale Clinical Study using ARB



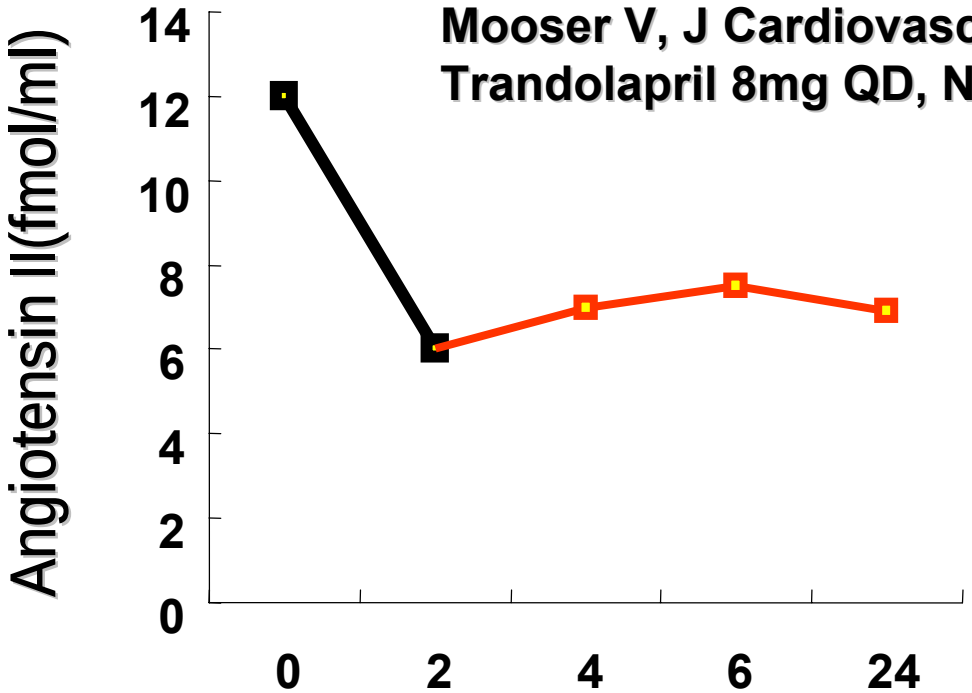
Renoprotective and Cardioprotective effect

Effect of ARB on proteinuria is dose-dependent



Weinberg M, KI, 2000

Chronic ACE inhibition dose not completely suppress Ang II

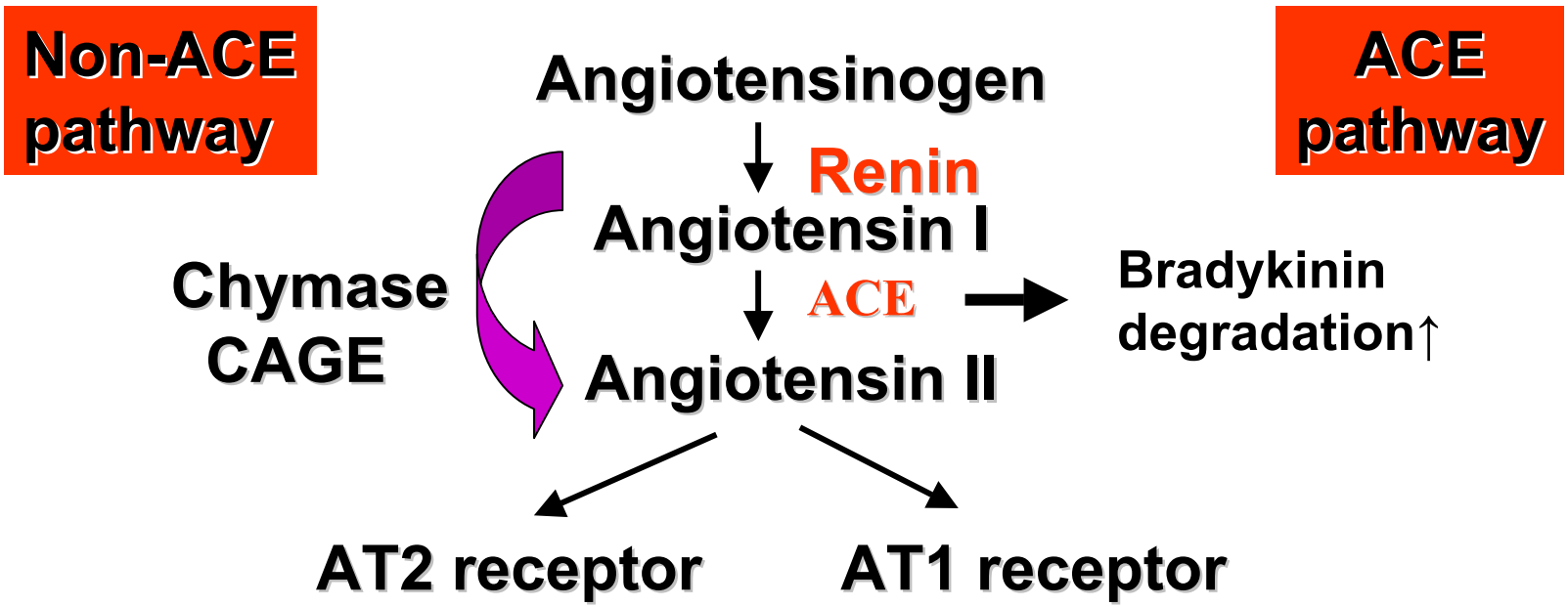


Mooser V, J Cardiovasc Pharmacol, 1990
Trandolapril 8mg QD, N=7 subjects for 10days

New strategies to improve RAS blockade

- **High dose ACEI or ARB**
- **Combination RAS therapy**

Dual therapy of ARB and ACEI



- ARB: Non-ACE pathway 차단
- ACEI: kinins production↑

SPECIAL COMMENTARY

Combination ACEI and ARB therapy: additional benefit in renoprotection?

Maarten W. Taal[a] and Barry M. Brenner[b]

Table 1. Clinical trials of combination angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy in non-diabetic chronic renal disease

Patients	Design	Duration	Outcome	Ref.
Non-diabetic CRD (n=11)	Observational		6 mm ↓ MAP UP ↓ 30%	27
IgA nephropathy (n=8) Normotensive UP 1–3 g/day	Observational	ACEI × 12 weeks Comb. × 4 weeks Losartan 50 mg × 12 weeks Comb. × 4 weeks ACEI or ARB double dose × 4 weeks	BP similar among groups UP 39% ↓ with ACEI UP 27% ↓ with ARB UP 73% ↓ with comb. Double dose → no benefit	28
CRD (n=60)	Randomized cross-over	3 months on ACEI 3 months on comb.	BP 6/3 mmHg ↓ with comb Greater UP ↓ with comb	29
CRD (n=108)	Randomized, open-label Val 160 mg vs Val 80 mg + Bz 5–10 mg vs Val 160 mg + BZ 5–10 mg	5 weeks (Comb. 4 weeks)	Greater BP ↓ with comb Greater UP ↓ with comb	31

ACEI, Angiotensin-converting enzyme inhibitor; BP, blood pressure; Bz, benazepril; comb., combination therapy; CRD, chronic renal disease; MAP, mean arterial pressure; UP, urinary protein; Val, valsartan.

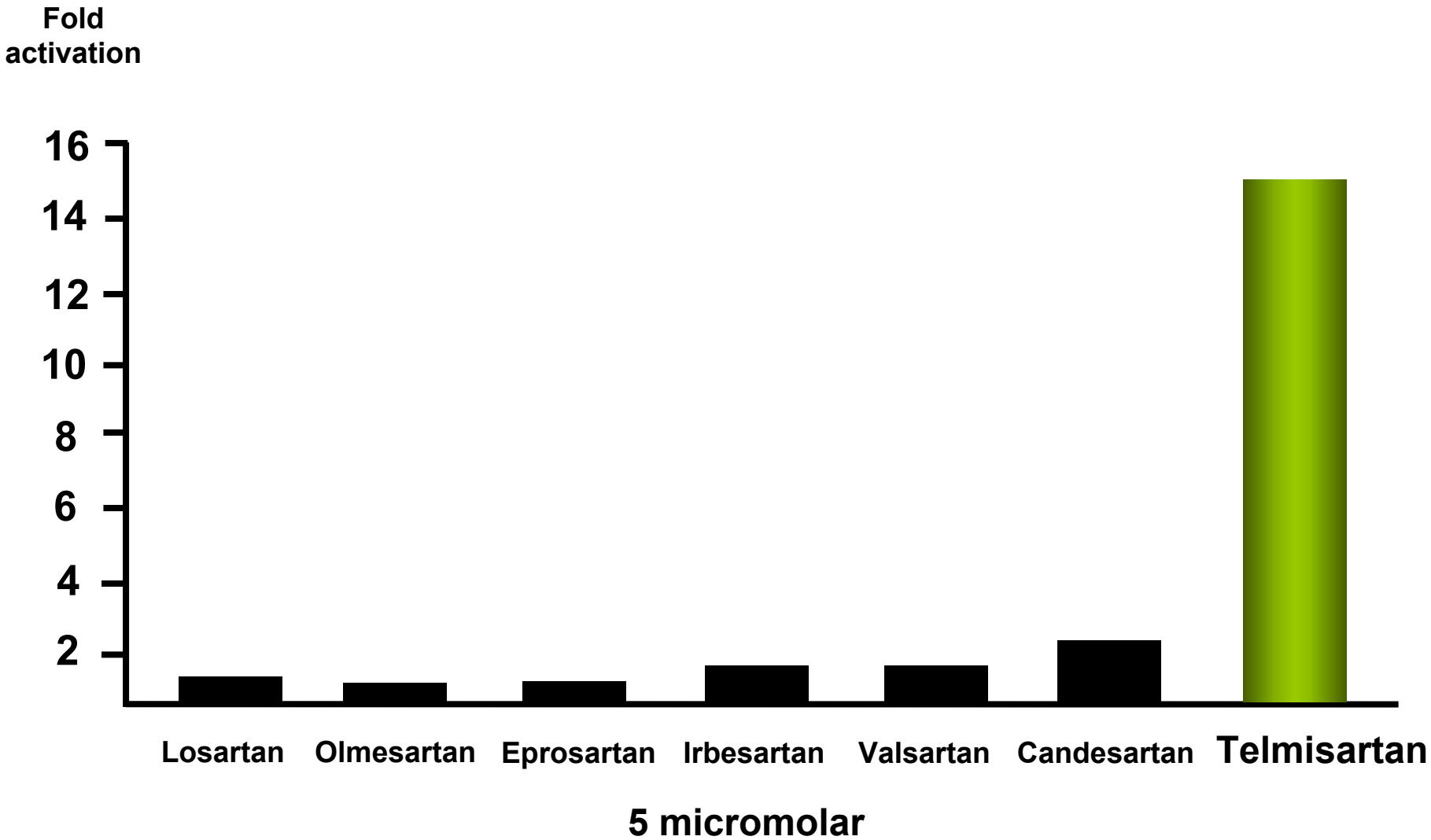
Dual blockade of RAS

- Greater reduction in BP
- Greater increase in renin activity
- Additive antiproteinuric effect
- Additive renoprotective effect


www.koreapen.com
Sartan’s War

Ability of Different ARBs To Activate PPARγ

(S.C. Benson et al., Hypertension, 43:993-1002, 2004)



PPARγ agonist: Thiazolidinediones:

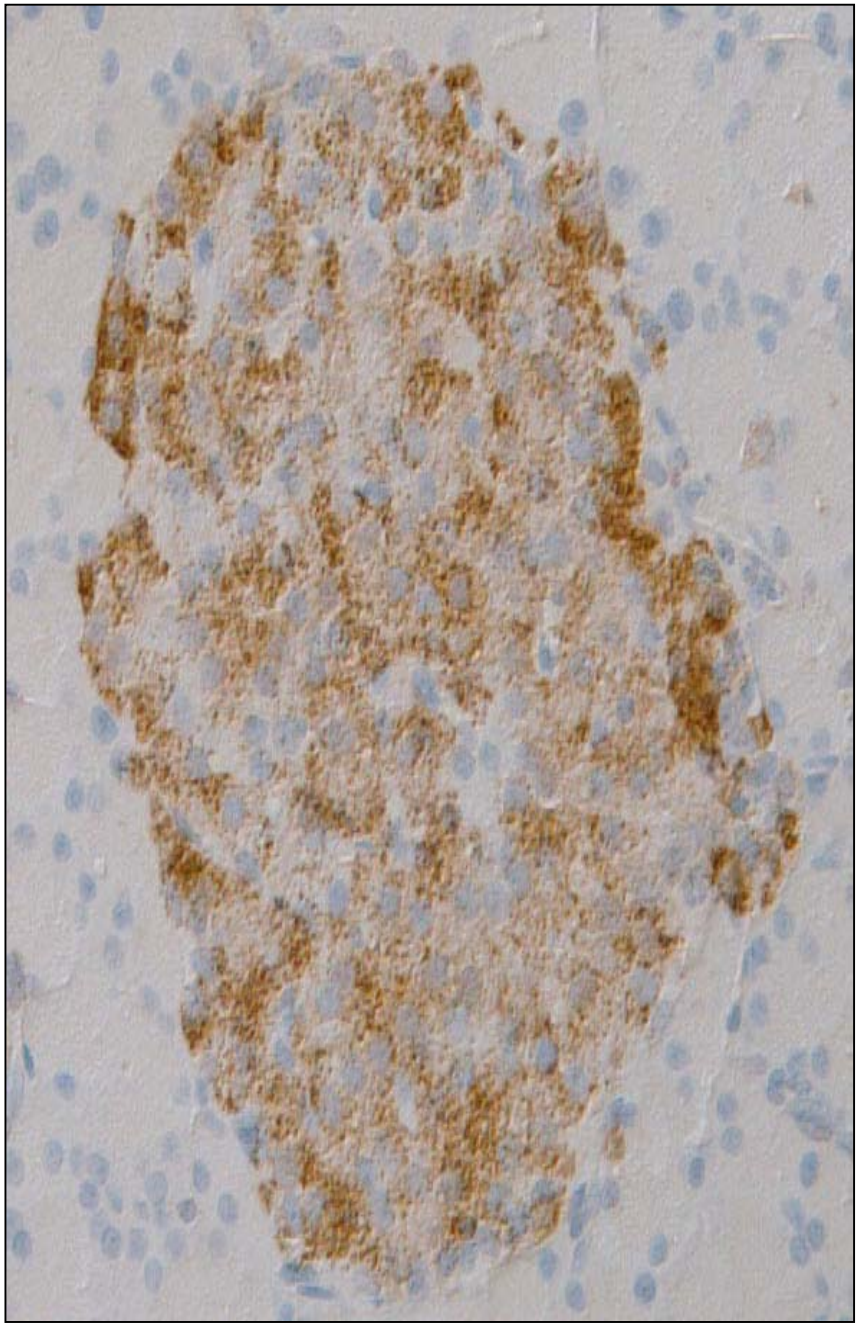
- Insulin sensitivity↑
- Endothelial dysfunction ↓
- Blood pressure ↓
- Hyperlipidemia ↓
- Inflammation and fibrosis ↓
- Anti-apoptotic effect

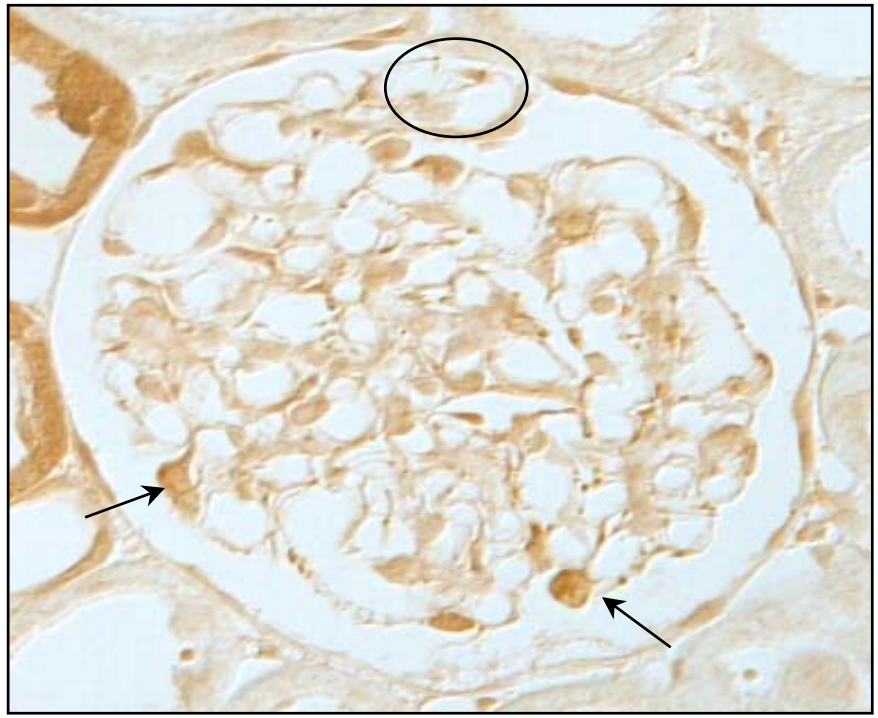
Beneficial and Deleterious Effects of Rosiglitazone on Hypertension Development in Spontaneously Hypertensive Rats

Lingyun Wu, Rui Wang, Jacques de Champlain, and Thomas W. Wilson

The antihypertensive effect of the peroxisome proliferator-activated receptor (PPAR)γ agonist rosiglitazone has been reported in patients with diabetes or obesity. The correlation of PPARγ expression with blood pressure and the therapeutic application of rosiglitazone in spontaneously hypertensive rats (SHR) were investigated in the present study. Systolic blood pressure of 21-week SHR was significantly higher than that of age-matched Wistar-Kyoto rats (WKY) (225 ± 5 *v* 144 ± 2 mm Hg, $P < .05$). Basal expression levels of PPARγ proteins in vascular tissues of 21-week SHR were significantly lower than that of age-matched 21-week WKY ($P < .05$). This reduced expression of PPARγ was not detected between 5- and 13- week SHR and age-matched WKY. Cardiac PPARγ expression was also not different among different age groups between SHR and WKY. Chronic treatment with rosiglitazone, but not PPARα agonist Wy14643, significantly retarded hypertension development and reversed abnormally faster heart rate in young SHR. An unfavorable effect of rosiglitazone treatment was the increased heart-to-body weight ratio accompanied by left ventricular hypertrophy. In conclusion, vascular PPARγ protein expression in adult SHR (21 weeks) is significantly decreased in comparison with the age-matched WKY. Chronic rosiglitazone treatment retards hypertension development, but the associated pro-hypertrophy effect calls for a cautious use of this thiazolidinedindione in the treatment of insulin resistance syndrome associated with hypertension. Am J Hypertens 2004;17:749–756 © 2004 American Journal of Hypertension, Ltd.

Key Words: Rosiglitazone, hypertension, ventricular hypertrophy, peroxisome proliferator-activated receptor (PPAR)α, PPARγ.






CCD
DT


IMCD

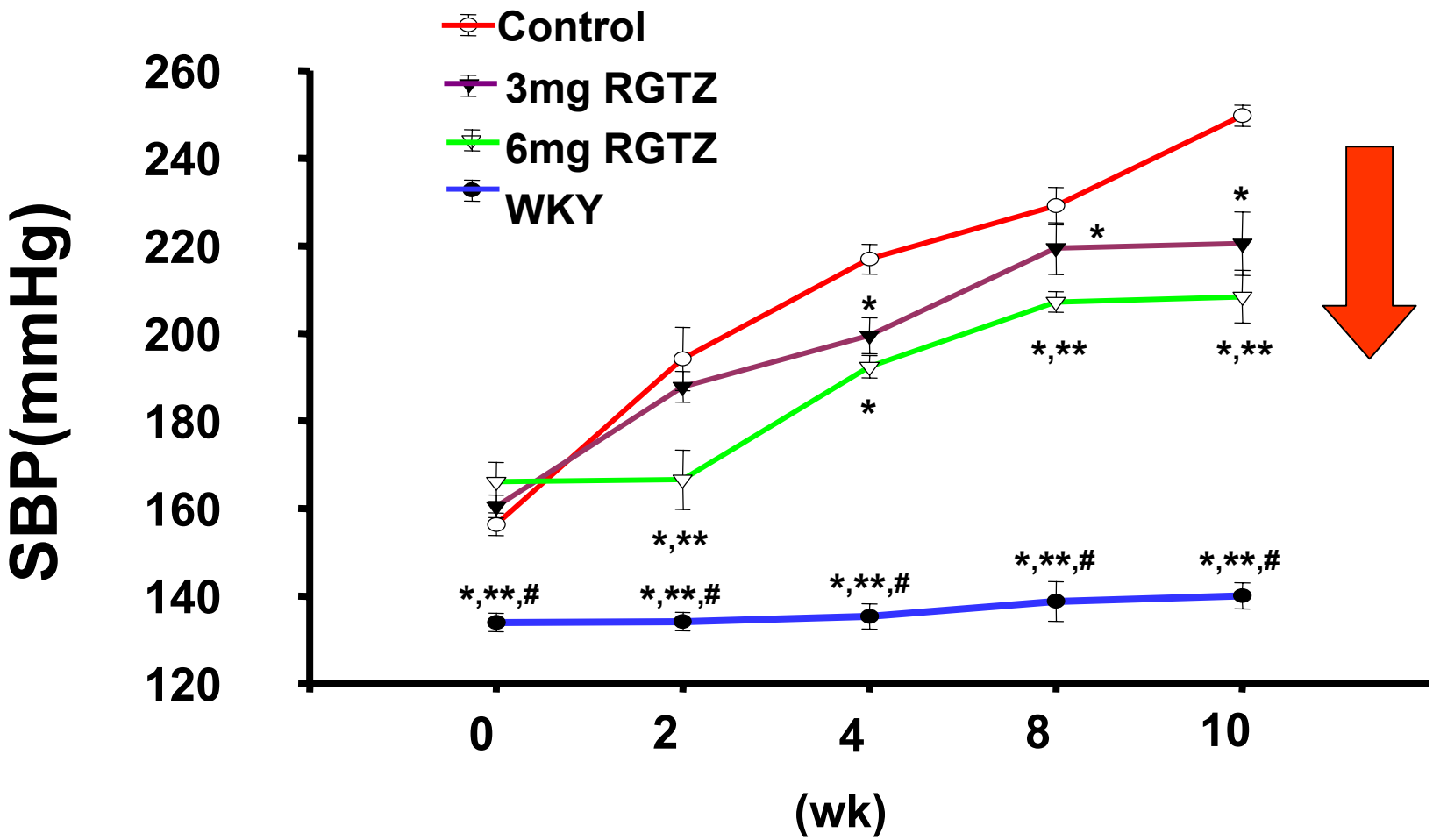
Effect of PPAR-γ Agonist on Hypertensive Nephropathy in Stroke Prone Spontaneously Hypertensive Rats on High-sodium Diet

WKY group	
SHRSP group	➢ **Without RGTZ** ➢ **With RGTZ** **- Low-dose (3mg/kg)** **- High-dose (6 mg/kg)**

N=6, each group

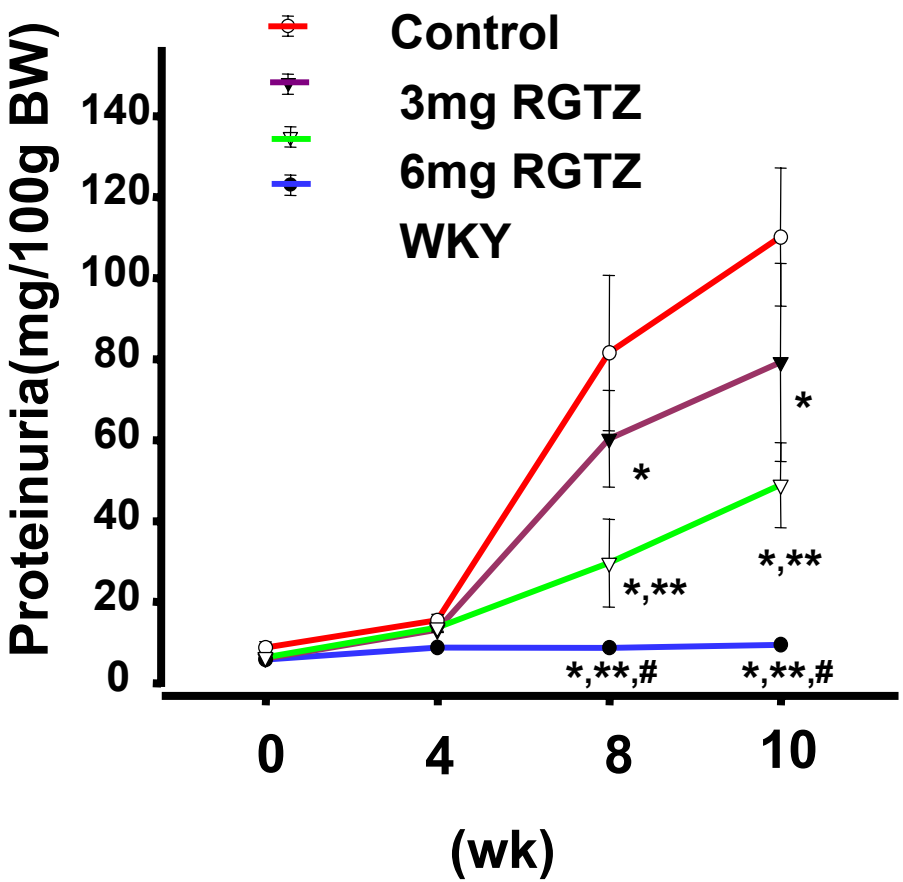
RGTZ: Rosiglitazone

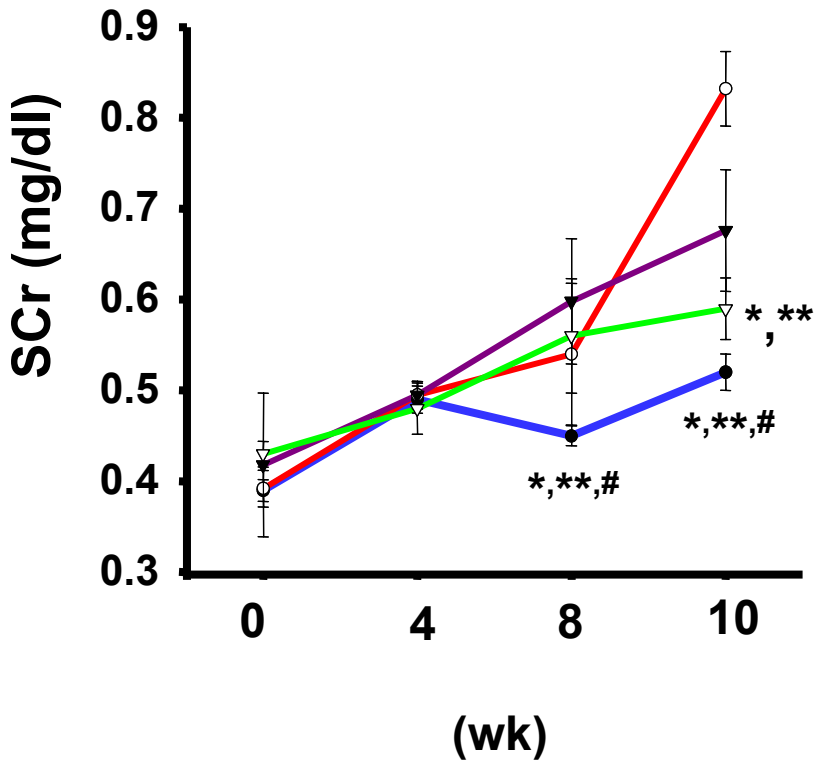
Systolic BP



* P < 0.05 vs. Control,** P < 0.05 vs. 3mg RGTZ, # P < 0.05 vs. 6mg RGTZ

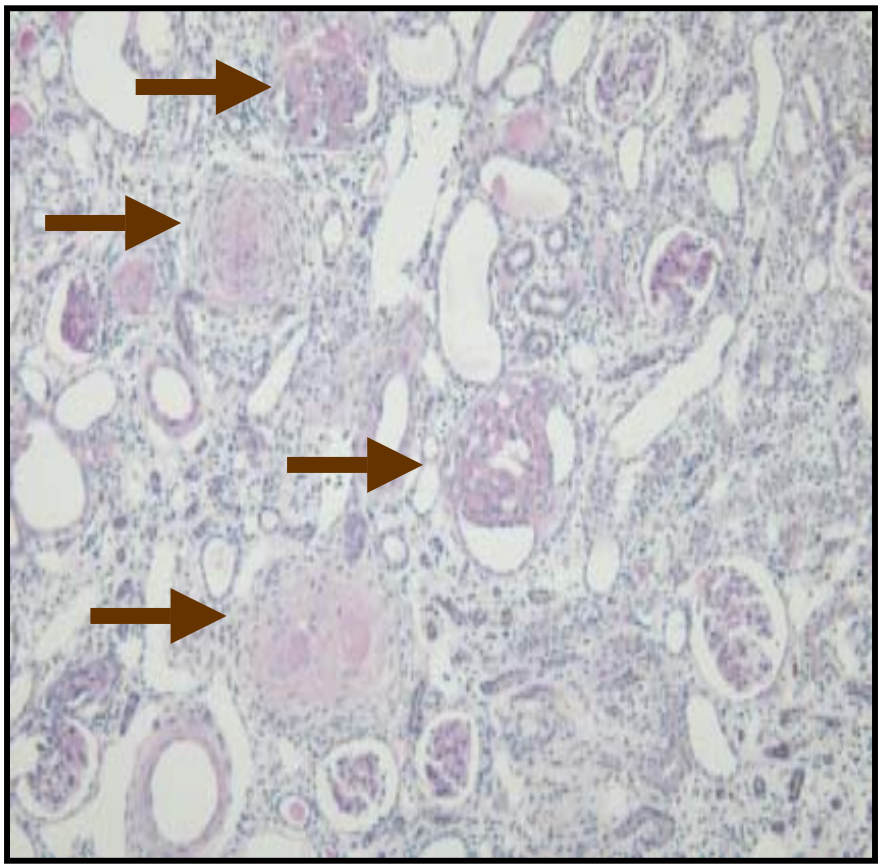
Proteinuria and Renal Function



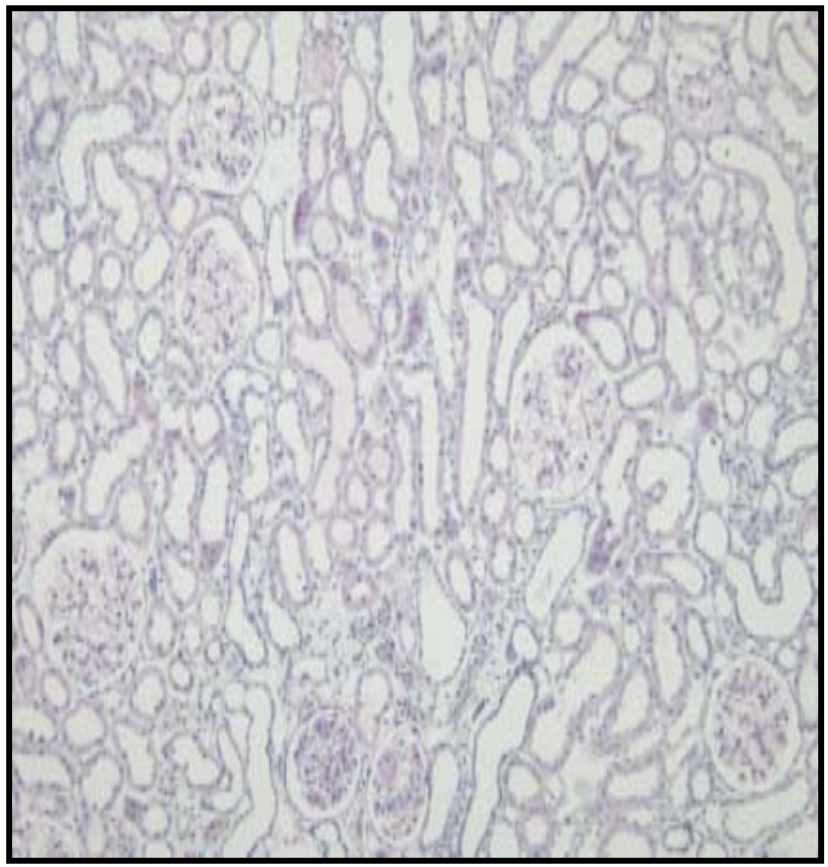


* P < 0.05 vs. Control,** P < 0.05 vs. 3mg RGTZ, # P < 0.05 vs. 6mg RGTZ

Glomerulosclerosis

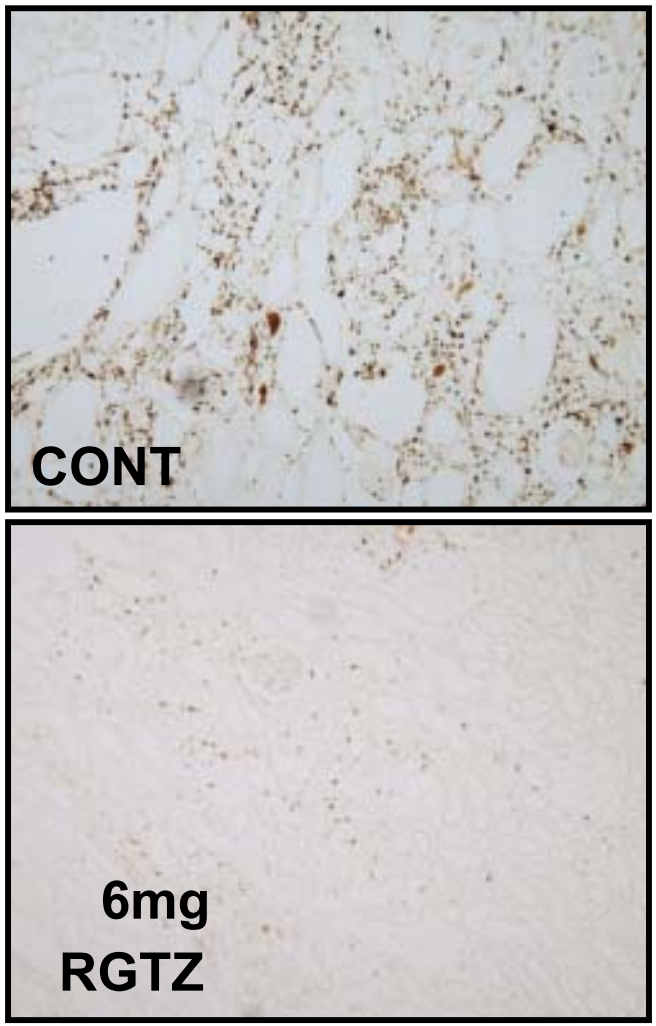


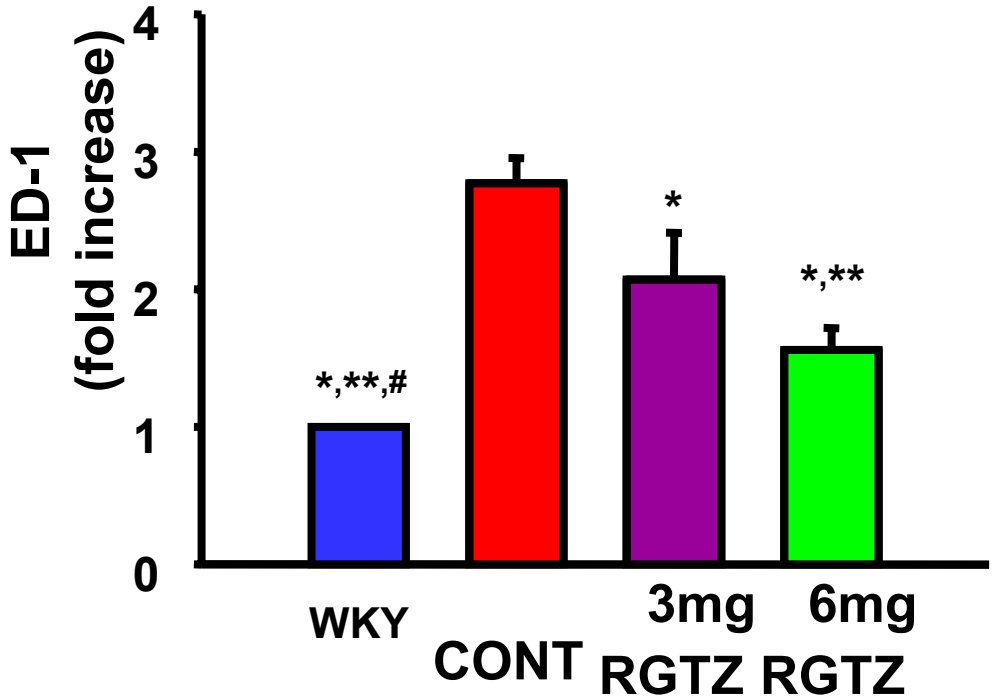
CONT



6mg RGTZ

Macrophage infiltration





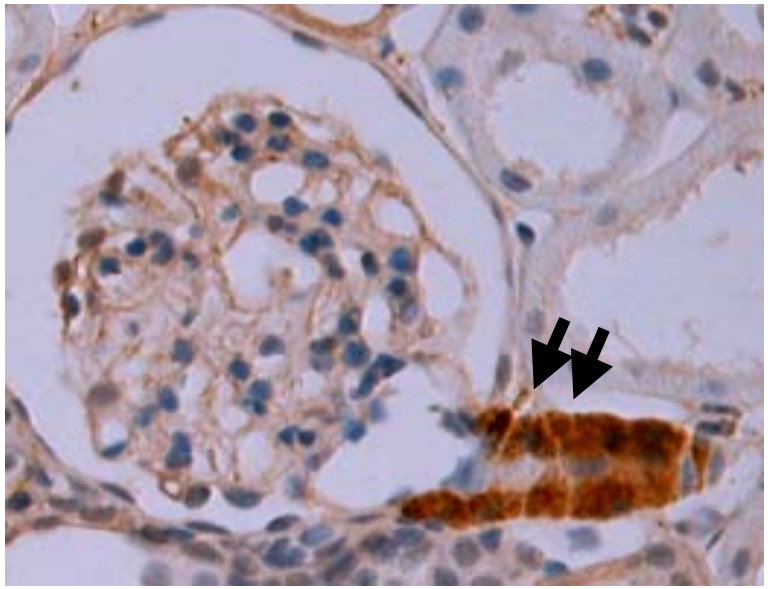
* P < 0.05 vs. Control

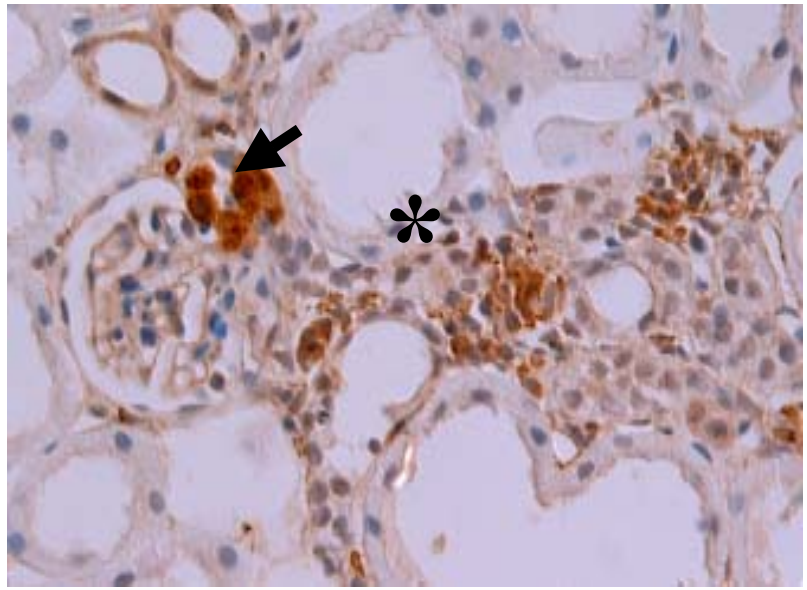
** P < 0.05 vs. 3mg RGTZ

\# P < 0.05 vs. 6mg RGTZ

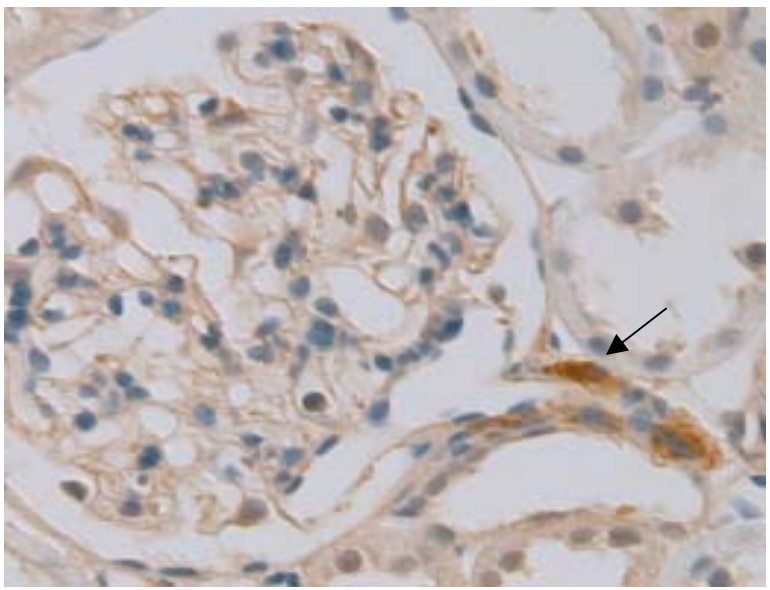
Effect of RGTZ on Angiotensin II Expression

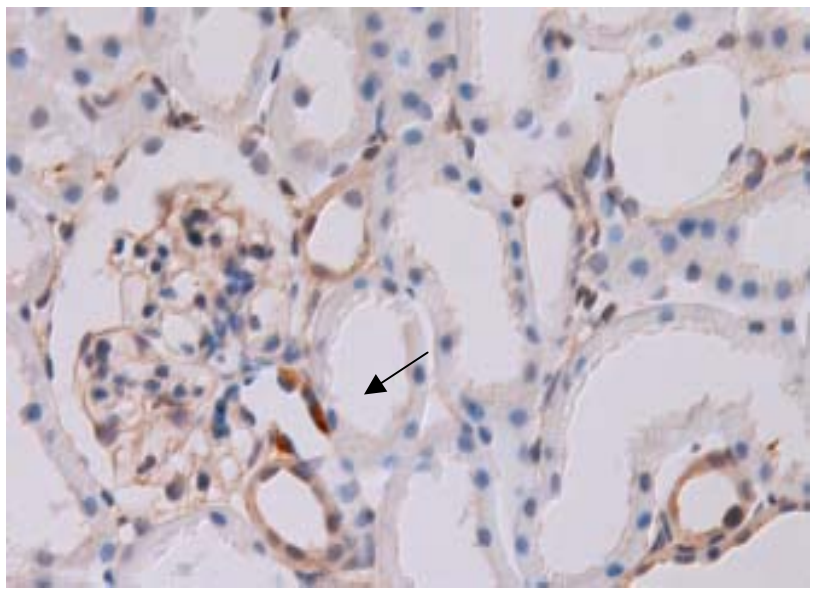
Control



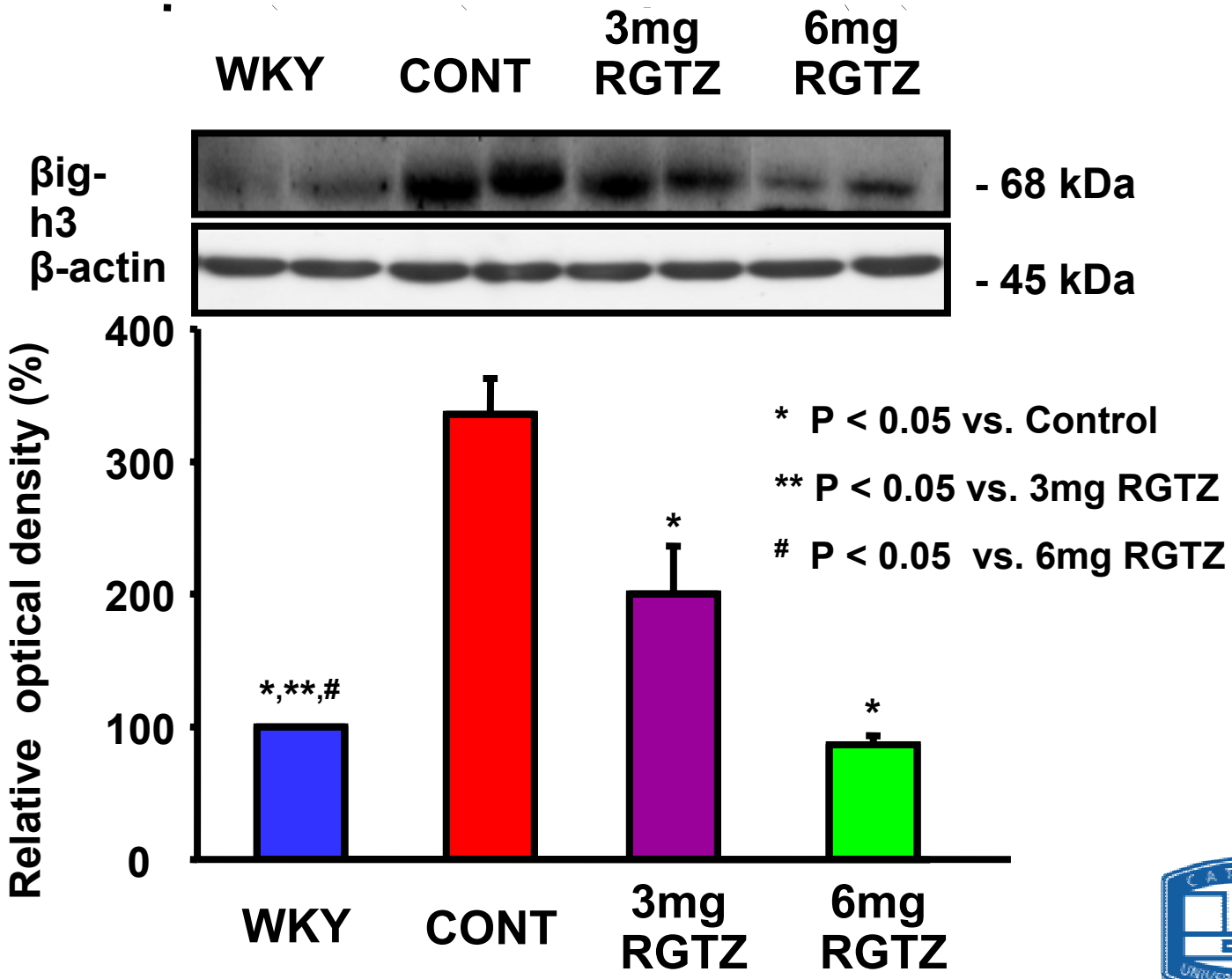


Control + RGTZ





TGFβ-igh3 expression



Summary

PPAR-γ

Anti-inflammation
↓Blood pressure

Hypertensive nephropathy

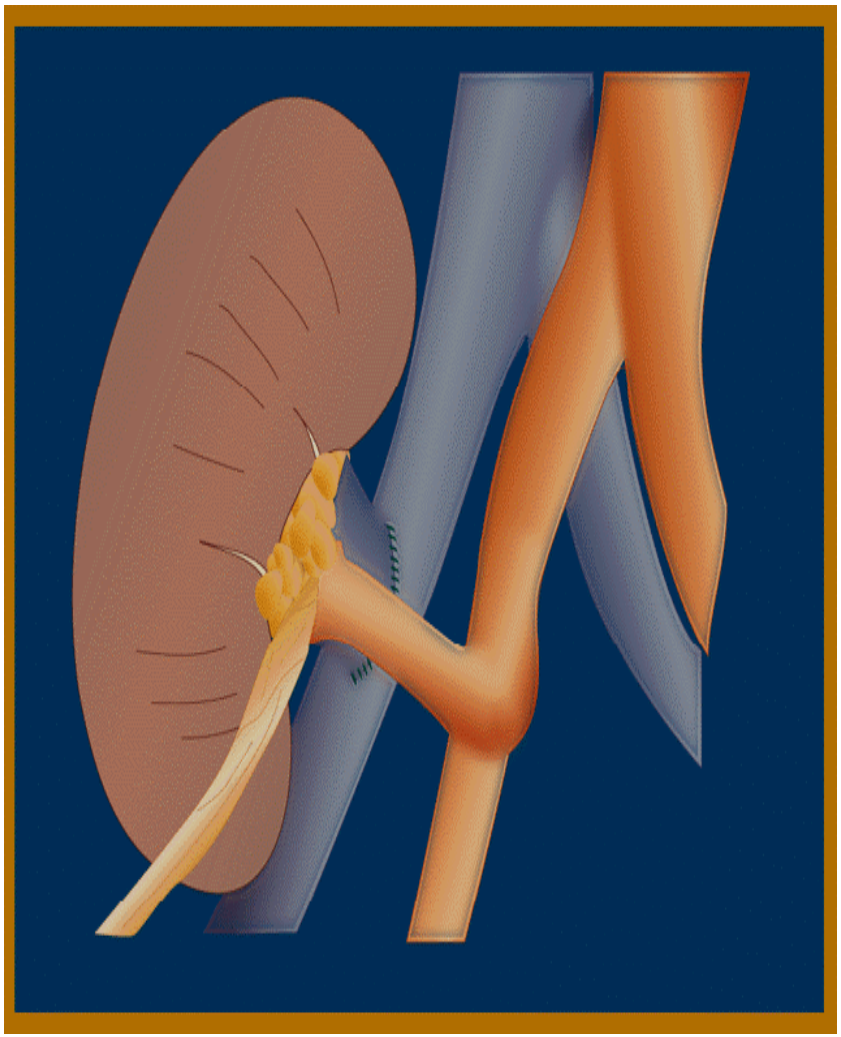
- **Renal Function↑**
- **Inflammation↓**
- **Glomerulosclerosis↓**
- **Fibrosis↓**

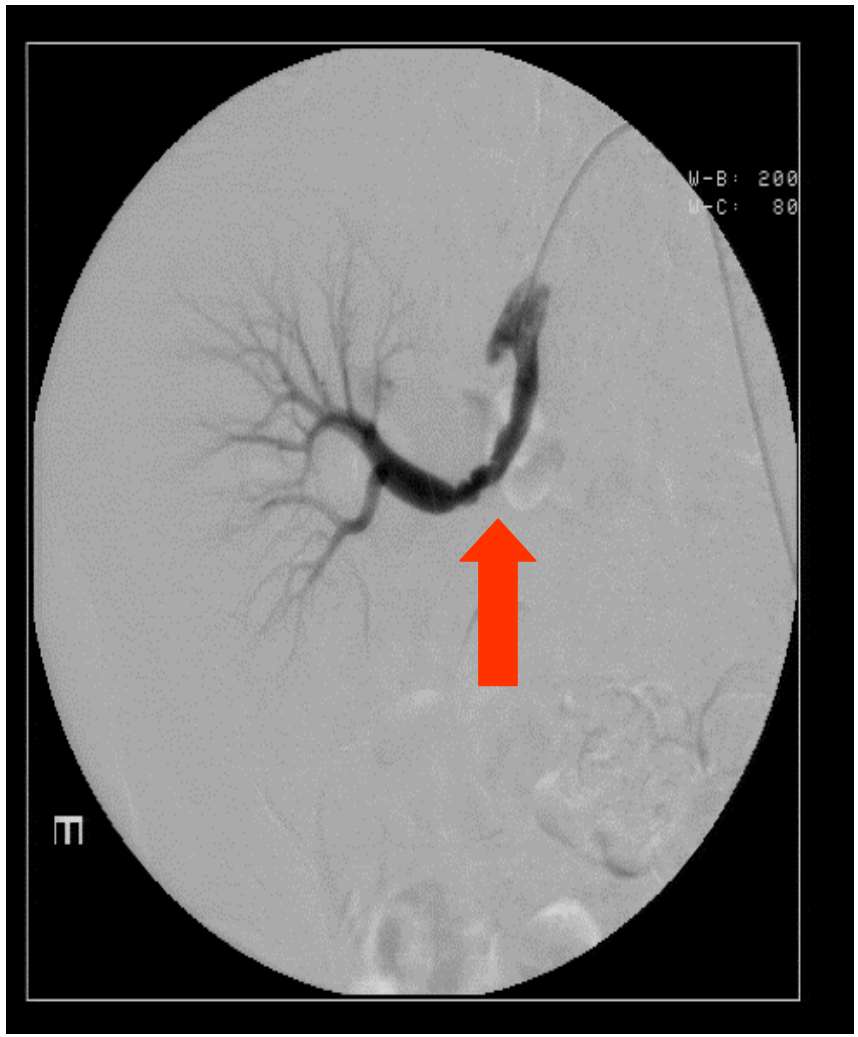
Adverse Effects of ACEI or ARB

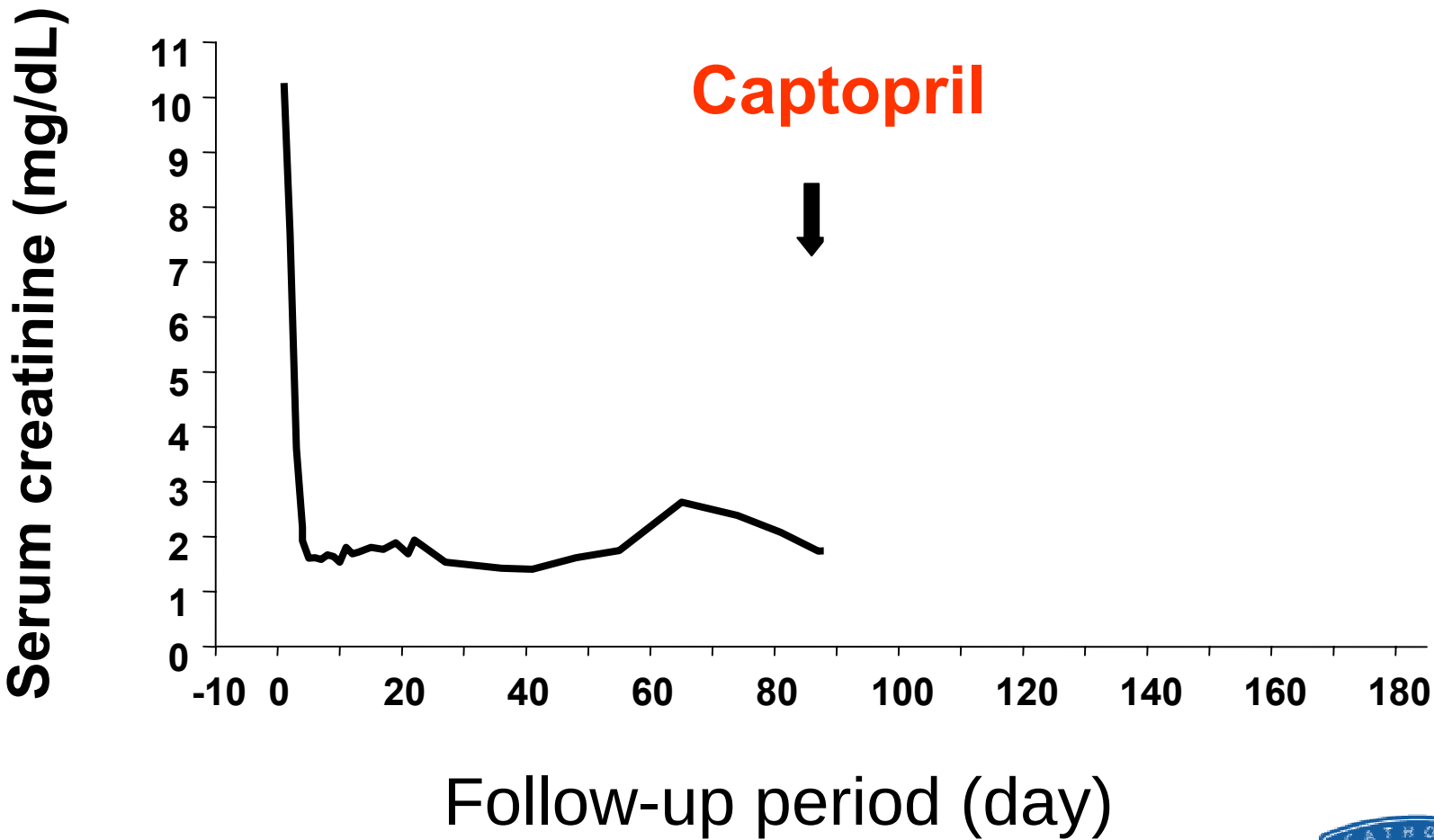
- Renal dysfunction
- Hyperkalemia

Risk factors for Renal dysfunction

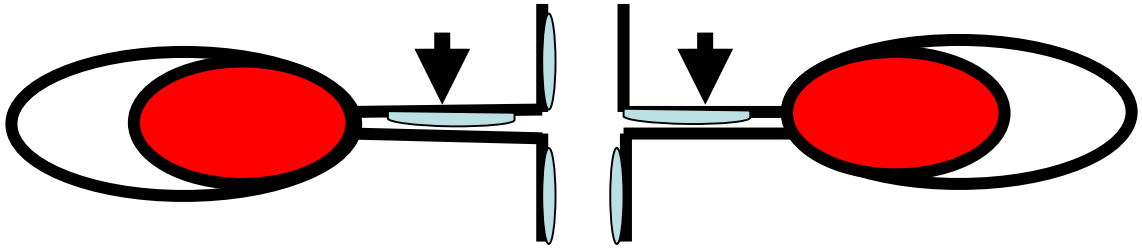
- Renal artery stenosis in single kidney
- Bilateral renal artery stenosis
- CHF + CKD
- Volume depletion
- Combination treatment of NSAID



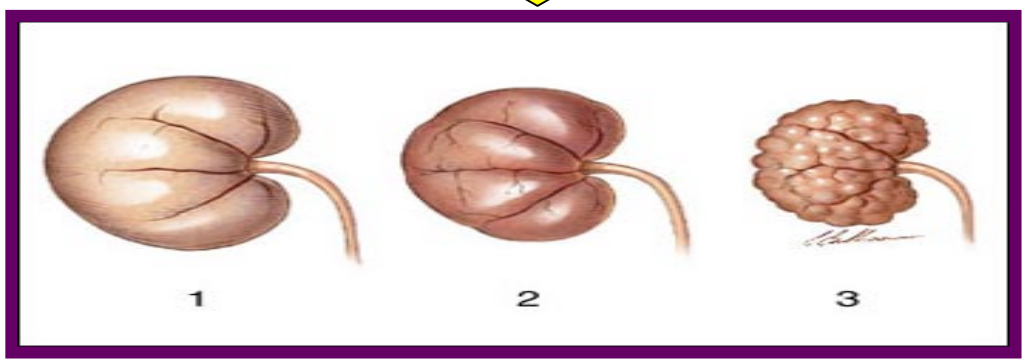

W-B: 200
W-C: 80


Captopril
Serum creatinine (mg/dL)
0
1
2
3
4
5
6
7
8
9
10
11
-10
0
20
40
60
80
100
120
140
160
180
Follow-up period (day)


다시는 ACEI 쓰지
않으리...



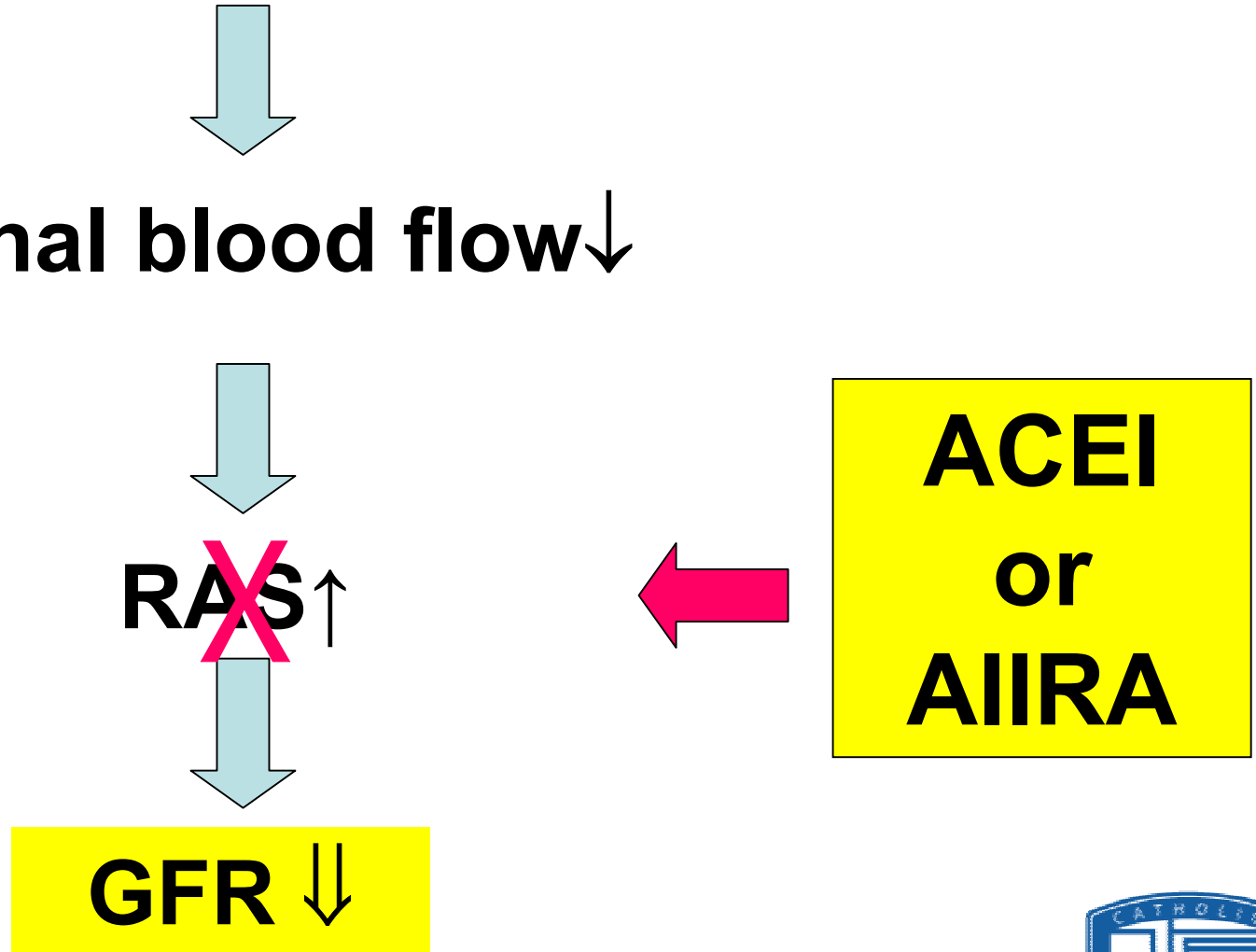
Bilateral renovascular disease



Ischemic Nephropathy

15% of ESRD in old-aged people

Bilateral renovascular disease



Pattern of Renal dysfunction is dependent upon baseline renal function

Renal Function	Tx duration (wk)	Serum creatinine level
Normal GFR	0-1	10% ↑
	2-	Stable
Decreased GFR	1-2	20% ↑(Rapid)
	3-4	10% ↑(Gradual)
	4-	Stable

Pitfalls in Serum Creatinine!!!!

Accurate measurement of GFR

Serum Creatinine level: 1.4 mg/dL

Cockcroft-Gault equation

[(140-Age) X BW(kg) X0.85(Female)

/[72X Serum Cr (mg/dL)]

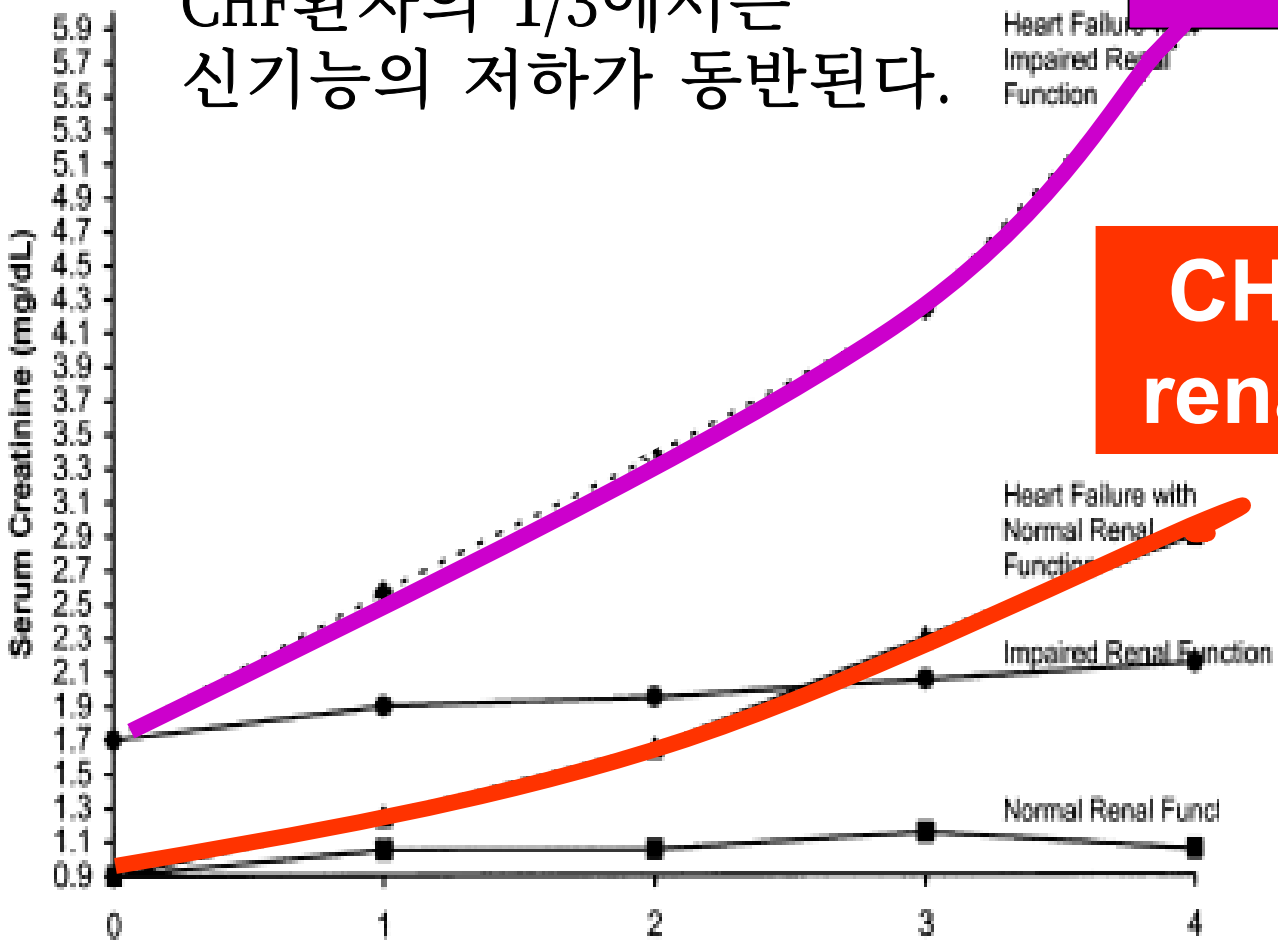
20세, 80kg: GFR=101 ml/min

80세, 40kg: GFR= 20 ml/min

CHF환자의 1/3에서는
신기능의 저하가 동반된다.

CHF+impaired renal function

CHF+normal renal function



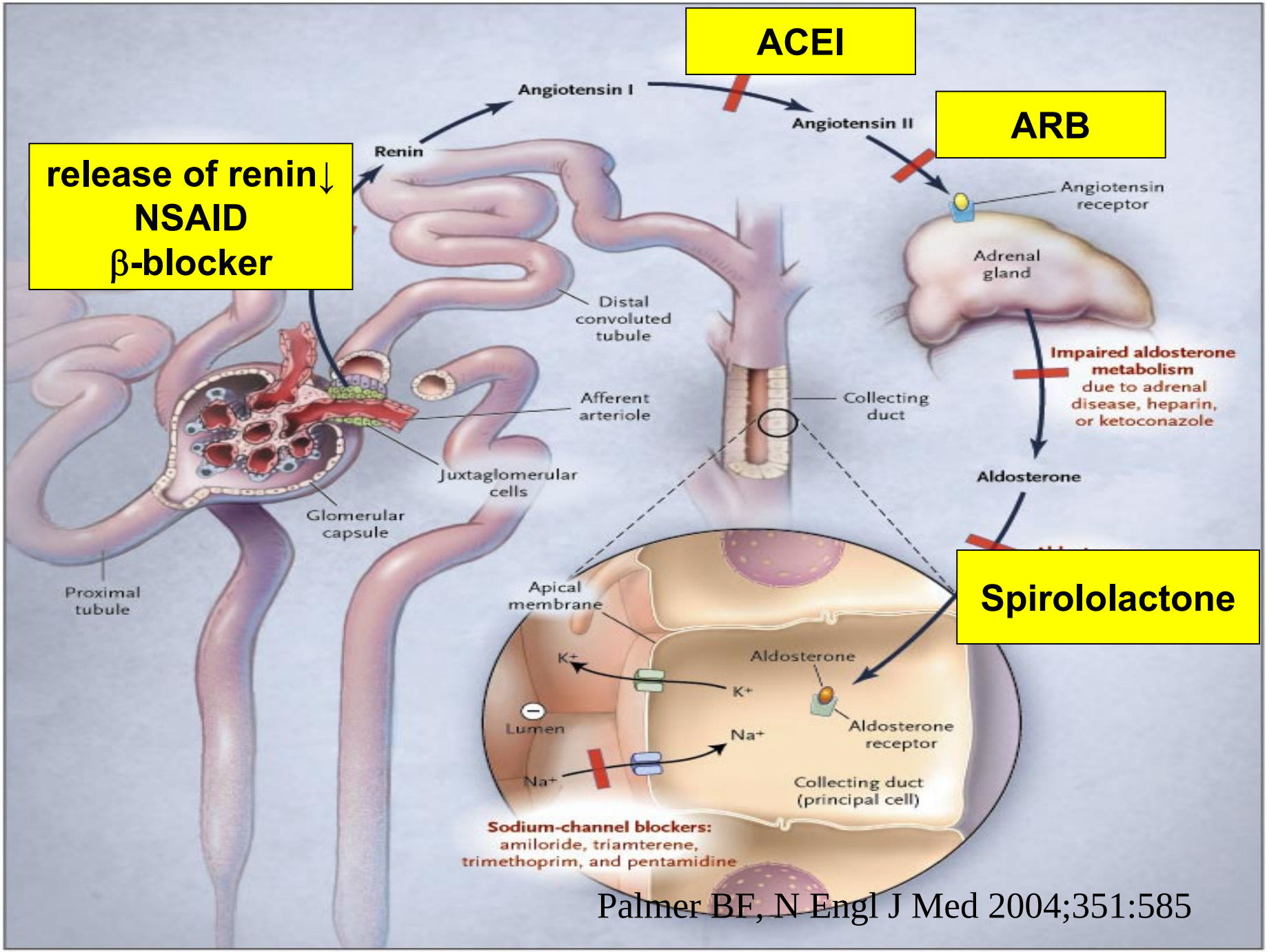
Impaired Renal Function

Normal Renal Function

Duration of ACEI treatment (week)

Guideline for ACEI or ARB

- **Measurement of GFR**
- **Evaluation of risk factors**
- **Initial dose: half dose**
- **Measure serum Cr: 1 wk after Tx**
- **Stop ARB if serum Cr>30% at 4 wks**



Palmer BF, N Engl J Med 2004;351:585

Risk factors for hyperkalemia with the use of drugs that interfere the RAS

- Chronic Kidney Disease (GFR<30 ml/min)
- Diabetes Mellitus
- Congestive heart failure
- Volume depletion
- Advanced Age

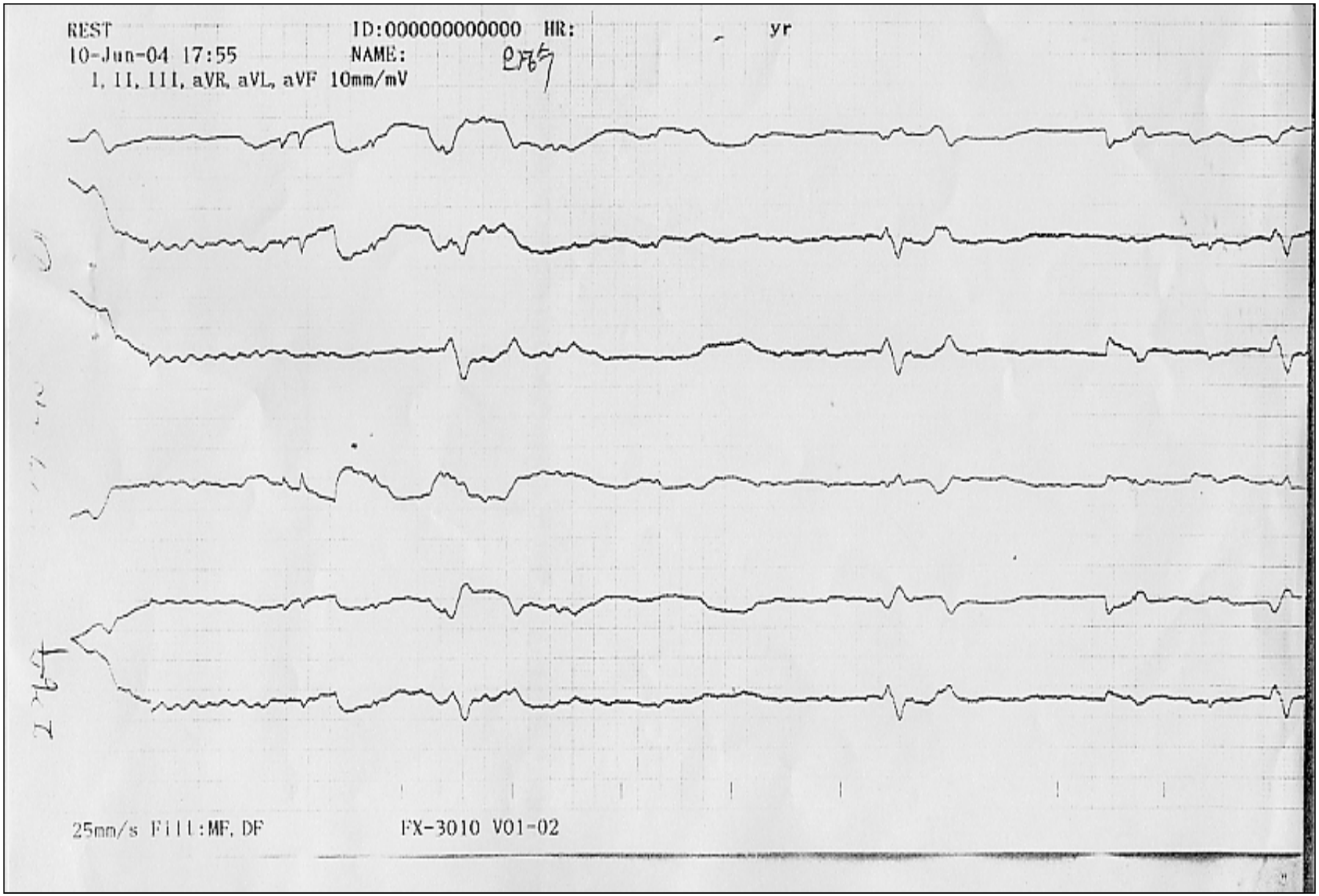
Case

- 69-year-old man
- Sudden Cardiac arrest on street
- P/H:DM and atrial fibrillation
- Lab. findings:

  Serum creatinine: 1.4 mg/dL

  Urine protein (++)

  Serum potassium: 10.1 mEq/L


REST
ID:000000000000 HR:
yr
10-Jun-04 17:55
NAME:
I, II, III, aVR, aVL, aVF 10mm/mV
25mm/s F111:MF, DF
FX-3010 V01-02

- Digoxin 0.25mg
- Spirolactone 50mg
- dilatren 50mg
- Candesartan 16mg
- Warfarin 2.5 mg

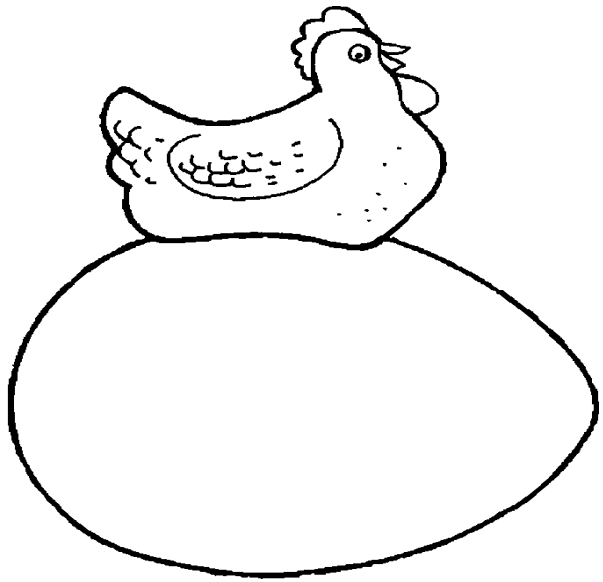
Why K=10.1?

- Old age
- Diabetes
- Impaired renal function (SCr=1.4)
- Type IV RTA (PRA: 0.1, Plasma Aldo: 30)
- Drug-induced hyperkalemia

Approach to Patients at Risk for Hyperkalemia caused by RAS inhibition-I

- Estimate GFR
- Low-dose ACEI or ARB
- Measure K^+ 1wk after initiating therapy
- Discontinue NSAID
- Thiazide or loop diuretic
- Correct metabolic acidosis

Hypertension

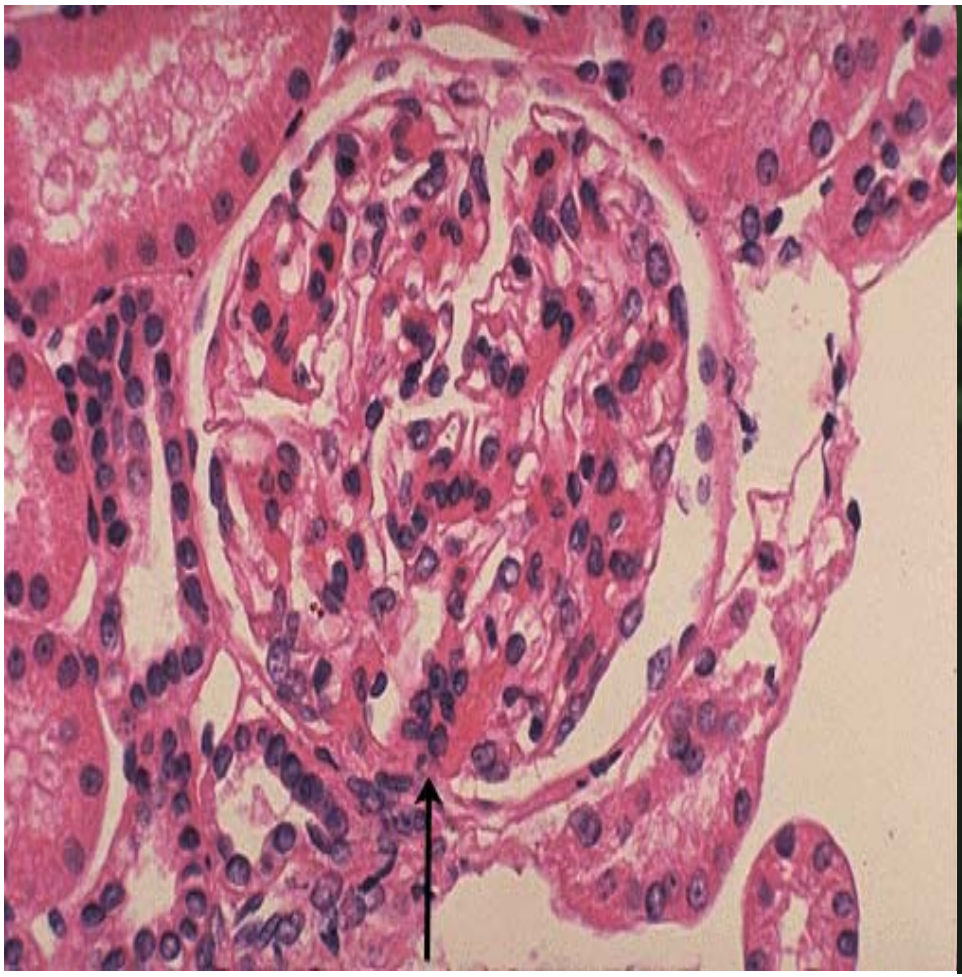


Proteinuria

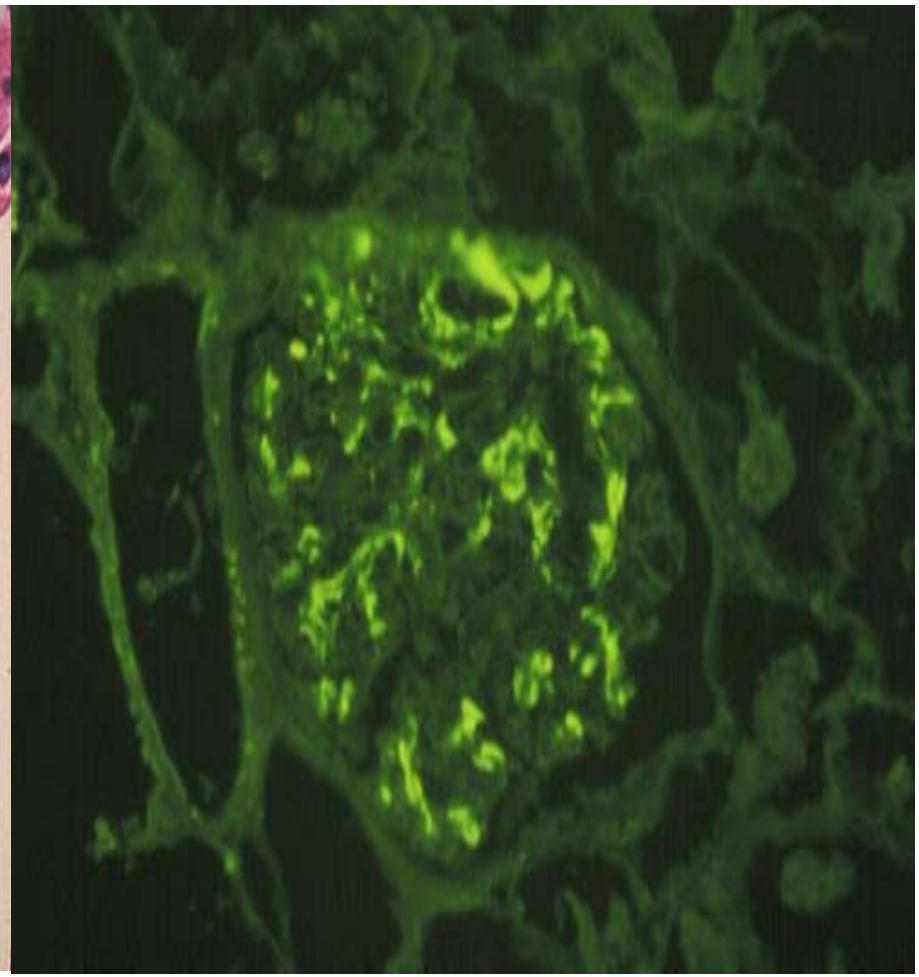
Case

- 47-year-old woman
- C/C: Exertional dyspnea
- P/H: Anti-HBP medication for 4yrs

  Proteinuria 15 years ago
- Urinalysis : Proteinuria (+++)
- SCr: 7.9 mg/dL (4 yrs ago: 1.1 mg/dL)



Mesangial proliferative glomerulonephritis



IgA deposits at mesangial area

사건번호:

조회의 내용

환자는 4년간 모병원 순환기 내과에서 혈압조절을 받아왔음.

최근 피곤함이 지속되어 외래 방문하였으나
담당의사가 학회 중으로 타 의사에게 진찰받은 결과
만성신부전으로 진단받음.

환자는 4년간 외래 방문하여 치료받았으나
신장기능의 저하에 대하여 의사로 부터 일체의 내용을 들은 바 없으며
신기능에 대한 검사를 받은 바 없음.

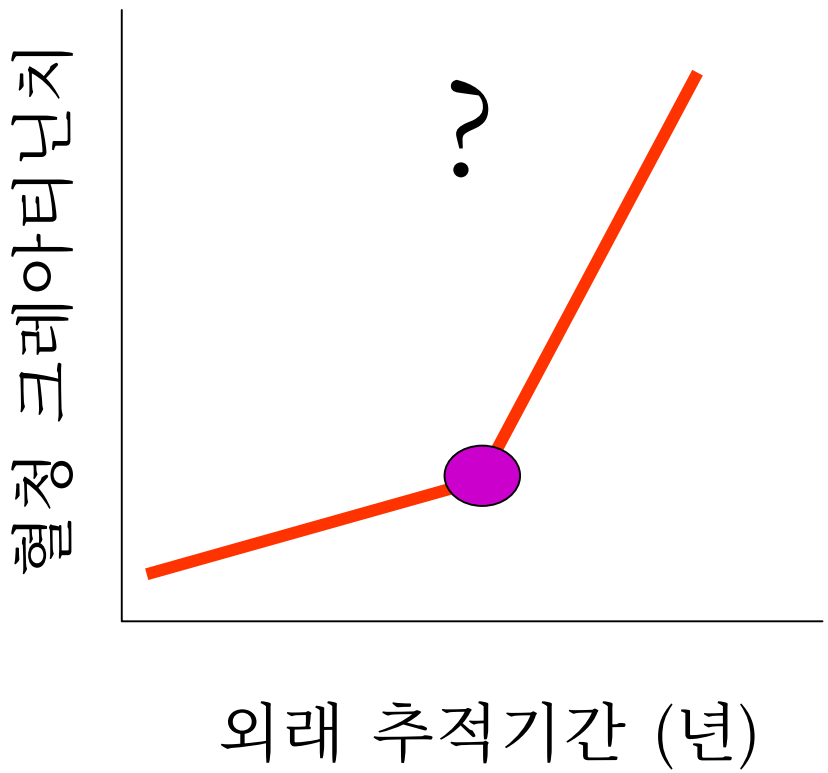
환자는 이후 투석치료 중 신장이식술 받음.

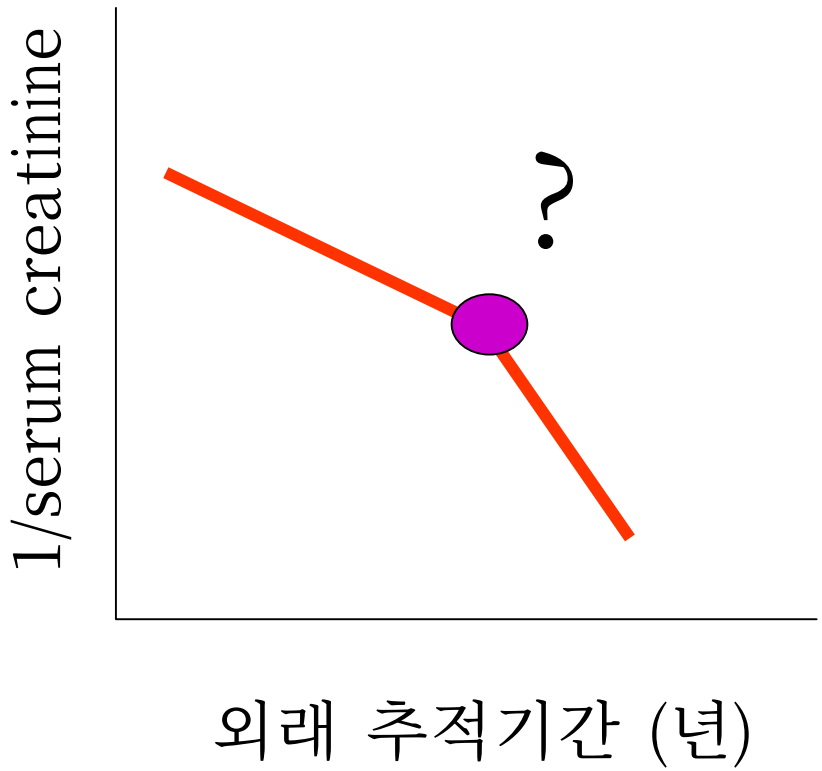
환자는 병원진찰에도 불구하고 신장에 대한 검사를 제대로 시행하지
않았기 때문으로 이에 대한 손해배상을 요구함.

Recommendation

- **Medical history of proteinuria or hematuria**
- **Renal biopsy: Proteinuria> 1.0 g/day**
- **Regular measurement of renal function and urinalysis**

Superimposed factors





Case

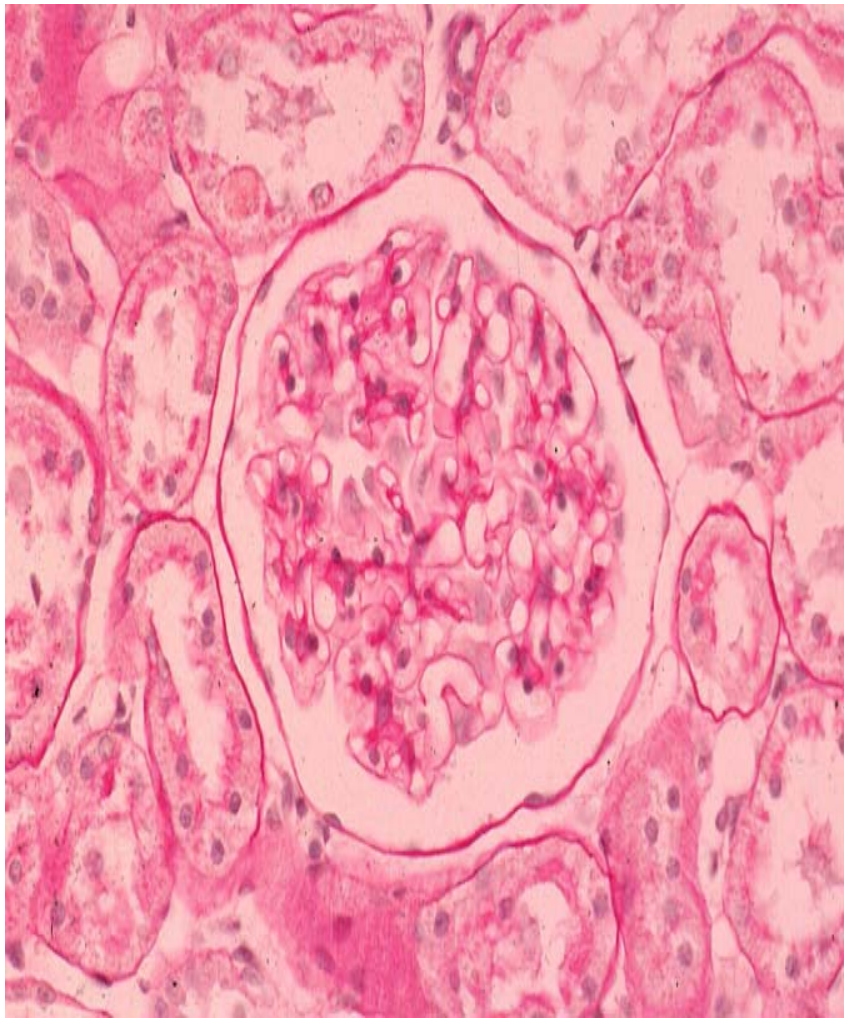
- 54-year-old woman
- C/C: Uncontrolled HBP and edema
- P/H: Anti-HBP medication for 4 yrs
- Urinalysis : proteinuria (++)
- Serum Creatinine 7.9 mg/dL

  (2 months ago: 1.2 mg/dL)

독수리의 눈, 예리한 판단

Guidelines for Evaluation of Aggravation of Renal Dysfunction

- Hypovolemia
- Uncontrolled hypertension
- Infection
- Obstructive nephropathy
- Nephrotoxic drugs
- Radiocontrast media
- Activation of underlying disease



Normal glomerulus

Crescentic glomerulus

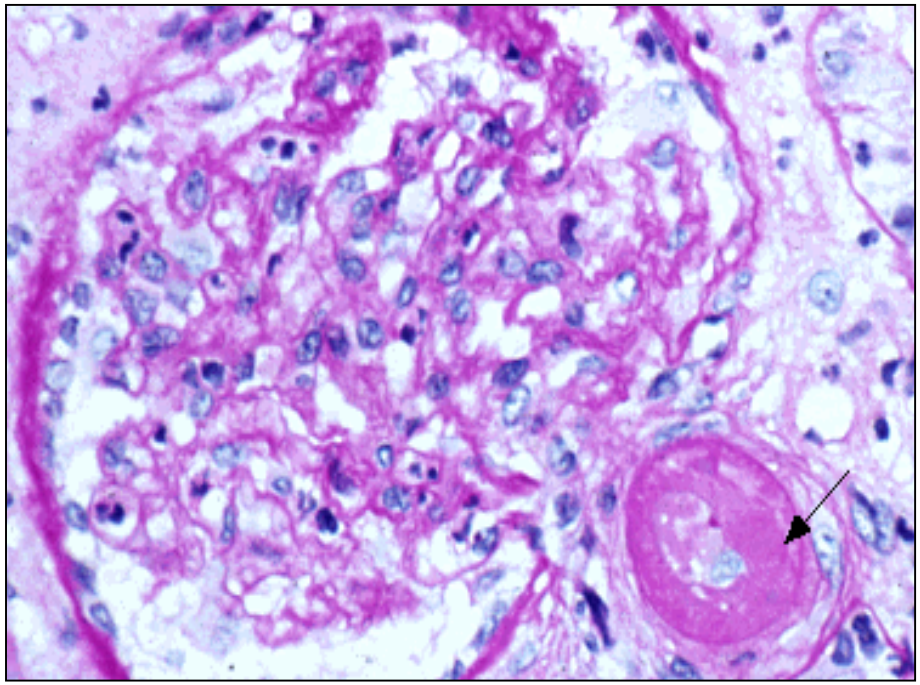
Recommendation

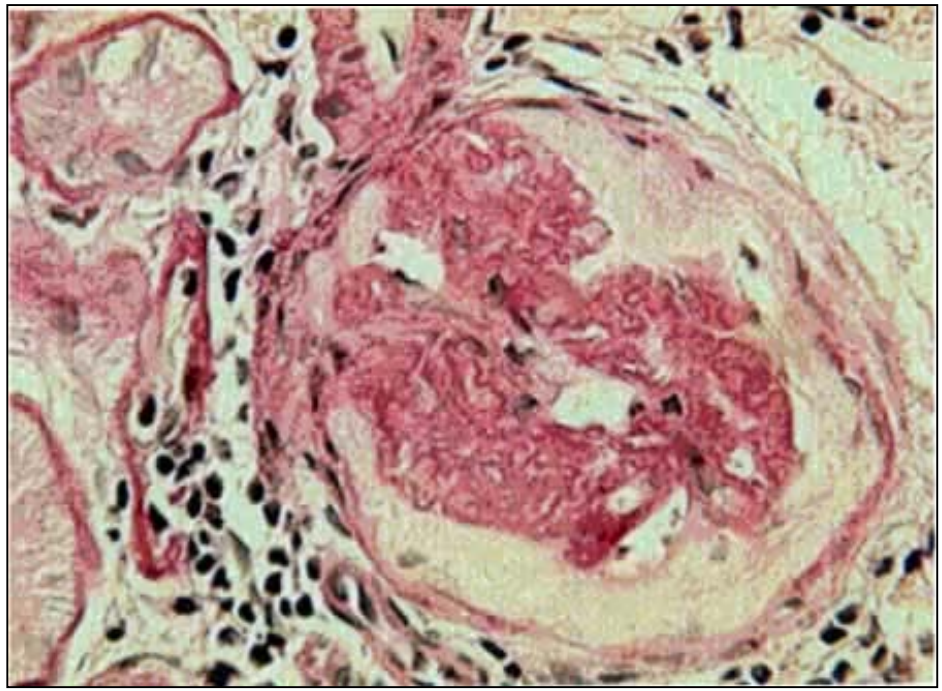
- Careful evaluation of superimposed factors is needed in patients with aggravation of renal dysfunction.
- Nephrology consultation for rapid deterioration of renal function without definite causes.

Patients with Severe Hypertension and Renal Failure

Case

- 36-year-old man
- C/C: Headache
- BP: 240 mg/150 mmHg
- Serum Cr: 10.4 mg/dL

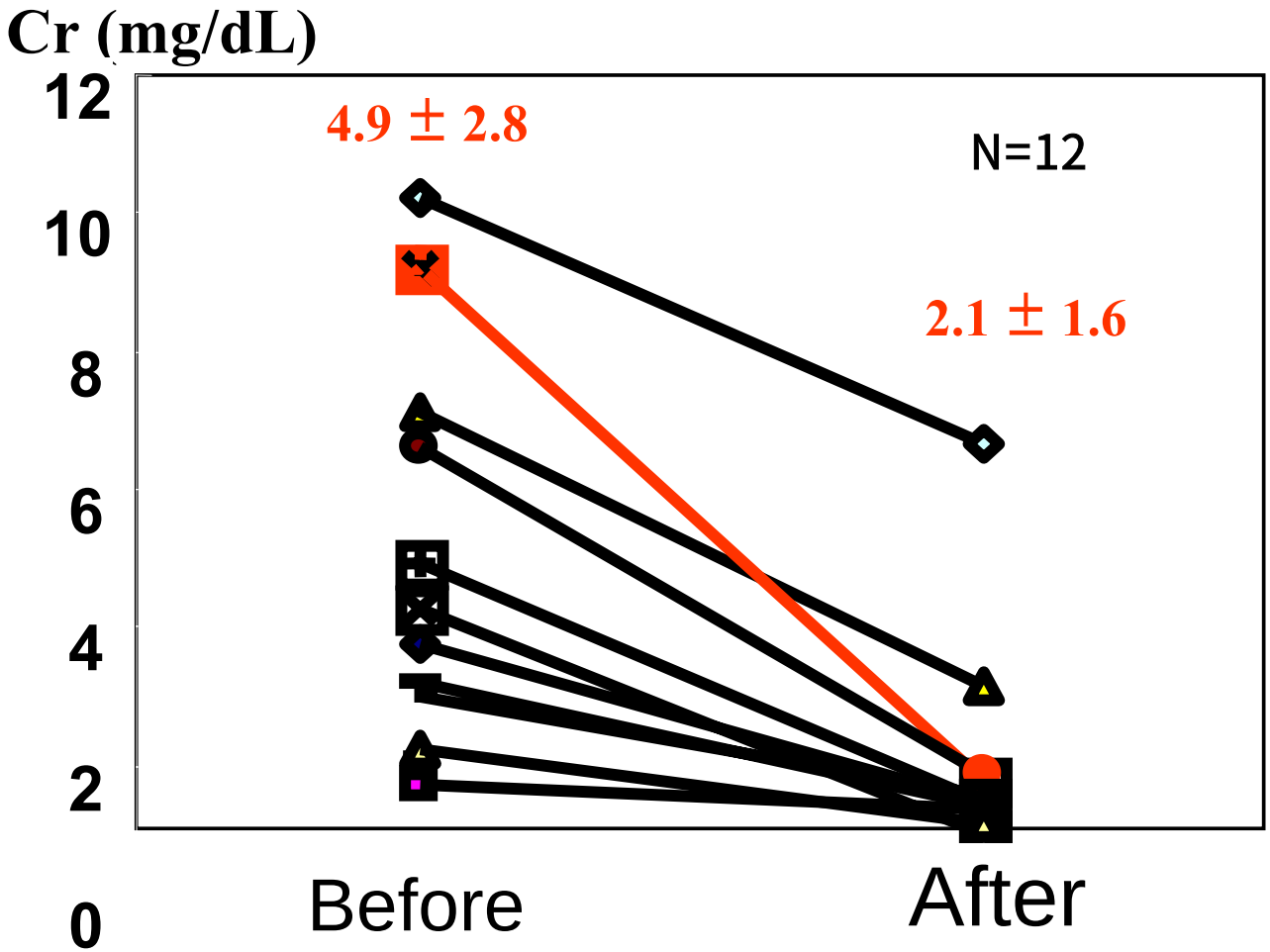




Five years later

Current BP: 140/90 mmHg

Current serum Cr: 1.8 mg/dL

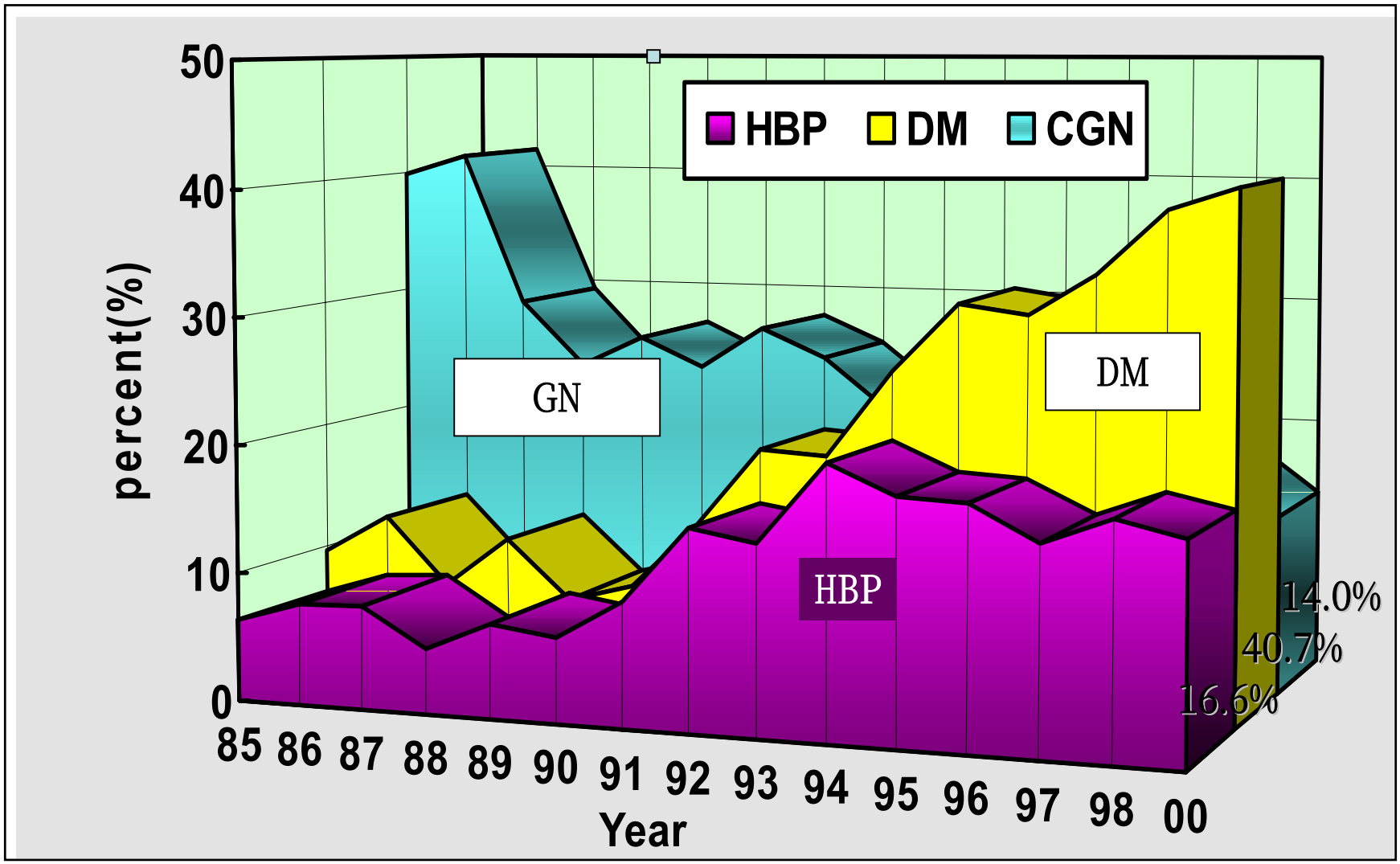


- 6 cases : hypertensive nephrosclerosis
- 4 cases : IgA nephropahty

Lesson

- **Renal failure in patients with severe hypertension is sometimes reversible.**
- **Hypertension is a common pathway of renal dysfunction in essential hypertension and glomerulonephritis.**

Major Causes of ESRD



Natural History of DM

Stage	Duration (year)	Clinical findings
1		Hemodynamics of recent-onset DM
2	1.5-5	Early renal involvement
3	5-15	Initial stage of nephropathy- Microalbuminuria
4	10-20	Overt Nephropathy (Nephrotic Syndrome, Hypertension)
5	>20	End-stage renal disease (Chronic renal failure)

Clinical Predictors for Progression to ESRD in IgA Nephropathy

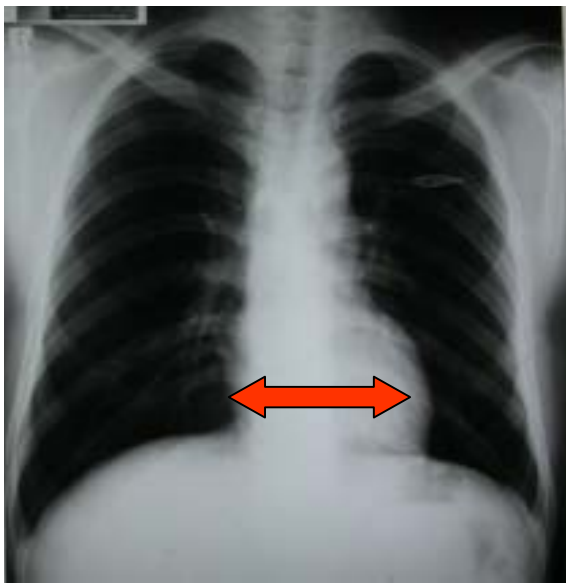
- **Hypertension**
- **Nephrotic-range proteinuria**
- **Renal insufficiency at presentation**

Frequent Complications in Dialysis

HD (% of Pts.)		PD (% of Pts.)	
Hypertension	3040 (43.7)	Hypertension	645 (26.2)
CHF	970 (13.9)	Peritonitis	397 (16.1)
Other G-I	617 (8.9)	CHF	136 (5.5)
Coronary Heart Dis	447 (6.4)	Coronary Heart Dis	117 (4.8)
Arrythmia	381 (5.5)	Other G-I	100 (4.1)
Viral Hepatitis B	347 (5.0)	CVA	90 (3.7)
Other Infection	338 (4.9)	Malnutrition	88 (3.6)
Uremic Dermatitis	321 (4.6)	Viral Hepatitis B	81 (3.3)
Ascites/Pleural Effusion	317 (4.6)	Other Infection	50 (2.0)
CVA	295 (4.2)	Uremic dermatitis	49 (2.0)
Pericardial Effusion	269 (3.9)	Tuberculosis	44 (1.8)
Peptic Ulcer	244 (3.5).	Pericardial Effusion	37 (1.5)

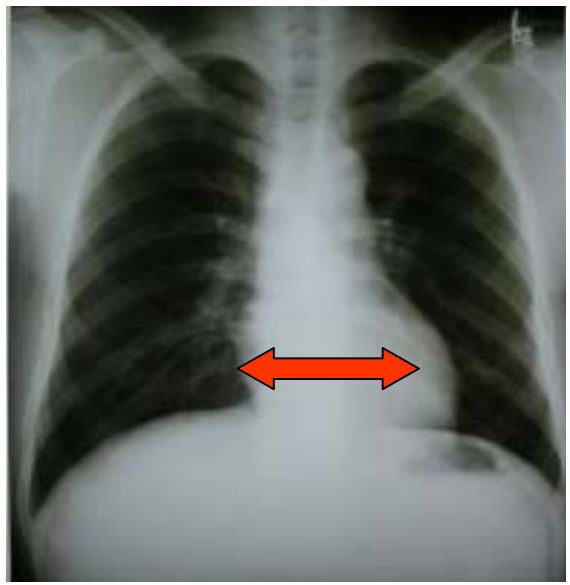
Patients number: HD =6956, PD=2460, Other GI=Gastrointestinal disease except peptic ulcer, CVA=cerebrovascular accident, Other infection= infection except pneumonia, tuberculosis, peritonitis and Herpes zoster .

Before dialysis



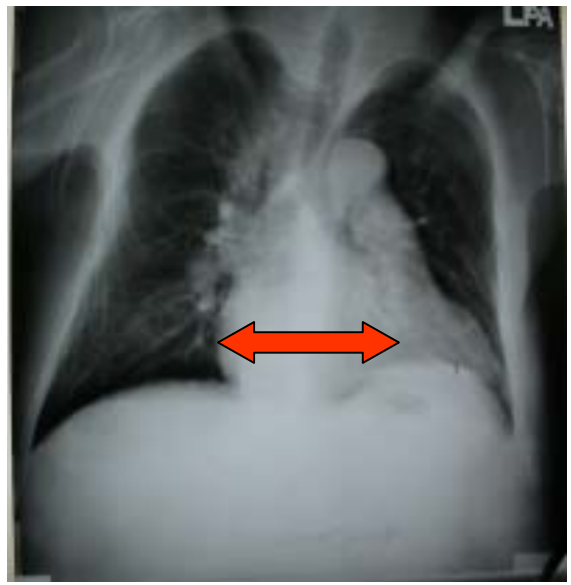
1986

7 yrs later



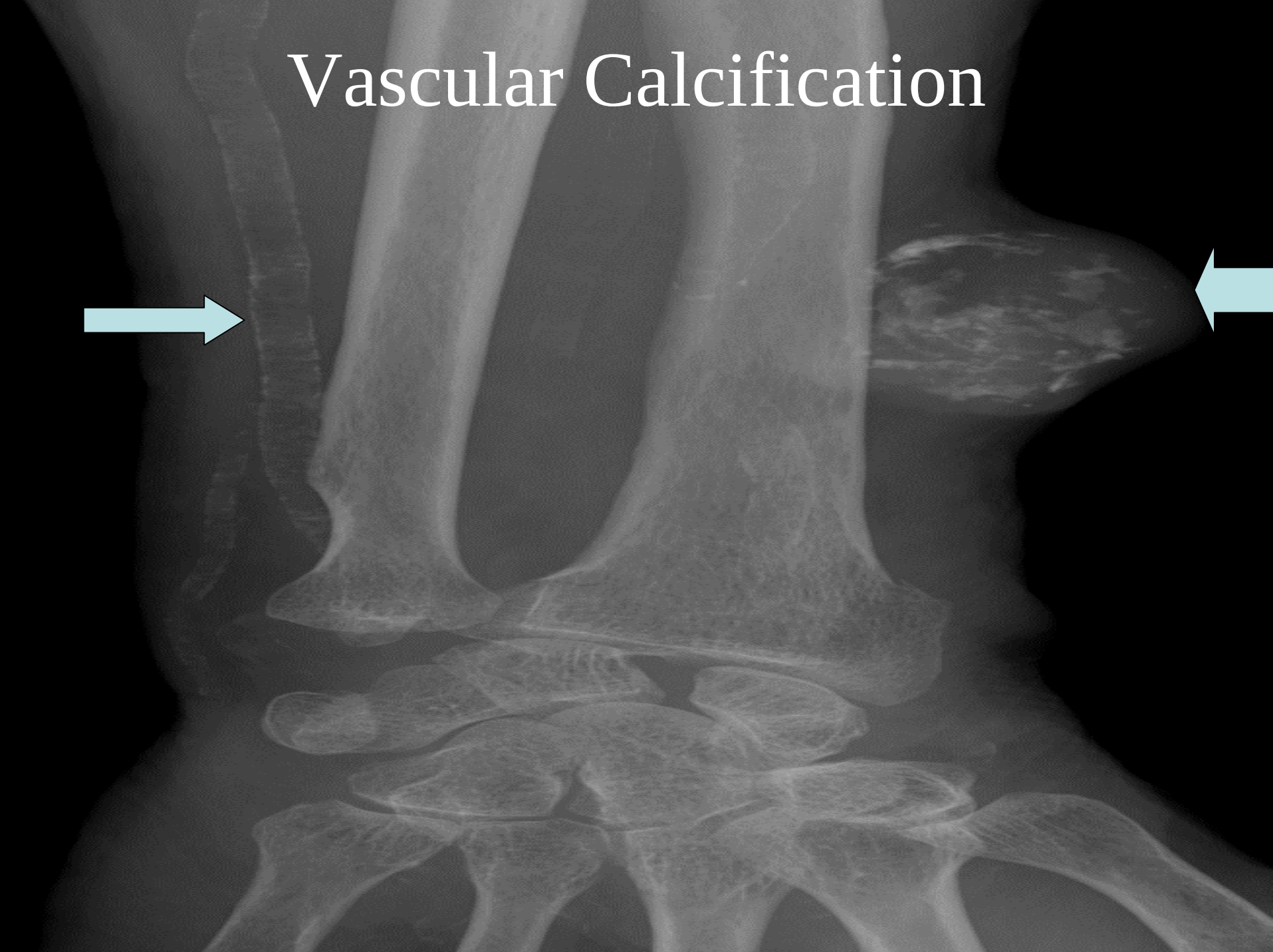
1993

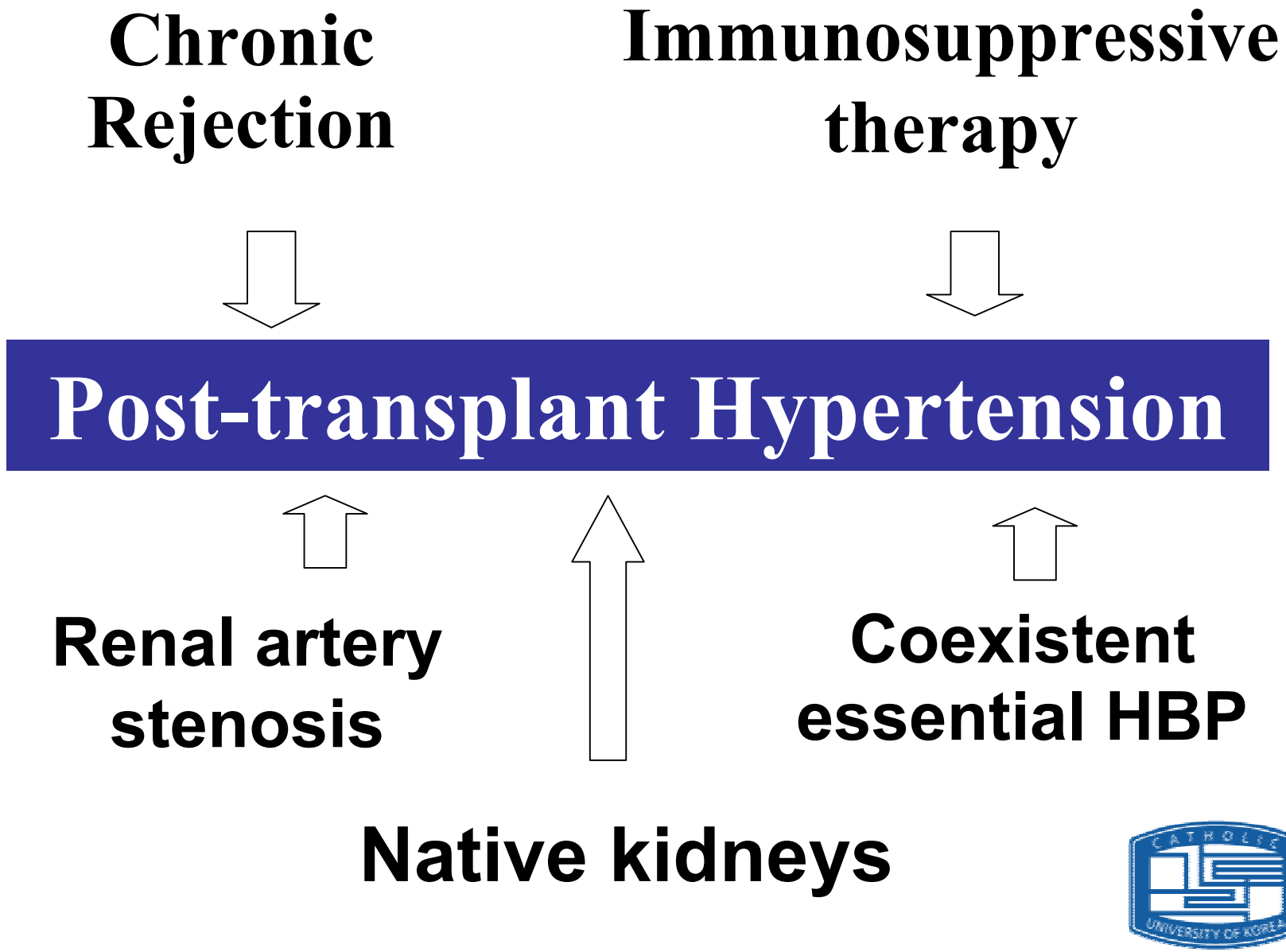
14yrs later



2000

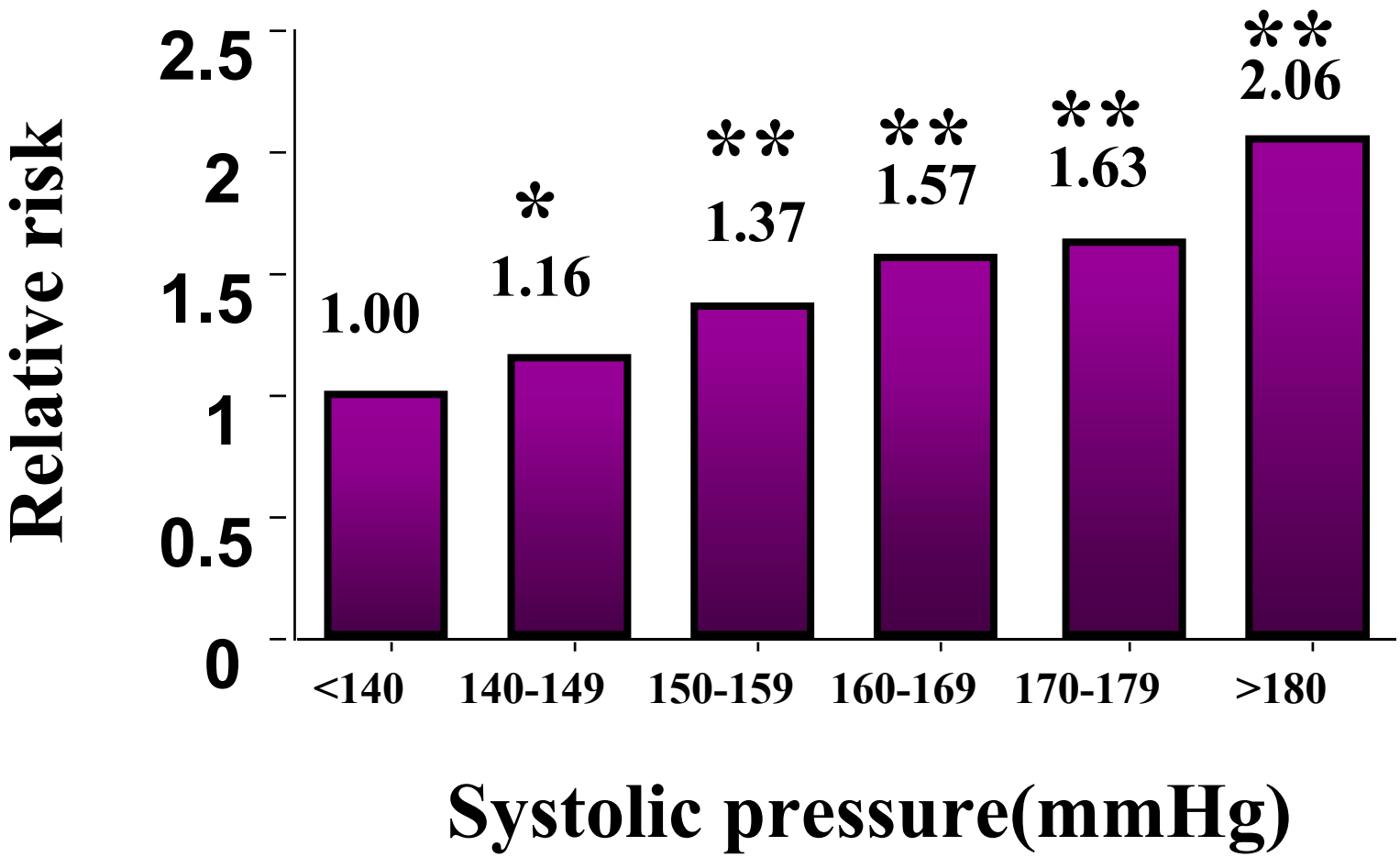
Vascular Calcification




Chronic Rejection
Immunosuppressive therapy
Post-transplant Hypertension
Renal artery stenosis
Native kidneys
Coexistent essential HBP

Effect of Blood pressure on chronic allograft nephropathy

Opelz G et al. Kidney Int 53:217-222, 1998



Hypertension in Nephrology Field

Cause of chronic renal failure

↓

Risk factor for progression of renal dysfunction

↓

Most common complication of dialysis patients

↓

Survival factor of transplanted kidney

HYPERTENSION

Cardio-Nephrologists