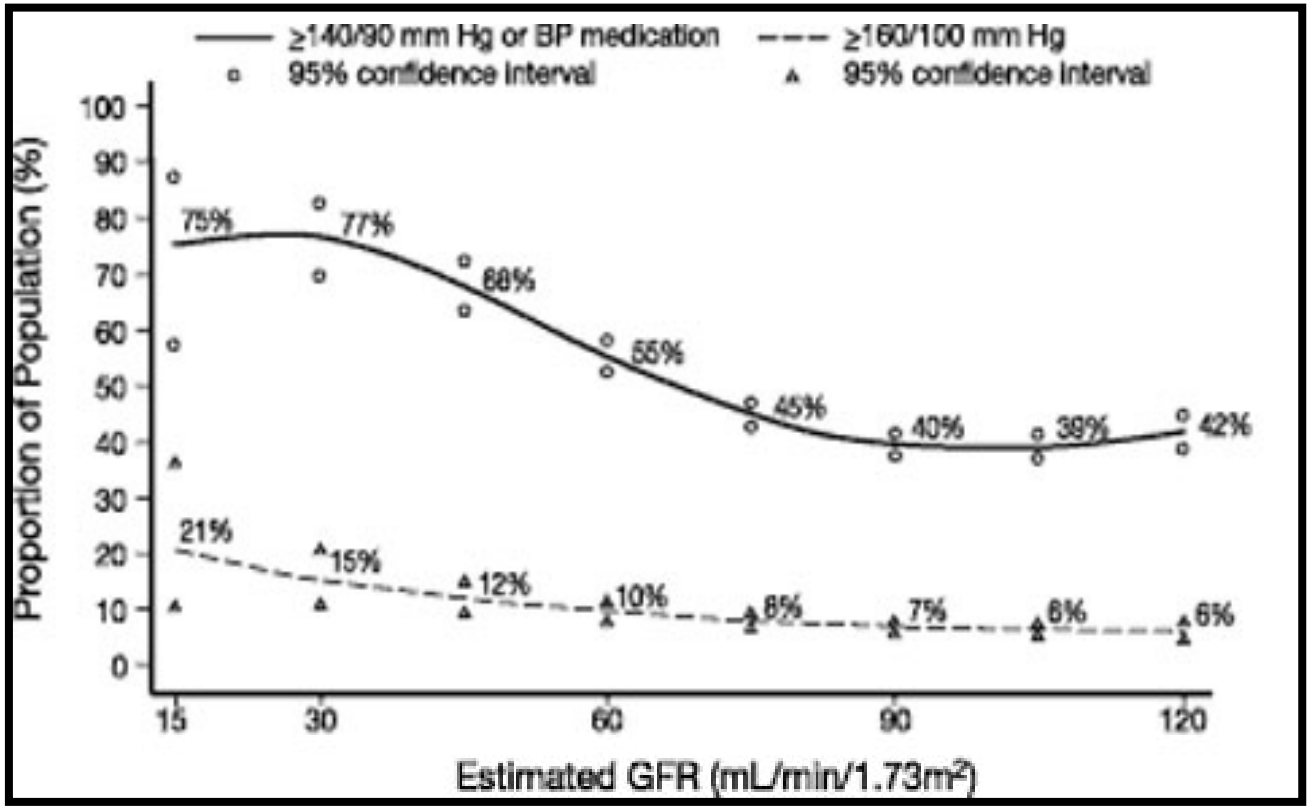
# Treatment of Hypertension in Chronic Kidney Disease( CKD )

**2010. 4. 16**

한림의대 신장내과

윤 종우

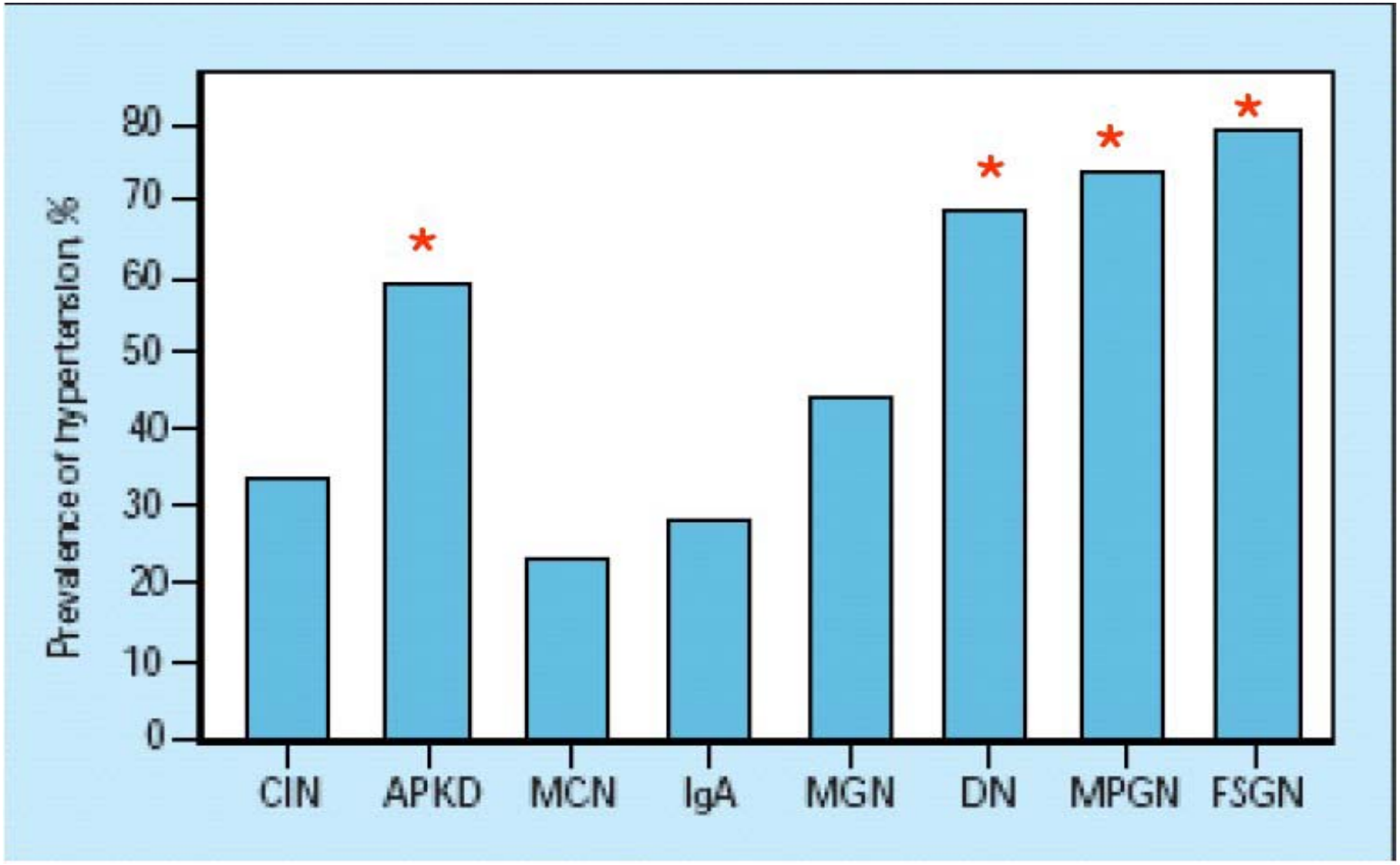
# Prevalence of Hypertension by level of GFR




**50 to 80 %of CKD patients**

*Am J Kidney Dis 39:S1-S266, 2002*

# Prevalence of Hypertension in specific disease



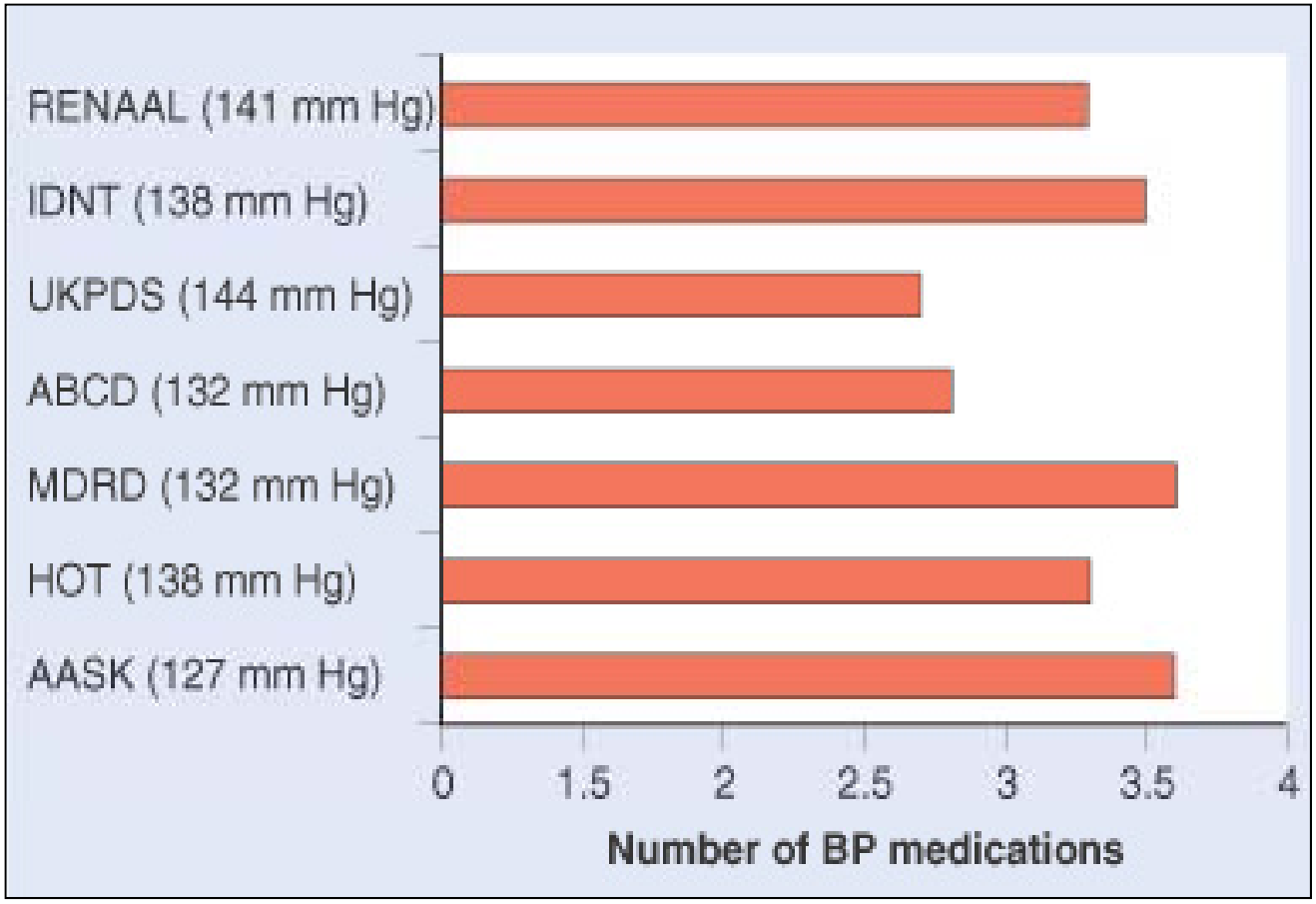
# Importance of BP Control in CKD

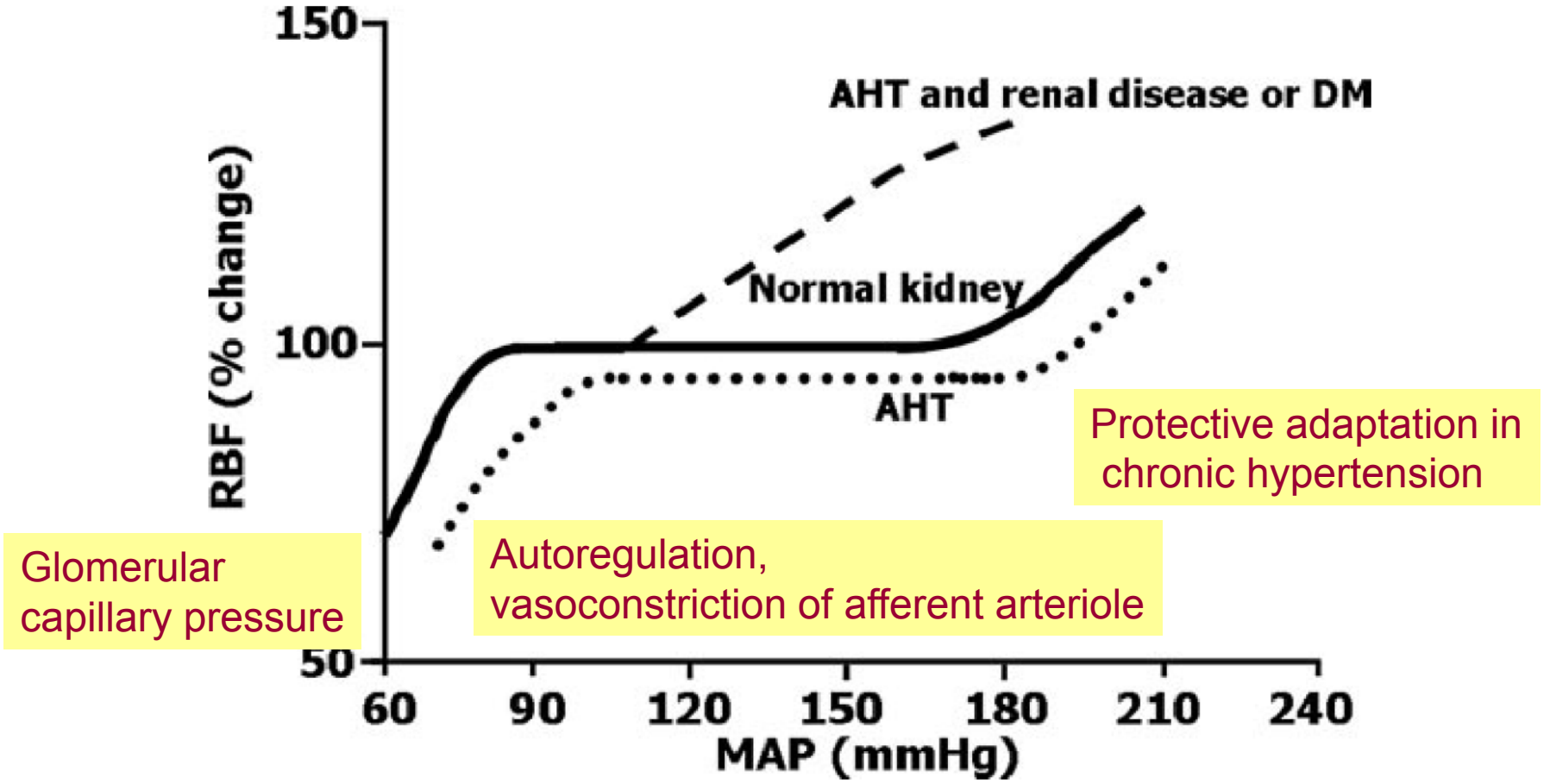
**Hypertension is…….**

- Independent factor **determining the rate of loss of renal function**
- Independent **risk factor for cardiovascular events** in patients with CKD

# Number of Antihypertensive Agents Used for Intensive BP Goals

**Multiple agents are required in 80-90% of CKD patients**






## Relationships between renal blood flow and systemic BP

Mechanical stretch of glomerular capillary and mesangial cells
repair response by fibrogenic cytokines, AngII and glomerulosclerosis

*Maura R. JASN 17:S98, 2006*

# Blood Pressure Target

**'< 130/80 mmHg' for all types of CKD (Diabetic or Nondiabetic Kidney Disease) with no relation to proteinuria.**

Consider lower SBP target ( < 125/75 mmHg ) for moderate proteinuria (spot urine total protein-to-creatinine ratio >1000 mg/g)

*K/DOQI Clinical Practice Guidelines, JNC 7 Report, ADA*

# BP Control and CKD Progression

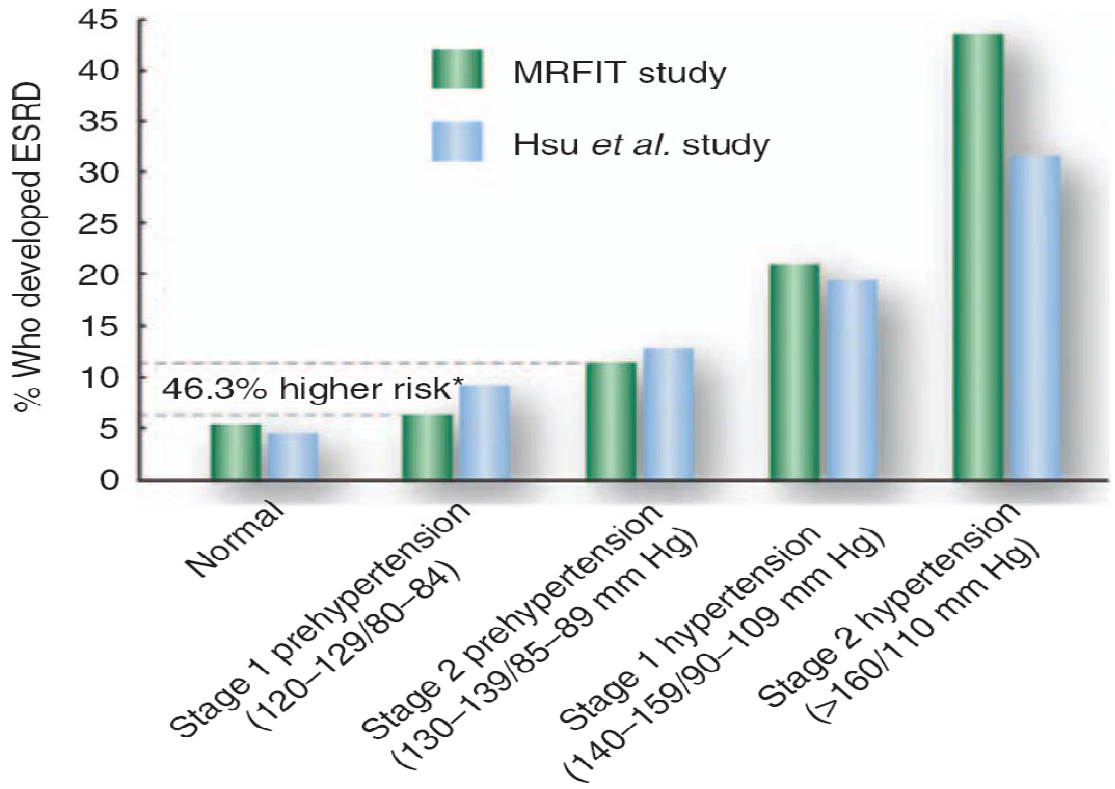


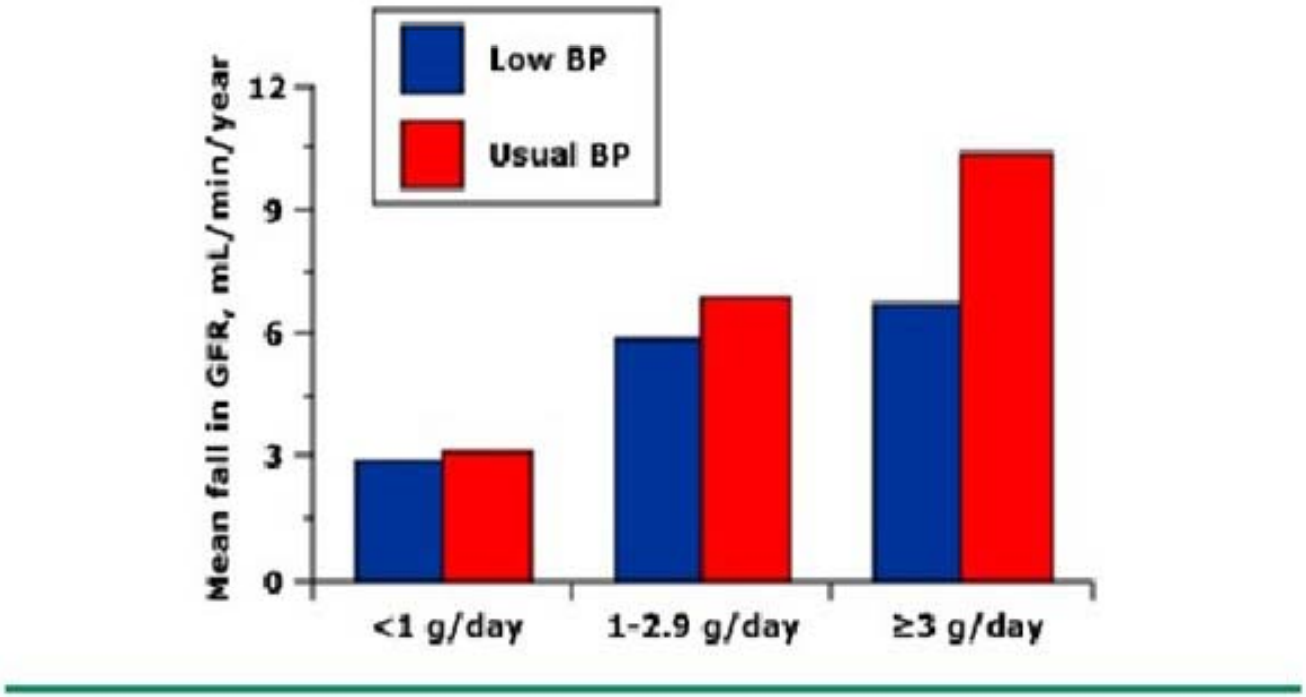

**Figure 1 | Age-adjusted rates of end-stage renal disease (ESRD) for prehypertension in the Multiple Risk Factor Intervention Trial (MRFIT) and Hsu *et al.*[3] analyses.** *Between the MRFIT prehypertensive cohorts, the risk for ESRD development was increased.

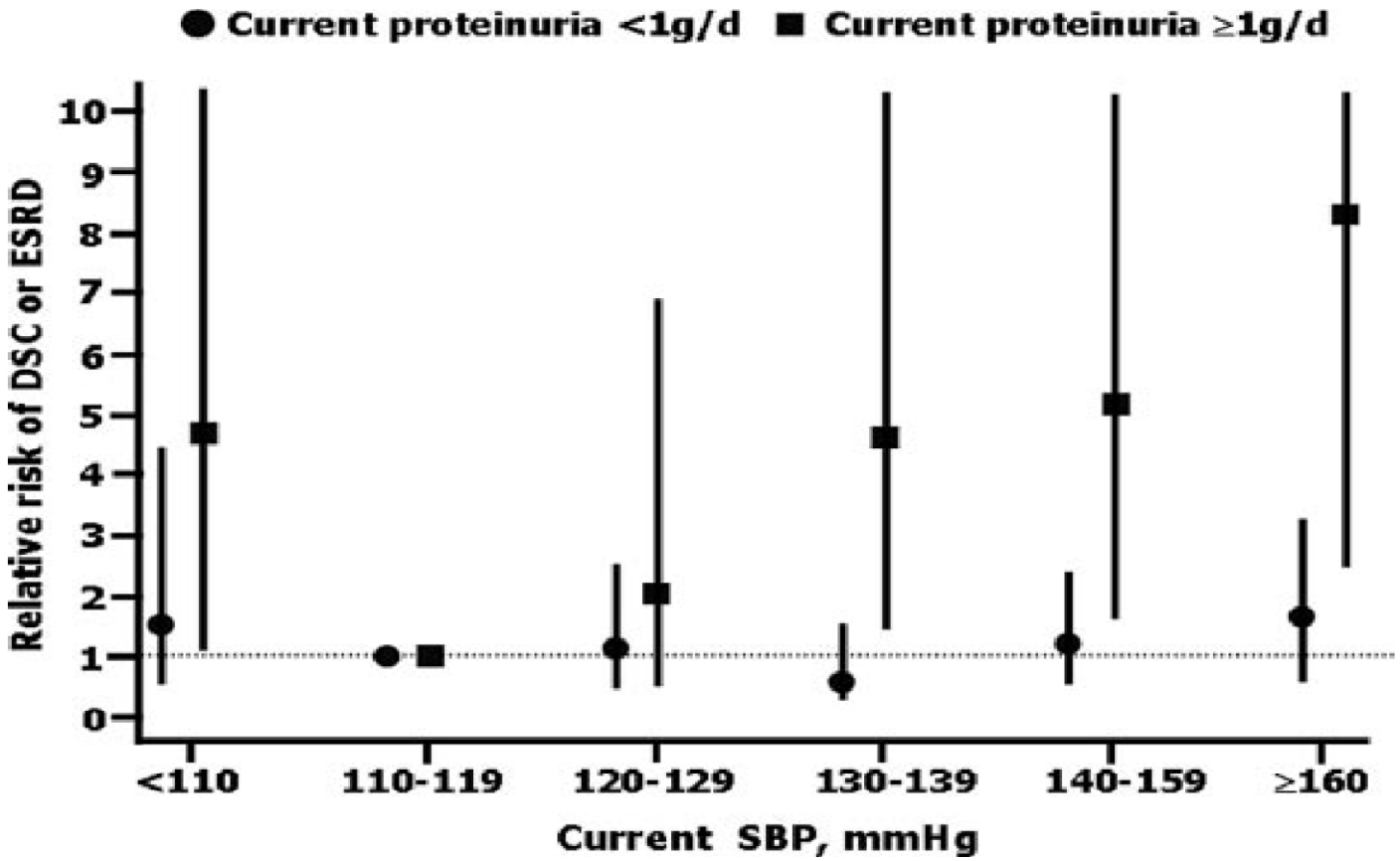
*Kidney Int 77: 194-200, 2010*

# The Effects of Dietary Protein Restriction and Blood-Pressure Control on the Progression of Chronic Renal Disease

*Saulo Klahr, Andrew S. Levey, Gerald J. Beck, Arlene W.*
*for The Modification of Diet in Renal Disease Study Group*

**Aggressive BP control preserves renal function in proteinuric patients**



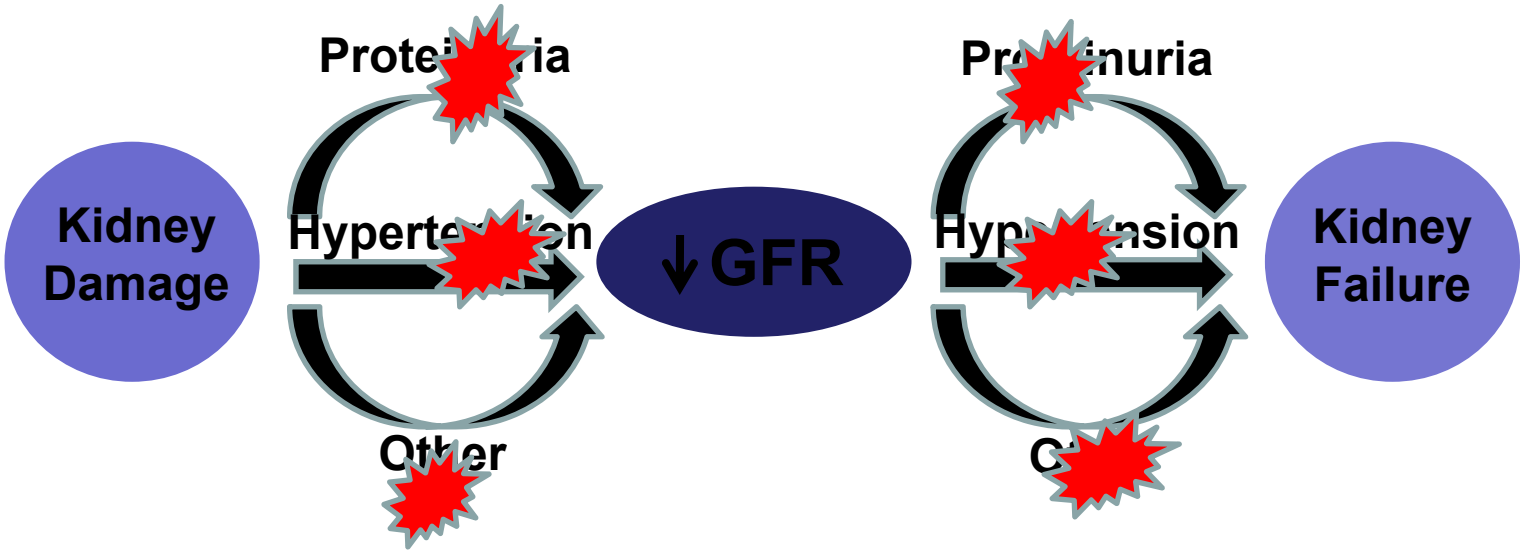



## Nephropathy progression according to current SBP and proteinuria

Risk for ESRD increased when SBP was <110 mmHg, especially in proteinuric patients, suggesting a J-curve behavior of the relationship between BP and the progression of renal disease

*Maura R. JASN 17:S98, 2006*

# Renal Disease and Hypertension
# -Core Concepts of Treatment-



# Preferred Agents: ACEI or ARB

Patients with diabetic kidney disease and nondiabetic kidney disease with spot urine protein-to-creatinine ratio >200 mg/g with or without hypertension should be treated with an **ACEI** or **ARB**.

- Titration: a minimum of 2 weeks (2-4 wks)

Preferred agents for CKD are defined as antihypertensive agents that slow progression of CKD in addition to lowering blood pressure and should be prescribed even in the absence of hypertension.

*K/DOQI Clinical Practice Guidelines*

# Beneficial Effects of ACE or AII inhibition

lowers the intraglomerular pressure, $P_{GC}$ via the dilatation of efferent arterioles.

Improve the size selectivity of the glomerulus

AII is a growth factor,
minimize glomerular and vascular hypertrophy
Accumulation ECM

# Use in advanced CKD:

## Whether the benefit from ACE inhibitor or ARBs extends to advanced CKD?

1. Given the increased risk of hyperkalemia.
2. Is there a serum creatinine concentration above which one would not use such therapy?

The NEW ENGLAND JOURNAL of MEDICINE

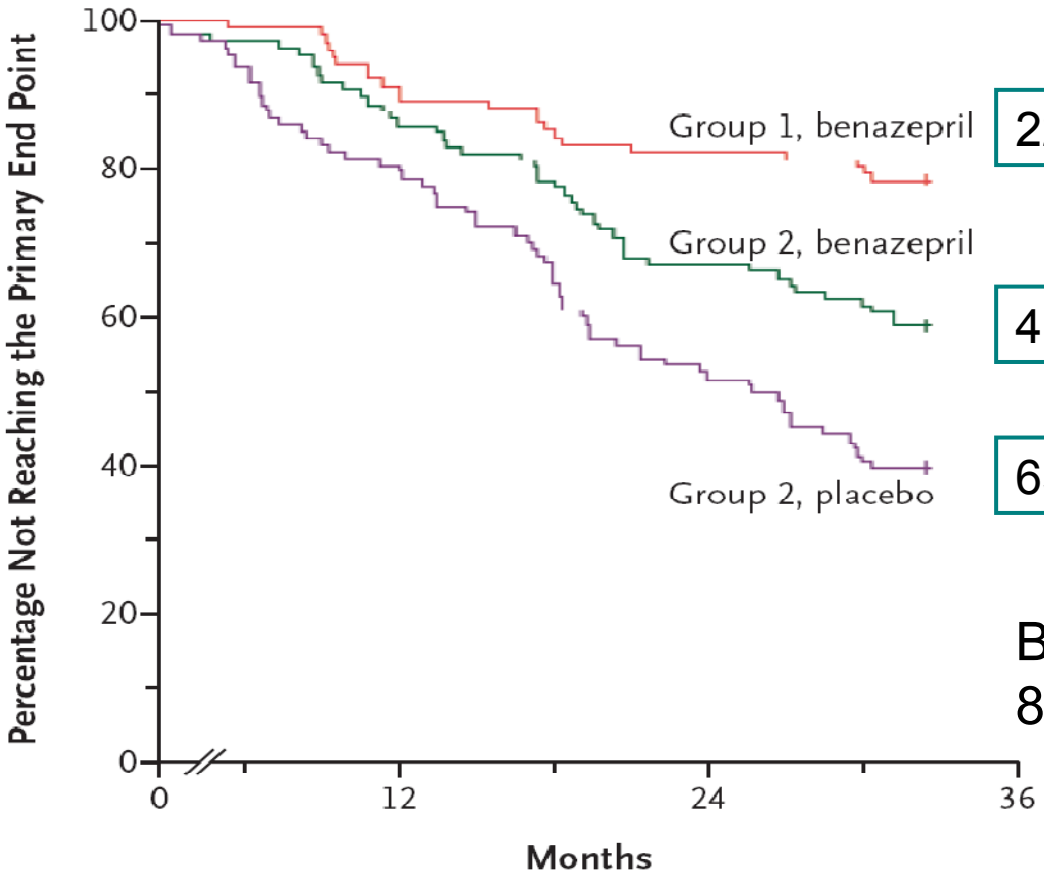
ORIGINAL ARTICLE

### Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Fan Fan Hou, M.D., Ph.D., Xun Zhang, M.D., Guo Hua Zhang, M.D., Ph.D., Di Xie, M.D., Ping Yan Chen, M.D., Wei Ru Zhang, M.D., Ph.D.

422 Non diabetic CKD, Cr1-3 and 3-5

*Fan FH. NEJM 2006;354:131-40*

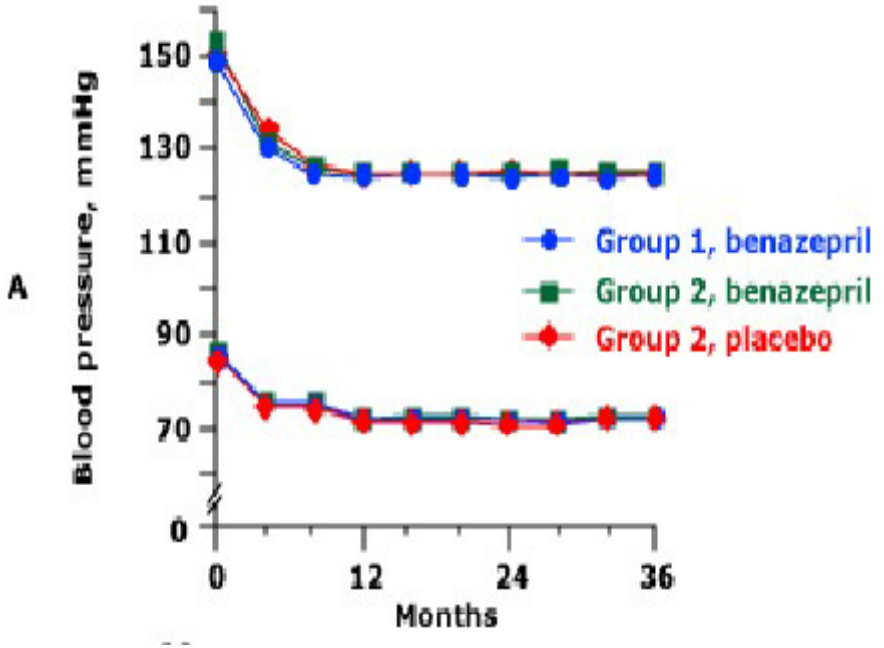


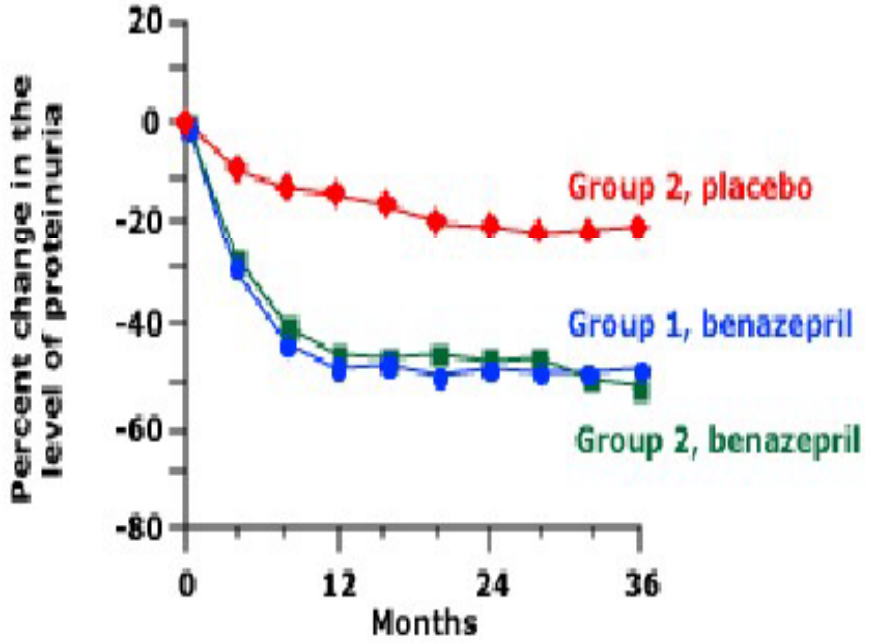

Benazepril 10mg bid
8 week run-in period

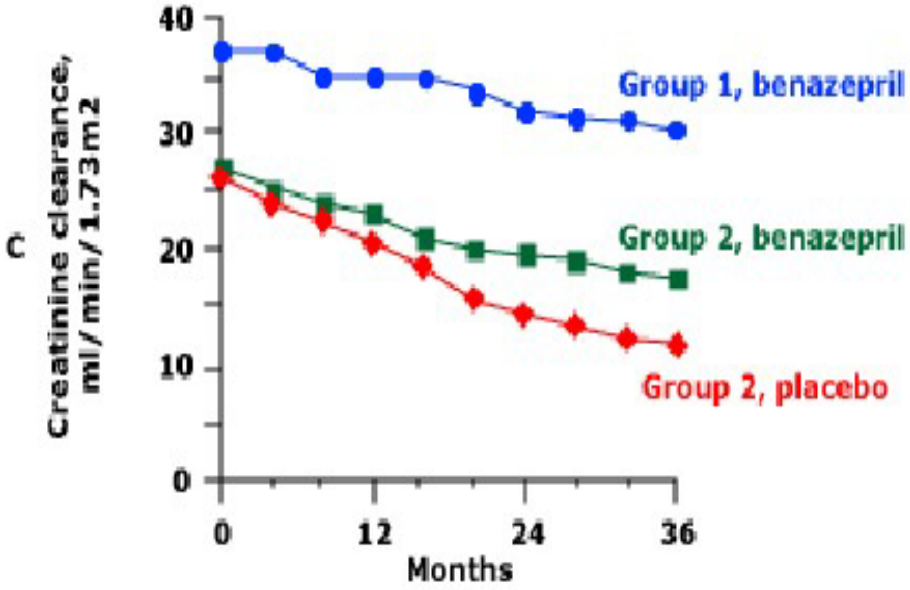
| No. at Risk | | | | |
|---|---|---|---|---|
| Group 1, benazepril | 102 | 96 | 84 | 40 |
| Group 2, benazepril | 107 | 96 | 73 | 32 |
| Group 2, placebo | 108 | 88 | 59 | 22 |

**Figure 2. Kaplan–Meier Estimates of the Percentage of Patients Not Reaching the Primary Composite End Point of a Doubling of the Serum Creatinine Level, End-Stage Renal Disease, or Death.**

Group 1 had a serum creatinine level of 1.5 to 3.0 mg per deciliter, and group 2 had a serum creatinine level of 3.1 to 5.0 mg per deciliter at baseline.




**Group 1 sCr 1.5 - 3 mg/dL**
**Group 2  sCr 3 – 5 mg/dL**

**Table 3. Adverse Events after Randomization.***

| Adverse Event | Group 1 (N=104) | Group 2 | |
|---|---|---|---|
| | | Benazepril (N=112) | Placebo (N=112) |
| | | *no. of events* | |
| Death | 0 | 1 | 0 |
| Nonfatal cardiovascular event | | | |
| Myocardial infarction | 3 | 5 | 8 |
| Heart failure | 1 | 3 | 5 |
| Stroke | 1 | 2 | 3 |
| Other adverse events | | | |
| Hyperkalemia† | 2 | 6 | 5 |
| Acute decline in renal function | 1 | 1 | 1 |
| Dry cough | 0 | 1 | 0 |
| Hypotension‡ | 1 | 0 | 0 |
| Total | 9 | 19 | 22 |

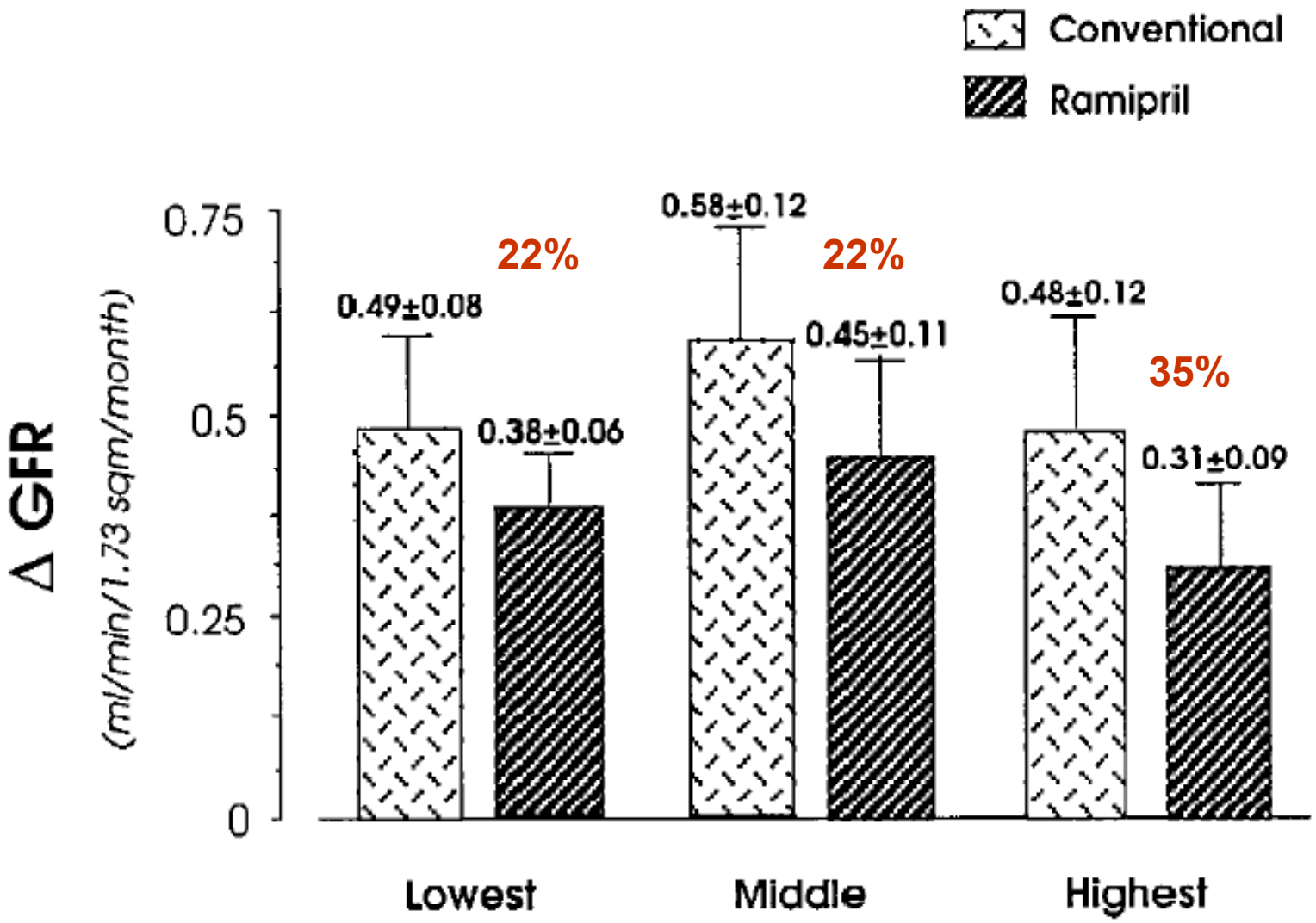
**Severe hyperkalemia, acute increase in serum creatinine** more than 30% were usually occurred within 1 month of run-in period

# ACE Inhibitors to Prevent End-Stage Renal Disease: When to Start and Why Possibly Never to Stop: A *Post Hoc* Analysis of the REIN Trial Results

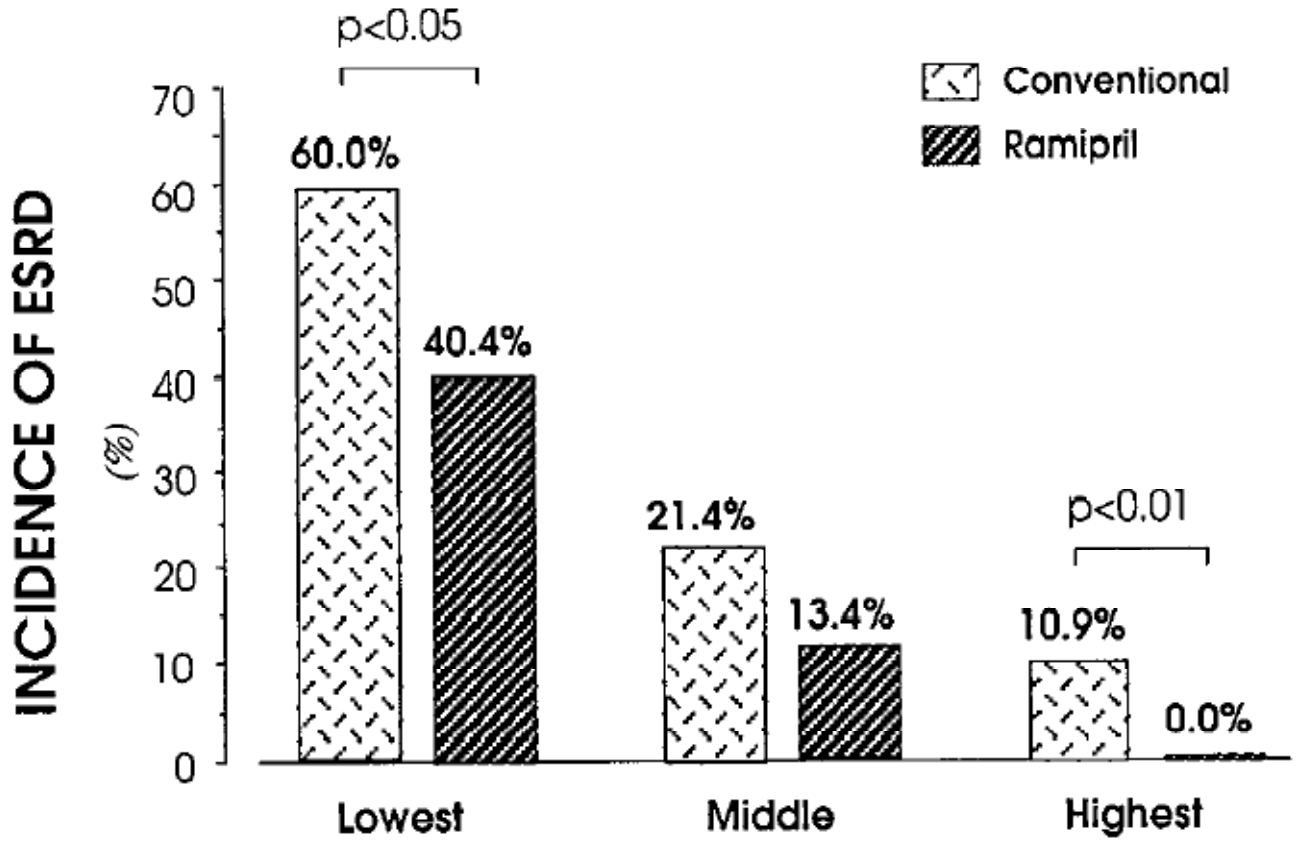
PIERO RUGGENENTI,*† ANNALISA PERNA,* and GIUSEPPE REMUZZI*†
on behalf of Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN)
**Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases, "Aldo e Cele Daccò" Villa Camozzi, Ranica, Italy; and †Unit of Nephrology, Ospedali Riuniti, Azienda Ospedaliera, Bergamo, Italy.*

*JASN 12:2832-37*

- 322 Non-diabetic proteinuric CKD and **different degrees of renal insuffiency**
- **Rate of GFR decline(ΔGFR)**
- **Incidence of ESRD**
- Ramipril or non ACEI treatment within three tertiles of basal GFR, 21-49 month




No significant difference among the groups




1. ACEI are worth using even in very advanced form of CKD GFR 10-30mL/min
2. Need not to withhold, even GFR approximates levels requiring replacement therapy

# Indication of Diuretics

**Patients with *nondiabetic kidney disease* with spot urine *total protein-to-creatinine ratio <200 mg/g* as first-line agent**

*K/DOQI Clinical Practice Guidelines*

# Effects of Diuretics

√ Reducing ECF volume

√ Potentiating the effect of ACEI and ARB

√ Reducing the risk of CVD in CKD (esp, thiazide)

Antiproteinuric effect is prominent on a relative volume depletion, **low sodium diet** or **treated with diuretics**.

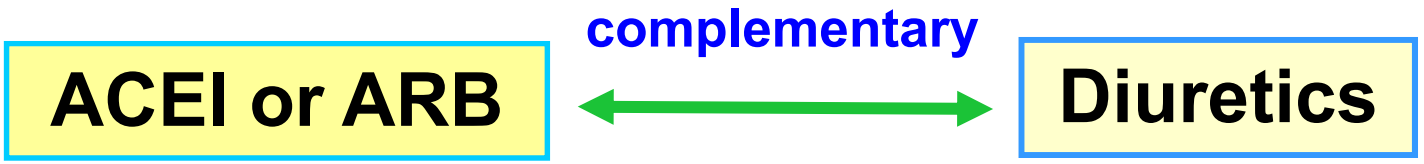
# Choice of Diuretics

Choice of diuretic agents depends on the level of GFR and need for reduction in ECF volume.

- **Thiazide diuretics:**
  - Once daily
  - **GFR≥30 mL/min/1.73 m2 (CKD Stages 1-3)**

- **Loop diuretics:**
  - Once to thrice daily
  - **GFR<30 mL/min/1.73 m2 (CKD Stages 4-5)**

# ACEI or ARB + Diuretics




Hyperkalemia
Less effect in low renin HTN
Anti-diabetogenic
Block RAS

Hypokalemia
Effective in low renin HTN
New-onset DM
Activating RAS

Nephrol Dial Transplant (2009) 24: 701–702
doi: 10.1093/ndt/gfn695
Advance Access publication 10 December 2008

# Should nephrologists use beta-blockers? A perspective

Rigas Kalaitzidis and George Bakris

Department of Medicine, Hypertensive Diseases Unit, University of Chicago School of Medicine, Chicago, IL, USA

# Sympathetic nerve system

**modulate renal function by its receptor**

- $\beta_1$ : Cardiac output and renin release
- $\alpha_1$ : Systemic and renovascular constriction
  vascular constriction
- $\beta_2$ : renovascular dilatation
  bronchial dilatation

# Sympathetic overactivity

- Commonly seen in chronic kidney disease (CKD) and is an important contributor to the

  **genesis of hypertension**,
  increasing the **risk of cardiovascular events**
  **increasing renal disease progression**

  Ang II-dependent and independent sympathetic hyperactivity

Activation of afferent signals from damaged kidneys,

⇩

spinal cord

⇩

hypothalamus,
(local catecholamine turnover is upregulated)

⇩

increased efferent sympathetic nerve traffic
into the periphery.

# Vasodilating β-blockers (Labeterol and carvedilol)

- Use of nonselective (propranolol) or selective (metoprolol, atenolol) β -blockers : Compensatory stimulation of the SNS and RAS, NE and renin release…..

activation of a-adrenergic receptors results in an **increase in systemic as well as RVR.**

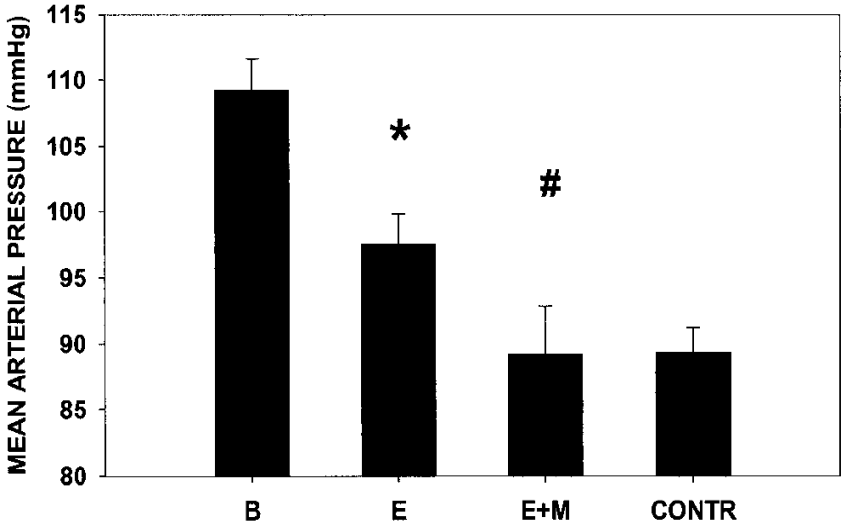
# Vasodilating β-blockers (Labeterol and carvedilol)

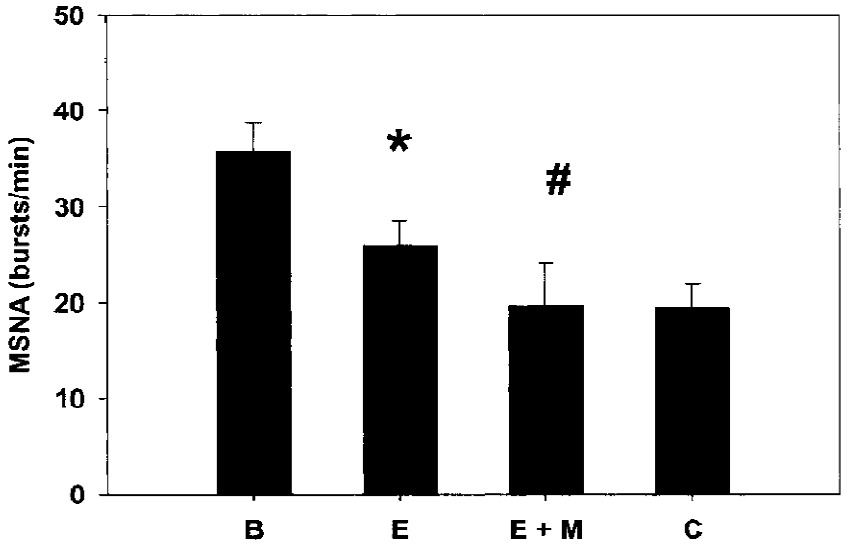
- better tolerability and different effects on renal hemodynamics as well as metabolic variables
- Relative $\alpha_1$-blocking effect
- Studies with carvedilol attenuate albuminuria reduction in CV events in CKD patients with hypertension

J Am Soc Nephrol 15: 2902–2907, 2004

# Moxonidine Normalizes Sympathetic Hyperactivity in Patients with Eprosartan-Treated Chronic Renal Failure

JUTTA NEUMANN,* GERRY LIGTENBERG,* LIAM OEY,†
HEIN A. KOOMANS,* and PETER J. BLANKESTIJN*
*Departments of *Nephrology and †Clinical Neurophysiology, University Medical Center, Utrecht, the Netherlands.*




**Sympatho-inhibitory effect of moxonidine**,
Imidazole I1 receptor mediated by brain stem receptors

Angiotensin-independent sympathetic activity

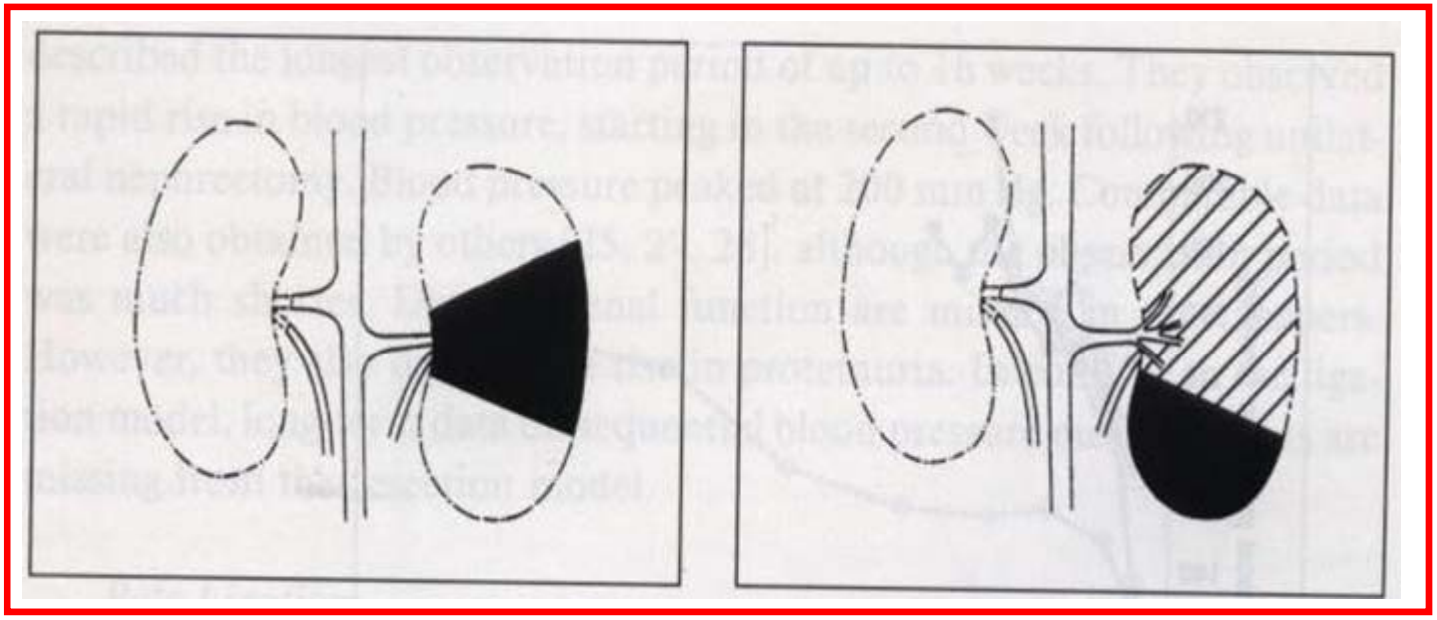
# Effects of Low Dose Sympathetic Inhibition on Glomerulosclerosis and Albuminuria in Subtotally Nephrectomized Rats

KERSTIN AMANN,*† LARS CHRISTIAN RUMP,§ AURELIA SIMONAVICIENE,* VITUS OBERHAUSER,§ SABINE WESSELS,* STEPHAN R. ORTH,‡ MARIE-LUISE GROSS,* ANDREAS KOCH,* GERHARD W. BIELENBERG,‖ JORGE P. VAN KATS,¶ HEIMO EHMKE,# GERHARD MALL,** and EBERHARD RITZ‡

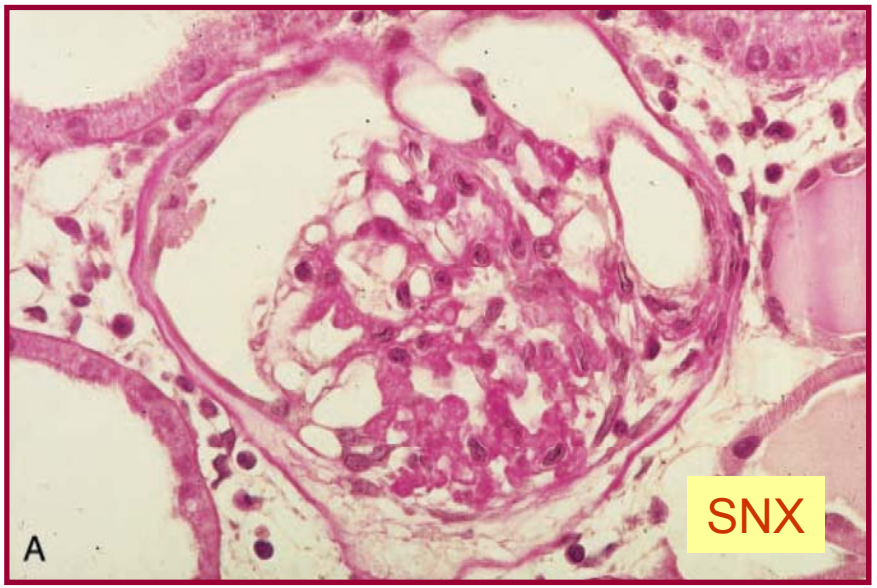
*Kerstin A. JASN 11;1469-78*

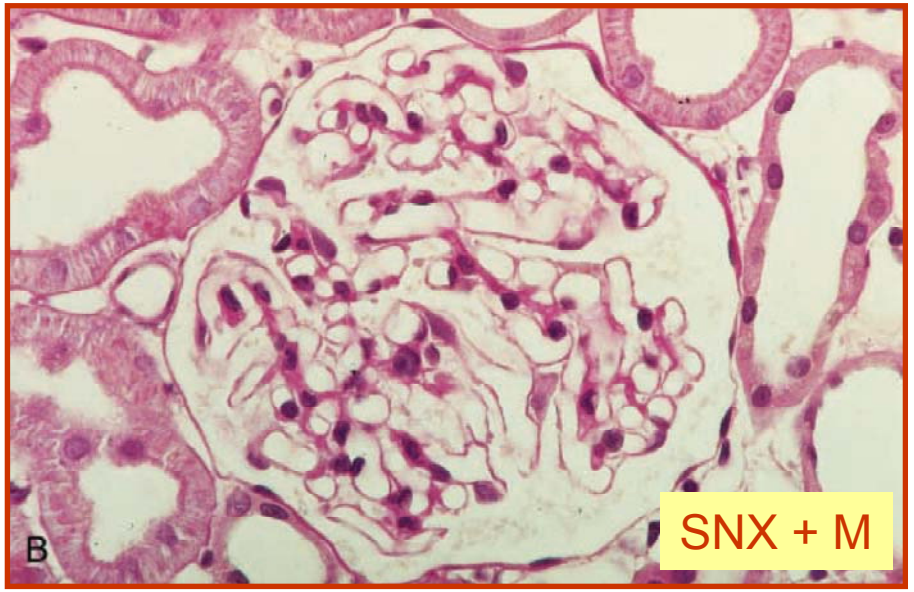
- SHR-SP, administeration moxonidine in a dose that failed lower systemic BP
- Potentially injurious BP-independent effect of sympathetic overactivity on progression of renal failure

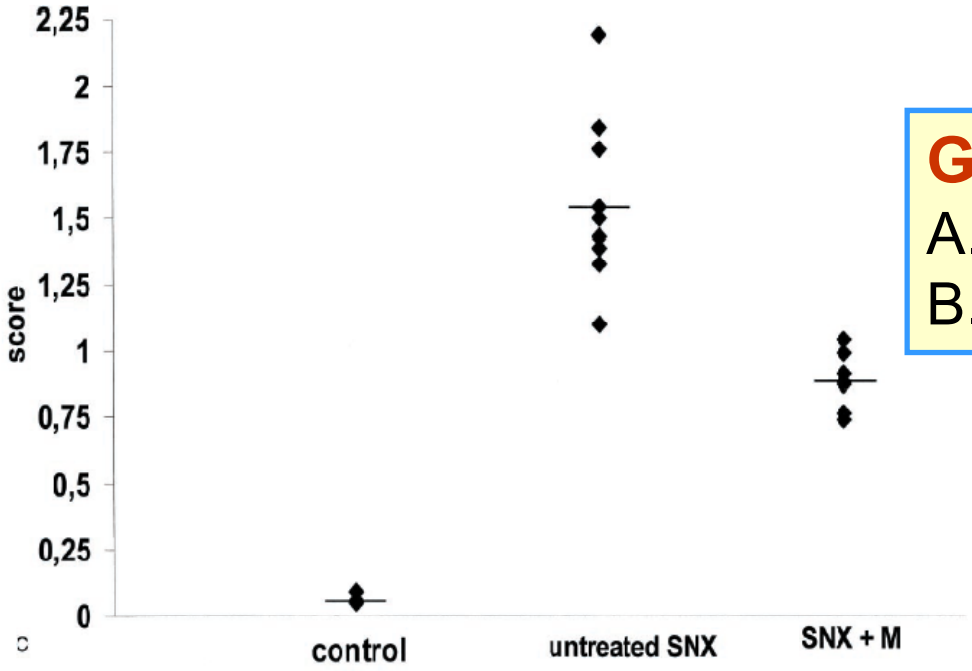
# 5/6 Nephrectomy model
# (Remnant kidney model)



**Pole resection**
**Pole ligation**
**Branch ligation**

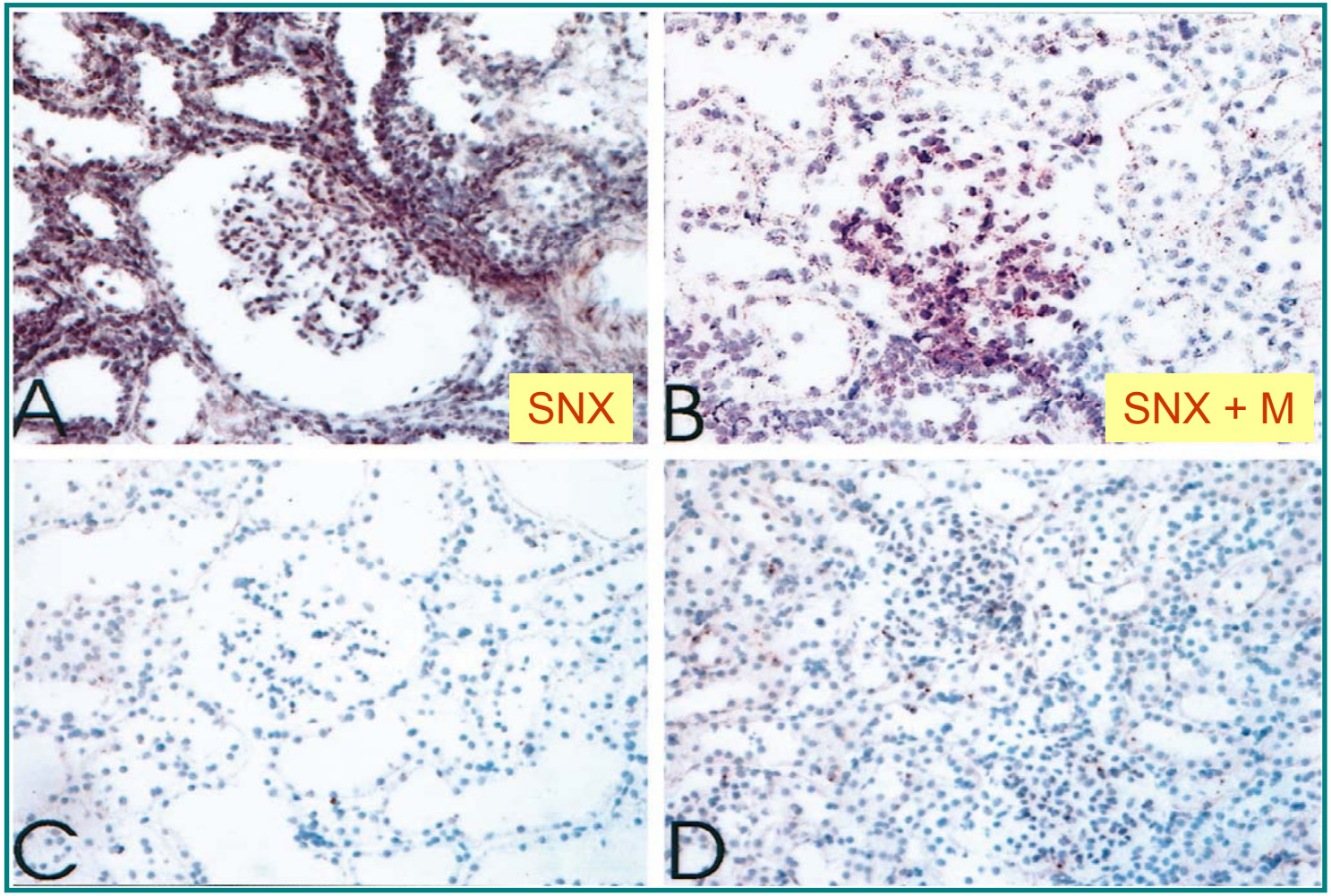


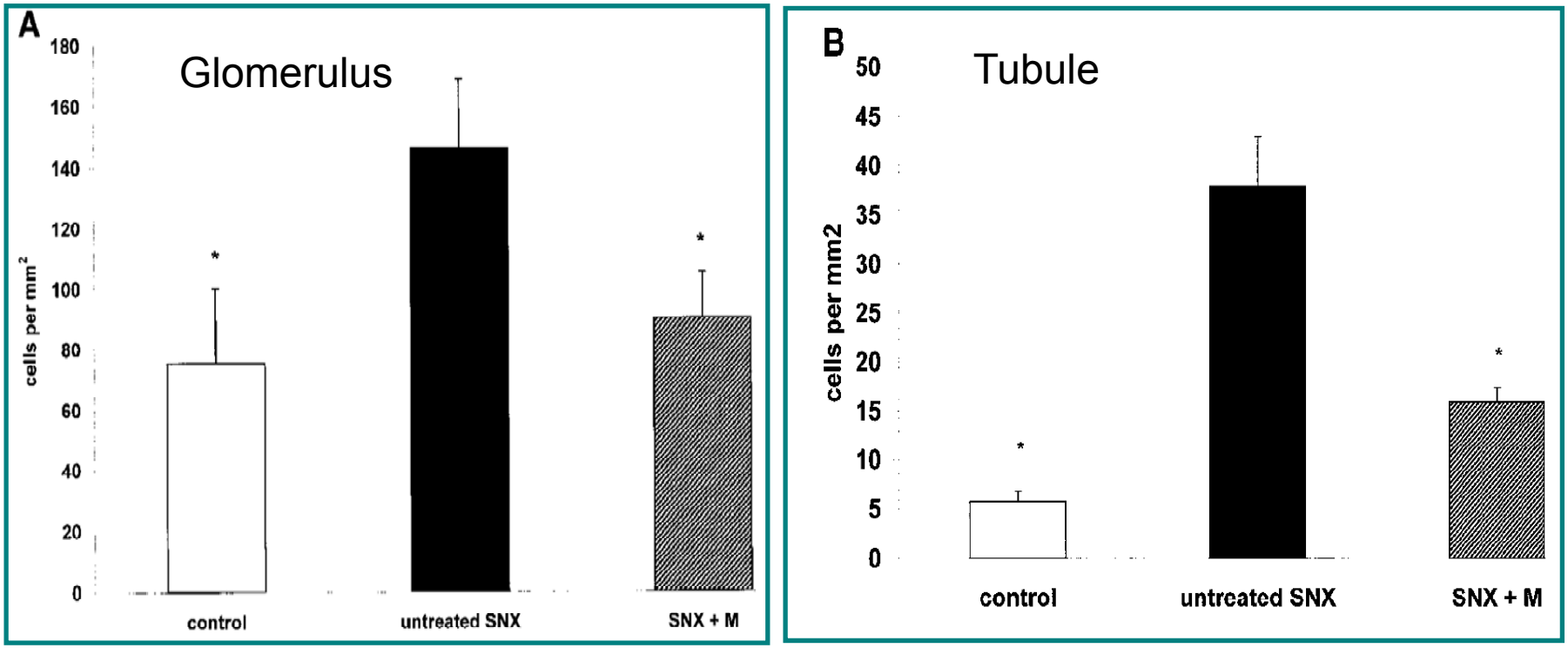

**Glomerulosclerosis index** of
A. 5/6 nephrectomized rat
B. moxonidine treated rat kidney

*Kerstin A. JASN 11;1469-78*



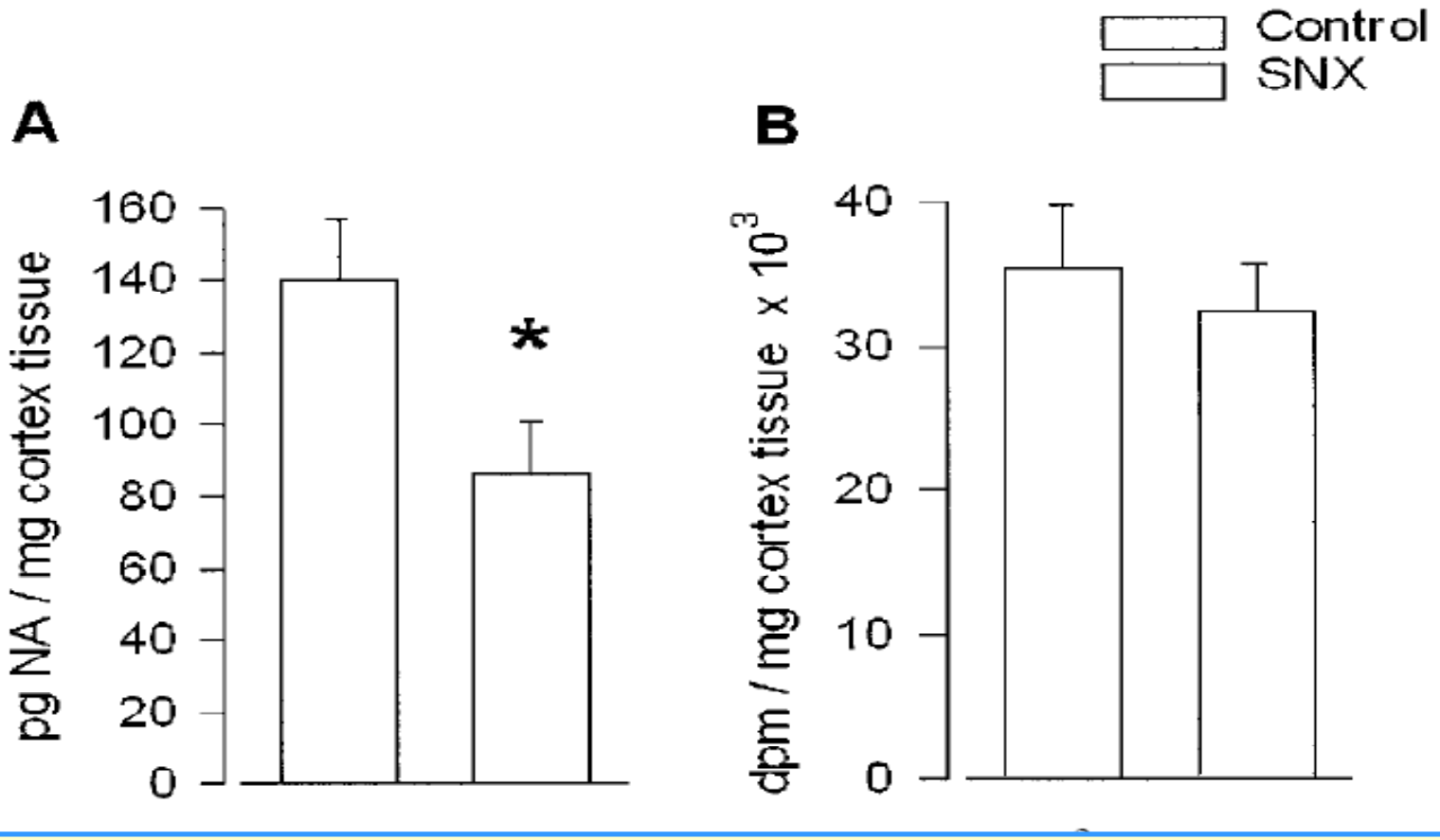

Nonradioactive *in situ* hybridization of
**transforming growth factor-b1 (TGF-b1) mRNA.**

*Kerstin A. JASN 11;1469-78*




**Average number of proliferating cell nuclear antigen (PCNA)-positive cells per mm² glomerular tuft area**

*Kerstin A. JASN 11;1469-78*




Endogenous NE content and [$^3$H]-NE uptake inrenal cortex

**Increased NE uptake and turn over, diminished NE content**

**Increased single nerve fiber activity in the kidney**

*Kerstin A. JASN 11;1469-78*

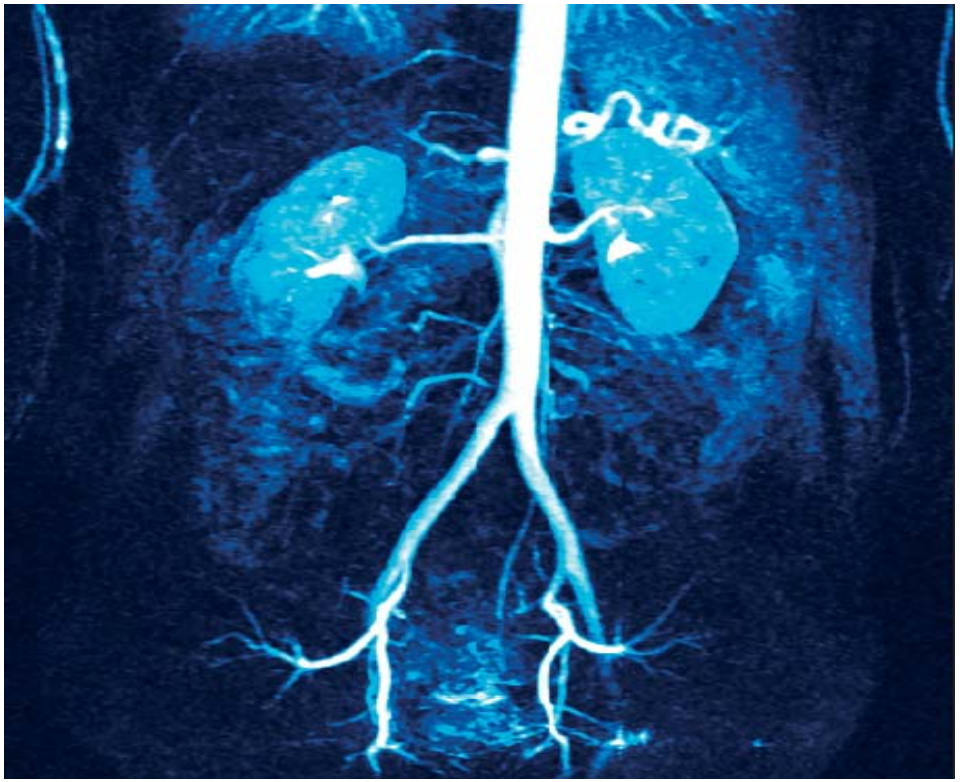
# Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

*Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler*

## Summary

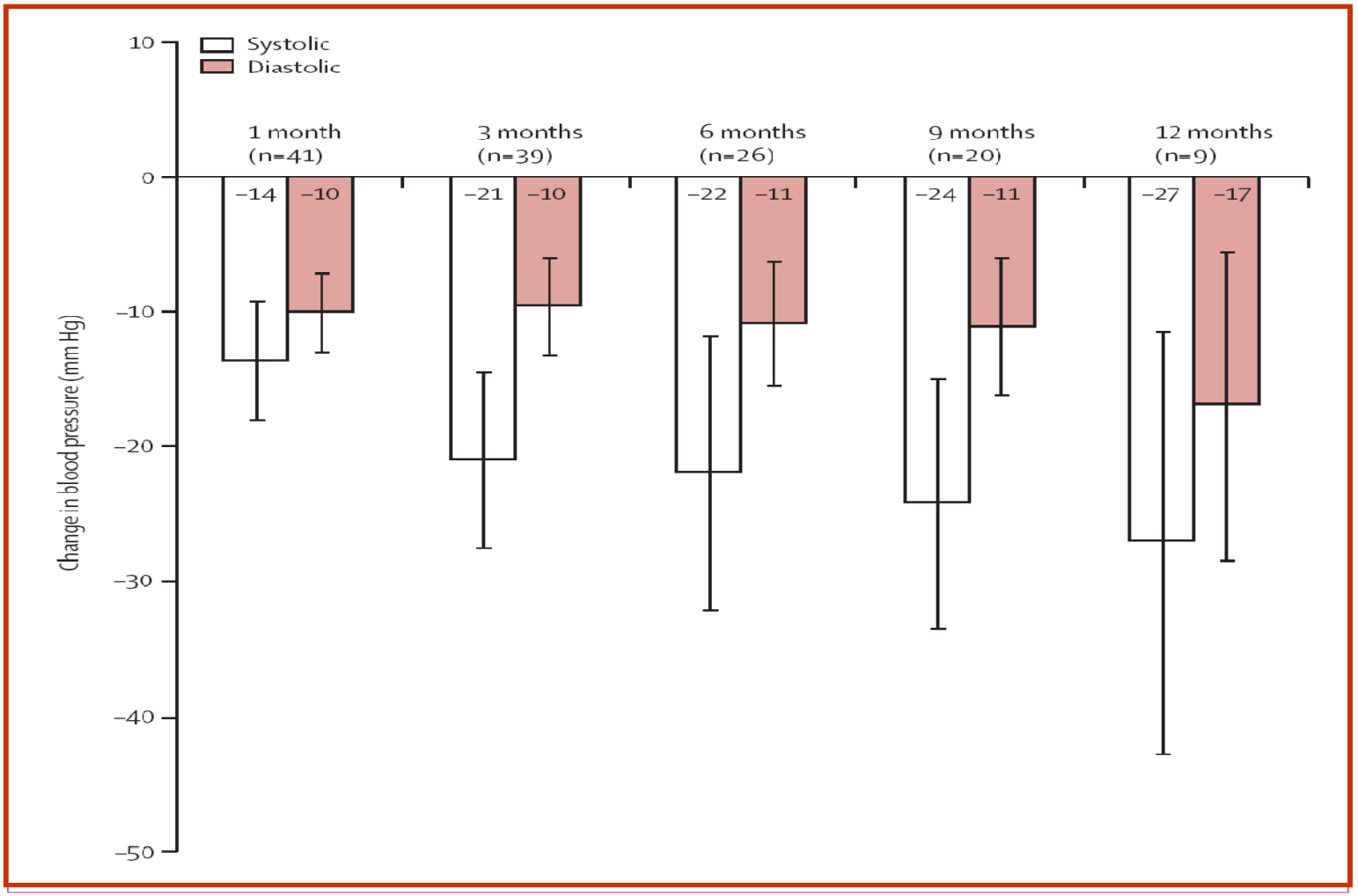
**Background** Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure ≥160 mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

*Lancet 2009;373:1275-81*



1. Renal sympathetic efferent and afferent nerves, lie within and immediately adjacent to the wall of the renal artery
2. Percutaneous, radiofrequency cather-based devervation, with both renal artery angiography
3. Ablation lasting up to 2 minuts, 8 watt, procedure 38 min

*Lancet 2009;373:1275-81*




BP reduction was preserved more than 1 year follow up period
Suggesting no nerve fiber recovery, regrowth, development of counter-regulatory BP elevating mechanism

*Lancet 2009;373:1275-81*

- **Safe, brief,  No long-term adverse effects**
  - 1 dissection, femoral access pseudoaneurysm
  - No renal artery aneurysm or stenosis
  - No substantial deterioration of GFR

- 47% reduction of renal noradrenalin release, indicating achiving **efferent renal denervation**

- **Beneficial effects beyond BP reduction**
  - 24% patients had 20% or more GFR improvement
  - LVH, Insuline resistence…?

*Lancet 2009;373:1275-81*

# Subclass of Calcium Channel Blockers

## Non-dihydropyridine vs. Dihydropyridine

- **Non-dihydropyridine:** decrease in proteinuria and renal injury, slow the progression to ESRD in diabetes and non-diabetic hypertensive proteinuric nephropathy

*Kidney Int 65: 1991-2002, 2004*

*Kidney Int 54: 1283-1289, 1998*

- **Dihydropyridine:** limited to CKD patients with persistent hypertension despite the use of ACEI, ARB, diuretics, non-dihydropyridine CCB, and BB

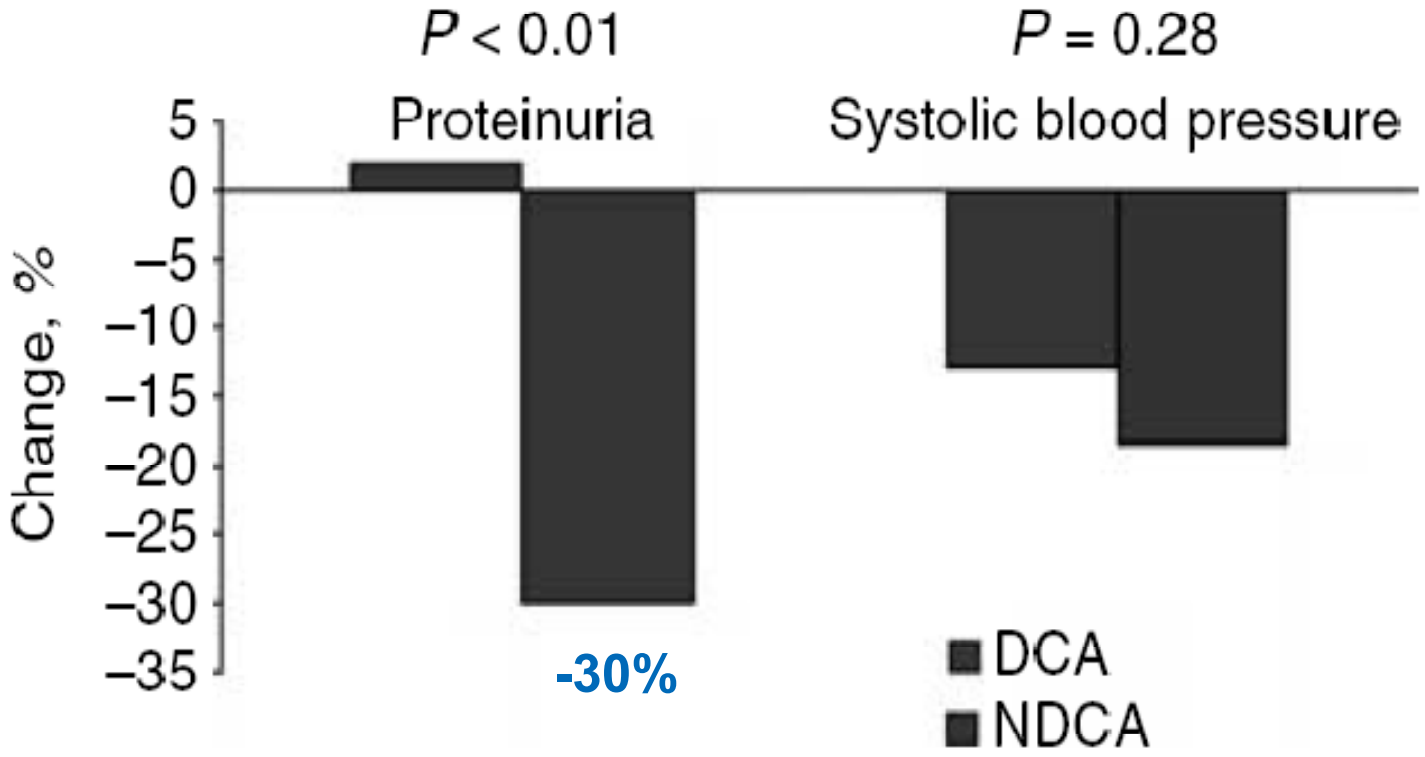
# Differential effects of calcium antagonist subclasses on markers of nephropathy progression

**GEORGE L. BAKRIS, MATTHEW R. WEIR, MICHELLE SECIC, BRETT CAMPBELL, and ANNETTE WEIS-MCNULTY**

*Rush University Hypertension Center, Chicago, Illinois; Division of Nephrology, University of Maryland, Baltimore, Maryland; Secic Statistical Consulting, Inc., Chardon, Ohio; College of Pharmacy, University of Illinois, Chicago, Illinois; and Johannes Gutenberg University, Mainz, Germany*

- Systemic review on proteinuria in hypertensive adults
- Diabetes and Non-diabetes
- Effects of each class on blood pressure( N =1338 )

  Proteinuria ( N = 510 )




**The change in proteinuria and systolic blood pressure**

NDCAs, alone or in combination with an ACEI/ARB are preferred agents to lower BP in hypertensive patients with nephropathy with proteinuria

# Ca channel blockers

**Non-dihydropyridine type**

Diltiazem: Reduce heart rate by inhibiting A-V conductance,
Verapamil

**Dihydropyridene type**

**L-type Ca channel blocker**

: Nifedipine, Amlodipine Nicardipine, Benidipine

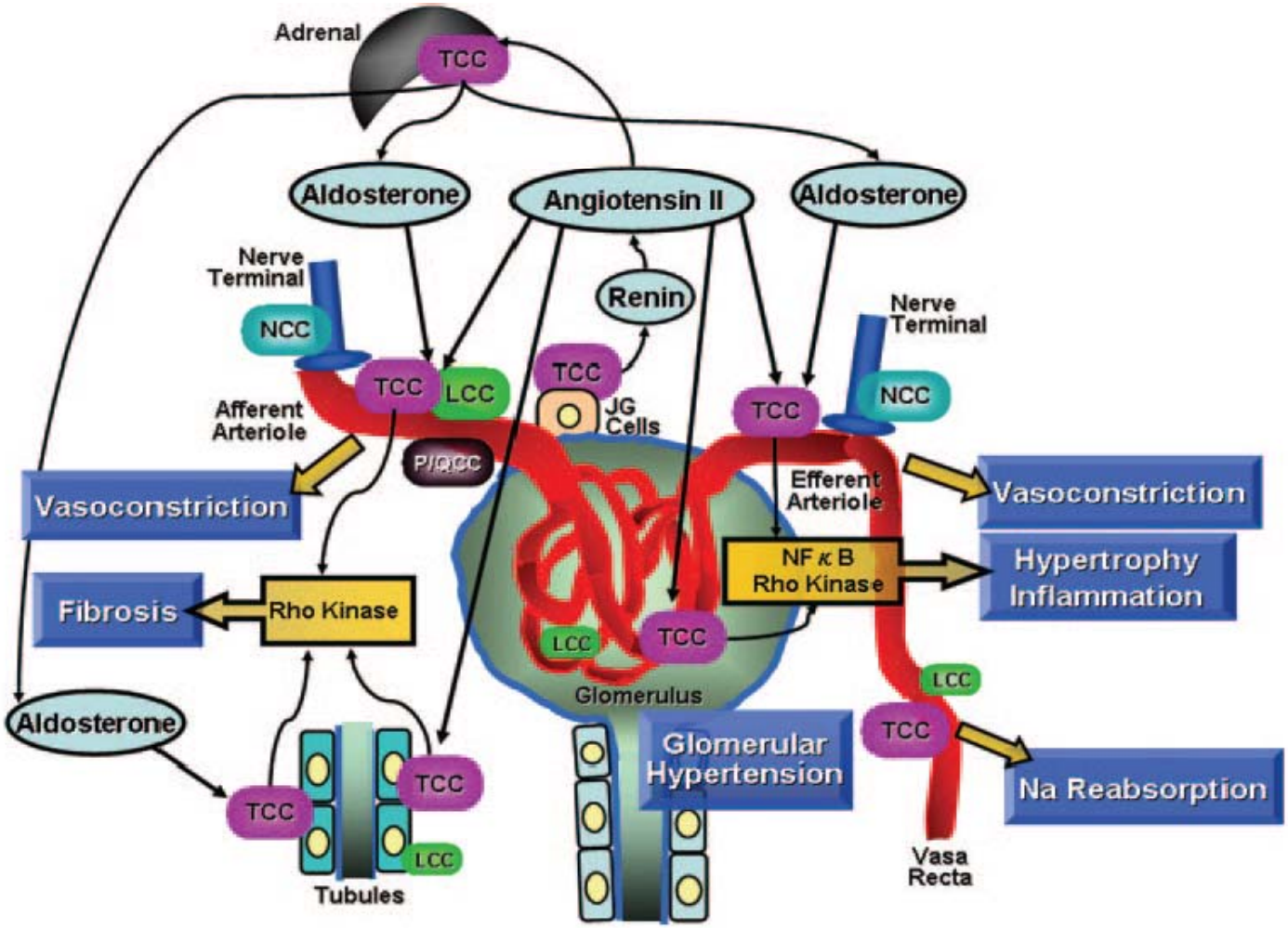
**L-type, N-type Ca channel blocker**

: Cilnidipine - Inhibit norepinephrine release at nerve end

**L-type, T-type Ca channel blocker**

: Efonidipine

# The role of L-/T-/N-type $Ca^{2+}$ channels in the pathophysiological process of renal injury



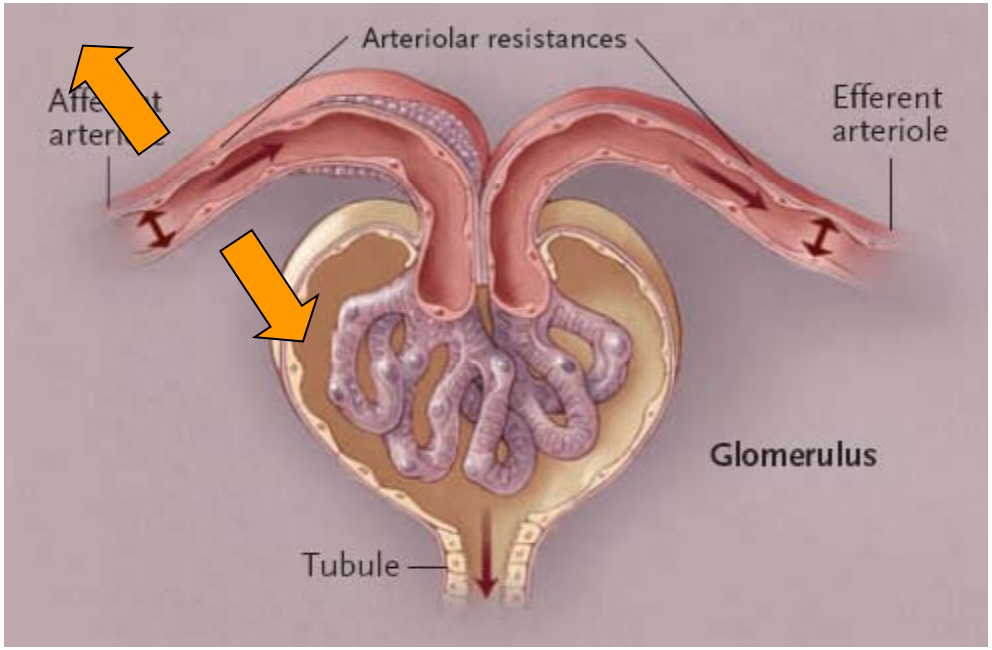
# (Conventional) L-type CCBs

- May act predominantly on the preglomerular (afferent) arterioles, renal vascular bed
- Marked increases in GFR & renal blood flow
- Elevate filtration fraction, a marker for glomerular capillary pressure

# Nifedipine

**Nifedipine acts exclusively on L-type $Ca^{2+}$ channels.**

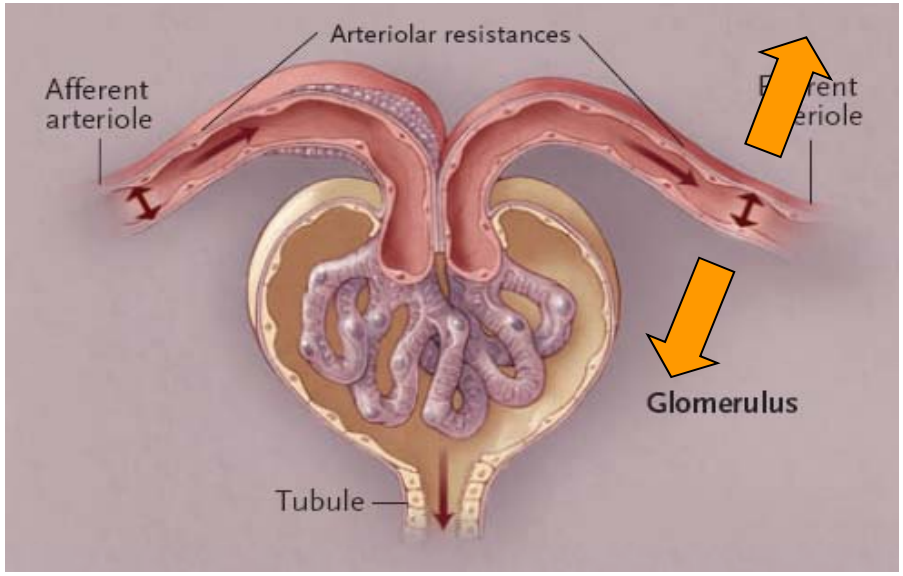
**Nifedipine** predominantly **dilates afferent arterioles** in the distribution of L-type $Ca^{2+}$ channels & suggests that it potentially **causes glomerular hypertension.**



# Recently developed T-type $Ca^{2+}$ channel blockers : mibefradil & efonidipine

Blocking action on **L-type** & **T-type $Ca^{2+}$ channels**

⇨ **vasodilation of afferent & efferent arterioles**




- decrease efferent arteriolar resistance
- increase renal plasma flow (**No significant changes in GFR**)

# Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease

T Fujita[1], K Ando[1], H Nishimura[2], T Ideura[3], G Yasuda[4], M Isshiki[1] and K Takahashi[1] on behalf of the Cilnidipine versus Amlodipine Randomized Trial for Evaluation in Renal Disease (CARTER) Study Investigators

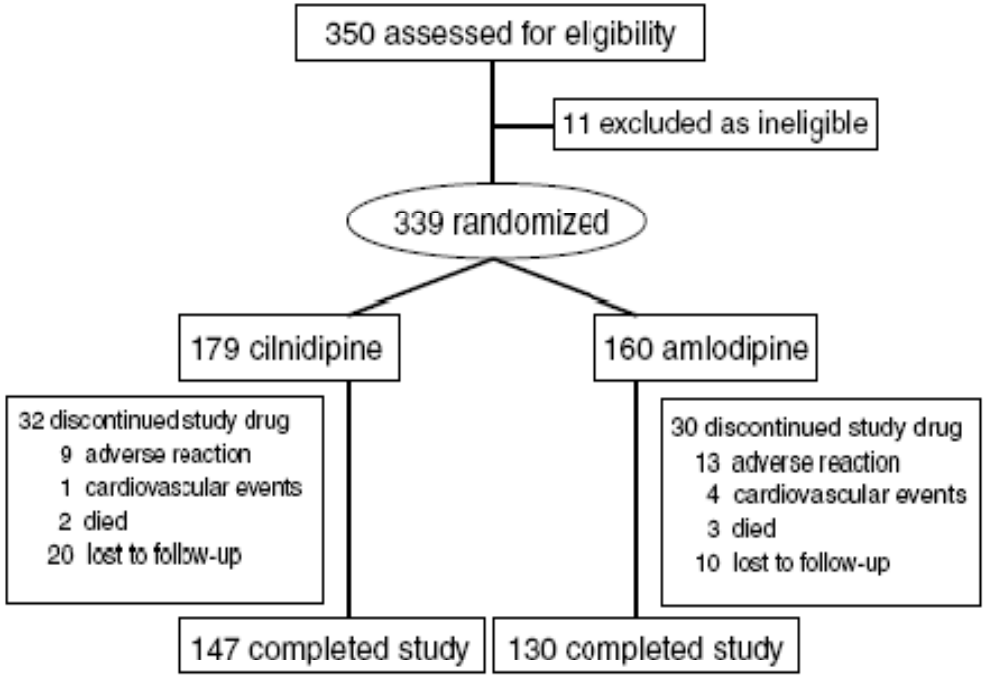
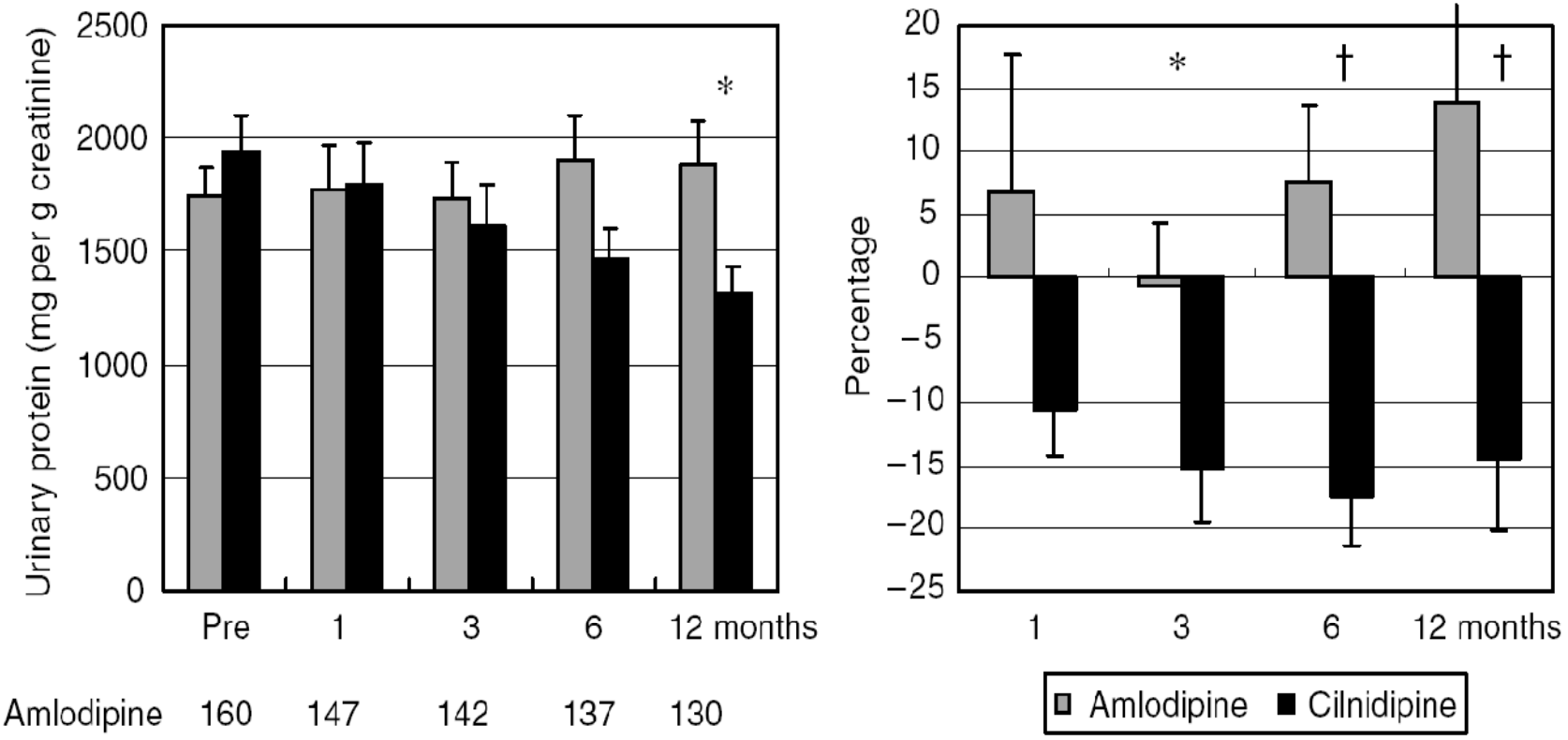



**Figure 1 | Flow of participants throughout the study.**




| | | | | | |
|---|---|---|---|---|---|
| Amlodipine | 160 | 147 | 142 | 137 | 130 |
| Cilnidipine | 179 | 168 | 168 | 160 | 146 |

Changes in urinary protein/Cr ratio during the treatment period

# Comparison between valsartan and valsartan plus cilnidipine in type II diabetics with normo- and microalbuminuria

K Katayama[1,3], S Nomura[1], H Ishikawa[2], T Murata[3], S Koyabu[3] and T Nakano[1]

*[1]First Department of Internal Medicine, Mie University, Mie, Japan; [2]Department of Public Health and Preventive Medicine, Mie University, Mie, Japan and [3]Department of Internal Medicine, Owase General Hospital, Mie, Japan*

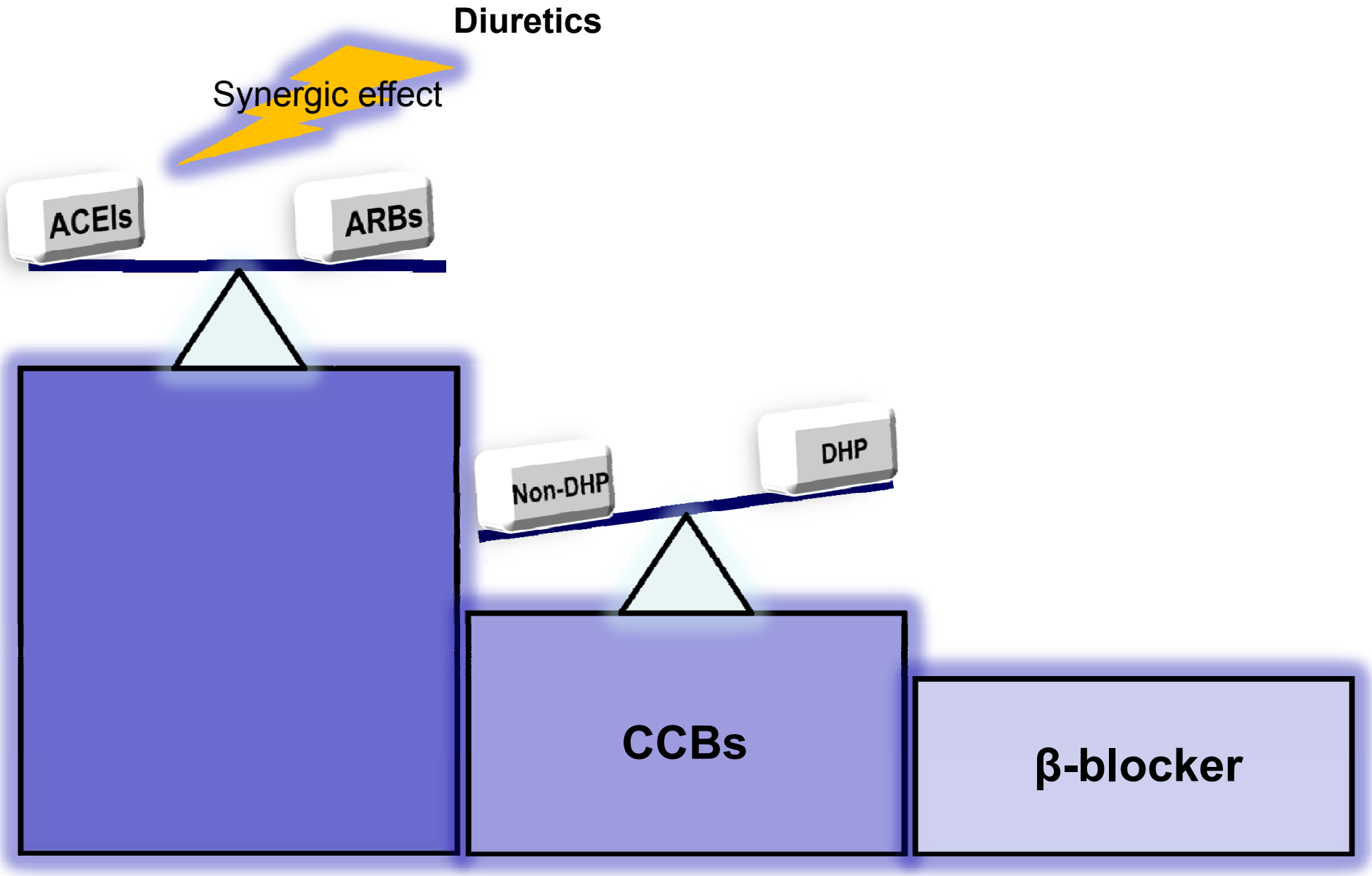
**ARB vs. ARB+Cilnidipine**

**당뇨병성 콩팥질환에서 요단백을 줄인다.**

with a combination therapy consisting of valsartan plus cilnidipine versus monotherapy with valsartan. An open-label, randomized controlled trial was conducted from

trial.[2] However, it is unclear as to whether the renoprotective effect of valsartan alone is sufficient. As a result, to achieve a clinically satisfactory decrease of microalbuminuria, it seems

# Renoprotective Effects



# Recommendations on Hypertension and Antihypertensive Agents in CKD

| Type of Chronic Kidney Disease | BP Target (mmHg) | Preferred Agent with (or without) hypertension | Other Agents to Reduce CVD Risk and Reach BP Target |
|---|---|---|---|
| Diabetic Kidney Disease | <130/80 | ACEI or ARB | Diuretic preferred, then BB or CCB |
| Nondiabetic Kidney Disease with Spot Urine Total Protein-to-Creatinine Ratio ≥200 mg/g | <130/80 | ACEI or ARB | Diuretic preferred, then BB or CCB |
| Nondiabetic Kidney Disease with Spot Urine Total Protein-to-Creatinine Ratio <200 mg/g | <130/80 | None preferred | Diuretic preferred, then ACEI, ARB, BB or CCB |

| CKD stage and GFR | Diuretics |
|---|---|
| Stages 1-3<br>GFR>30 mL/min/1.73 $m^2$ | Thiazide diuretic |
| Stages 4-5<br>GFR<29 mL/min/1.73 $m^2$ | Loop diuretic |

*JNC 7 Report, K/DOQI Clinical Practice Guidelines*

# Take Home Message

- Diabetic, Non-diabetic CKD 모두 목표혈압은 130/80mmHg이하이며 proteinuria가 1gram/day이상인 경우 목표 혈압을 125/75mmHg 까지 낮추도록 노력한다.
- ACEI/ARB를 우선 사용하며 투석직전의 advanced CKD까지 hyperkalemia등 부작용에 주의하며 사용한다.

- 혈압과 단백뇨의 조절이 만족스럽지 못할때 우선 salt restriction을 강조하고 다음으로 diuretics를 우선 추가한다. GFR>30mL/min인경우 thiazide, GFR<30mL/min인경우 loop diuretics를 사용하고 K sparing diuretics는 사용하지 않는다.

- N-DHP CCB가 단백뇨를 감소시키는 보고가 있어 선호된다
- CKD환자의 경우 sympathetic hyperactivity가 흔하기 때문에 금기증이 없는경우 α block 효과가 있는 **β-**blocker가 선호되며 N-type이나 T-type CCB의 사용을 고려할 수 있다.