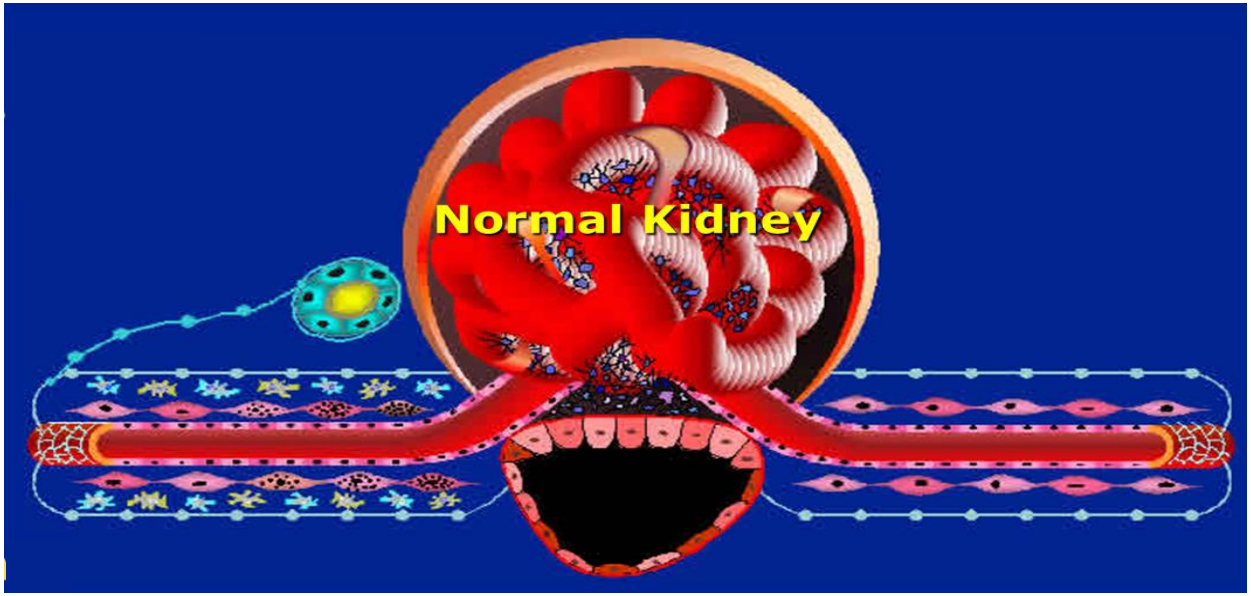
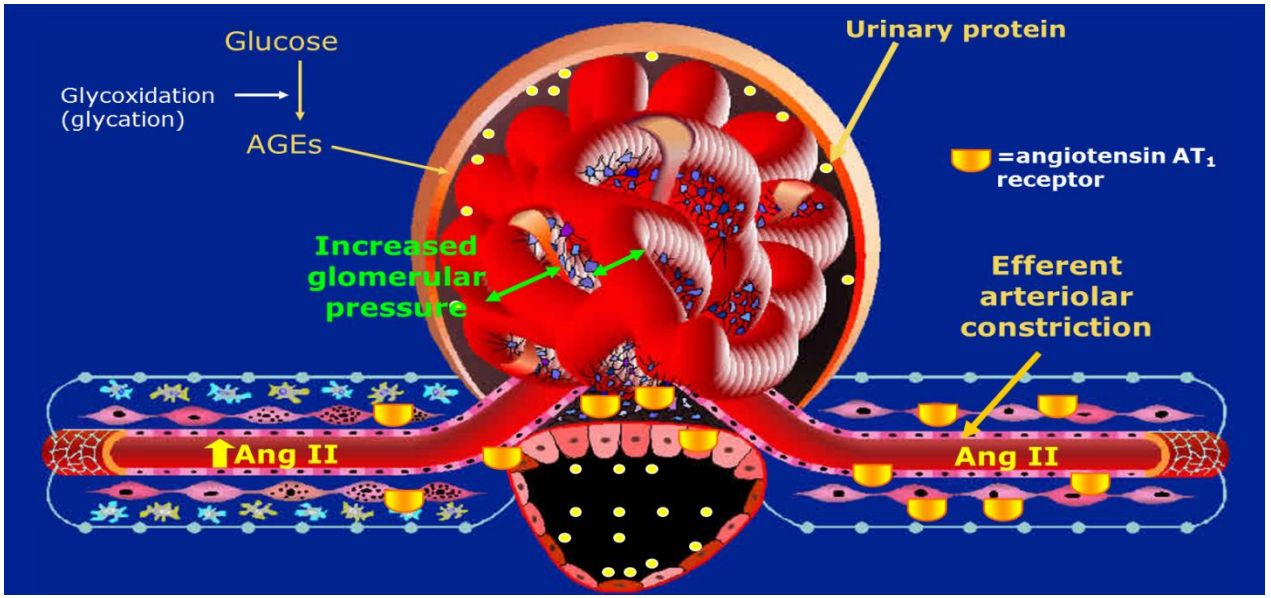
“Hypertension Misattributed Kidney Disease””



Conventional Wisdom: Hypertension Causes Chronic Kidney Disease
Hypertension may be an initial manifestation of primary kidney injury
Treatment of Hypertension Ameliorates Progression of CKD



Specificity of APOL1 Disease Associations

Robust Associations:

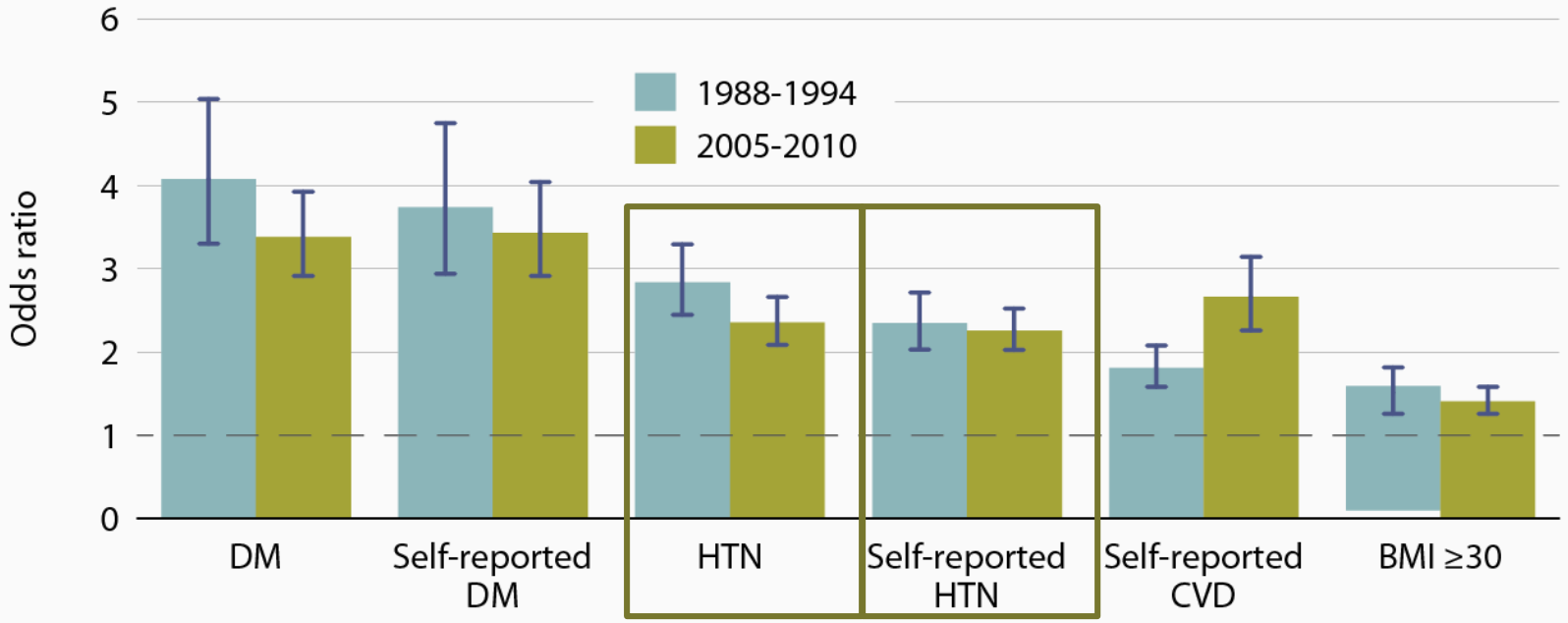
- **Hypertension with Chronic Kidney Disease in African Ancestry population (Hypertension "Misattributed" Chronic Kidney Disease)**
- **FSGS – primary non-monogenic [especially Collapsing Glomerular Nephropathy (CGN)]**
- **HIV Associated Nephropathy (HIVAN)**
- **Progression of SLE Nephropathy**
- **Sickle Cell Nephropathy**

Weak or no associations:

- **Diabetic Nephropathy – Shlush et al and 2010 and multiple studies**
- **IgA Nephropathy (Patera et al. JASN 2012)**

Adjusted odds ratios of CKD in NHANES participants, by risk factor

Figure 1.4 (volume 1)



NHANES III (1988-1994) & 2005-2010 participants age 20& older. Adj: age, gender, & race.

Kidney International (2012)

Hypertension-misattributed kidney disease in African Americans

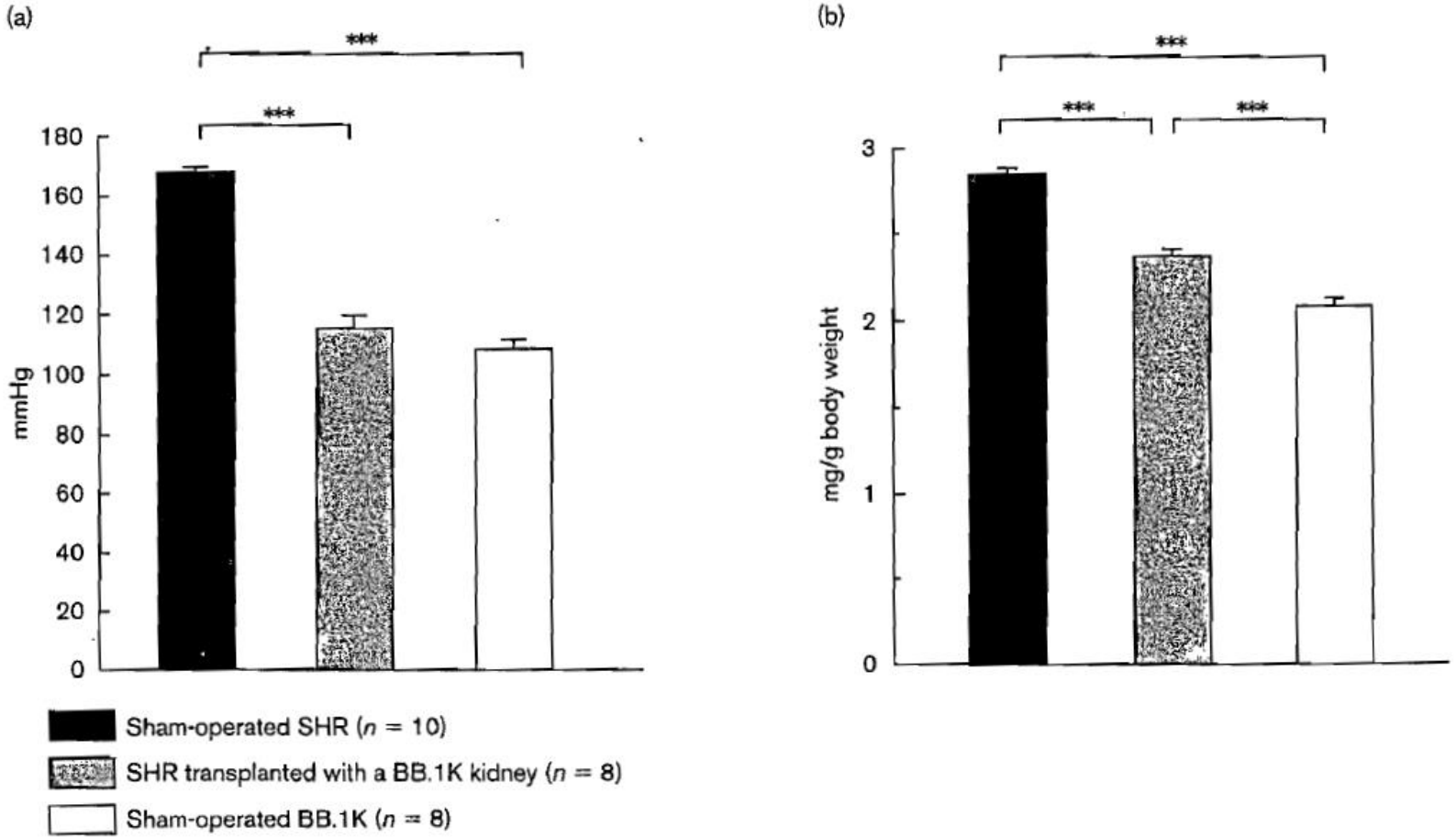
Karl L. Skorecki[1] and Walter G. Wasser[2]

Three years of population genetics research suggests that:

1) **Common genetic variants markedly increase the risk for Chronic Kidney Disease (CKD)**
2) **In turn hypertension is an early consequence cause rather than cause of CKD in at least a subset of African ancestry individuals**
3) **Not surprising that antihypertensive therapy does not slow progression of CKD to ESKD (AASK study and Lipkowitz et al KI 2012)**
4) **What about other global populations?**

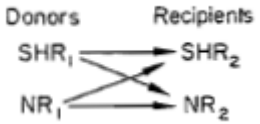
Long-term arterial pressure in spontaneously hypertensive rats is set by the kidney

Olaf Grisk[a], Ingrid Klöting[b], Jürgen Exner[a], Simone Spiess[a], Ralf Schmidt[a], Dirk Junghans[c], Gerd Lorenz[c] and Rainer Rettig[a]



Clinical Science and Molecular Medicine (1974) **47**, 435–448.

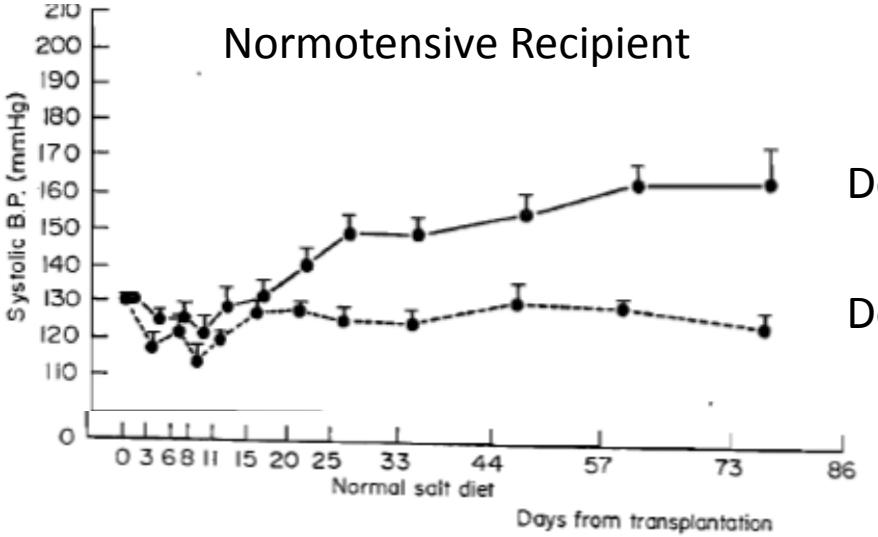
BLOOD PRESSURE CHANGES PRODUCED BY KIDNEY CROSS-TRANSPLANTATION BETWEEN SPONTANEOUSLY HYPERTENSIVE RATS AND NORMOTENSIVE RATS



G. BIANCHI, U. FOX, G. F. DI FRANCESCO,
A. M. GIOVANETTI AND D. PAGETTI

Istituto di Clinica Medica I e Semeiotica Chirurgica dell'Università di Milano, Laboratori di Farmacologia della Lepetit S.p.A., Milano, Italy

Normotensive Recipient



Donor kidney SHR

Donor kidney normotensive

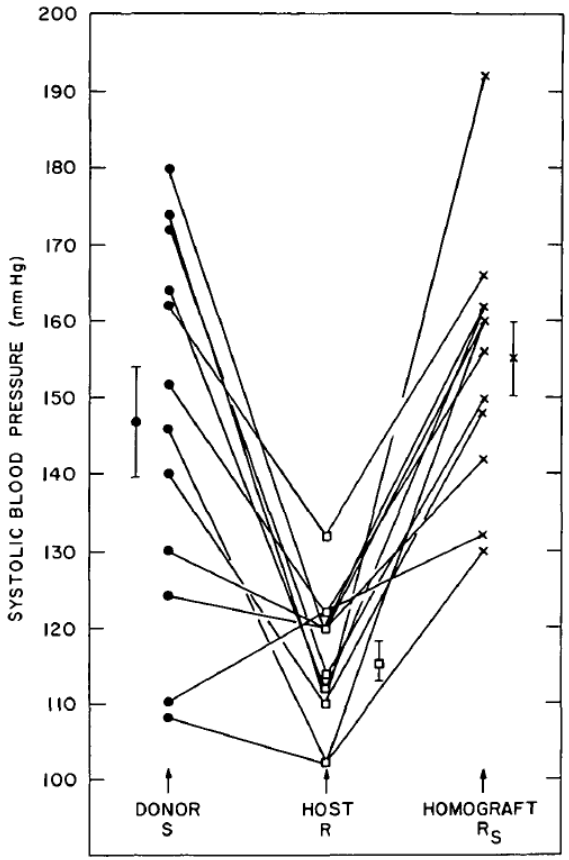
Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

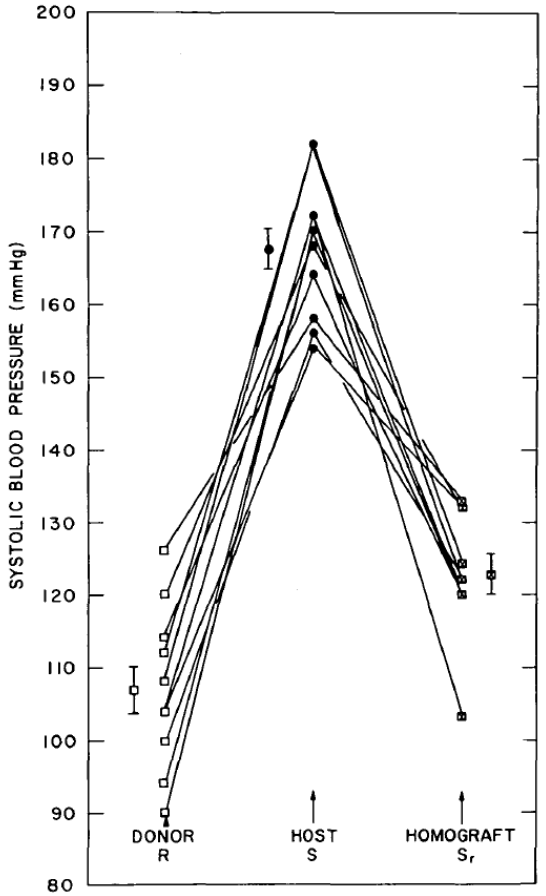
American Heart Association

Primary role of renal homografts in setting chronic blood pressure levels in rats.

L K Dahl and M Heine

Circ Res. 1975;36:692-696





Walker WG et al JAMA 268:3085-3091 1992

Renal Function Change in Hypertensive Members of the Multiple Risk Factor Intervention Trial

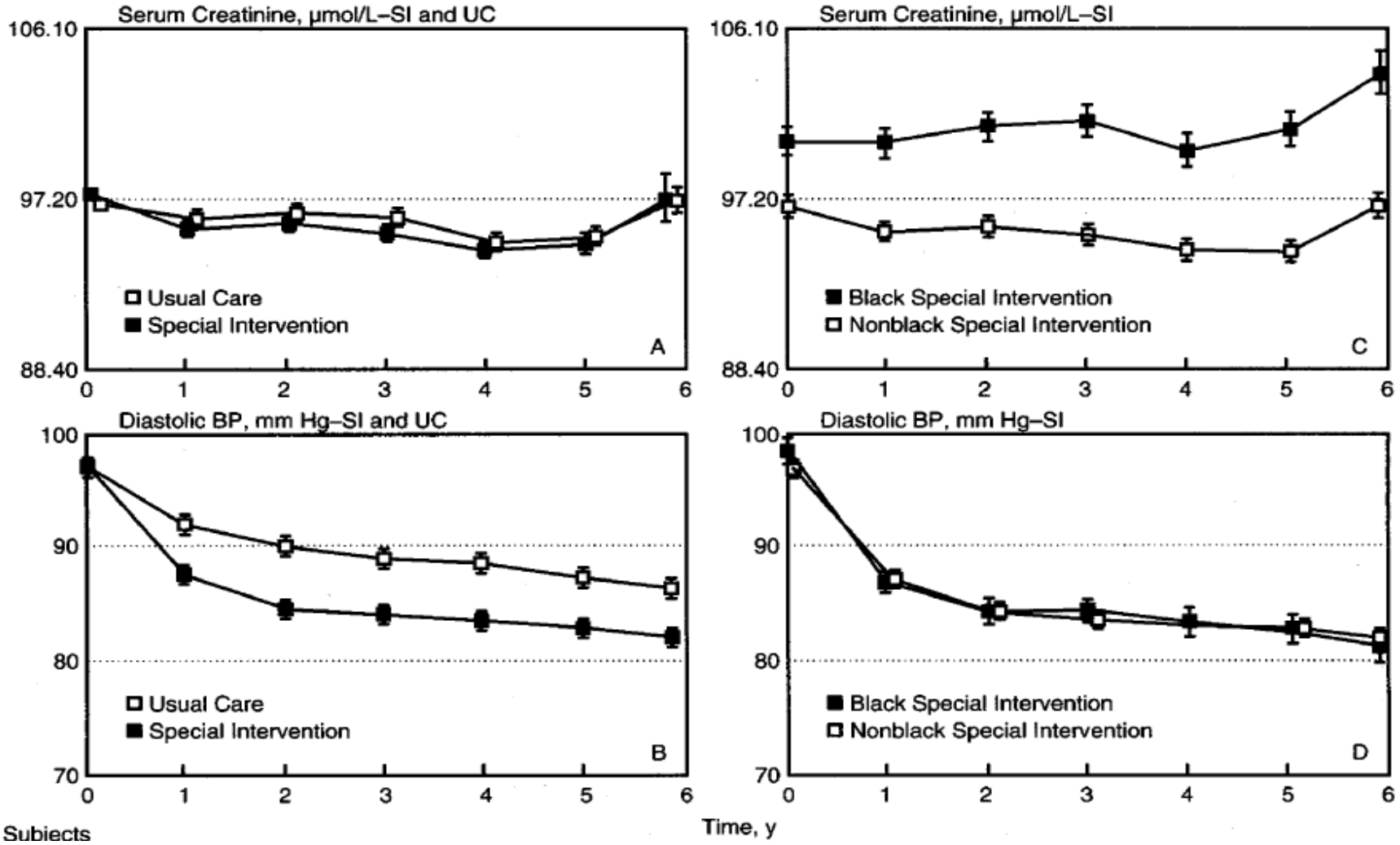
Racial and Treatment Effects

Table 1.—Serum Creatinine Level at Baseline, Change After 6 Years of Follow-up, and Reciprocal Creatinine Slope for MRFIT SI and UC Hypertensive Participants* by Level of Systolic Blood Pressure at Baseline

Baseline Systolic Blood Pressure, mm Hg	No.	Average Baseline Creatinine, mg/dL (μmol/L)	Change in Creatinine, mg/dL (μmol/L) (6 y–Baseline), Mean±SE	Reciprocal Creatinine Slope, $(mg/dL)^{-1}$ $(Year)^{-1}$, Mean±SE
<140	2495	1.11 (98.1)	−0.015 (1.3)±0.003 (0.26)	+0.0018±0.0006
140-159	2485	1.09 (96.4)	+0.006 (0.5)±0.003 (0.26)	0.0009±0.0006
>160	543	1.10 (97.2)	+0.062 (5.5)±0.030 (2.60)	−0.0035±0.0012
P value for difference among groups			<.001	<.001

Walker WG et al JAMA 268:3085-3091 1992

Renal Function Change in Hypertensive Members of the Multiple Risk Factor Intervention Trial

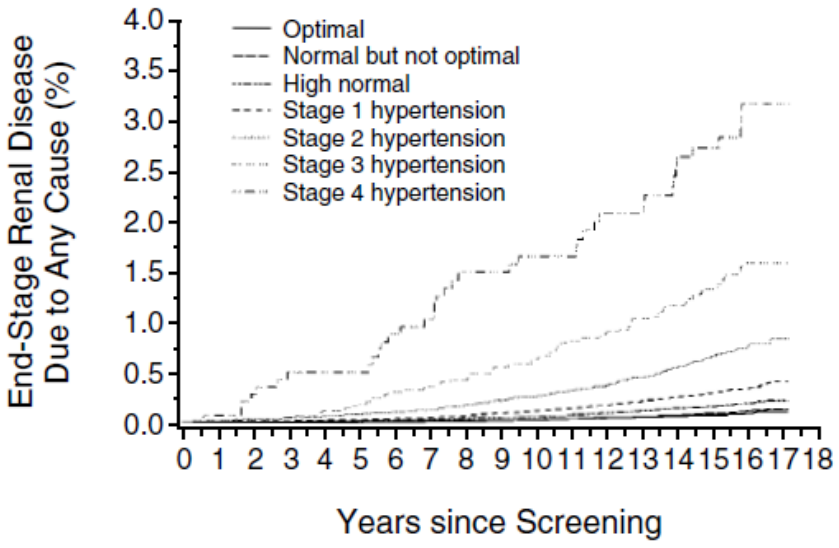


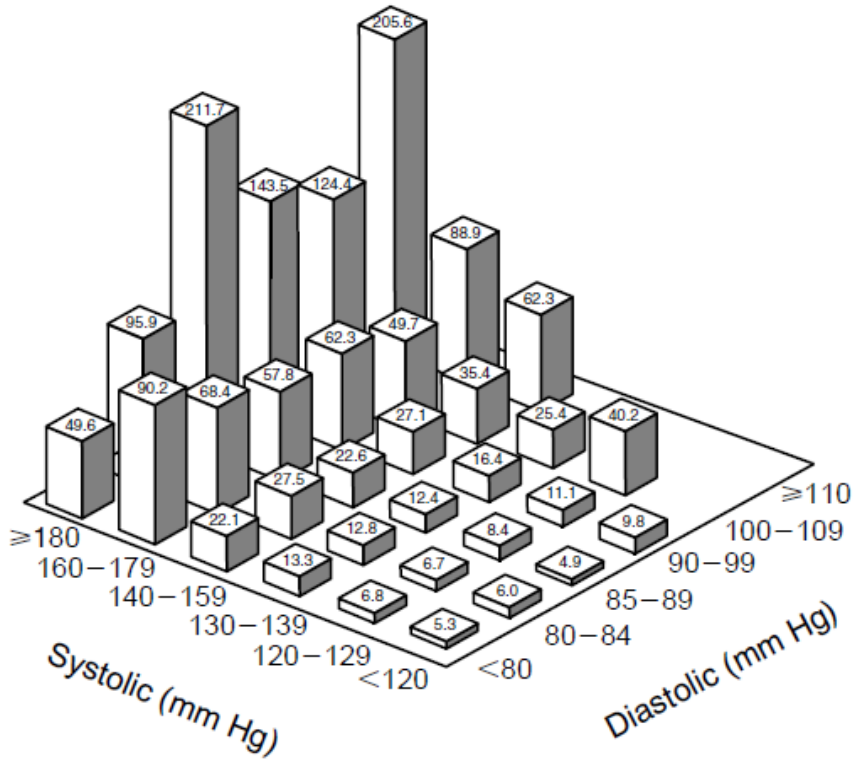
ers of Subjects

(N Engl J Med 1996;334:13-8.)

BLOOD PRESSURE AND END-STAGE RENAL DISEASE IN MEN

MICHAEL J. KLAG, M.D., M.P.H., PAUL K. WHELTON, M.D., BRYAN L. RANDALL, M.S., JAMES D. NEATON, PH.D., FREDERICK L. BRANCATI, M.D., M.H.S., CHARLES E. FORD, PH.D., NEIL B. SHULMAN, M.D., AND JEREMIAH STAMLER, M.D.



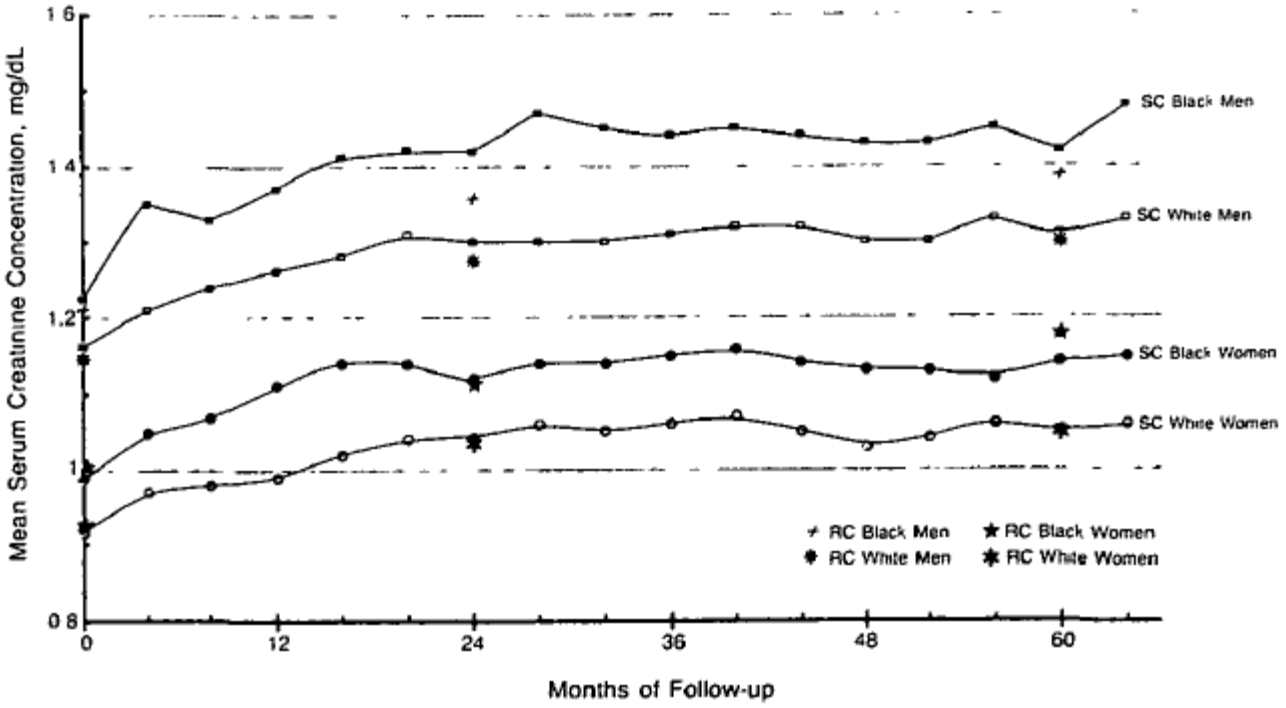


Shulman et al 1989

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group.



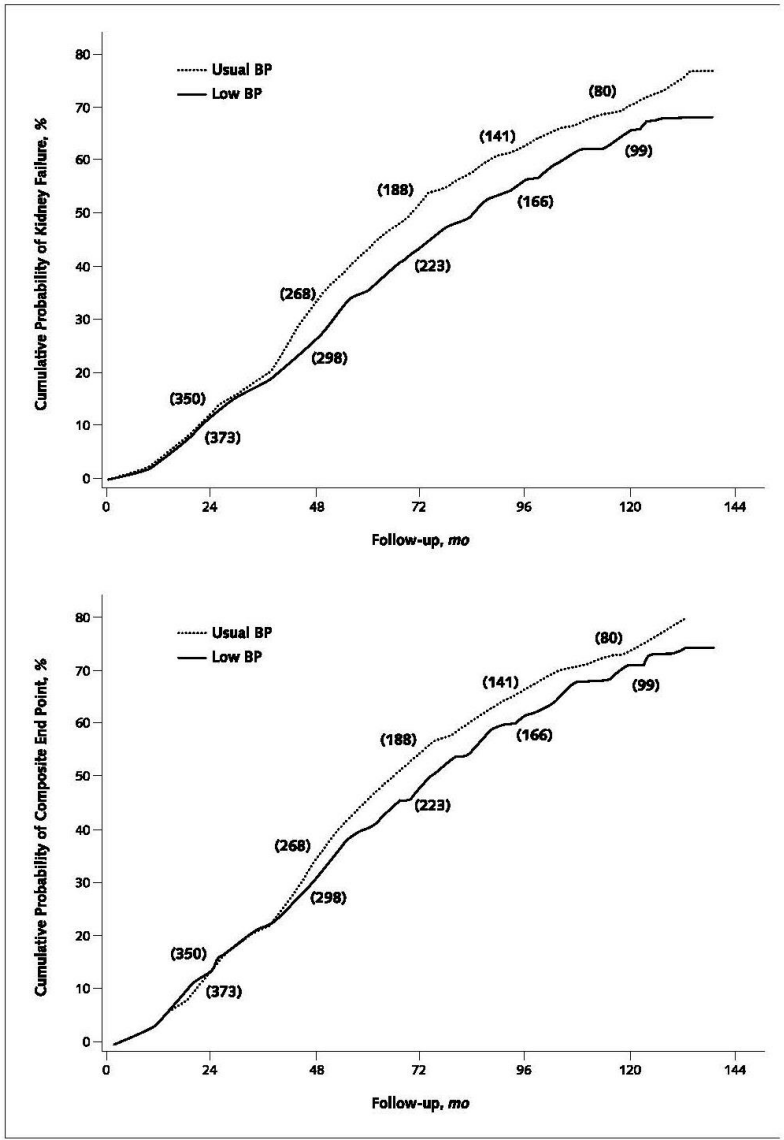
Stated Conclusions from MRFIT

"….Effective blood pressure control was associated with stable or improving renal function in nonblacks but not in blacks. These findings emphasize the importance of blood pressure control to maintain adequate renal function in hypertensive white men and raise important questions about the relationship of pressure reduction and renal function change in blacks……"

The Effect of a Lower Target Blood Pressure on the Progression of Kidney Disease: Long-Term Follow-up of the Modification of Diet in Renal Disease Study

Mark J. Sarnak, MD; Tom Greene, PhD; Xuelei Wang, MS; Gerald Beck, PhD; John W. Kusek, PhD; Allan J. Collins, MD; and Andrew S. Levey, MD

Mark J et al. Ann Intern Med. 142:342-351,2005



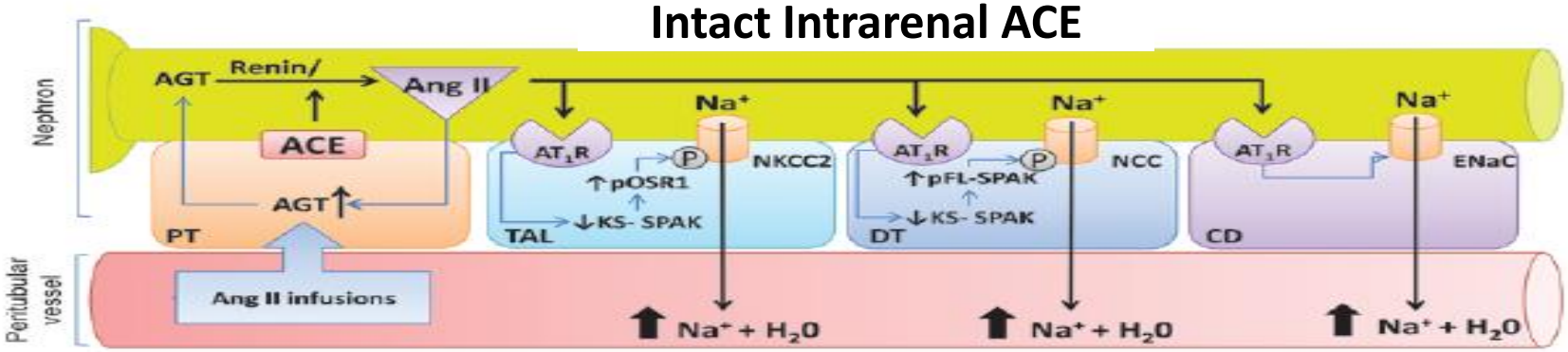
Critique of Inferences from Modification of Diet in Renal Disease study

Tobe S. et al. Open Medicine 2012;6(4)e130 Clinical Practice Tobe et al.

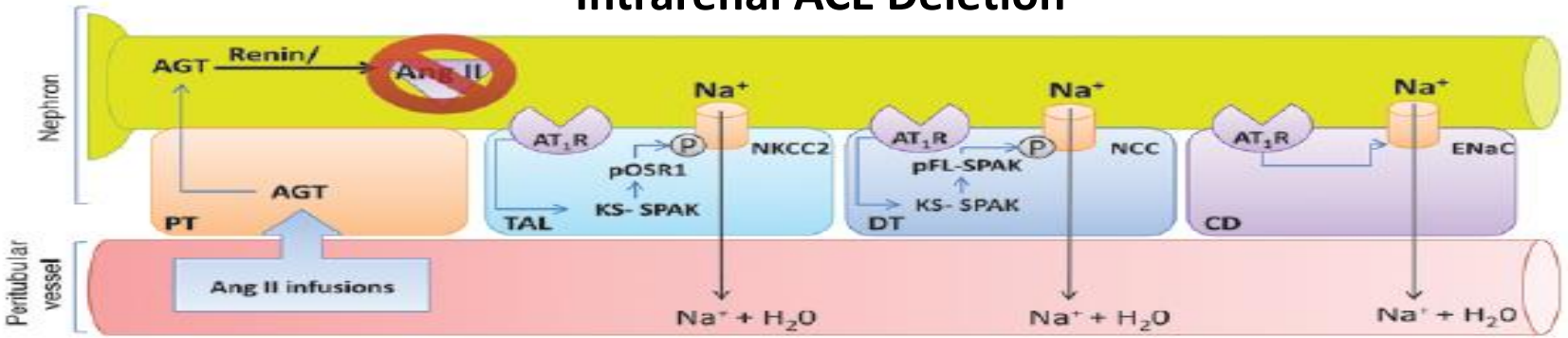
- **Not trial but only long-term non-trial follow up demonstrated that individuals who had been randomly assigned to the group with the low BP target had a lower hazard of kidney failure, ad difference not apparent during the trial.**
- **No information about the therapy, BP targets, BP achieved for each group after completion of the trial.**
- **Proteinuria interaction was a post-hoc subgroup analysis and that randomization was not stratified on the basis of pre-specified level of proteinuria.**
- **There was no *a priori* power calculations done for the subgroups and no adjustment was made for multiple testing.**
- **Use of ACE inhibitors was higher in the patients assigned to the low BP target, and this may very well have influenced outcomes.**

Inhibition of intra-renal ACE may be crucial to slowing of CKD progression at least in proteinuric (hypertensive) patients

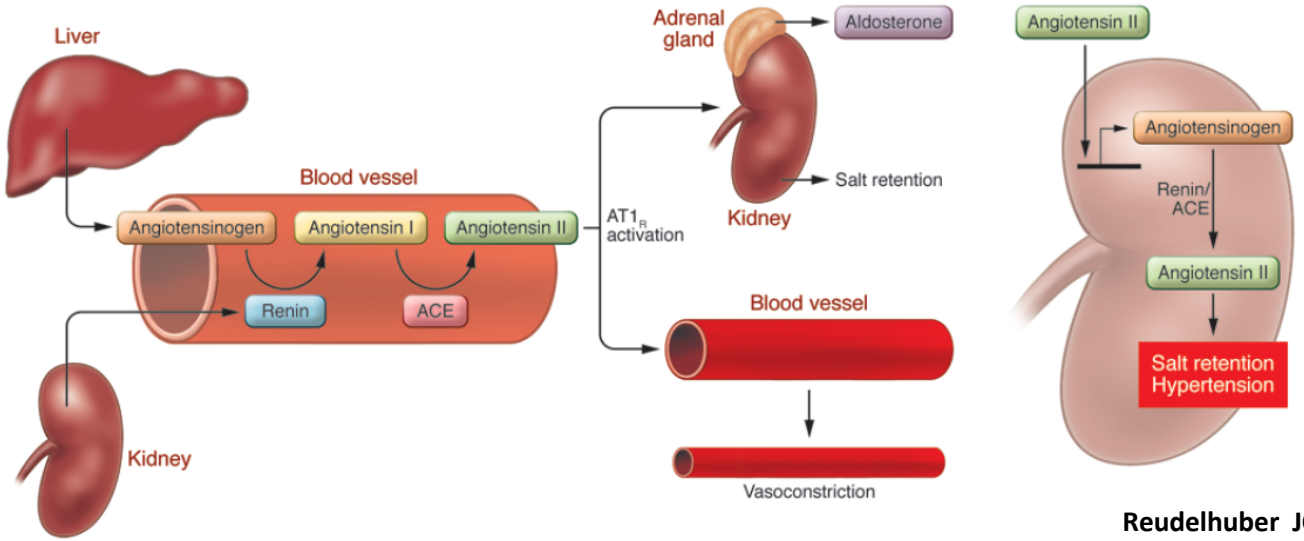
Intact Intrarenal ACE



Intrarenal ACE Deletion



Gonzalez-Villalobos R et al JCI 2013



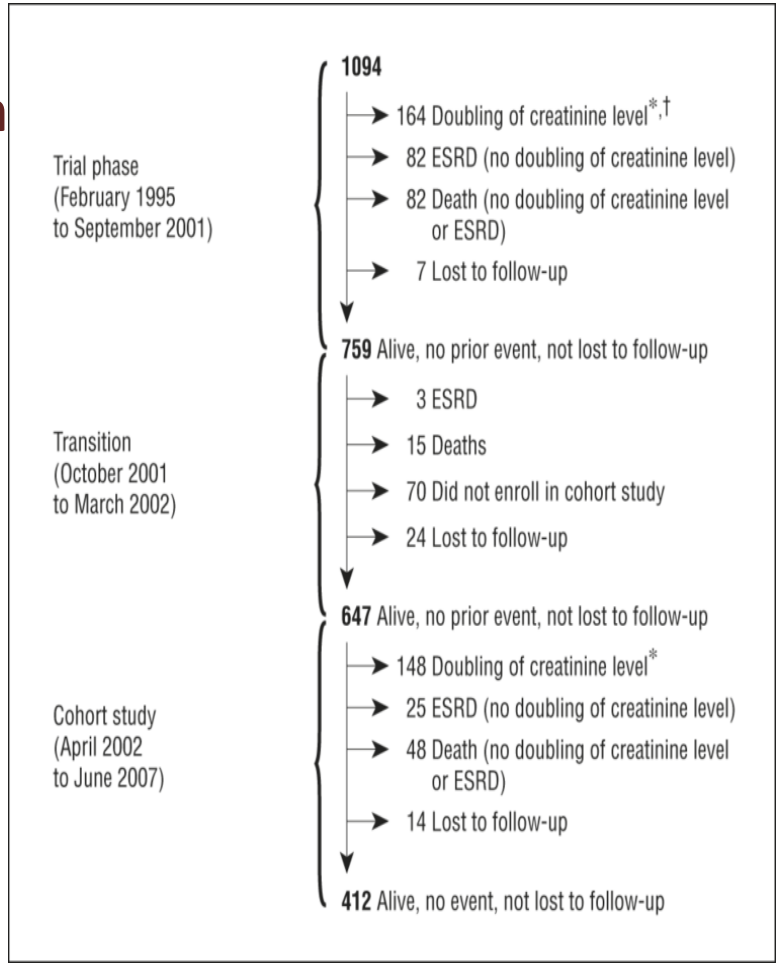
Reudelhuber JCI 2013 Commentary

Stated Conclusions from MRFIT

"….Effective blood pressure control was associated with stable or improving renal function in nonblacks but not in blacks. These findings emphasize the importance of blood pressure control to maintain adequate renal function in hypertensive white men and raise important questions about the relationship of pressure reduction and renal function change in blacks……"

African American Study of Kidney Disease (AASK)-Clinical Trial

- AASK Trial Phase → 3 x 2 factoral design
- Anti-hypertensive drug regimens:
  - ACEI (ramipril)
  - dihydropyridine CCB (amlodipine)
  - beta-blocker (metoprolol)
- The BP control levels:
  - usual goal (MAP 102 - 107 mmHg)
  - lower goal (MAP 92 mmHg)
- Cohort phase



African American Study of Kidney Disease (AASK)-Clinical Trial

OUTCOME MEASURES

- **Primary outcome → rate of change in renal function as measured by GFR, assessed by**

  I^{125} -iothalamate clearance

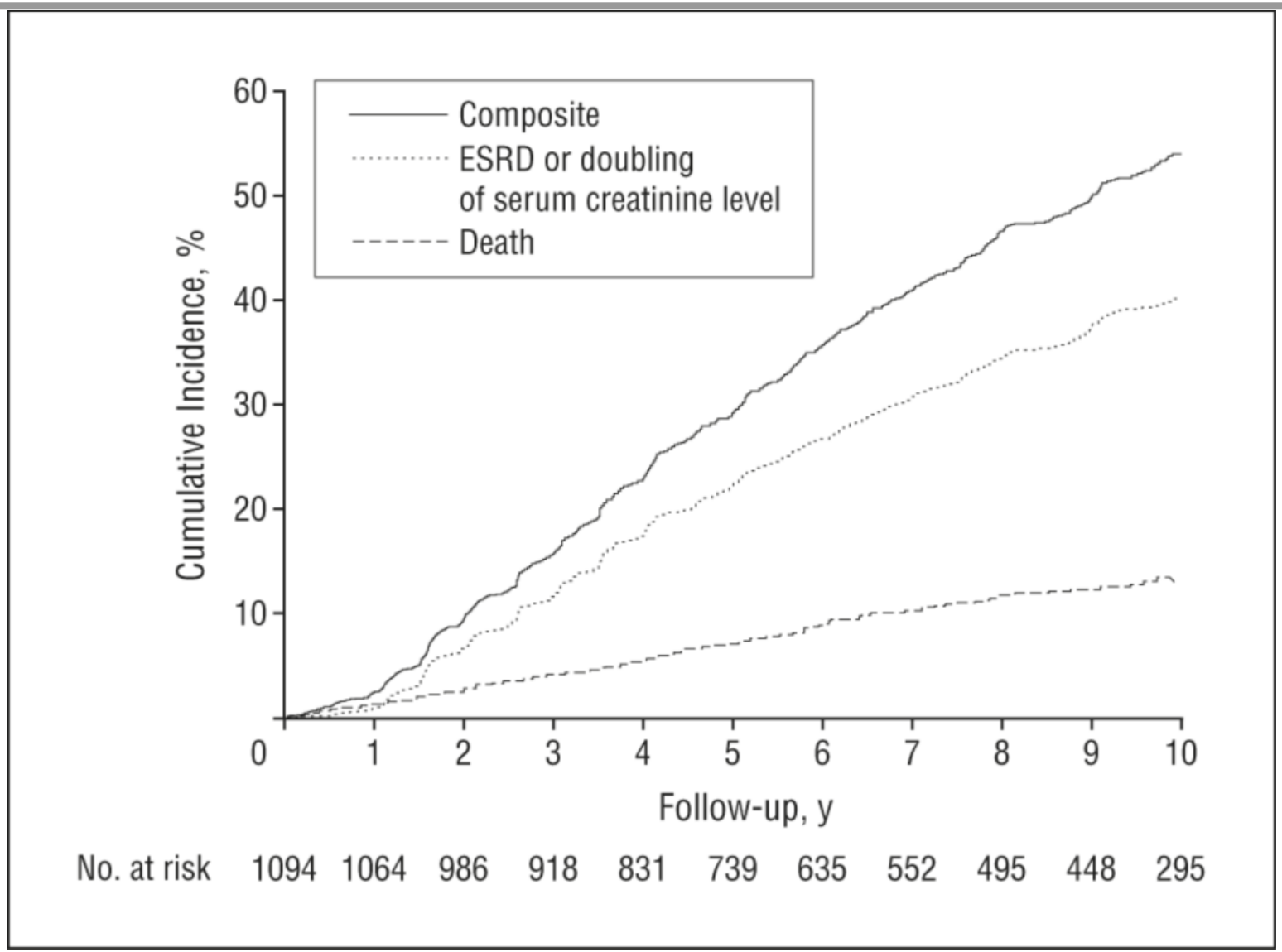
- **Secondary outcome → composite including the following events:**

  (*1*) reduction in GFR by 50%,

  (*2*) end-stage renal disease,

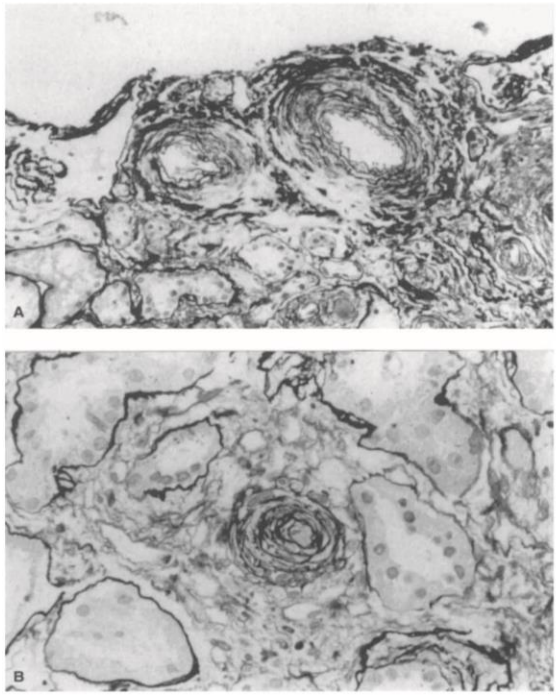
  (*3*) death

Cumulative Incidence of Renal Outcomes

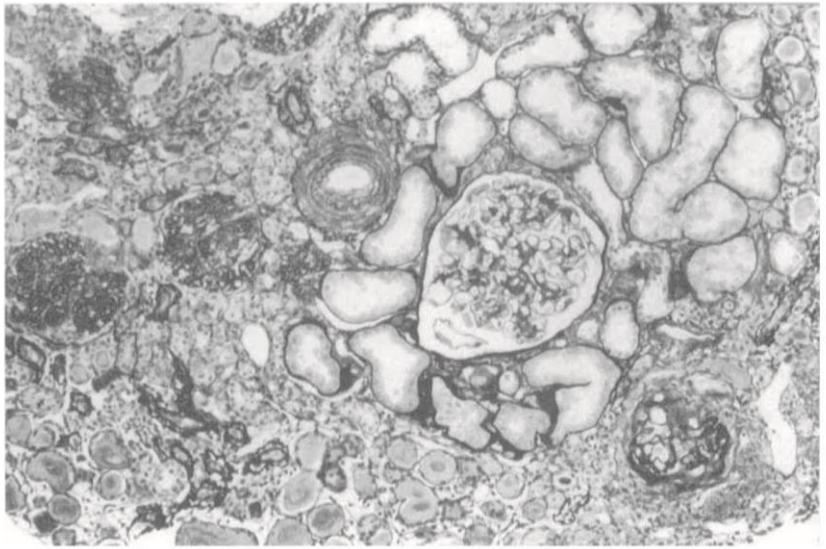


Arch Intern Med. 2008;168(8):832-839.
doi:10.1001/archinte.168.8.832

Arterial (A) and arteriolar (B) lesions



Severe global glomerulosclerosis and patchy interstitial fibrosis with tubular atrophy



Biopsy Lesions

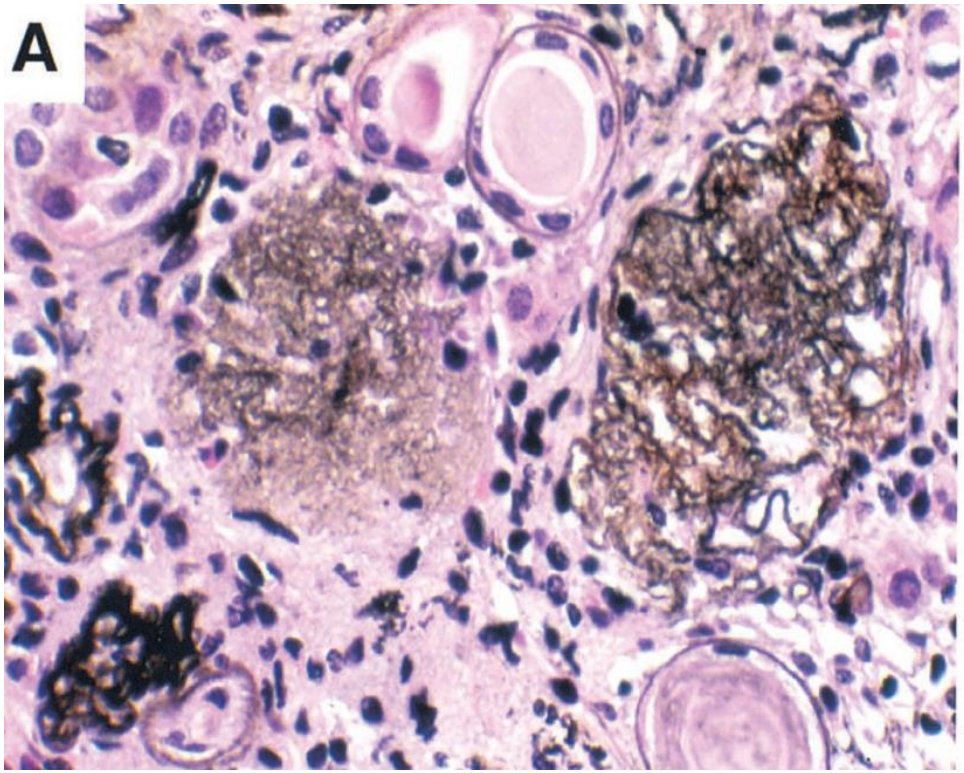
	Severity of vascular lesion			
	Mild	Moderate	Severe	Total
Arteriolosclerosis ± arteriosclerosis	10	15	8	33
Arteriolosclerosis ± arteriosclerosis + segmental glomerulosclerosis	3	1	1	5
Additional lesions				
Global glomerulosclerosis				35
Segmental glomerulosclerosis				5
End stage kidney				1
Mesangiopathic glomerulonephritis				1
GBM thickening				1
Cholesterol embolus				2

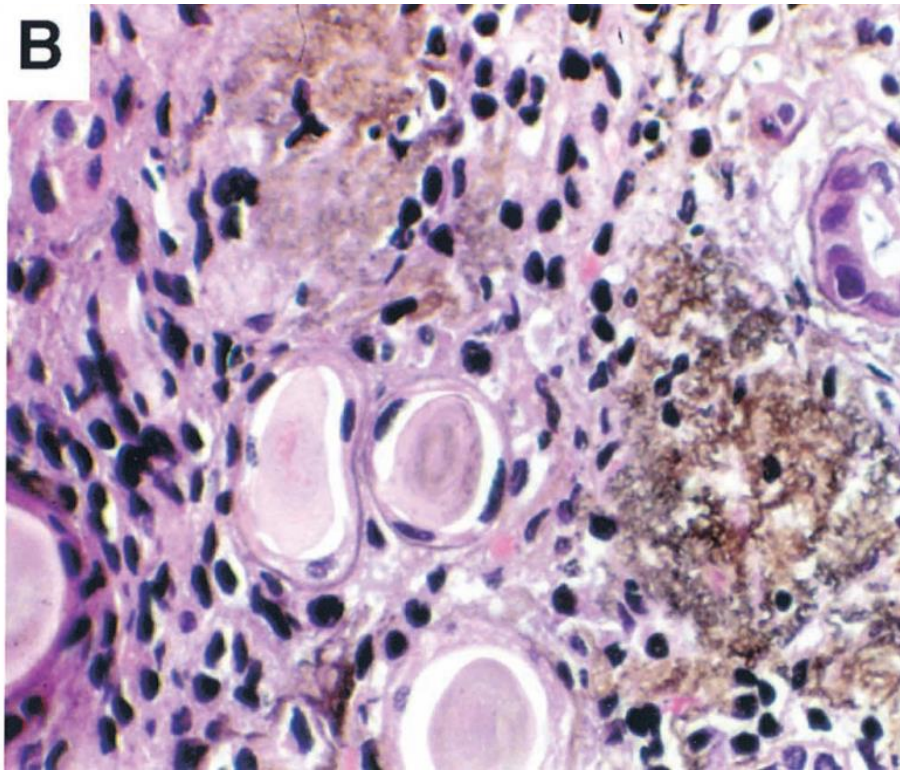
Abbreviation is: GBM, glomerular basement membrane

y International, 51: 244-252, 1997

Hypertensive nephrosclerosis in African Americans versus Caucasians

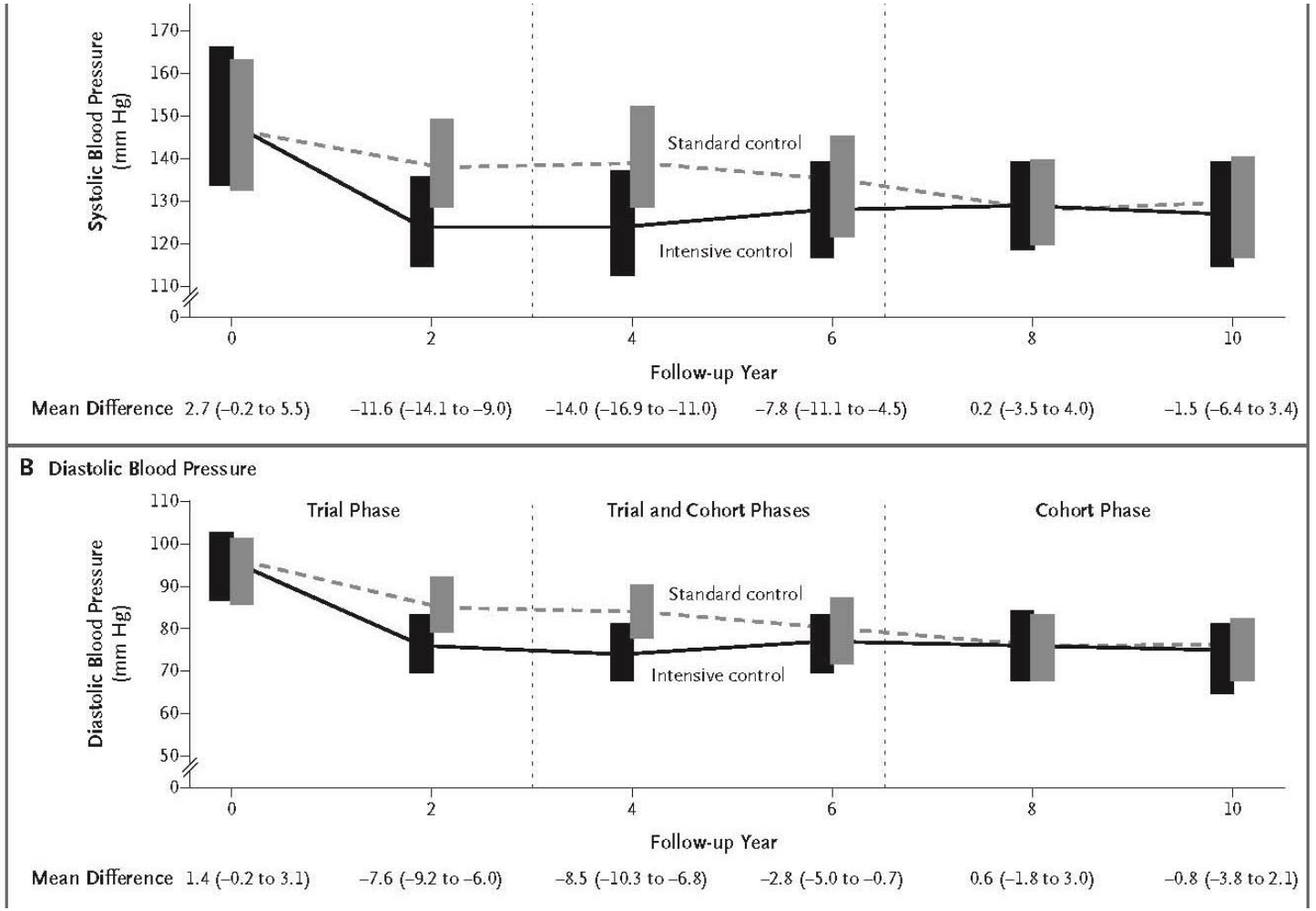
Marcontoni et al KI 2002





“Disappearing Glomeruli”

Blood-Pressure Levels in Patients with Chronic Kidney Disease



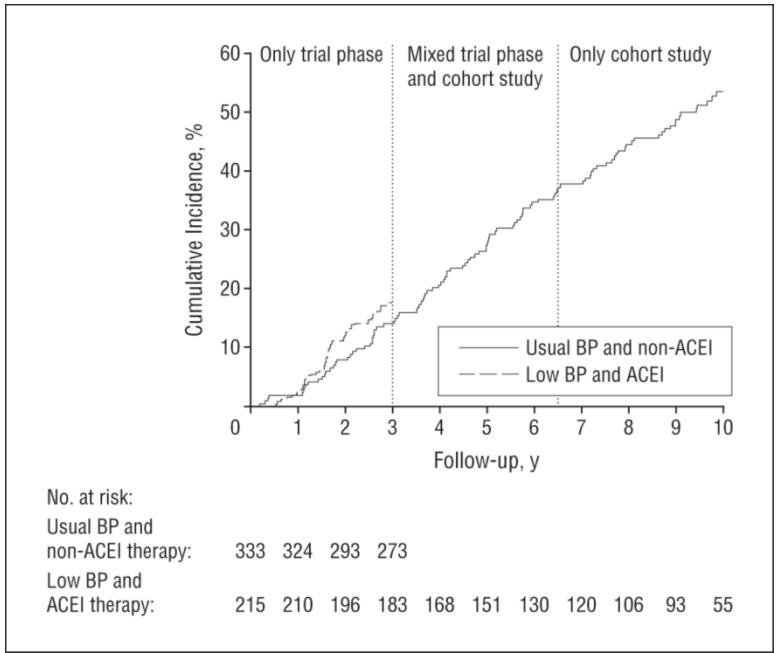
ACEI Usage

Appel LJ et al. N Engl J Med 363:918-929, 2010

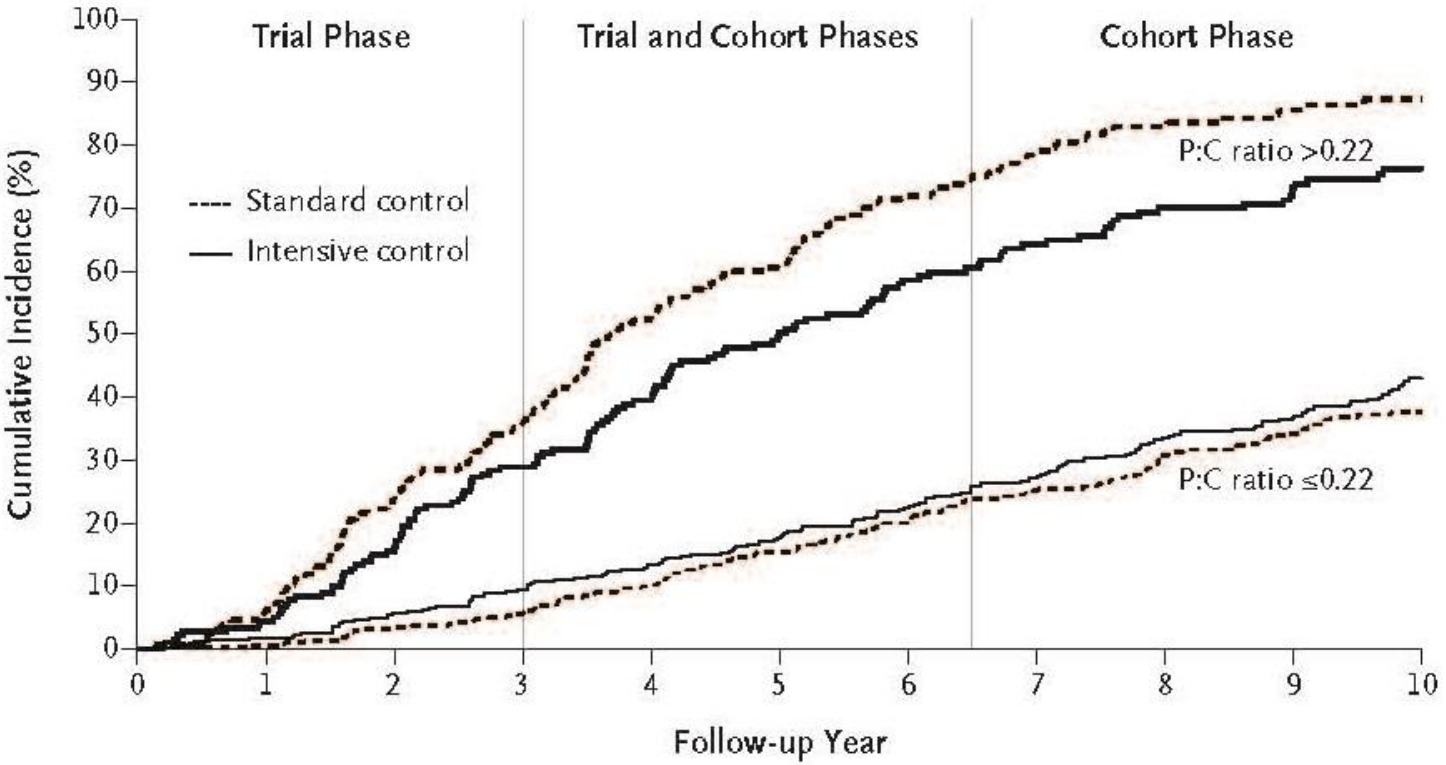
Specifically in the Trial Phase:

- Ramipril reduced the risk of clinical renal events (50% or 25 cc/min/1.73 m2 decline in GFR,ESKD or death) by 48% compared with the calcium channel blocker, and by 22% compared with the beta blocker
- A low BP goal conferred no additional benefit over a conventional goal

ACEI particularly slowed CKD progression in patients with protein creatinine ratio greater than 0.22.



Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

Appel LJ et al. N Engl J Med 363:918-929, 2010

MAJOR CLINICAL EPIDEMIOLOGY FINDING

- In both trial and cohort phases, there was no significant between-group difference in the risk of the primary outcome (hazard ratio in the intensive-control group, 0.91; P = 0.27).

- However, the effects differed according to the baseline level of proteinuria (P = 0.02 for interaction), with a potential benefit in patients with a protein-to-creatinine ratio of > 0.22 (hazard ratio, 0.73; P = 0.01).

Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans

AASK Trial and Cohort (1094)

+ WKFU Controls (970 no clinically overt kidney disease, 410 queried about BP 490 with hypertension without clinical kidney disease

Lipkowitz et al. KI 2013

Chromosome 22 genotype results

Gene	SNP	C22 position	Risk allele	Risk allele fraction, cases	Risk allele fraction, controls	*P*-value, recessive model	OR, recessive model	95% CI
APOL1	rs16996616	36661891	A	0.09	0.07	3.18E-01	2.1	(0.49, 9.04)
*APOL1*G1	rs73885319	36661906	G	0.28	0.21	2.97E-06	3.47	(2.06, 5.85)
*APOL1*G1	rs60910145	36662034	G	0.28	0.20	2.77E-06	3.54	(2.09, 6.00)
*APOL1*G2	rs71785313	36662051	C	0.16	0.13	1.46E-01	1.72	(0.83, 3.57)
APOL1G1G2				0.44	0.34	1.39E-08	2.57	(1.85, 3.55)

APOL1 SNP	*P*-value, cases/ controls	Odds ratio	95% CI
rs16996616	2.44E-01	2.49	(0.54, 11.55)
rs73885319 (G1)	1.87E-04	2.78	(1.62, 4.76)
rs60910145 (G1)	1.69E-04	2.83	(1.65, 4.88)
rs71785313 (G2)	2.85E-01	1.50	(0.72, 3.14)

Table 6 | Effects of *APOL1*, blood pressure target, and medication class on rate of decline of GFR in the AASK Trial

		Slope of iothalamate GFR			
Medication class	BP arm	*APOL1* non-risk	*APOL1* risk	*P*-value	Heterogeneity *P*-value
ACE inhibitor	Low	−1.47 ± 0.22	−2.68 ± 0.40	0.0202	
	Usual	−1.50 ± 0.23	−2.84 ± 0.41	0.0023	
β-Blocker	Low	−1.59 ± 0.24	−2.22 ± 0.41	0.3776	
	Usual	−2.01 ± 0.24	−2.70 ± 0.40	0.1736	
Calcium channel blocker	Low	−2.05 ± 0.34	−2.72 ± 0.60	0.2542	
	Usual	−2.18 ± 0.33	−3.17 ± 0.62	0.2050	
Meta-analysis				4.29E-05	0.6257

Heterogeneity P-values comparing usual and low BP treatment arms on the basis of APOL1 risk and nonrisk were nonsignificant, revealing that the effect of the APOL1 risk variants on BP effect did not differ by treatment arm (heterogeneity P=0.6240 systolic BP; P=0.3721 diastolic BP; P=0.4447 mean BP).

What about Hypertension without overt (non-biopsy) manifestations of CKD?

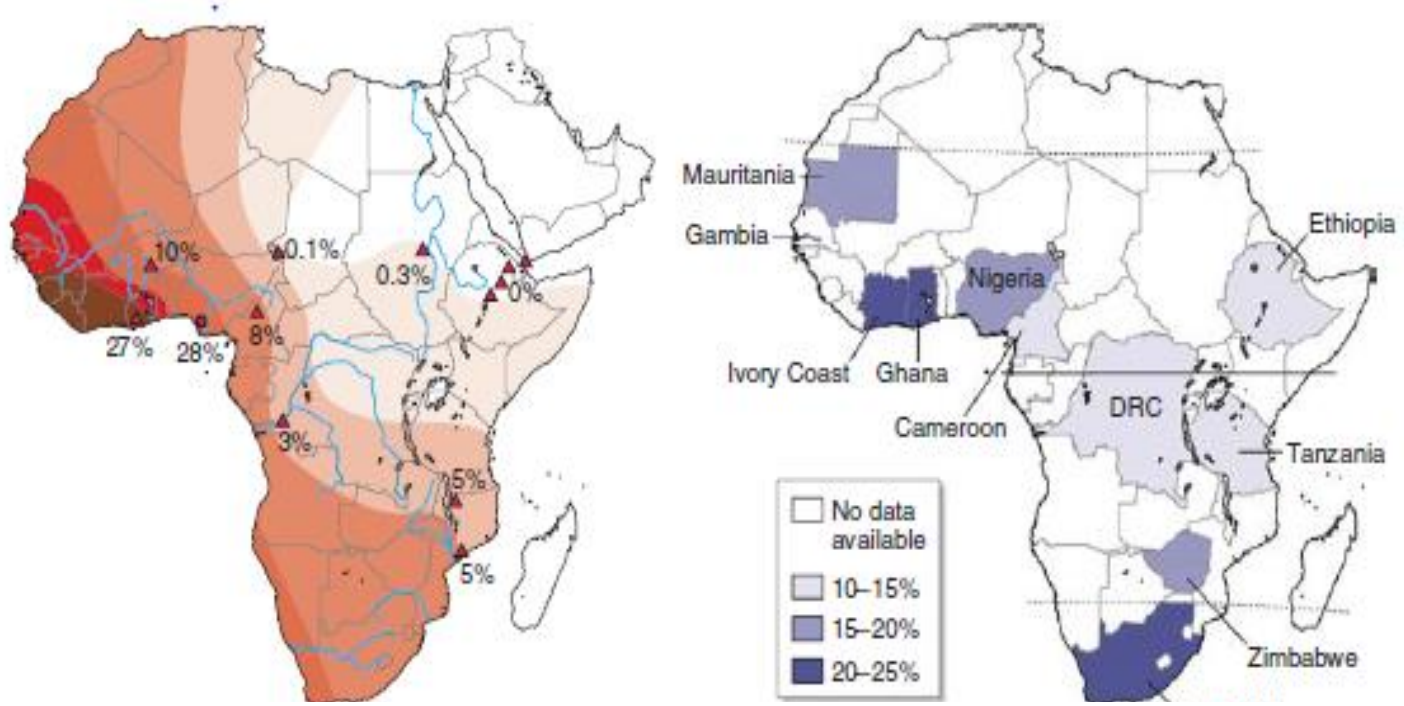
- Of the controls, 410 were questioned about the presence of hypertension, and of these 41.7% (171) reportedly were hypertensive based on physician report or the use of antihypertensive medications.
- No association was found with APOL1 Genotype

but

- Underpowered and ascertainment imprecise

Hypertension-misattributed kidney disease

Study in Africa:



Distribution of APOL1 Risk Alleles and Hypertension in Continental African Nations

Conclusions

- Progressive kidney disease attributed to hypertensive nephrosclerosis in AASK participants, particularly in those with higher baseline levels of proteinuria, appear to reside in this disease spectrum of APOL1 association.
- African Americans with hypertension-attributed CKD have poor BP response to many BP agents and rapid CKD progression.

- In AASK trial subjects with normal urine protein-creatinine excretion fail to respond to intensive BP reduction. (AASK patients with elevated protein-creatinine ratio did show some response to ACE-I).

- African Americans show different histopathology than Europeans (showing more global glomerulosclerosis)--indicates a different disease.

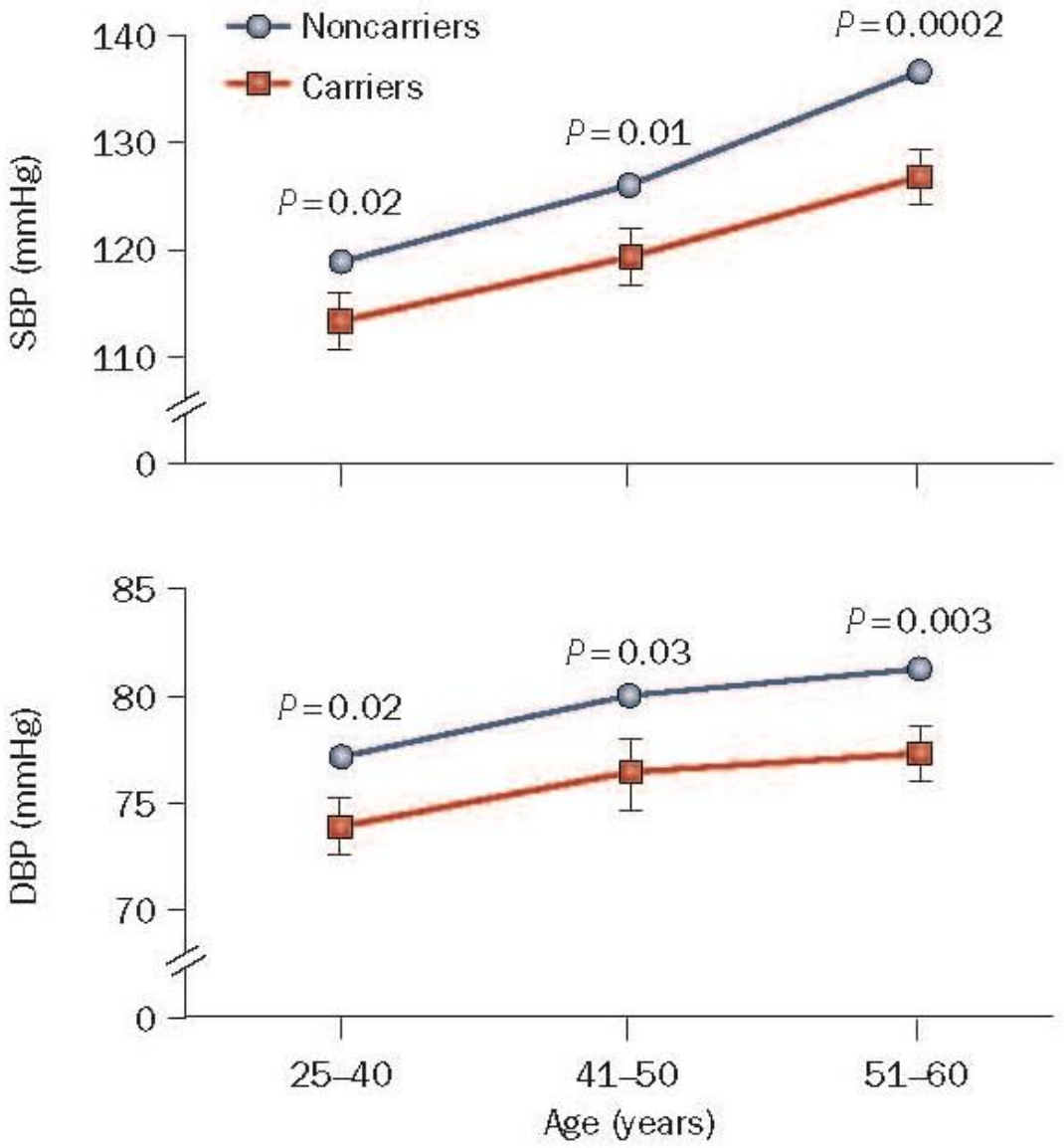
Hypertension-Misattributed Chronic Kidney Disease

- **PARADIGM SHIFT: Examining genetic epidemiology in an AASK case-control study design shows that APOL genetic risk is proximate to the hypertension & kidney disease.**

- **Unclear if African Americans with no APOL risk alleles will respond to anti-hypertensive agents similar to Europeans.**

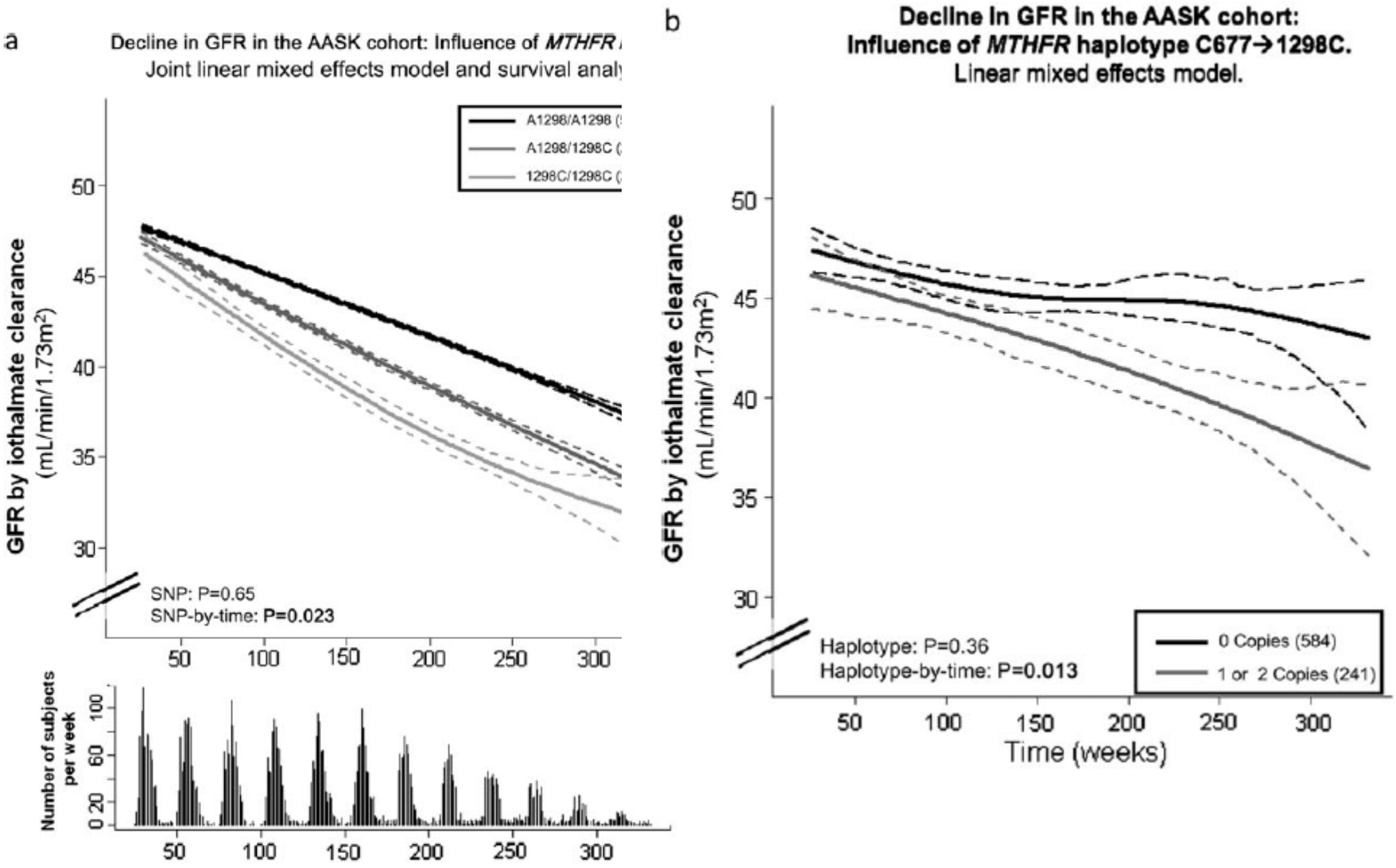
- **Clinical studies will need to stratify for APOL1 genotype and other relevant genetic variants**

Influence of SLC12A3, SLC12A1 and KCNJ1 functional coding sequence variants on blood pressure



Ji, W. et al. Nat. Genet. 40, 592–599 (2008).30

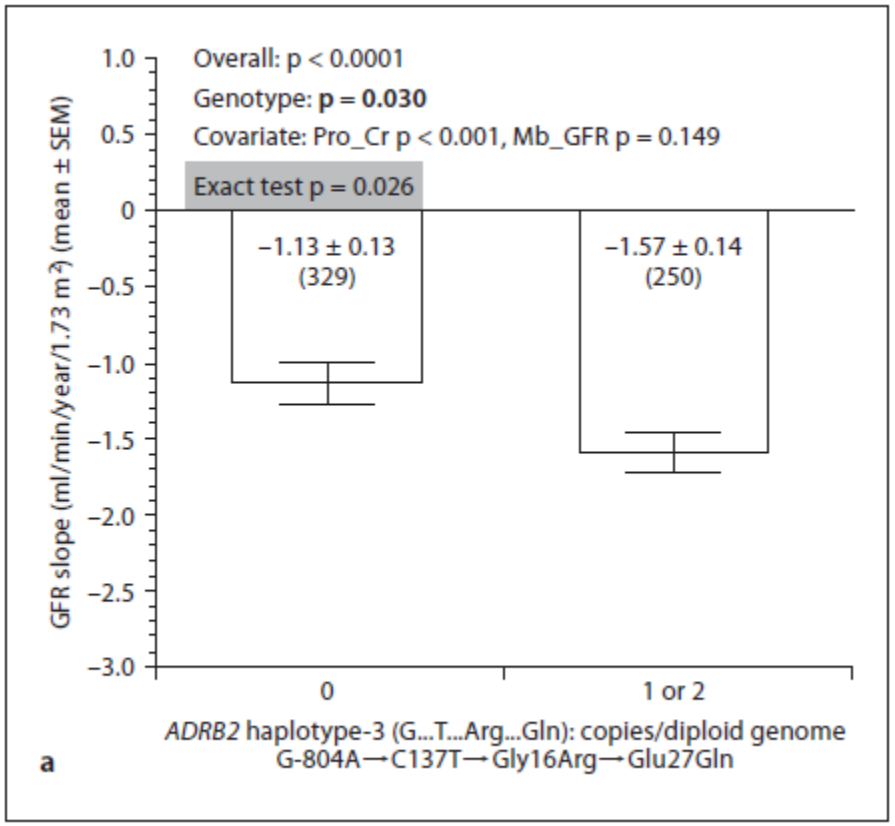
Methylenetetrahydrofolate reductase (MTHFR) polymorphism A1298C (Glu429Ala) predicts decline in renal function over time in the African-American Study of Kidney Disease and Hypertension (AASK) Trial and Veterans Affairs Hypertension Cohort

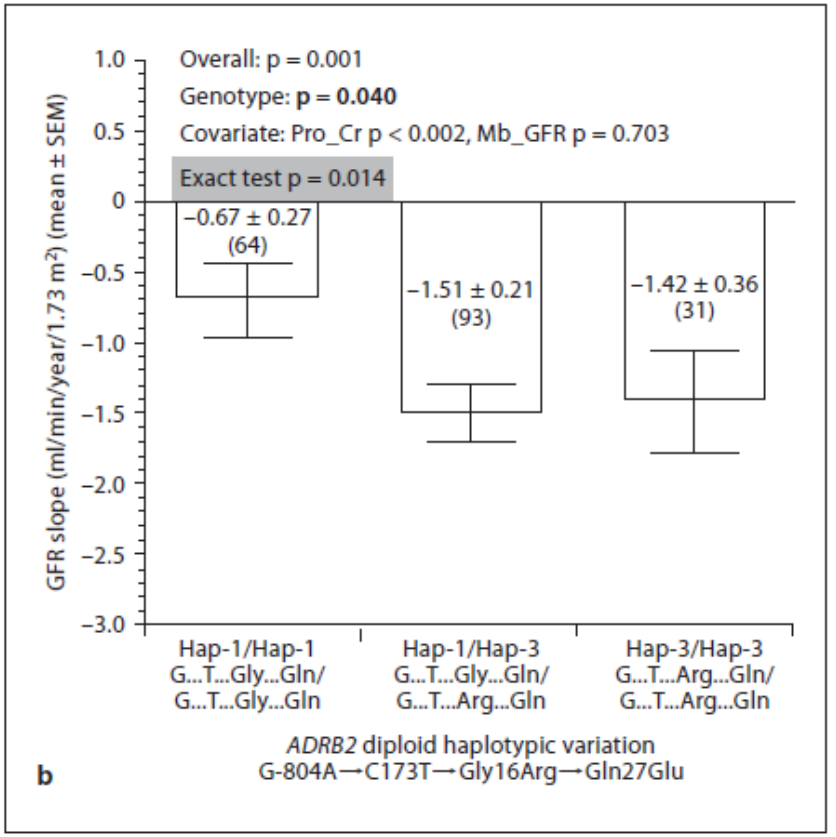


Fung M et al. Nephrol Dial Transplant (2012) 27: 197–205

Progression of Chronic Kidney Disease: Adrenergic Genetic Influence on Glomerular Filtration Rate Decline in Hypertensive Nephrosclerosis

Chen et al Am J Nephrol 2010;32:23–30

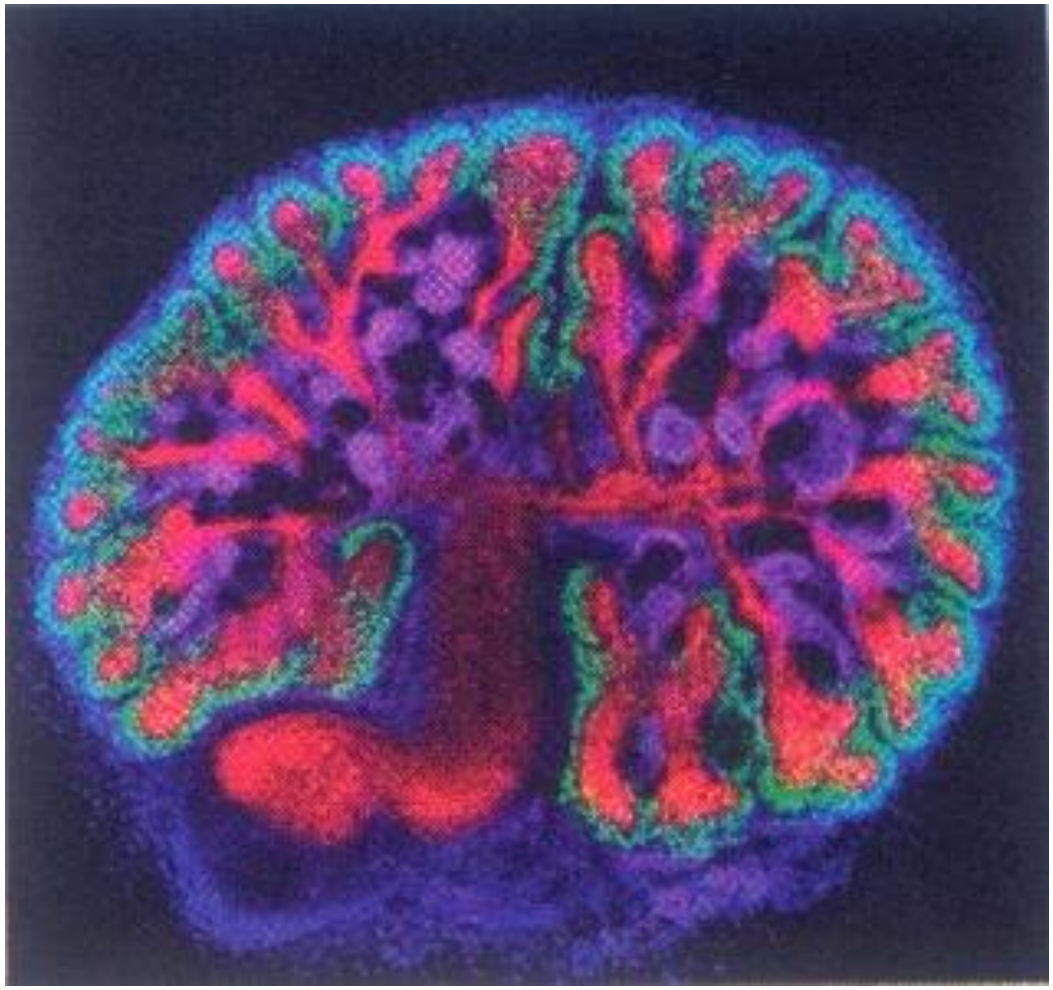




Gene-by-Drug Interaction in Proteinuric Subgroup

Gene variants	Two-way ANOVA
*ADRB2*_Gln27Glu	0.037 ($p < 0.05$)
*ADRB2*_HAP1	0.001 ($p < 0.05$)

The Kidneys are the Brains of Cardiovascular Health




Köszönöm
Szépen
Thanks
תודה
شُكْرًا جزيلا
Merci