

Recent advances in the treatment of
hypertension with renal disease:
peculiarities for the African descent
population

JM KRZESINSKI

Professor of Nephrology

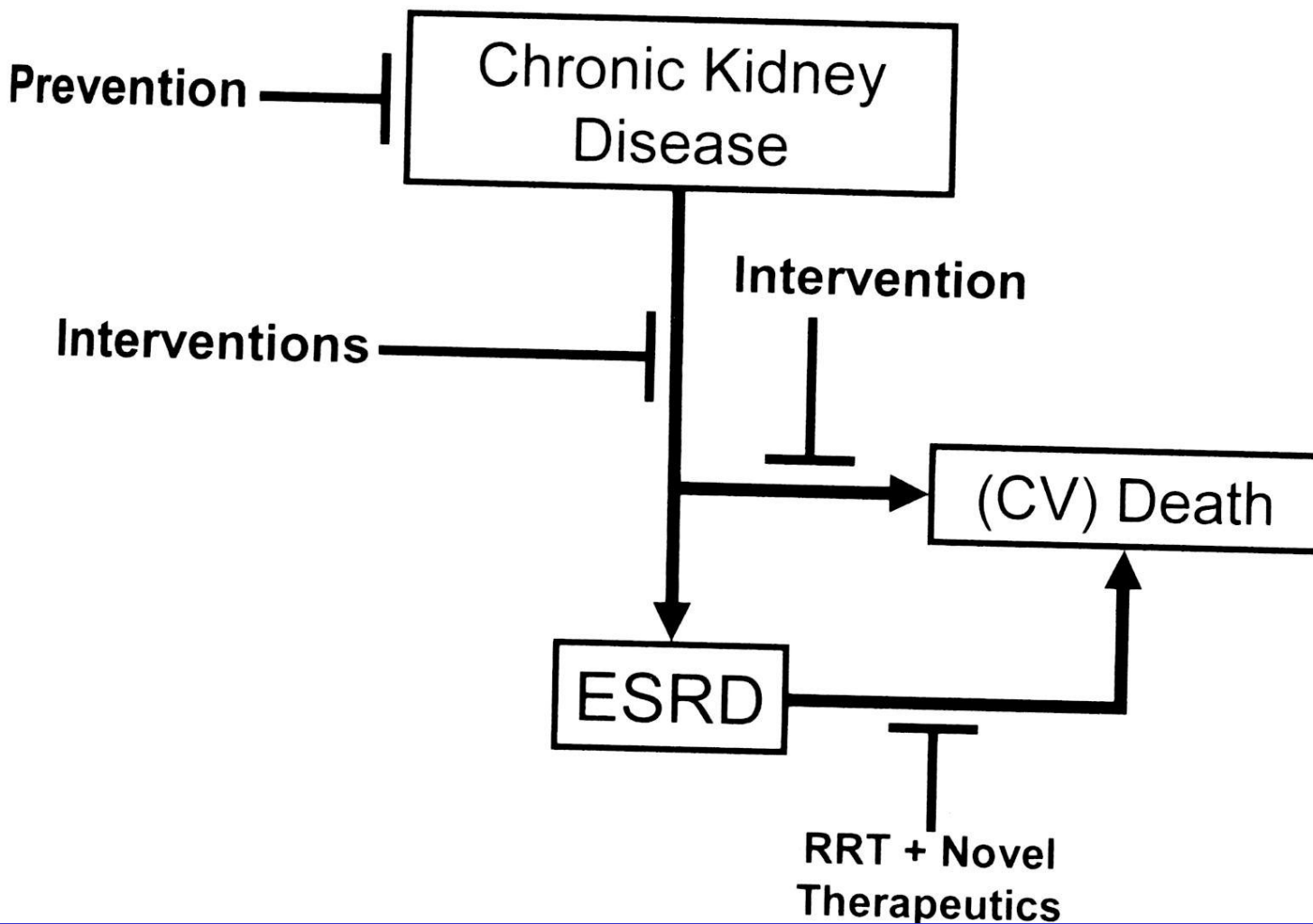
University of Liège

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

New Paradigm

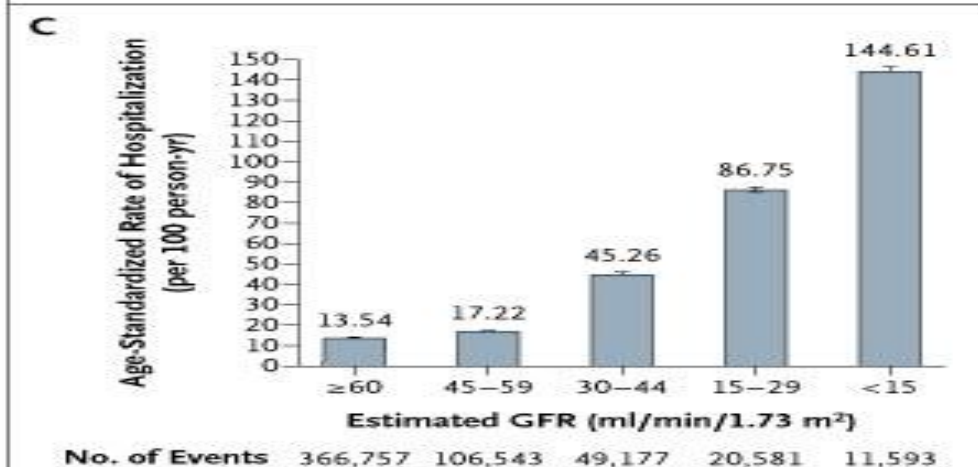
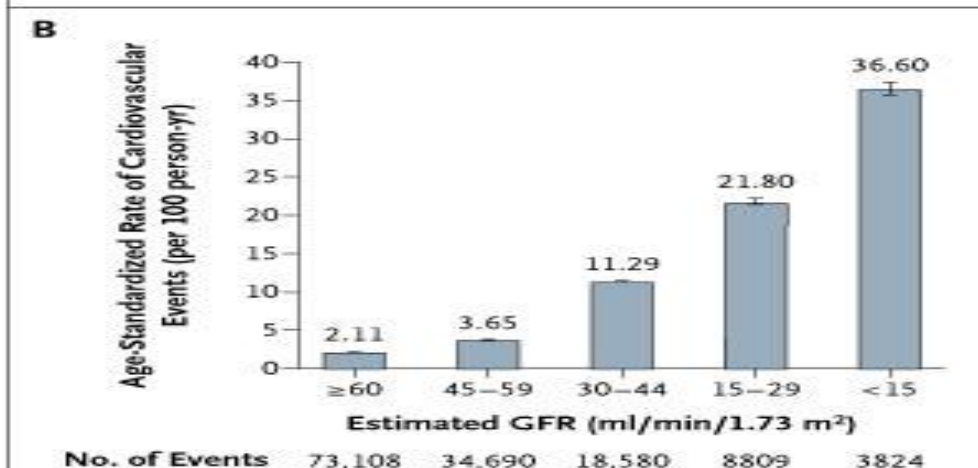
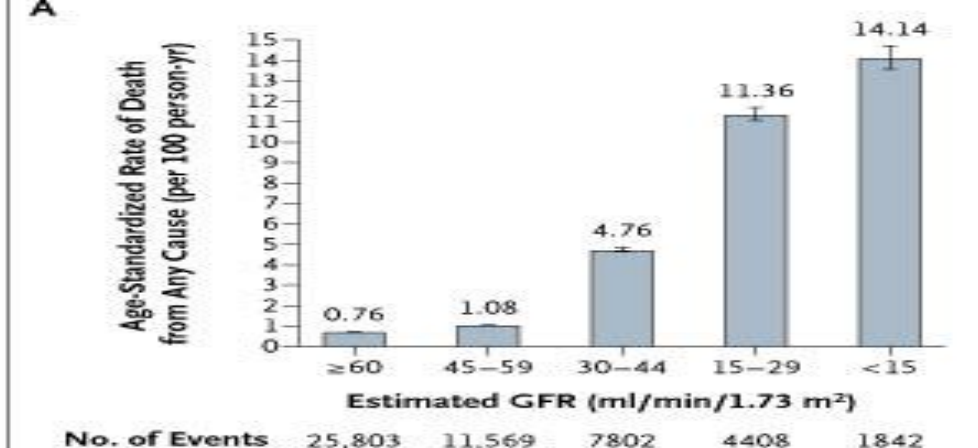


Age-Standardized Rates According to the Estimated GFR (MDRD) among 1,120,295 Adults

Death from Any Cause
(Panel A),

Cardiovascular Events
(Panel B),

Hospitalization
(Panel C)



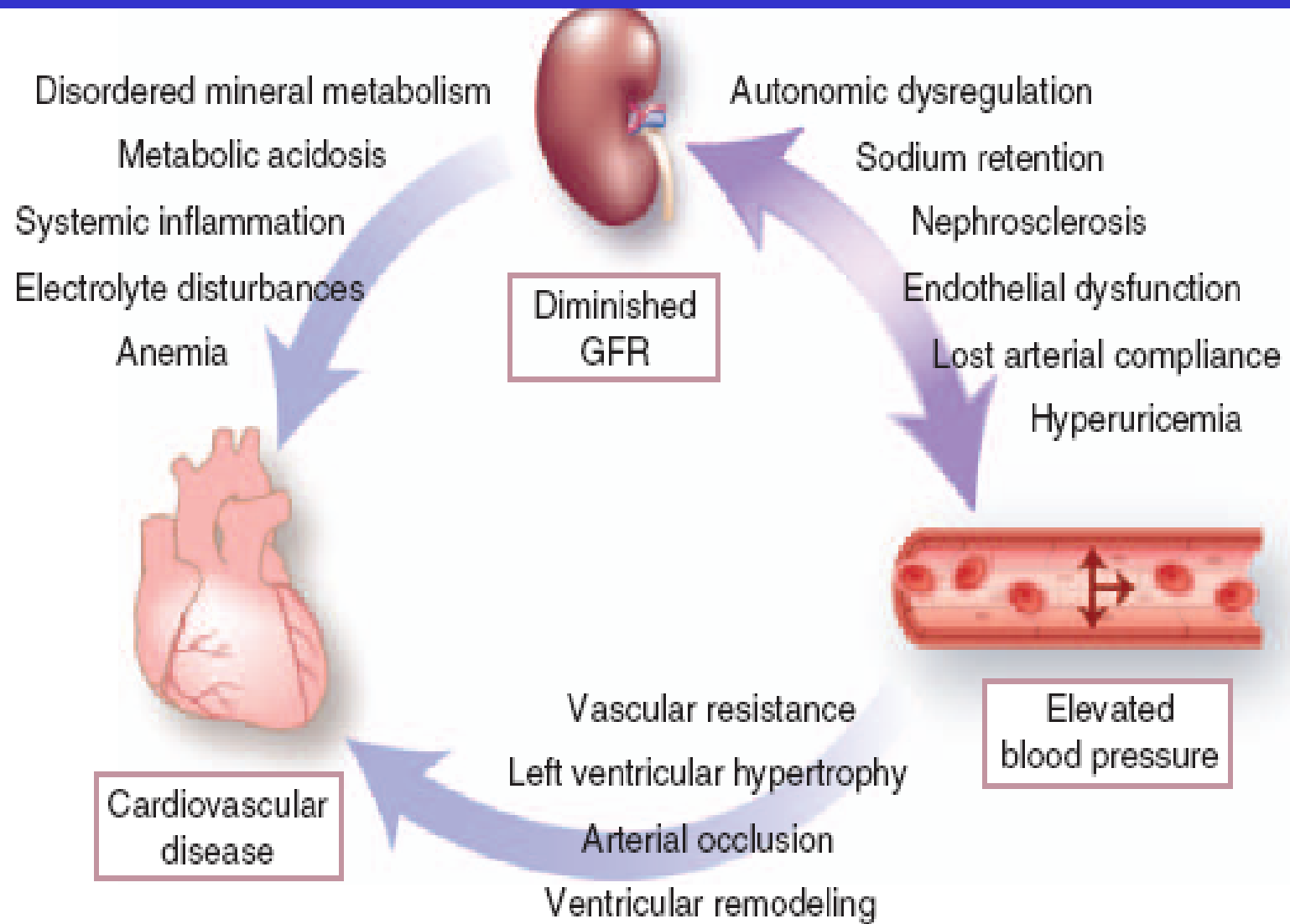
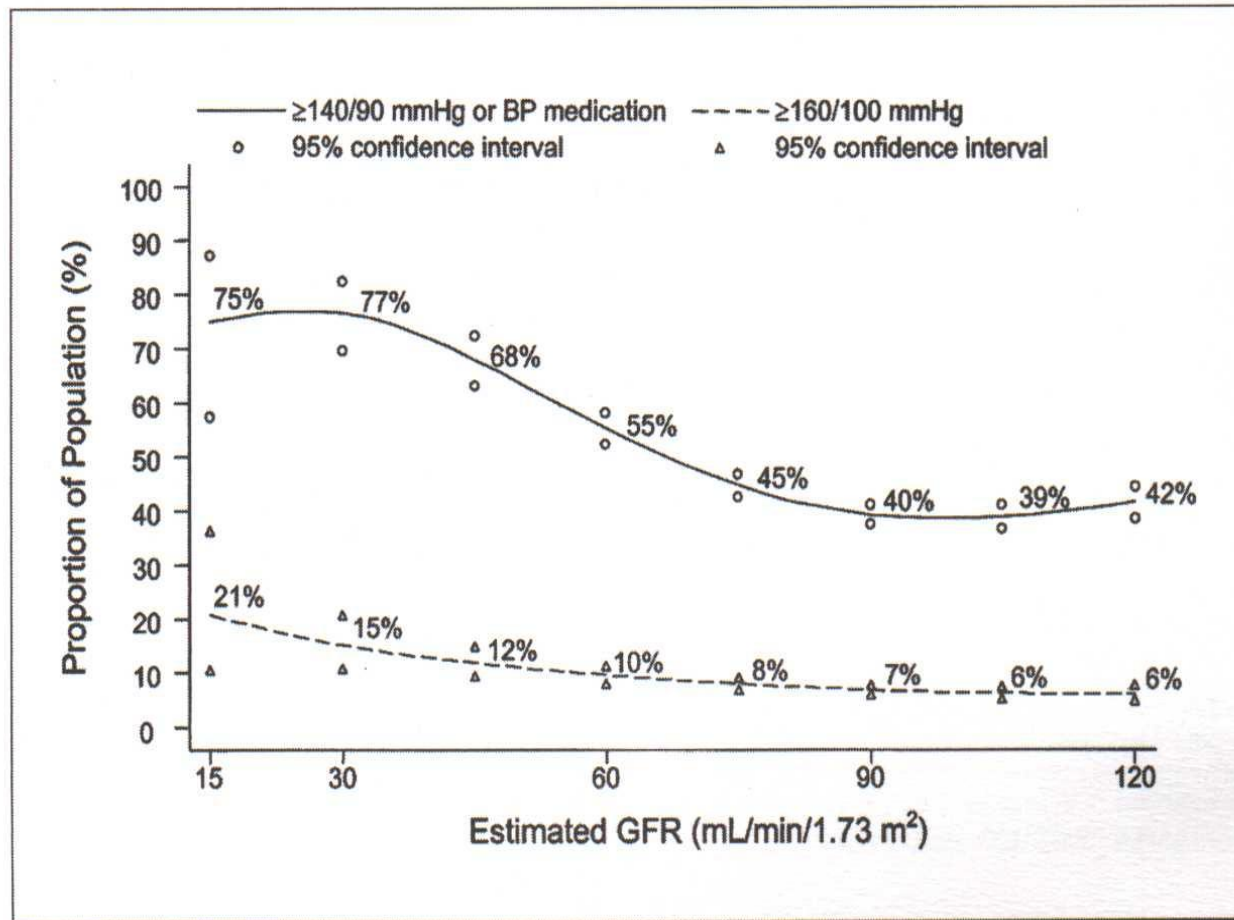


Figure 1 | Joint contribution of CKD and hypertension to cardiac risk. CKD, chronic kidney disease; GFR, glomerular filtration rate.

Figure E.2. Prevalence of High Blood Pressure by Level of GFR, Adjusted to Age 60 Years (NHANES III)



Prevalence of hypertension by level of GFR, adjusted to age 60 years in NHANES III. GFR was estimated using the abbreviated MDRD Study equation. Hypertension was defined as JNC >Stage 1 (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or taking medications for hypertension) or JNC >Stage 2 (systolic blood pressure >160 or diastolic blood pressure >100 mm Hg). Values are adjusted to age 60 years using a polynomial regression. 95% confidence interval are shown at selected levels of estimated GFR. Reproduced with permission.

Incidence of ESRD

(Klag et al JAMA 1997)

- Black Americans have a 2-4 fold higher incidence of ESRD compared with Whites
- When GFR is between 60-80 ml/min, the Black population presents higher systolic BP and diabetes mellitus prevalence, albuminuria and hyperuricemia (Peralta et al NDT 2010).
- Higher death risk than W before ESRD!

Racial Differences in Mortality Among Those with CKD

Rajnish Mehrotra,^{*†} Dulcie Kermah,[‡] Linda Fried,[§] Sharon Adler,^{*†} and Keith Norris^{†‡}

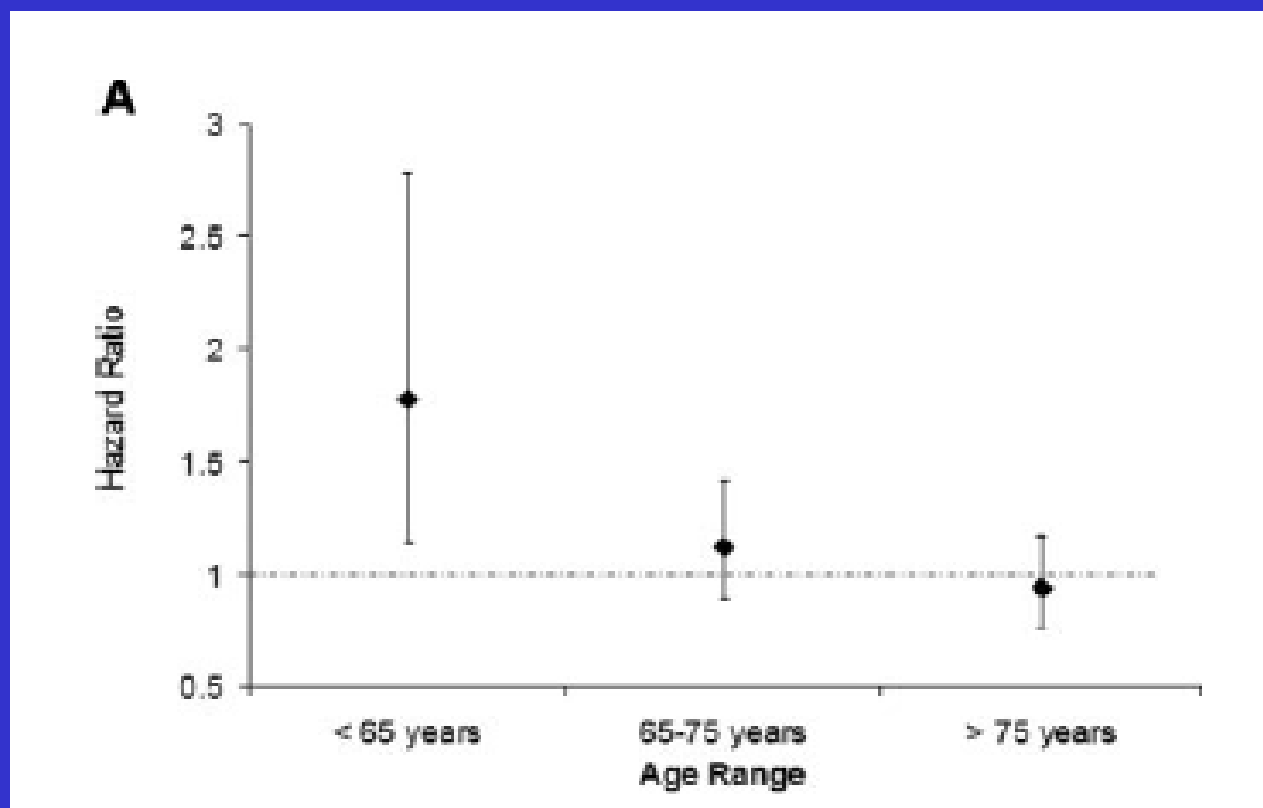


Figure 2. (A) Effect of age on the differences in outcomes among whites and black individuals with CKD enrolled in the NHANES III. The HR for all-cause mortality, adjusted for age and gender, among black individuals in different age categories were as follows: <65 yr 1.78 (95% CI 1.14 to 2.78); 65 to 75 yr 1.12 (95% CI 0.89 to 1.42) and >75 yr 0.94 (95% CI 0.76 to 1.17). (B)

HTN nephrosclerosis in AA

R Toto KI 2003

- Incidence of HTN is 5 times higher as cause of ESRD in AA compared to non AA
- HTN is more severe, develops earlier and is more difficult to control in AA
- Role of socioeconomic status and access to medical care, high salt intake, obesity, low nephron number, genetic predisposition?

Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States

MD Hughson¹, R Douglas-Denton², JF Bertram² and WE Hoy³

KI 2006

Table 9 | Distribution of hypertensive and non-hypertensive subjects having N_{glom} above and below the group mean (white subjects, 30-65 years old)

	N_{glom}	
	<855 755	>855 755
Hypertensive	17 (28%)	7 (12%)
Non-hypertensive	14 (23%)	22 (37%)

The distribution of values between rows and columns is significantly different. $\chi^2=4.675$, $P=0.031$.

Table 8 | Distribution of hypertensive and non-hypertensive subjects having N_{glom} above and below the group mean (African Americans, 30-65 years old)

	N_{glom}	
	<899 360	>899 360
Hypertensive	23 (37%)	18 (29%)
Non-hypertensive	11 (18%)	10 (16%)

The distribution of values between rows and columns is not significantly different; $\chi^2=0.00008$, $P=0.993$.

Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States

MD Hughson¹, R Douglas-Denton², JF Bertram² and WE Hoy³

KI 2006

Whites

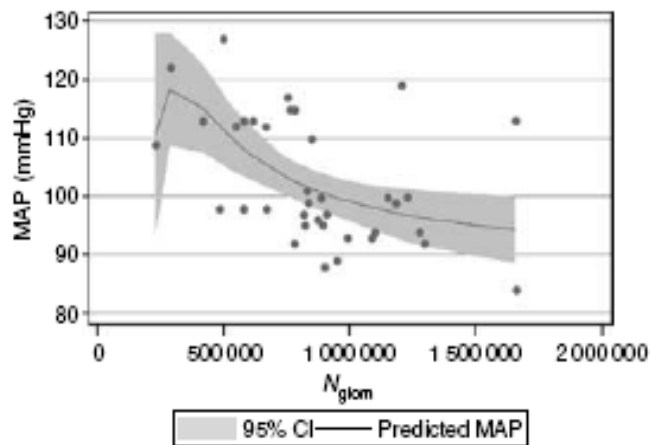


Figure 5 | MAP plotted against total right kidney glomerular number (N_{glom}) for white subjects 30–65 years of age. A significant inverse relationship is found between N_{glom} and MAP ($r = 0.4551$, $P = 0.0047$) in which high N_{glom} predicts low MAP. Note that two patients with >1 million glomeruli have high MAP and that blood pressures are considerably lower than for African Americans.

AA

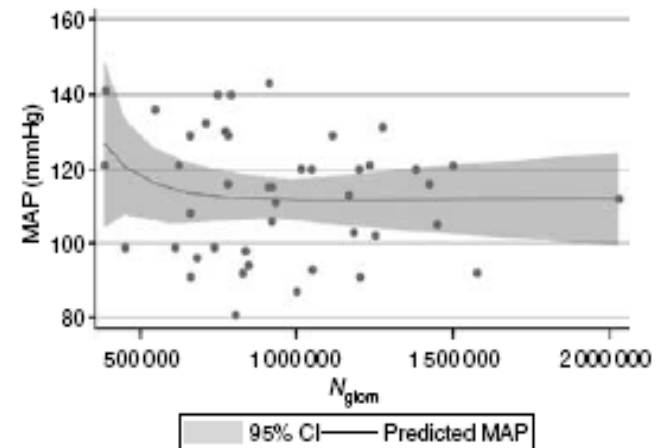


Figure 4 | MAP plotted against total right kidney glomerular number (N_{glom}) for African Americans 30–65 years of age. There is no significant relationship between N_{glom} and MAP ($r = -0.1367$, $P = 0.3822$). Several patients have $MAP \geq 120$ mmHg and $N_{glom} > 1$ million, and normotensive patients are found with low N_{glom} .

Polymorphisms in the non-muscle myosin heavy chain 9 gene (*MYH9*) are strongly associated with end-stage renal disease historically attributed to hypertension in African Americans

Barry I. Freedman¹, Pamela J. Hicks², Meredith A. Bostrom², Mary E. Cunningham³, Yongmei Liu³, Jasmin Divers³, Jeffrey B. Kopp⁴, Cheryl A. Winkler⁵, George W. Nelson⁵, Carl D. Langefeld⁶ and Donald W. Bowden^{1,2,6}

Thus, hypertension-associated ESRD in African Americans is substantially related to *MYH9* gene polymorphisms and this may explain the poor response to blood pressure control in those diagnosed with hypertensive nephrosclerosis. It is possible that many African Americans classified as having hypertension-associated ESRD have occult *MYH9*-associated segmental or global glomerulosclerosis. Our study shows that gene-environment and/or gene-gene interactions may initiate kidney disease in genetically susceptible individuals, because African Americans homozygous for *MYH9* risk alleles do not universally develop kidney disease.

Kidney International (2009) **75**, 736–745; doi:10.1038/ki.2008.701;
published online 28 January 2009

Hum Genet

DOI 10.1007/s00439-010-0861-0

SHORT REPORT

Missense mutations in the *APOL1* gene are highly associated with end stage kidney disease risk previously attributed to the *MYH9* gene

Shay Tzur · Saharon Rosset · Revital Shemer · Guennady Yudkovsky ·
Sara Selig · Ayele Tarekegn · Endashaw Bekele · Neil Bradman ·
Walter G. Wasser · Doron M. Behar · Karl Skorecki

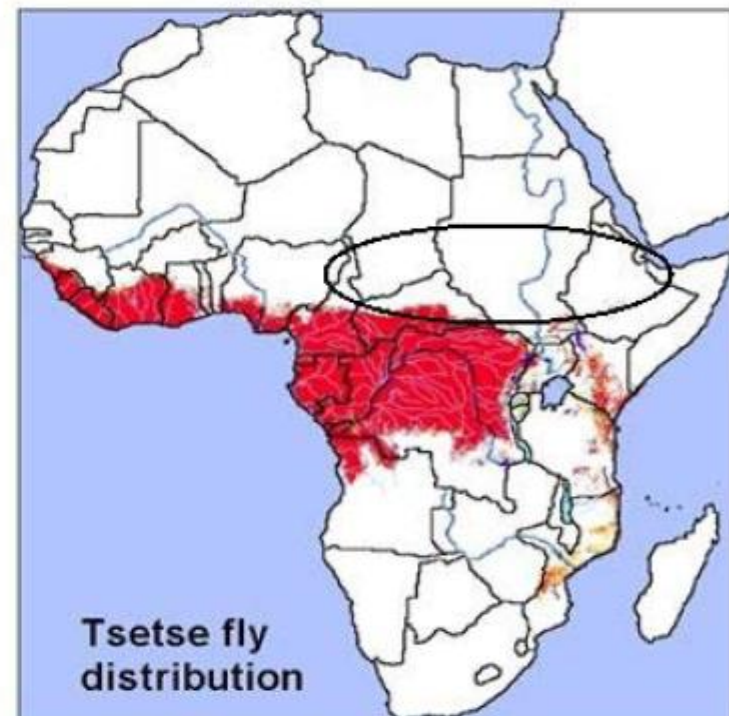
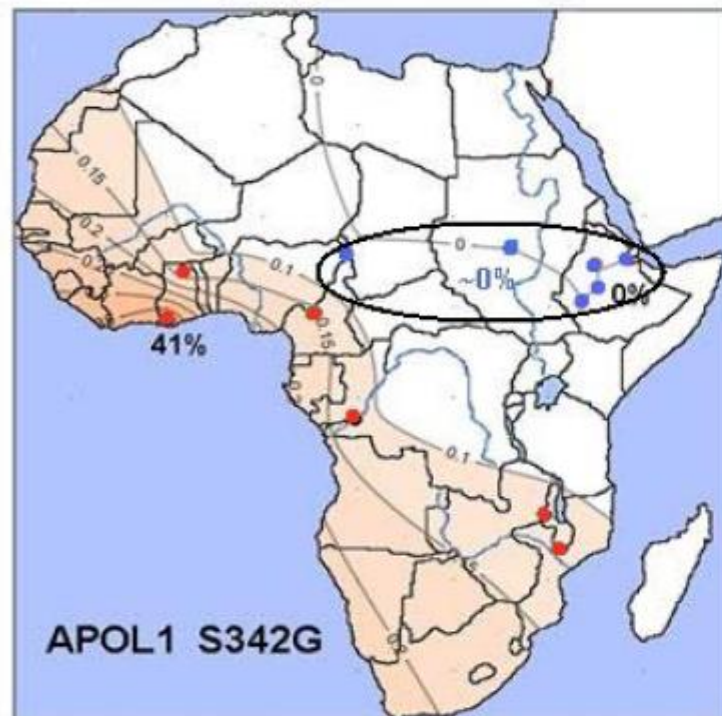
Chromosome 22

Received: 7 June 2010 / Accepted: 6 July 2010

Population Genetic Structure in Chronic Kidney Disease: The MYH9 - APOL1 Example

Saharon Rosset^{1,6}, Shay Tzur^{2,6}, Doron M Behar^{3,4}, Walter G Wasser⁵, Karl Skorecki^{2,3,7}

Figure 5. Spatial allele frequency distributions of APOL1 S342G in comparison to the distribution of the tsetse fly (*Glossina fuscus*).



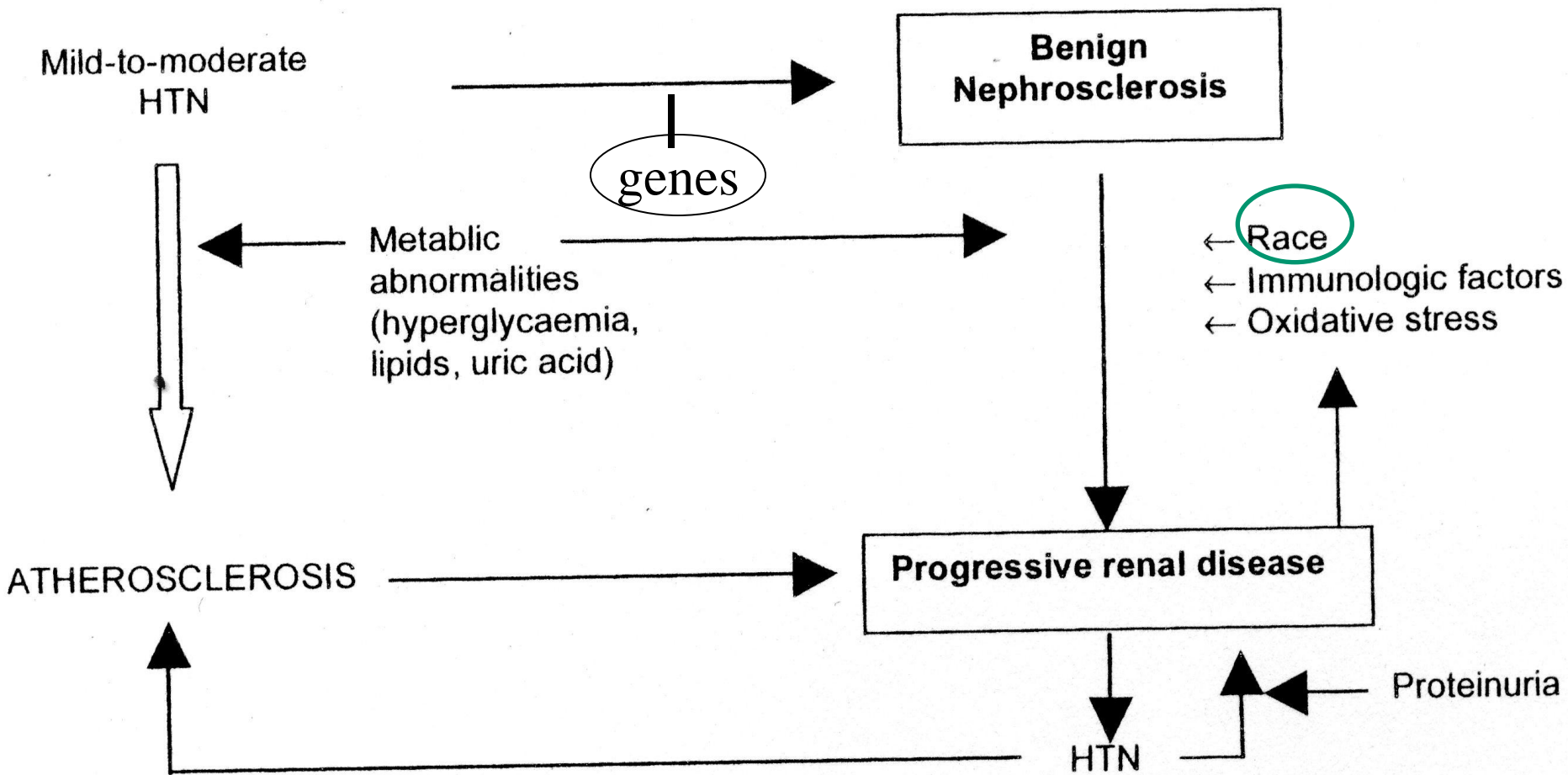


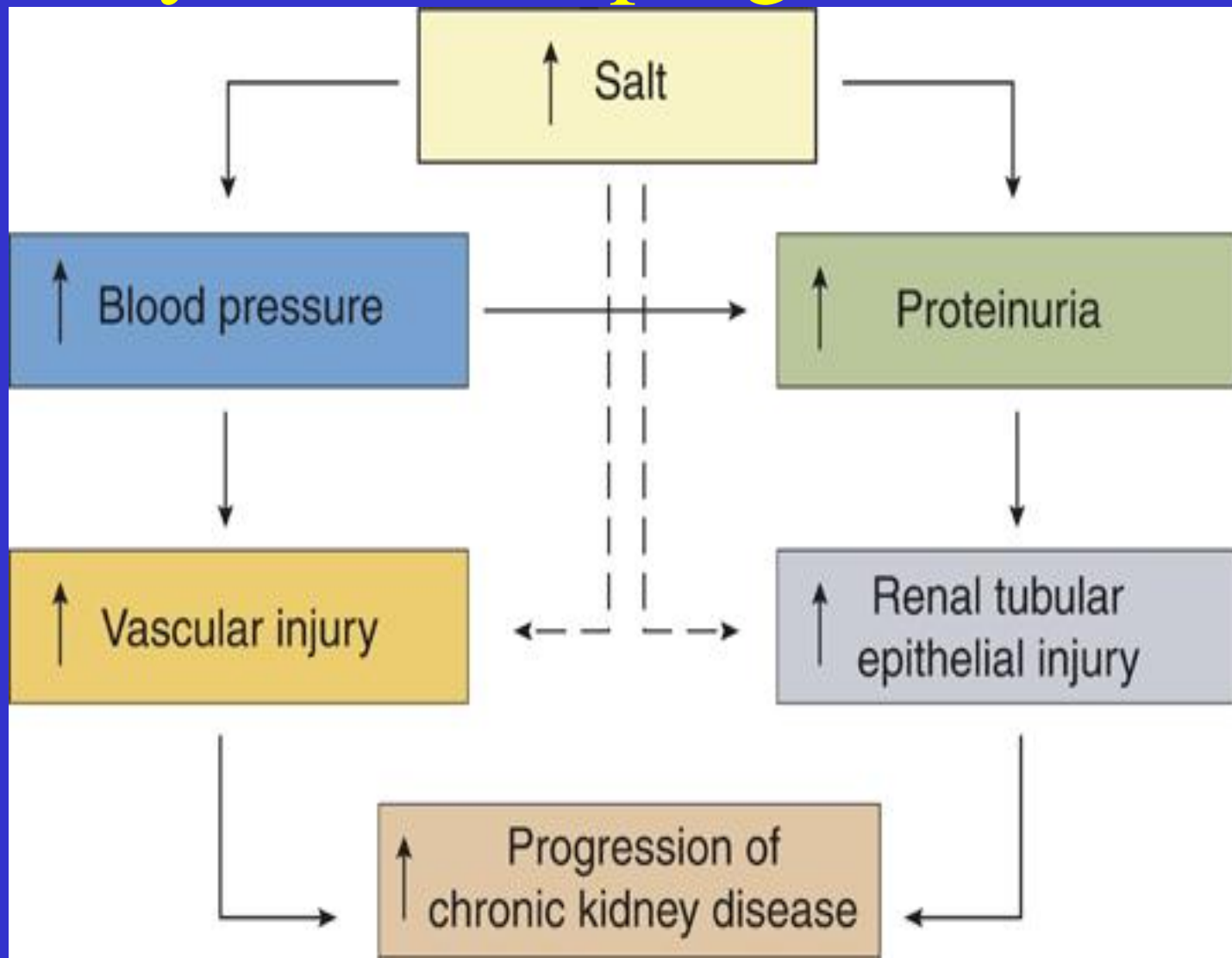
Figure 1 : Relation between Hypertension and Chronic Kidney Disease

How to manage HTN with CKD:

Dietary approach

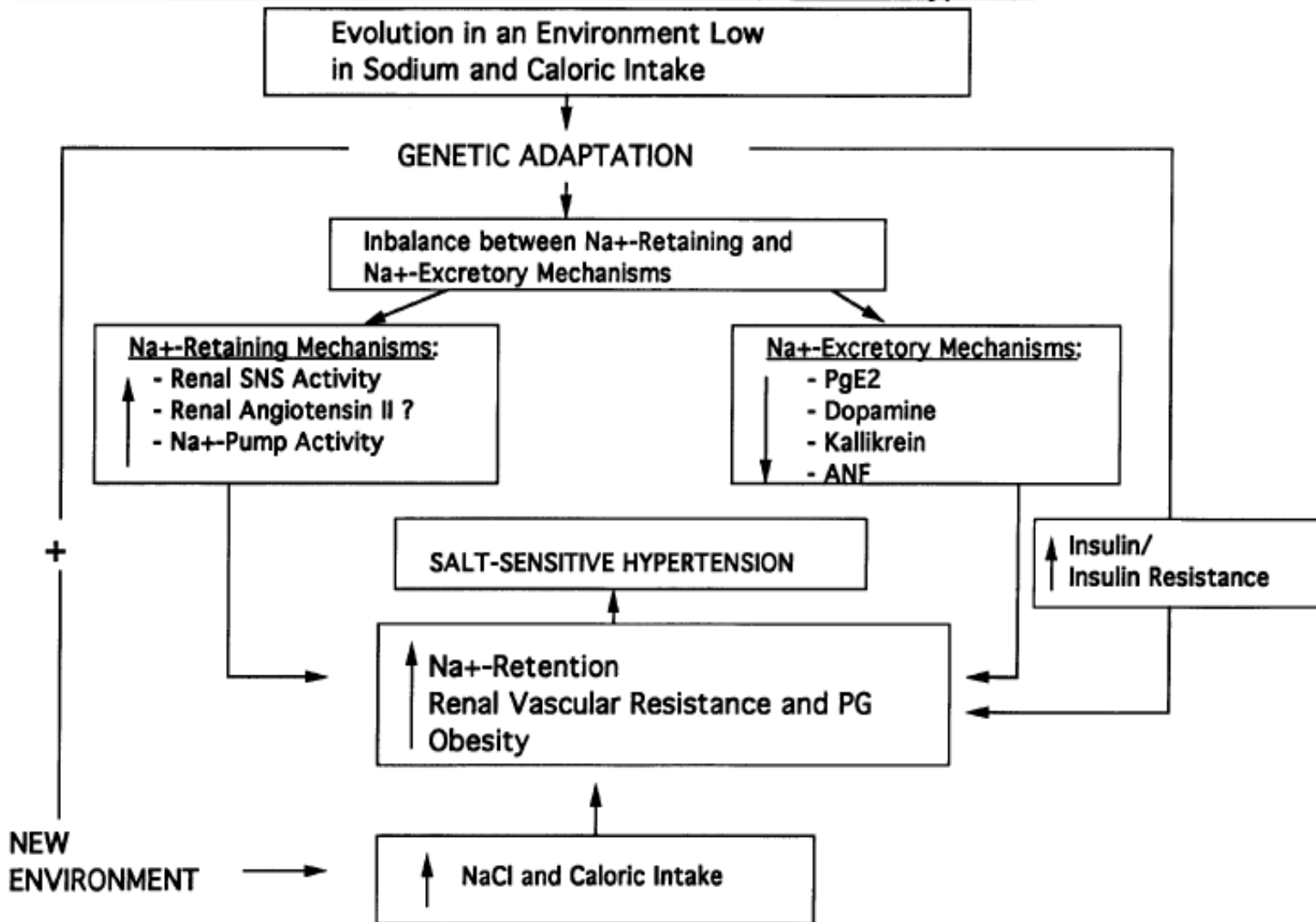
- Low salt diet
- DASH diet (fruits, vegetables, fresh low fat dairy products)
- Physical activity and low caloric diet
- Low proteins (if proteinuria) and low lipids in the diet

Role of sodium intake in the renal dysfunction progression



Why is salt-sensitive HTA so common in Blacks? (Campese NDT 1996)

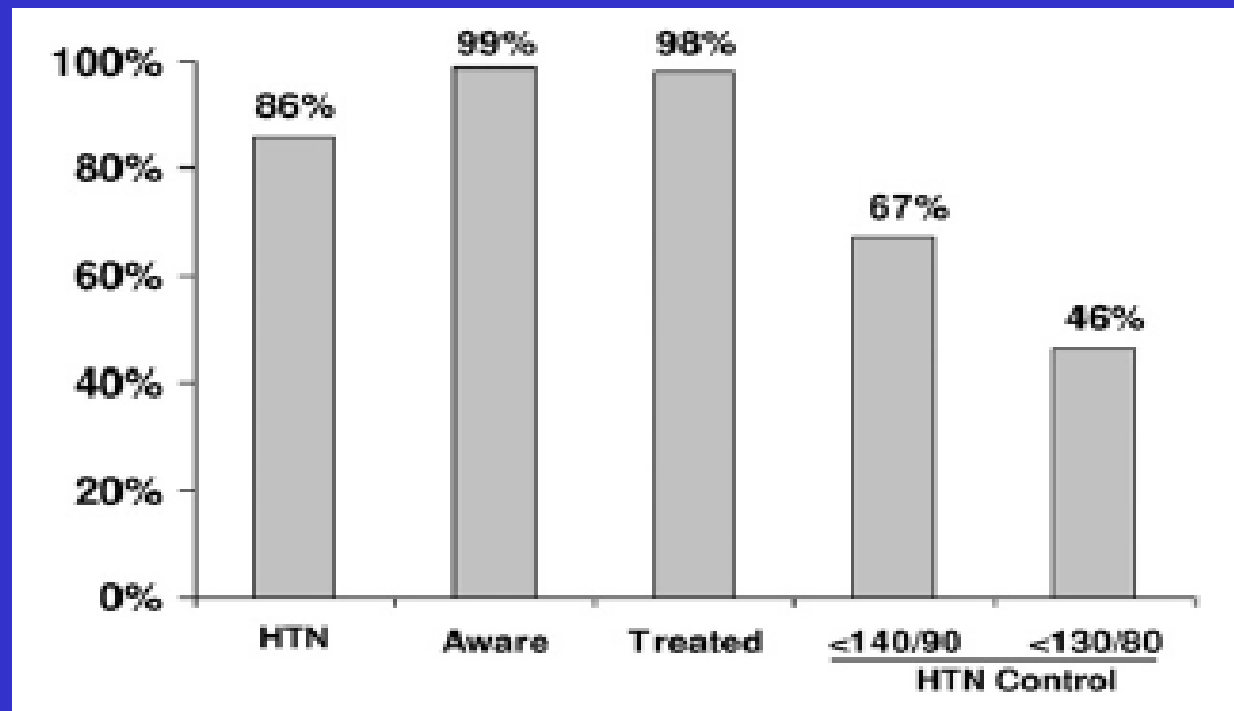
PATHOPHYSIOLOGY OF HYPERTENSION IN AFRICAN-AMERICANS: An Hypothesis



How to manage HTN with CKD: Target BP and first line anti HTA drug

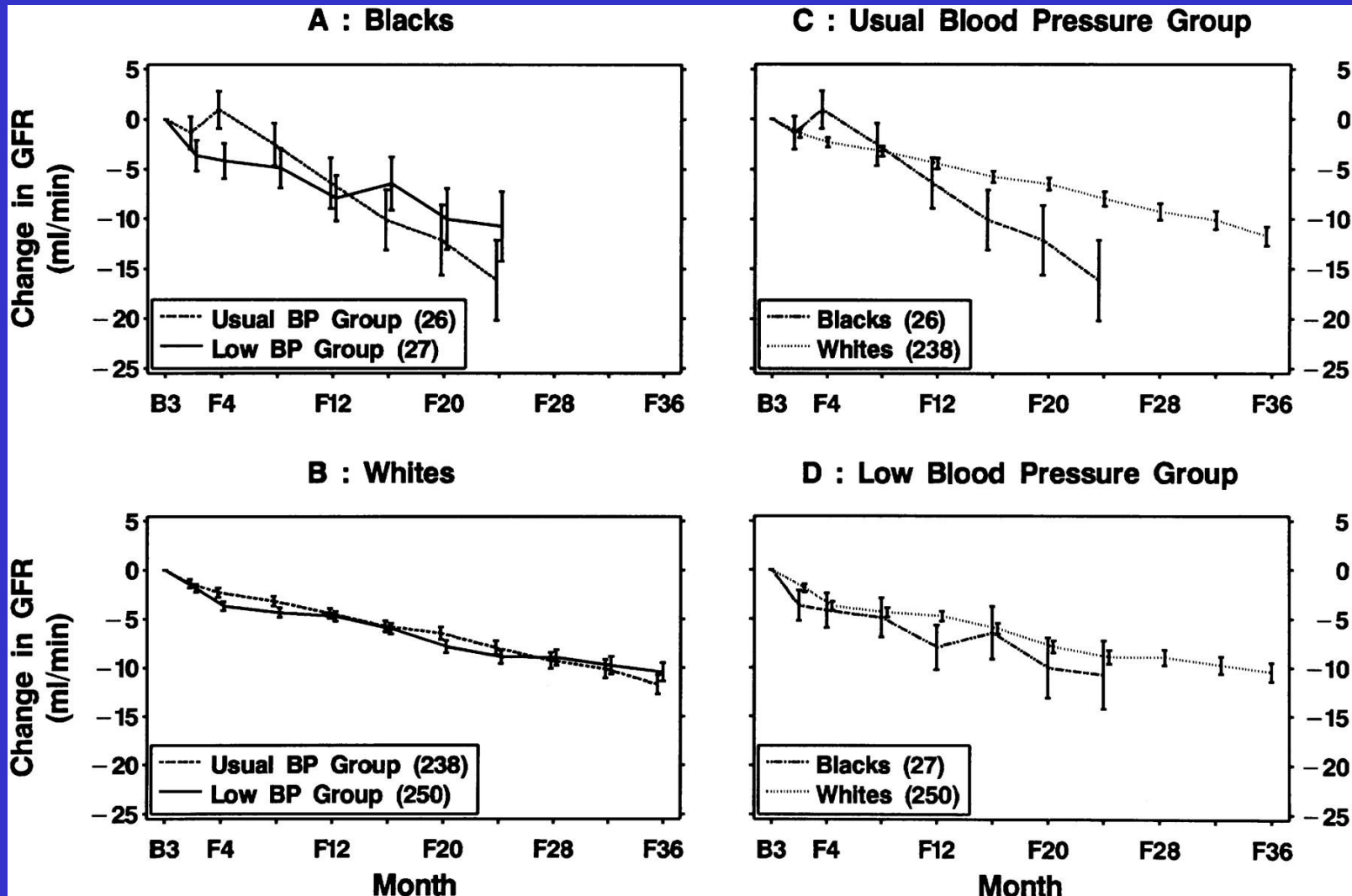
- Target BP < 130/80 mmHg (or even lower)
- RAS blocker must be the first choice!

Hypertension Awareness, Treatment, and Control in Adults With CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study



Conclusions: Despite almost universal hypertension awareness and treatment in this cohort of patients with CKD, rates of hypertension control were suboptimal. *Am J Kidney Dis* 00:00-00 ©2009 by the National Kidney Foundation, Inc

Estimated mean change in GFR in stage 3 CKD according to BP target (MDRD study)



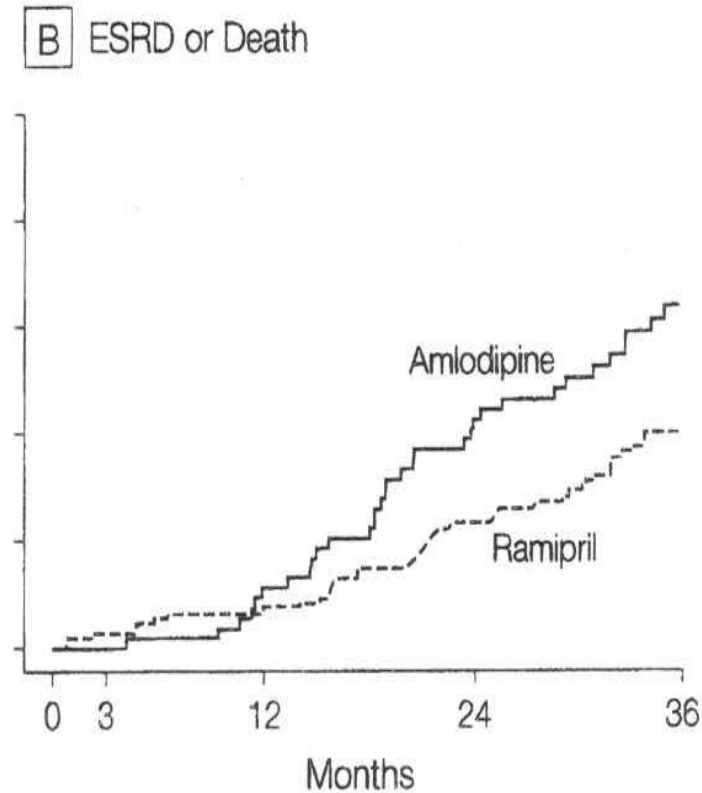
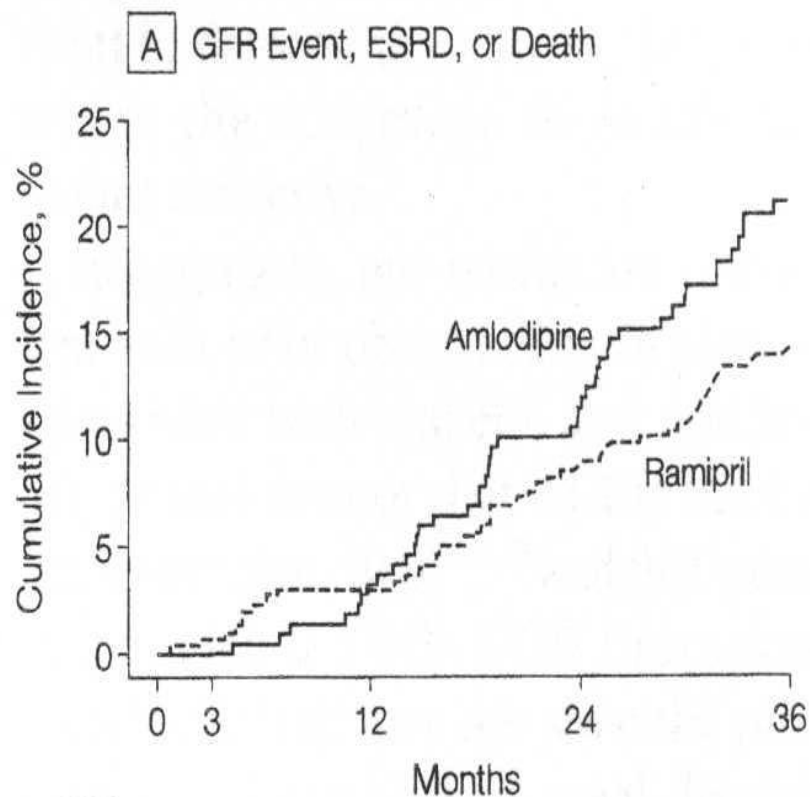
Hebert, L. A. et al. Hypertension 1997;30:428-435

UBP: 140/90
LBP: 125/75

Successful BP control in the AASK study (Wright et al Arch Int Med 2002)

- 1094 AA HT, GFR between 20-65 ml/min/1.73m² due to HTA
- DB Randomization to goal mean BP of either 102-107 mmHg (**usual MAP goal**) or 92 mmHg or less (**low MAP goal**) with either metoprolol, ramipril or amlodipine (+ if needed furosemide, doxazosin, clonidine or hydralazine)
- 79% achieved a BP < 140/90 mmHg after 14 months
- Mean antiHT agents : 3

Figure 3. Cumulative Incidence of Renal Events and Death



No. at Risk	0	3	12	24	36
Amlodipine	216	209	191	131	216
Ramipril	432	422	391	278	432

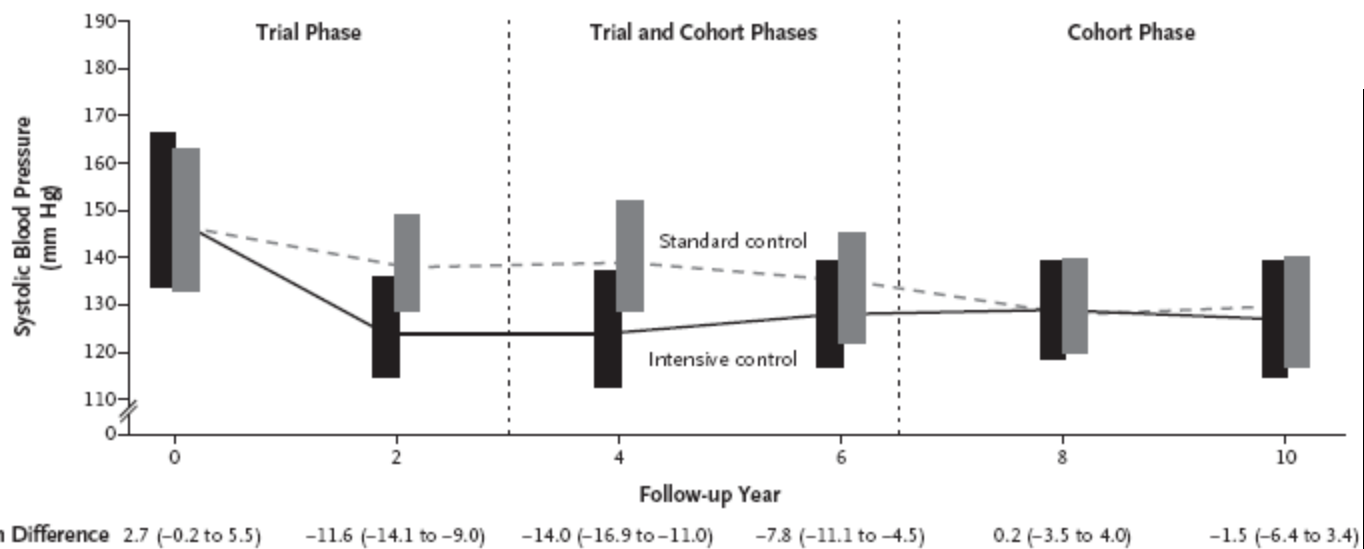
GFR indicates glomerular filtration rate; ESRD, end-stage renal disease. The adjusted risk reduction for ramipril vs amlodipine for the GFR event, ESRD, or death composite outcome was 38% (95% confidence interval [CI], 13%-56%; $P = .005$) (A) and for ESRD or death was 41% (95% CI, 14%-60%; $P = .007$) (B). The risk reductions are adjusted for baseline levels of log transformed urine protein-creatinine ratio, history of heart disease, mean arterial pressure, sex, and age.

Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease

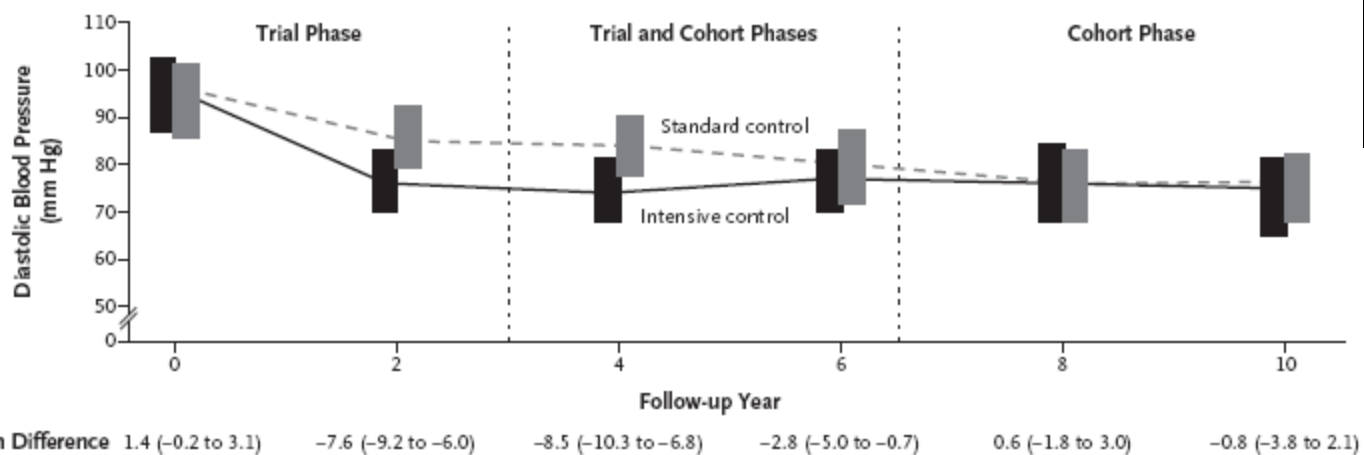
N ENGL J MED 363;10 NEJM.ORG SEPTEMBER 2, 2010

AASK Collaborative Research Group*

A Systolic Blood Pressure



B Diastolic Blood Pressure



Phase 1
BPst 141/86
BPi 131/78

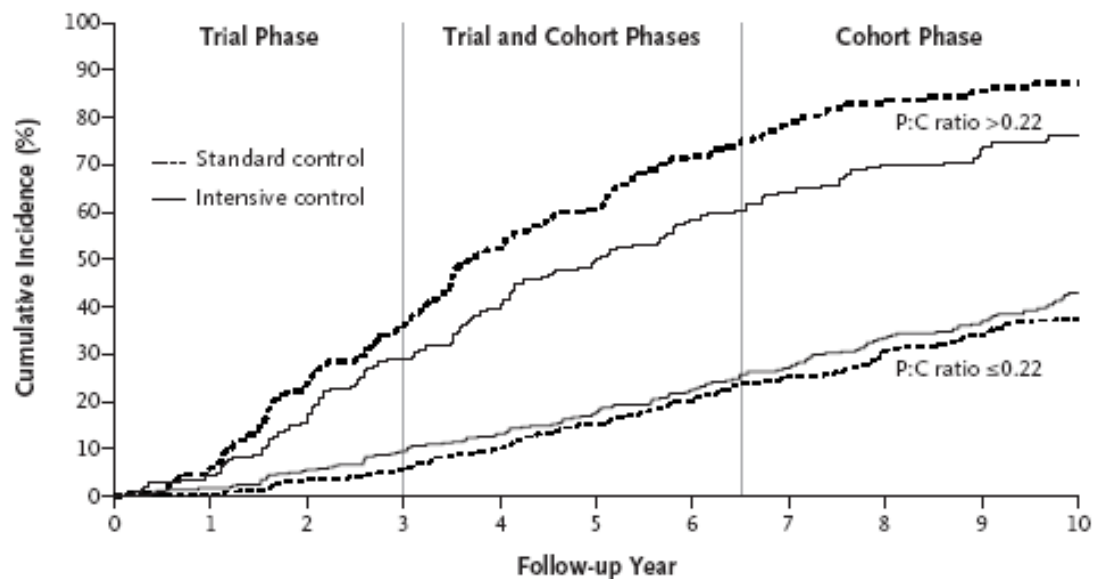
Phase 2
BP 134/78

Figure 1. Blood-Pressure Levels in Patients with Chronic Kidney Disease.

Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease

AASK Collaborative Research Group*

N ENGL J MED 363;10 NEJM.ORG SEPTEMBER 2, 2010



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

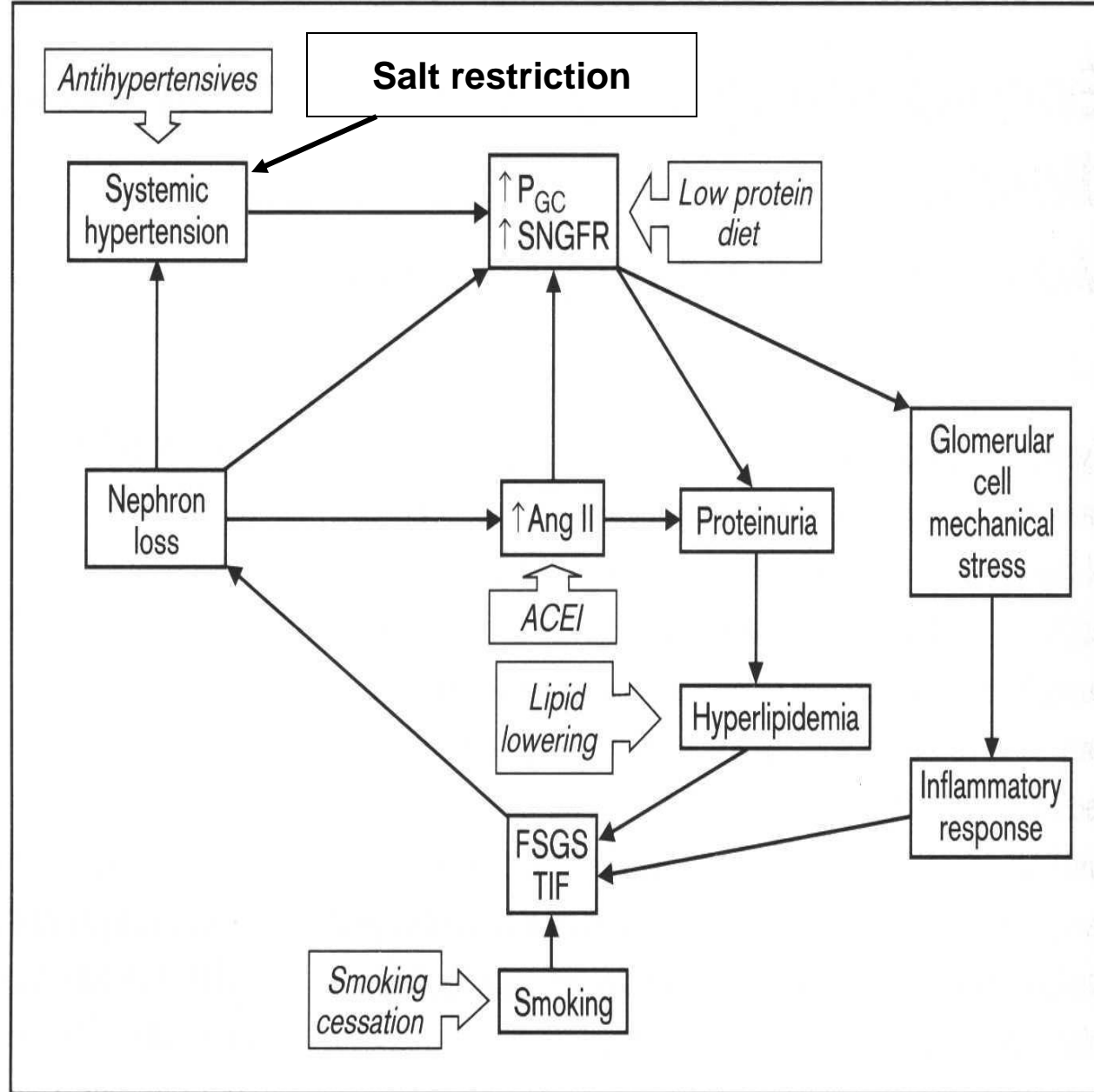
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

CONCLUSIONS

In overall analyses, intensive blood-pressure control had no effect on kidney disease progression. However, there may be differential effects of intensive blood-pressure control in patients with and those without baseline proteinuria. (Funded by the

Figure 1. Proposed mechanisms resulting in a common pathway of progressive nephron loss in chronic renal disease

The actions of different interventions in interrupting this pathway are shown in italics. ACEI, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; FSGS, focal and segmental glomerulosclerosis; P_{GC} , glomerular capillary hydraulic pressure; SNGFR, single-nephron glomerular filtration rate; TIF, tubulointerstitial fibrosis.



**In CKD Blacks,
need for lower target
BP, thus insist on
low salt diet, RAS
blocker and add
other antiHTA
(Diuretics, BBI,
CCBI)**

Other interventions to reduce the risk of CKD progression

- HyperPTH (Ca, Vit D, low P diet)
- Anemia (Iron, ESA)
- Metabolic acidosis (NaHCO₃)
- If necessary, statins and natural vit D

Vit D, a new hope for CKD prevention (with RAS inhibitors)

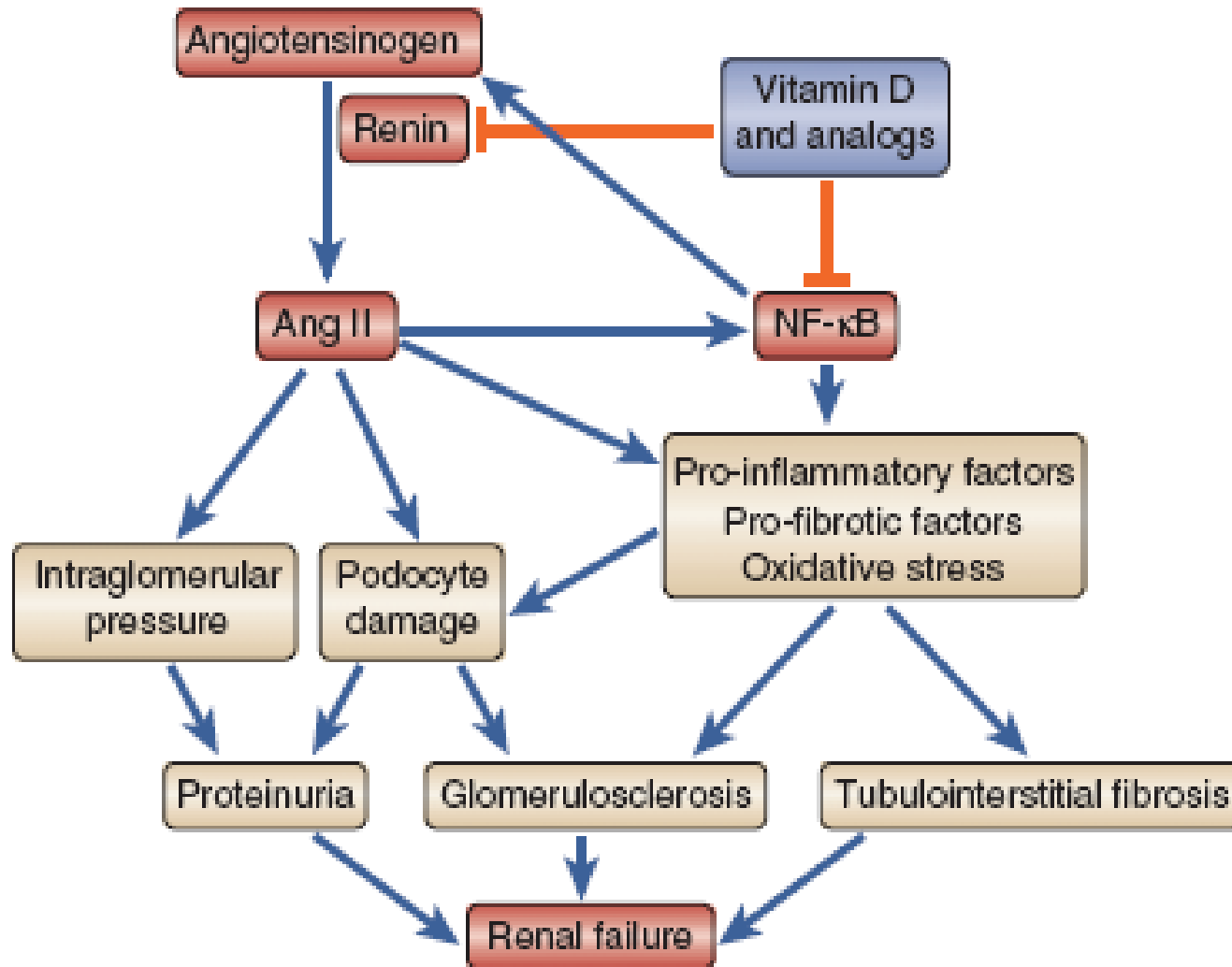


Figure 2 | Mechanism of renoprotection by vitamin D and its analogs. The renin-angiotensin system and the NF-κB activation

Conclusions

Hypertension is frequent in Chronic Kidney Disease.

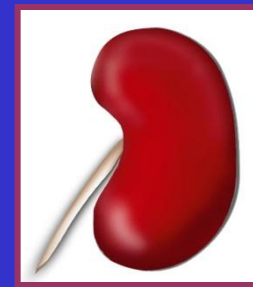
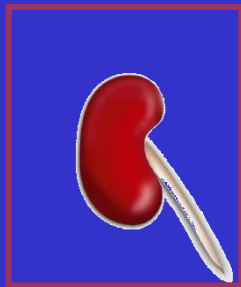
In Blacks, a genetic predisposition to HT nephrosclerosis explains the high prevalence of ESRD and some resistance to treatment.

Blood pressure control (target < 130/80 mmHg) slows the rate of decline in renal function, especially when proteinuria is present

A Dash diet with Low salt is recommended!

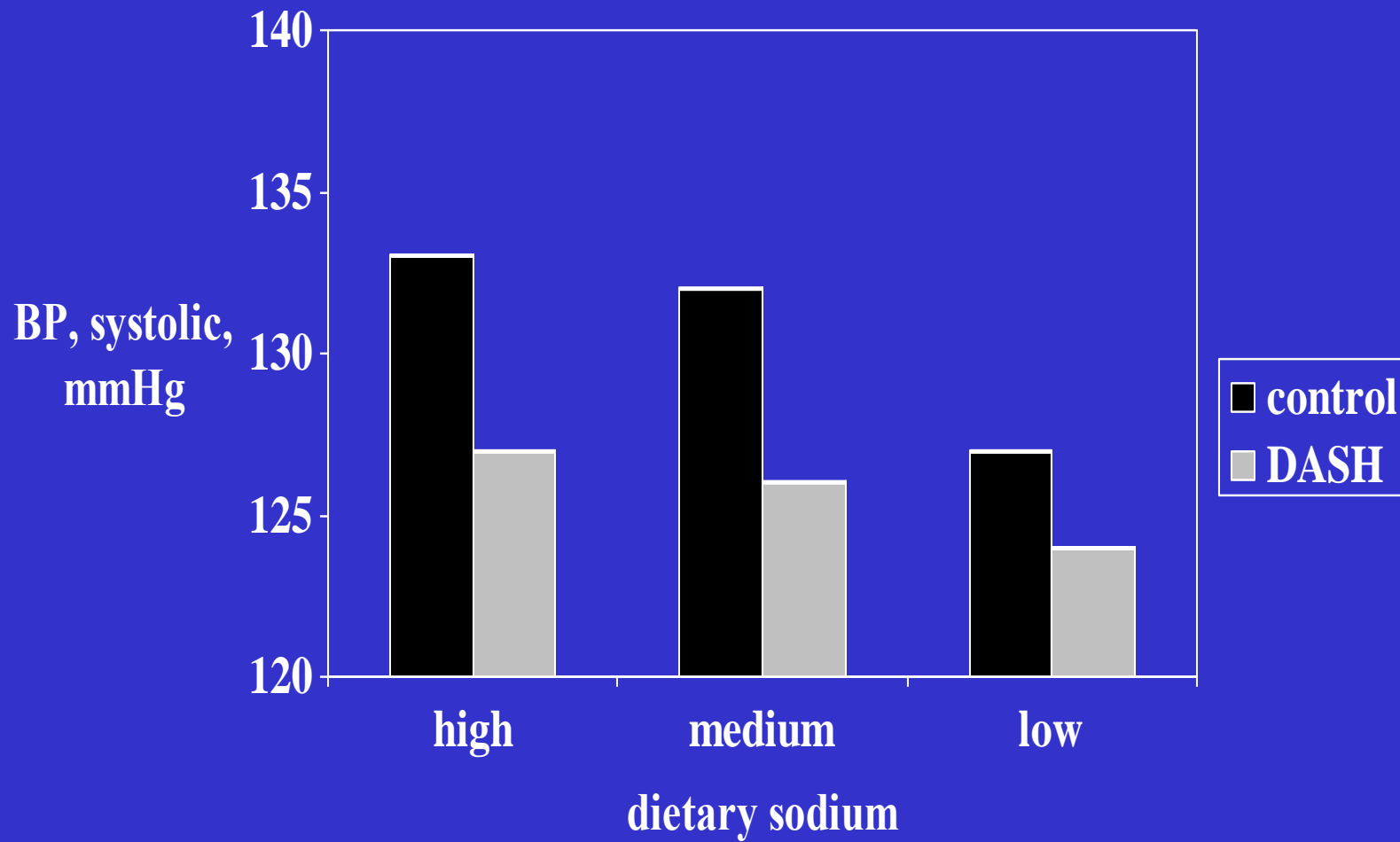
Multiple antihypertensive drugs are often required to achieve BP goal (Renin-angiotensin inhibitors, Calcium channel blockers and Diuretics)

EPIDEMIOLOGY of CHRONIC KIDNEY DISEASE IN KINSHASA (République Démocratique du Congo)



Thank you for your attention

Effect of different sodium intakes on BP (Sacks et al NEJM 2001)



Corin: new insights into the natriuretic peptide system

Qingyu Wu^{1,2}, Ye Olivia Xu-Cai³, Shenghan Chen¹ and Wei Wang¹

Kidney International (2009) **75**, 142–146;

Natriuretic peptides are important in regulating salt and body-fluid balance. In cells, these peptides are made as precursor forms that are converted to active forms by proteolytic processing. Corin is a transmembrane serine protease identified in the heart. Corin converts pro-atrial natriuretic peptide (pro-ANP) to active ANP in a sequence-specific manner. In mice, lack of corin prevents the conversion of pro-ANP to ANP and causes salt-sensitive hypertension. The hypertensive phenotype is exacerbated when the mice become pregnant. In humans, single nucleotide polymorphisms in the corin gene have been identified in African Americans with hypertension and cardiac hypertrophy. These data indicate that corin is important in maintaining normal blood pressure *in vivo* and that corin deficiency may contribute to hypertension and heart disease in patients.

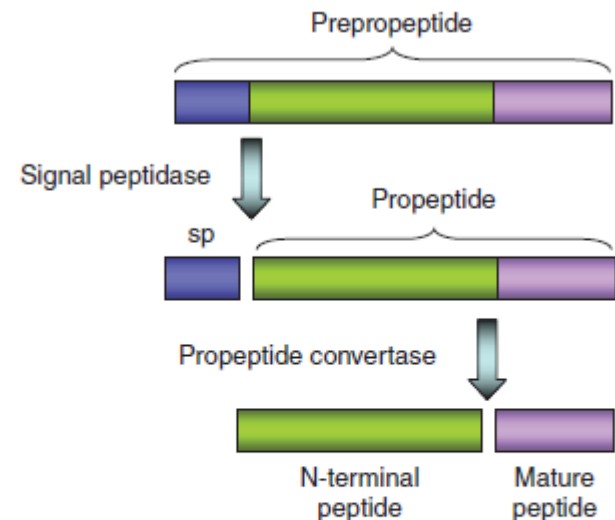


Figure 1 | Processing of natriuretic peptides. Natriuretic peptides are synthesized as prepropeptides. The signal peptide (sp) is removed by signal peptidase. The propeptide is cleaved by propeptide convertase to produce an inactive N-terminal peptide and a C-terminal mature peptide that is biologically active.

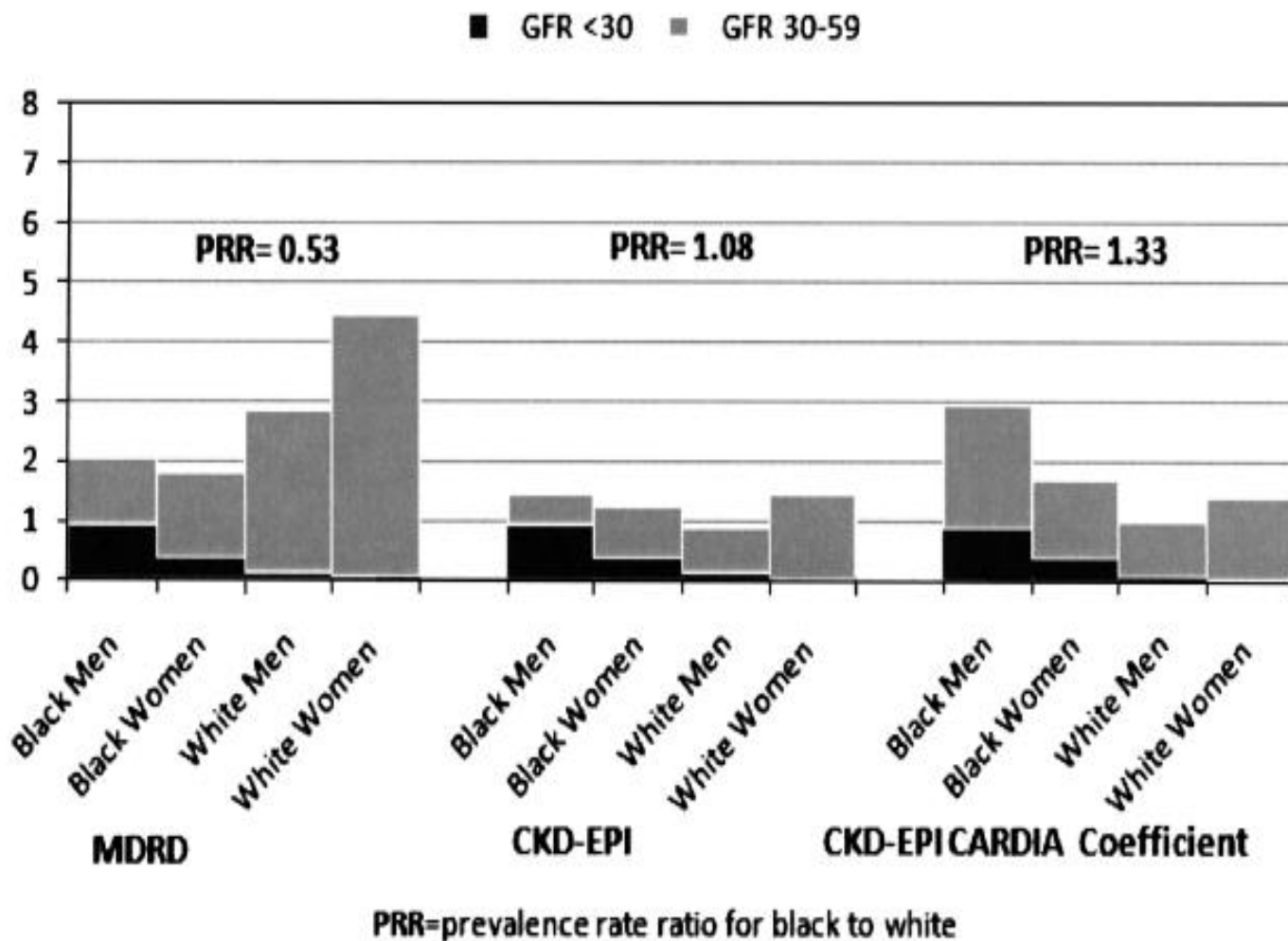
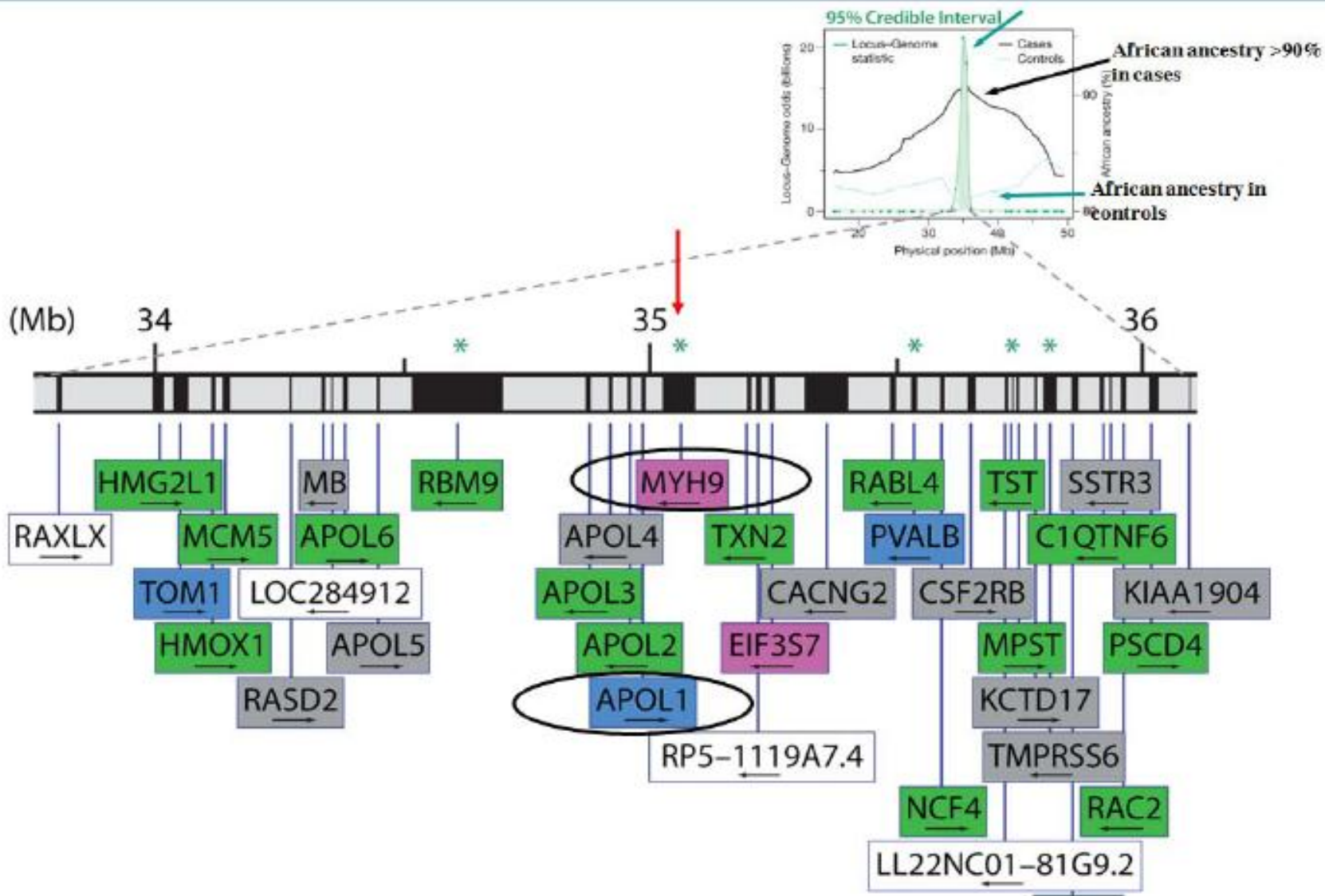


Fig. 1. Prevalence of CKD (GFR <60 mL/min/1.73 m²) by race and gender using MDRD, CKD-EPI equation and CKD-EPI equation with CARDIA-derived coefficient.

Table 3.3. Outcomes studies with primary CKD progression end point in which post hoc analyses showed significant risk reduction for CKD progression with proteinuria reduction

Study	Treatment Groups	Mean Follow-up	Change in Proteinuria	Relevant Outcomes
AASK	Ramipril, metoprolol, or amlodipine with conventional or intensive blood pressure targets	4 years	-20% for ramipril -14% for metoprolol +58% for amlodipine ^a	Ramipril slowed the progression of renal disease more than the other groups

Figure 3. Admixture (MALD) ESKD associated region: centered on *MYH9*; 34 other genes were found in the 2 mb 95% confidence interval



Adapted with permission from Kopp et al. 2008¹⁹.