Kidney Disease , Hypertension and Cardiovascular Risk

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Chronic Kidney Disease
Definition

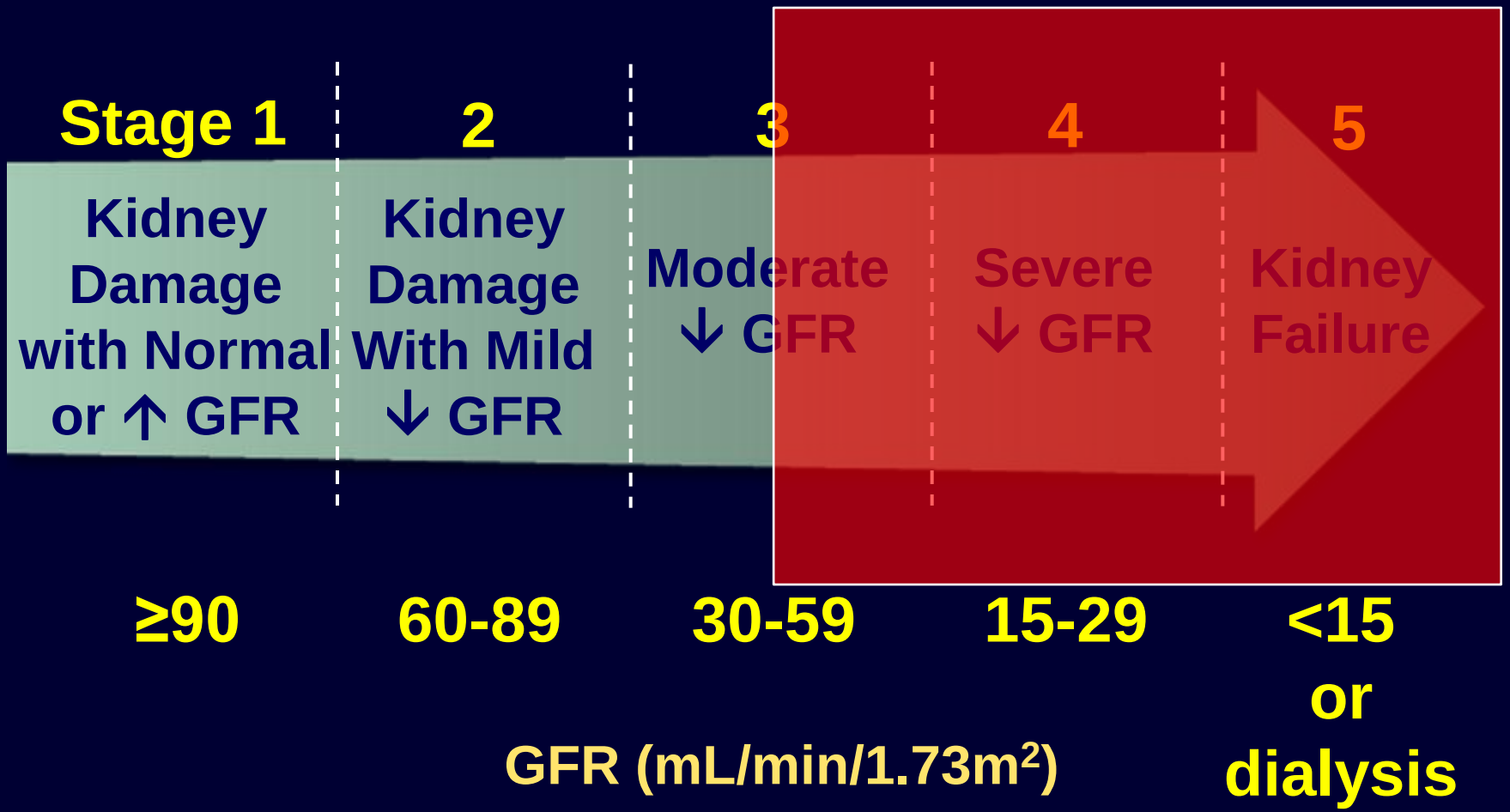
Kidney damage for ≥ 3 months

- Structural or functional abnormalities with or without decreased GFR
  - Pathological abnormalities
  - Abnormal blood or urine tests
  - Abnormal imaging

GFR <60 mL/min/1.73m2 for ≥ 3 months

K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. NKF 2002

The Five Stages of CKD



Awareness of CKD per CKD Stage

	Stage 1 and ACR 30 mg/g	Stage 2 and ACR 30 mg/g	Stage 3	Stage 4	Stage 5
2000–2002					
Number	190	313	2113	112	25
(% aware)	3.16 (0.66–5.65)	2.56 (0.80–4.31)	4.45 (3.57–5.33)	15.18 (8.50–21.85)	40.00 (20.40–60.74)
2003–2005					
Number	**1,187**	**1,846**	**6,753**	**315**	**53**
(% aware)	**4.55 (3.36–5.74)**	**5.25 (4.24–6.27)**	**5.69 (5.13–6.24)**	**38.10 (32.72–43.47)**	**47.10 (33.60–60.74)**

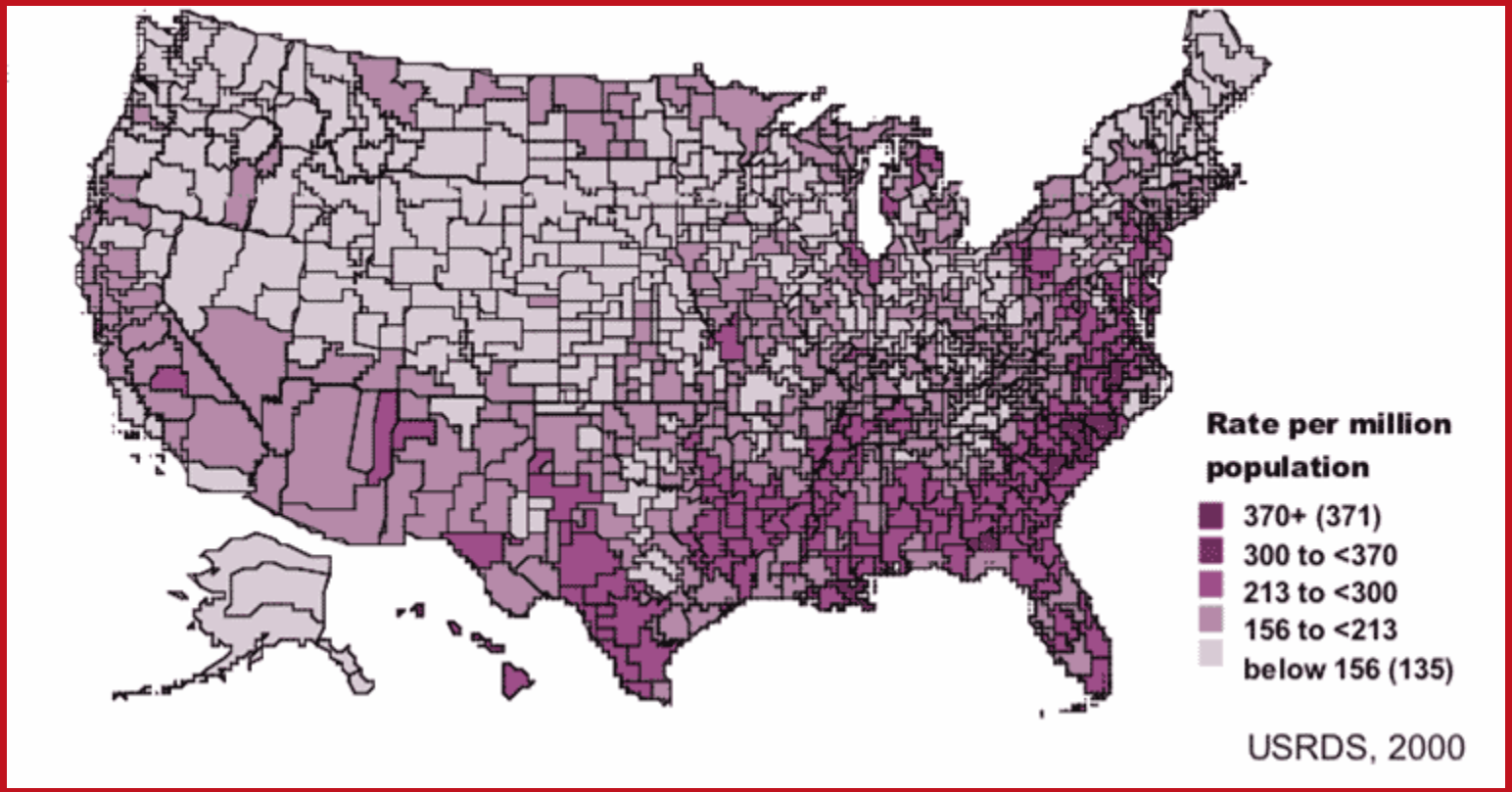
Values shown are number or percent (95% confidence interval); awareness defined as a positive response to the question :*Have you ever been told you have kidney disease*?
Albumin-creatinine ratio in mg/g may be converted to mg/mmol by dividing by 8.84.

Saabs G et.al. Am J Kidney Dis. 2008;52:382-386

NKDEP

Incidence of Kidney Failure

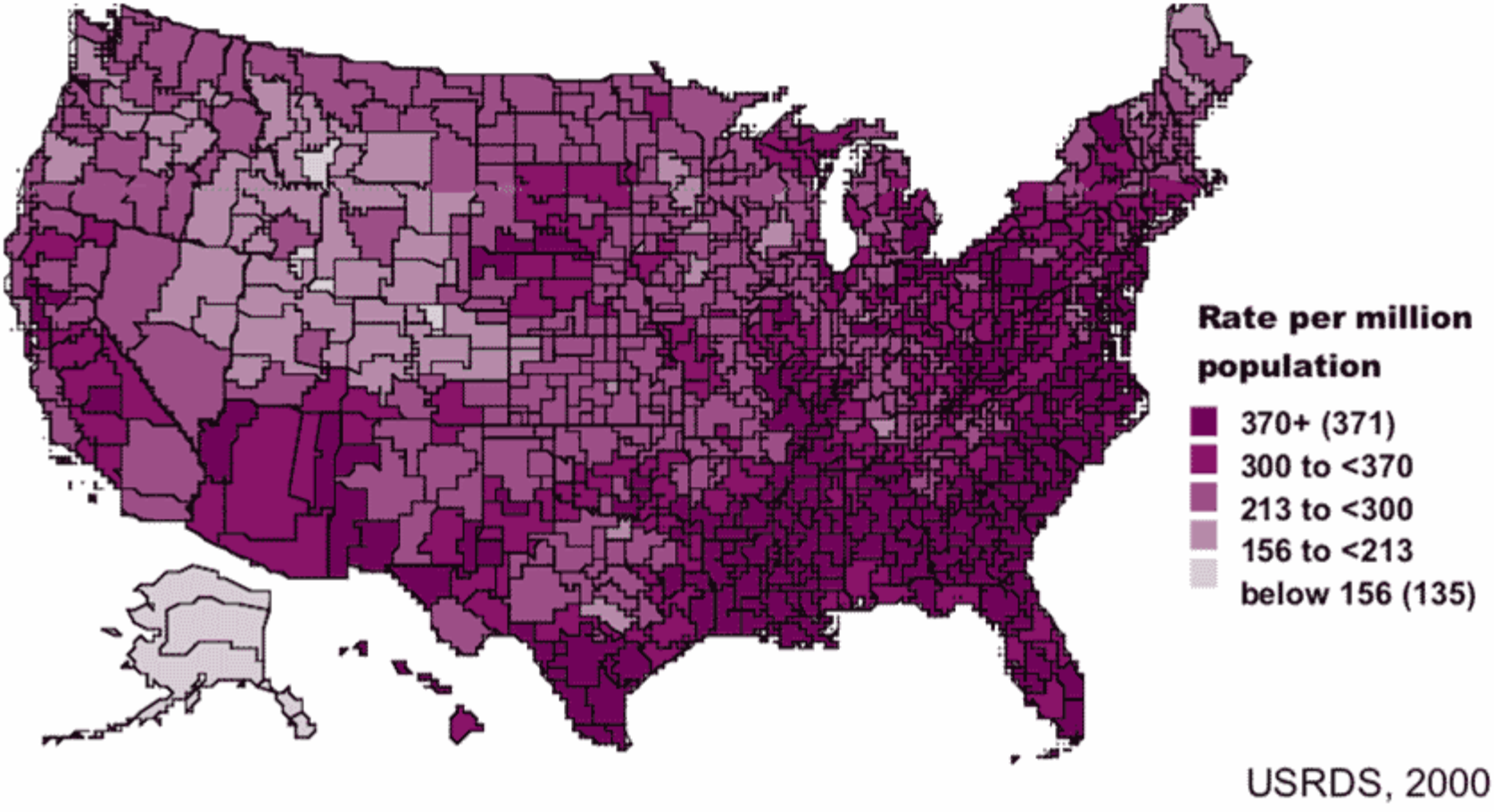
per million population, 1990, by HSA, unadjusted



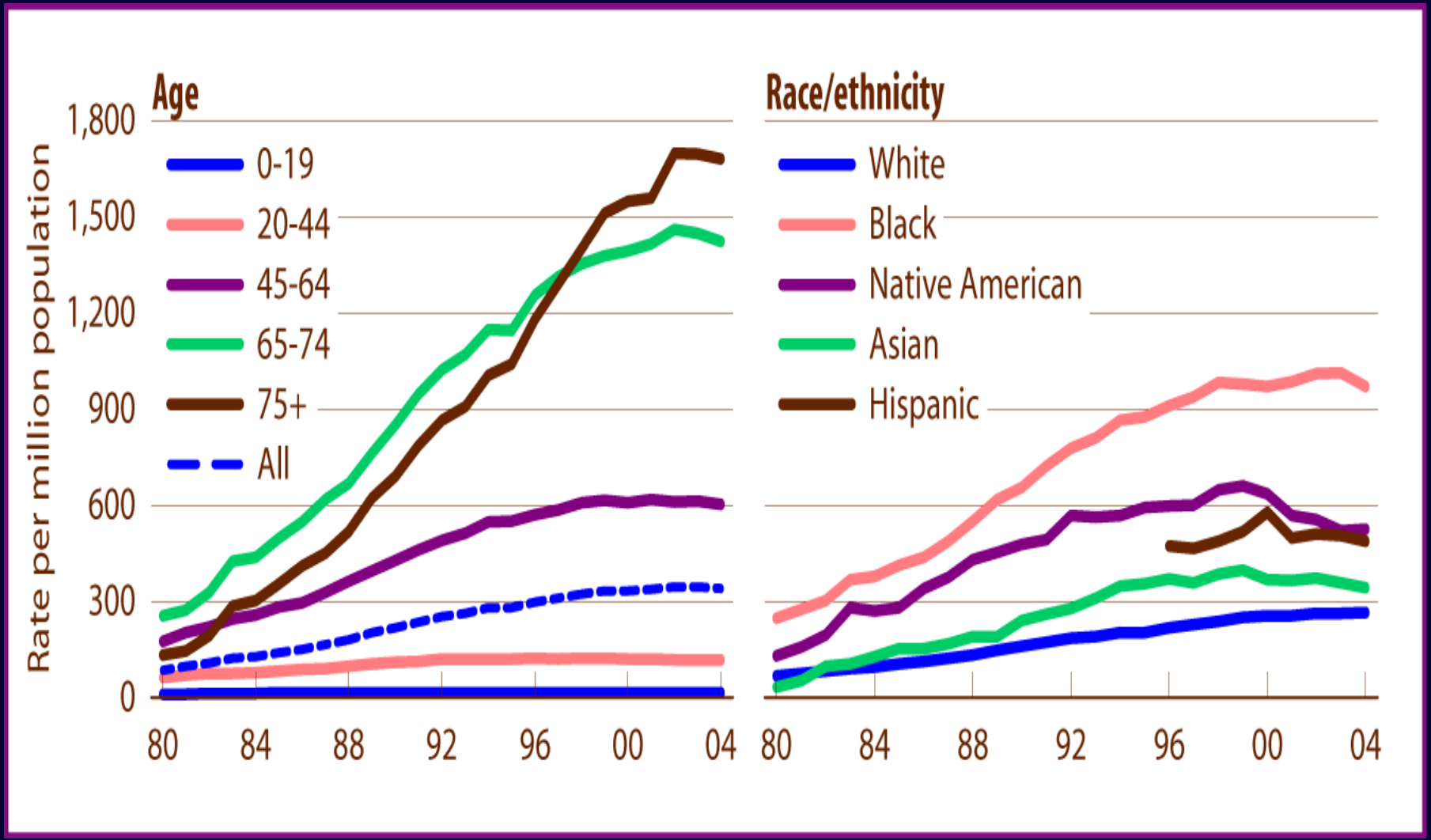
NKDEP

Incidence of Kidney Failure

per million population, 2000, by HSA, unadjusted



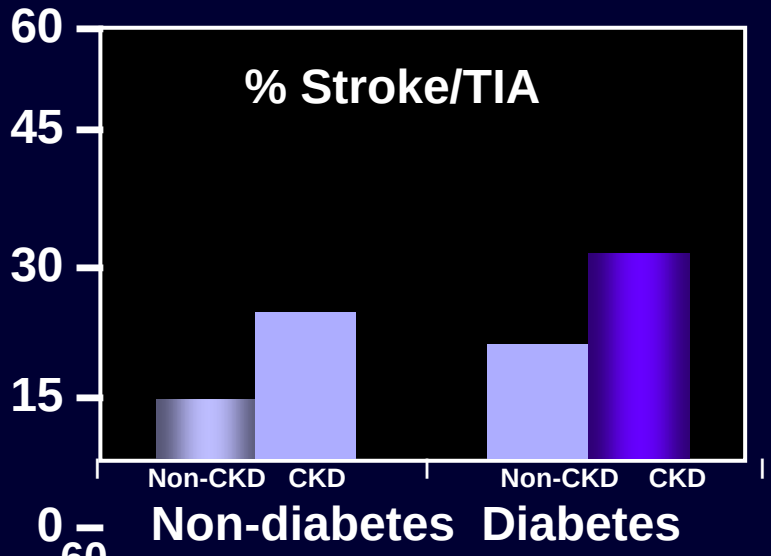
ESRD Incident Rates
Adjusted by Age & Race/Ethnicity

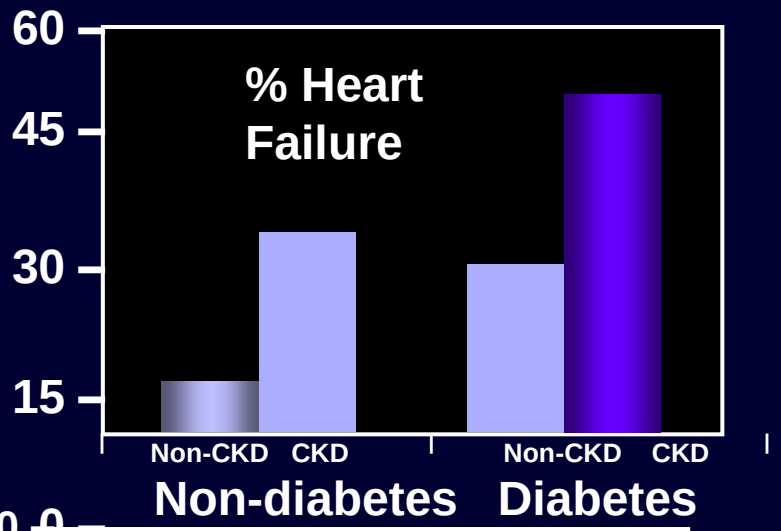


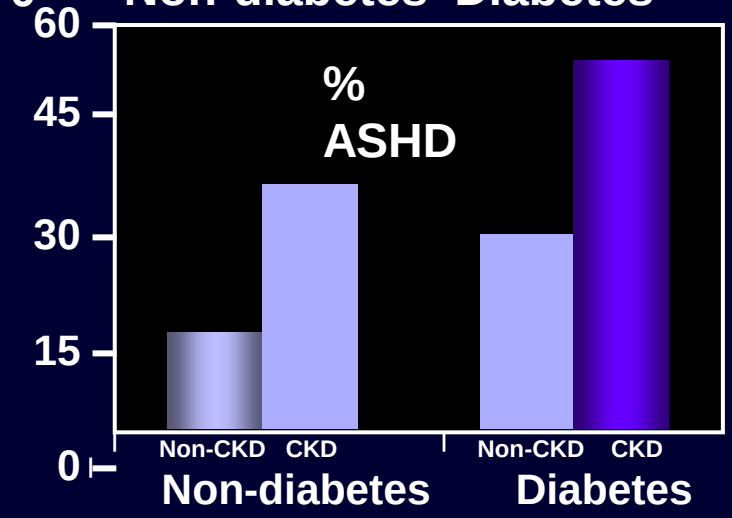
2006 ADR USRDS

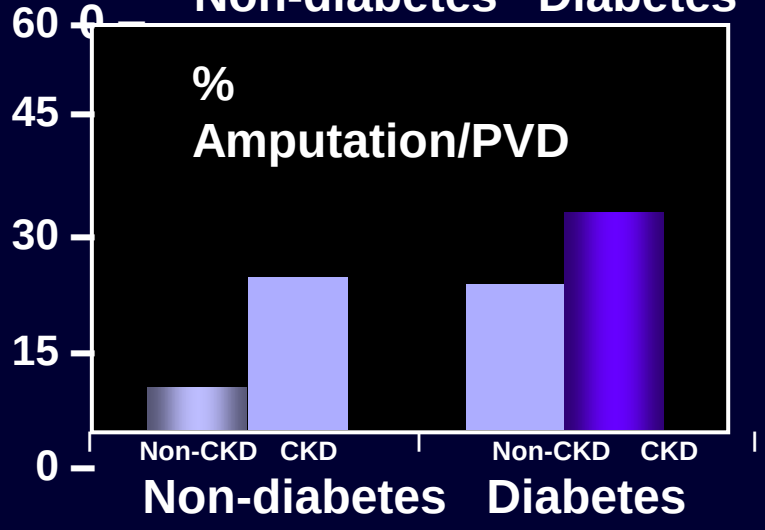
Cardiovascular Comorbidities,

5% Medicare Sample, by Diabetes and CKD Status 1999-2000









USRDS, 2000.

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

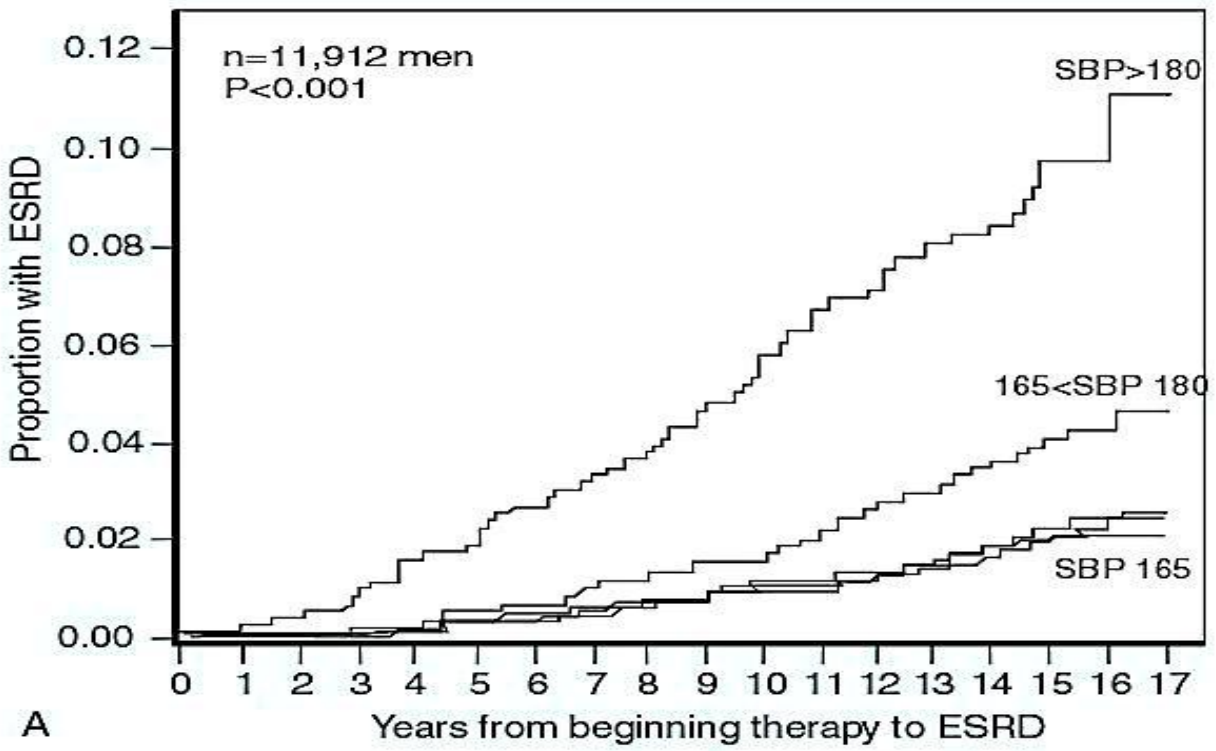
† This group served as the reference group.

Go, A. S. et al. N Engl J Med 2004;351:1296-1305

Risk Factors for CKD

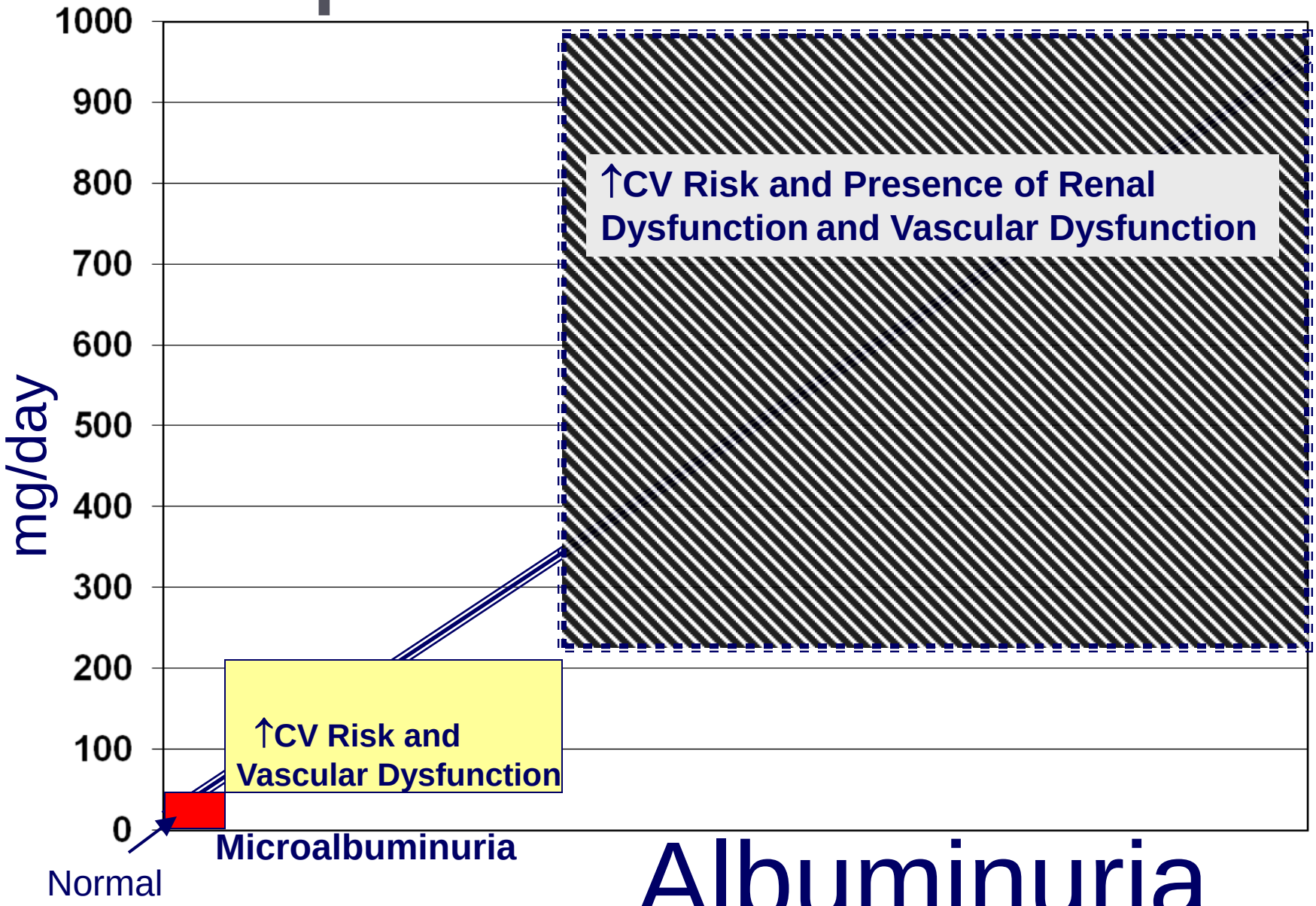
- Diabetes
- Hypertension
- Older age
- Family history of kidney disease or diabetes
- Male gender
- Racial/Ethnic Background:
  - African American
  - Native American
  - Asian-American
  - Pacific Islander
  - Latin American
- Tobacco Use

17 Year Follow-Up from VA Hypertension Clinics on ESRD

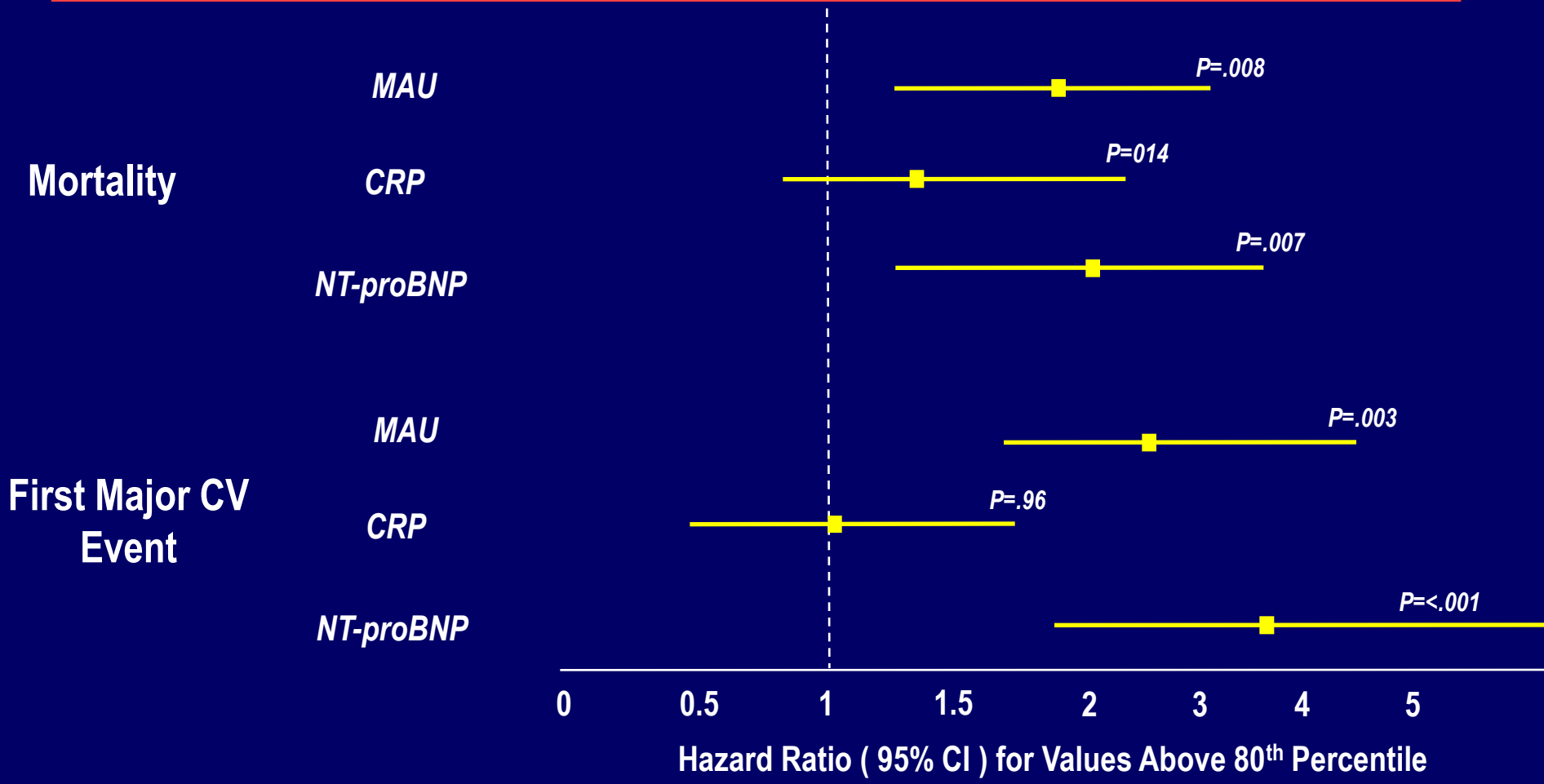


H. M. Perry, Jr., et.al Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 25 (4 Pt 1):587-594, 1995.

The Spectrum of Albuminuria



Use of MAU, CRP, and BNP as Predictors of Mortality and CV Events



Adjusted for age, sex, smoking, DM, HTN, Afib, LVEF<50%, LVH, total cholesterol, serum creatinine. Mortality analysis based on 91 deaths, and CV event data based on 63 events due to missing covariates. The 80th percentile corresponds to values more than 5.85 pg/mL for NT-proBNP, 5.76 mg/L for CRP, and 18.4 mg/g for MAU.

Kistorp K, et al. *JAMA*. 2005;293:1609-1616.

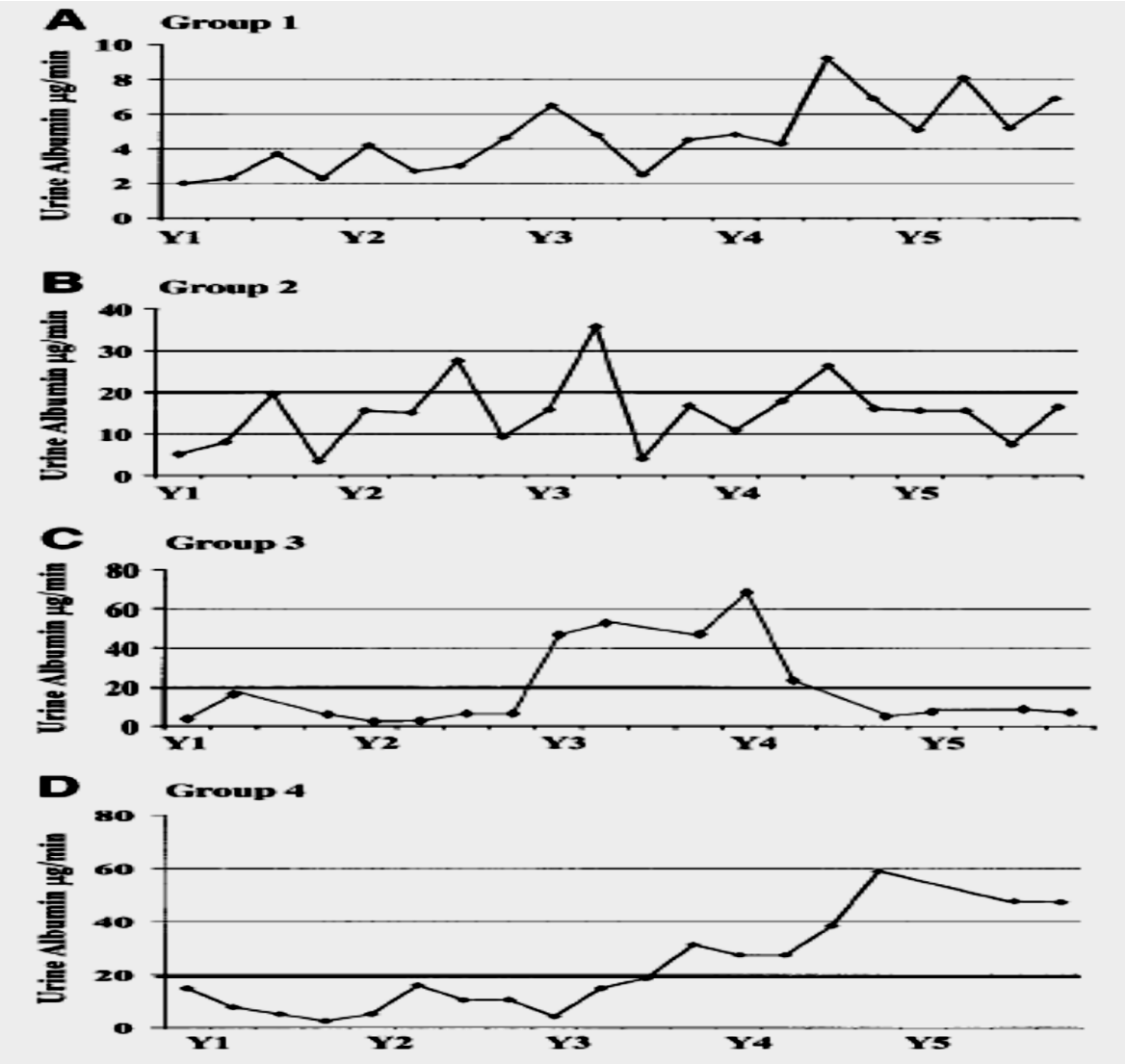
VOLUME FRACTION OF THE MESANGIUM (Vv Mes) IN THREE GROUPS OF DIABETIC PATIENTS

Chavers BM *et al. N Eng J Med* 1989;320:966

The Early Natural History of Nephropathy in Type 1 Diabetes: Predictors of 5-Year Urinary Albumin Excretion Rate Patterns in Initially Normoalbuminuric Patients

Steinke J et.al. Diabetes 2005;54:2164

All Groups had mesangial expansion and **stable** GFR at 5 years



Clinical Trials and Renal Outcomes Based on Proteinuria Reduction

Increased Time to Dialysis

(30-35% proteinuria reduction)

- Captopril Trial-N Engl J Med, 1993
- AASK Trial-JAMA, 2001
- RENAAL-N Engl J Med, 2001
- IDNT-N Engl J Med, 2001

No Change in Time to Dialysis

(NO proteinuria reduction)

- DHPCCB arm-IDNT
- DHPCCB arm-AASK

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) **Hot Topics in Hypertension**
Hanley and Belfus, Philadelphia, 2004, pp.249-252.

Meta-analysis of Trials on Proteinuria Reduction with RAS Blockade-Ratio of means (95% CI)* for change in proteinuria, by randomized therapy, over two follow-up intervals

Randomized Therapy	1-4 Months	5-12 Months
ARBs vs placebo	0.57 (0.47–0.68)	0.66 (0.63–0.69)
ARBs vs ACE-I	0.99 (0.92–1.05)	1.08 (0.96–1.22)
ARBs vs CCBs	0.69 (0.62–0.77)	0.62 (0.55–0.70)
ARB+ACE-I vs ARBs	0.76 (0.68–0.85)	0.75 (0.61–0.92)
ARB+ACE-I vs ACE-I	0.78 (0.72–0.84)	0.82 (0.67–1.01)

Bold=significant P<0.01 at 5-12 Months

Kunz R et al. ***Ann Intern Med*** 2008; 148:30-48

Design of Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)

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Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can slow the progression of diabetic nephropathy. Even with ACEI or ARB treatment, the proportion of patients who progress to end-stage renal disease (ESRD) remains high. Interventions that achieve more complete blockade of the renin–angiotensin system, such as combination ACEI and ARB, might be beneficial. This approach may decrease progression of nondiabetic kidney disease. In diabetic nephropathy, combination therapy decreases proteinuria, but its effect in slowing progression is unknown. In addition, the potential for hyperkalemia may limit the utility of combined therapy in this population. VA NEPHRON-D is a randomized, double-blind, multicenter clinical trial to assess the effect of combination losartan and lisinopril, compared with losartan alone, on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria.

The primary endpoints are time to (1) reduction in estimated GFR (eGFR) of > 50% (if baseline < 60 ml/min/1.73 m^2); (2) reduction in eGFR of 30 ml/min/1.73 m^2 (if baseline ≥ 60 ml/min/1.73 m^2); (3) progression to ESRD (need for dialysis, renal transplant, or eGFR < 15 ml/min/1.73 m^2); or (4) death. The secondary endpoint is time to change in eGFR or ESRD. Tertiary endpoints are cardiovascular events, slope of change in eGFR, and change in albuminuria at 1 yr. Specific safety endpoints are serious hyperkalemia (potassium > 6 mEq/L, requiring admission, emergency room visit, or dialysis), all-cause mortality, and other serious adverse events.

This paper discusses the design and key methodological issues that arose during the planning of the study.

Clin J Am Soc Nephrol 4: 361–368, 2009. doi: 10.2215/CJN.03350708

In 2003, approximately 50% of incident ESRD was due to diabetes; of these cases, 90% were due to type 2 diabetes (1). The overall rate of ESRD secondary to diabetes has risen 68% since 1992 (1). Use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can slow the progression of diabetic kidney disease. For example, the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study examined losartan *versus* placebo added to a standard antihypertensive regimen in 1513 individuals with type 2 diabetes and overt nephropathy (2). Losartan decreased the risk of doubling of serum creatinine, ESRD, or death by 16%; decreased the risk of doubling of serum creatinine by 28%; and decreased the risk of ESRD by 25% compared with placebo. In the Irbesartan in Diabetic Nephropathy (IDNT) study, which examined irbesartan *versus* amlodipine *versus* placebo in 1715 individuals with overt nephropathy, use of ARBs decreased the risk of doubling of serum creatinine, end-stage renal disease or death by 20%, decreased the risk of doubling of serum creatinine by 33% and decreased the risk of end-stage renal disease by 23% compared with placebo (3). Despite the benefit of ARBs

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Fried L et.al. Clin J Am Soc Nephrol 4: 361–368, 2009

Aldosterone Blockade

- RALES (Pitt B et.al. N Engl J Med 1999)
- EPHESUS (Pitt B et.al. N Engl J Med, 2003)
- EPHESUS -K(Pitt B et.al. Circulation, 2008)
- Meta-analysis-antiproteinuric effects (Bomback A Am J Kidney Dis 2008)

Odd Ratio of Hyperkalemia Development following Aldosterone Antagonism in Nephropathy

Variable	Odds Ratio	P value
Baseline eGFR $\leq$45 ml/min/1.73m^2 + serum potassium >4.5 mEq/L	8.71 (2.89-24.8)	<0.0001
Baseline eGFR $\leq$45 ml/min/1.73m^2 + >30% reduction in eGFR	7.76 (2.13-29.8)	<0.0001
Baseline eGFR $\leq$45 ml/min/1.73m^2	2.97 (1.14-21.3)	<0.001
Baseline eGFR $\leq$45 ml/min/1.73m^2 + >15 mmHg in systolic BP	3.98 (0.89-27.1)	0.09

Khosla N et.al. Am J Nephrol 2009;30:418

Major Factor Limiting Antiproteinuric Effects of RAS Blockade

- SALT

Sodium Intake Limits Antiproteinuric Effects of RAS Blockade

- Sodium Intake Above 4 grams per day reduces antiproteinuric effects of RAS Blockade by up to 50%-

(Heeg et.al Kidney International, 1989;36:272)

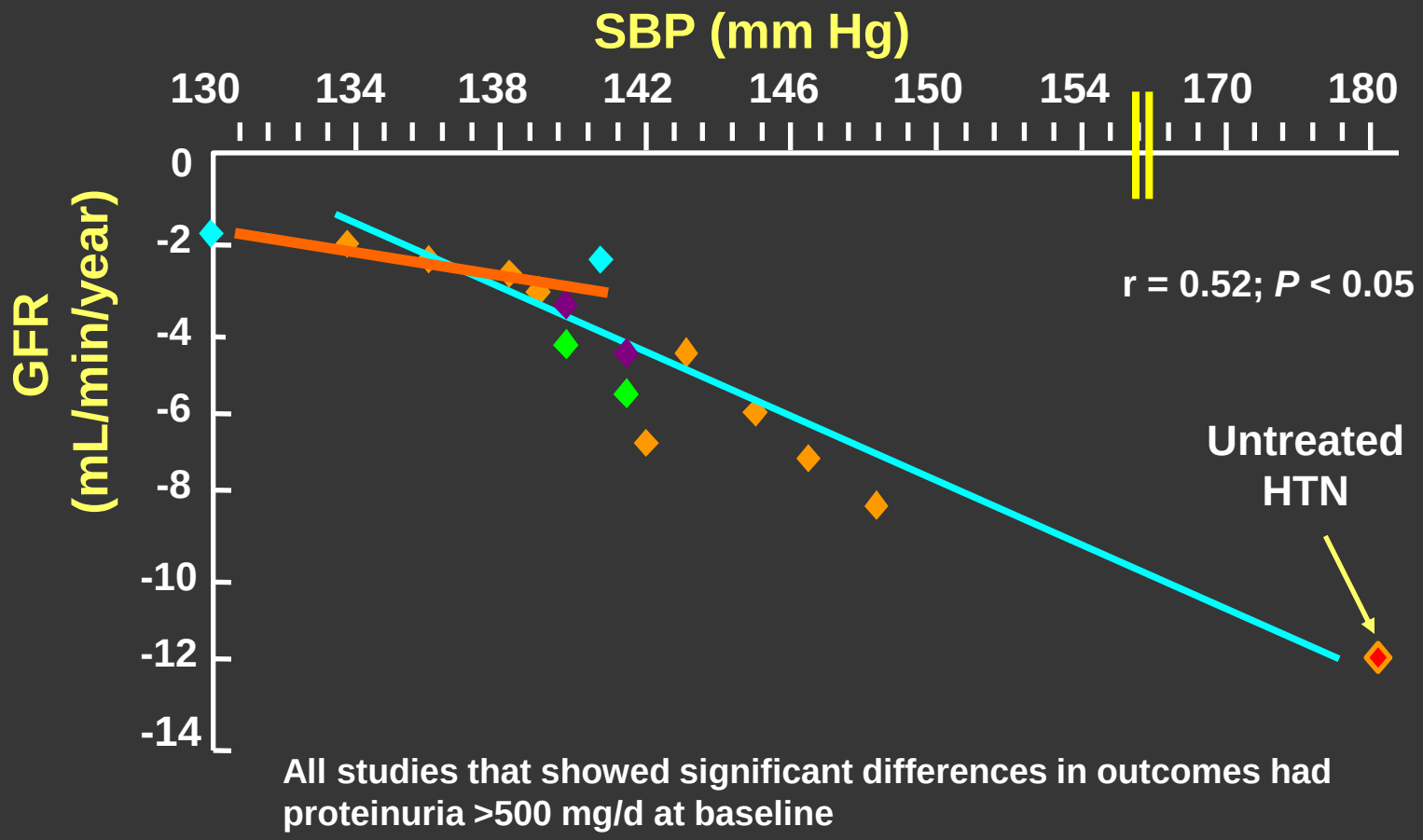
- Use of thiazide diuretics only partially restores antiproteinuric effect

(Buter, H. et.al. Nephrol Dialysis & Transpl 1998:16;1682)

- Mechanism for increased sodium on proteinuria is thought to be related to increased oxidant stress (partially) and increases in blood pressure (partially)

(Mishra I et.al. Curr Hypertens Rep 2005;7:385;Laffer C et.al. Hypertension 2006;47:434)

Summary of Studies on Nephropathy Progression



Modified from Bakris GL et.al.Am J Kidney Dis, Sept. 2000 MDRD, N Engl J Med, 1993; AIPRI, N Engl J Med, 1996; REIN, Lancet,1997;AASK, JAMA 2002;Captopril Trial, N Engl J Med, 1993;Hannadouche et.al B Med J, 1994; Bakris et.al Kidney Int., 1996;Bakris et.al Hypertension, 1997;IDNT- NEJM, 2001;RENAAL-NEJM, 2001; ABCD, Diabetes Care (Suppl), 2000

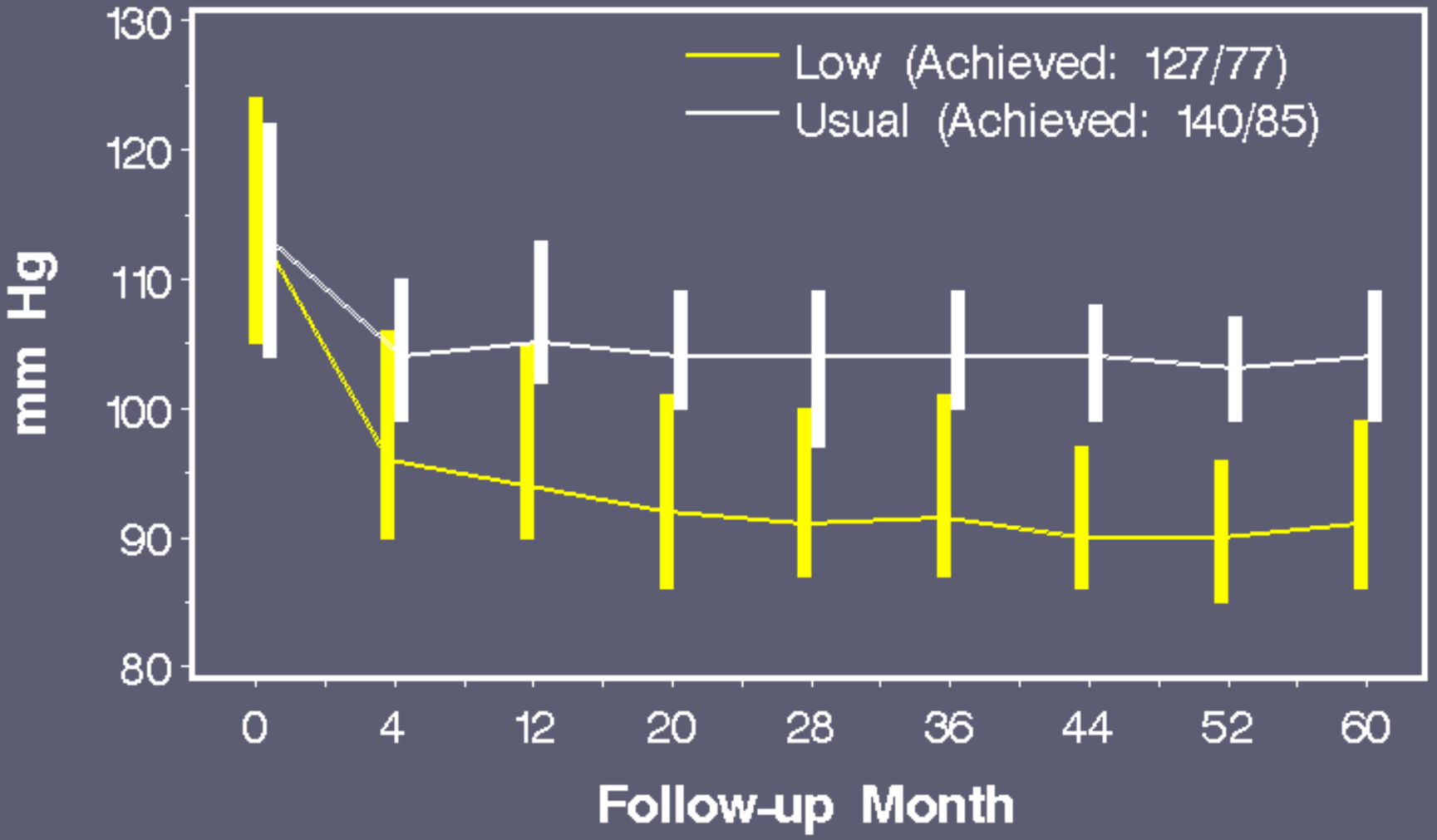
2 Phases of AASK

- *Trial with a 2 x 3 factorial design (completed Sept 2001)*
  - 1,094 African-Americans with non-diabetic, hypertensive CKD (GFR of 20-65 ml/min/1.73 m^2)

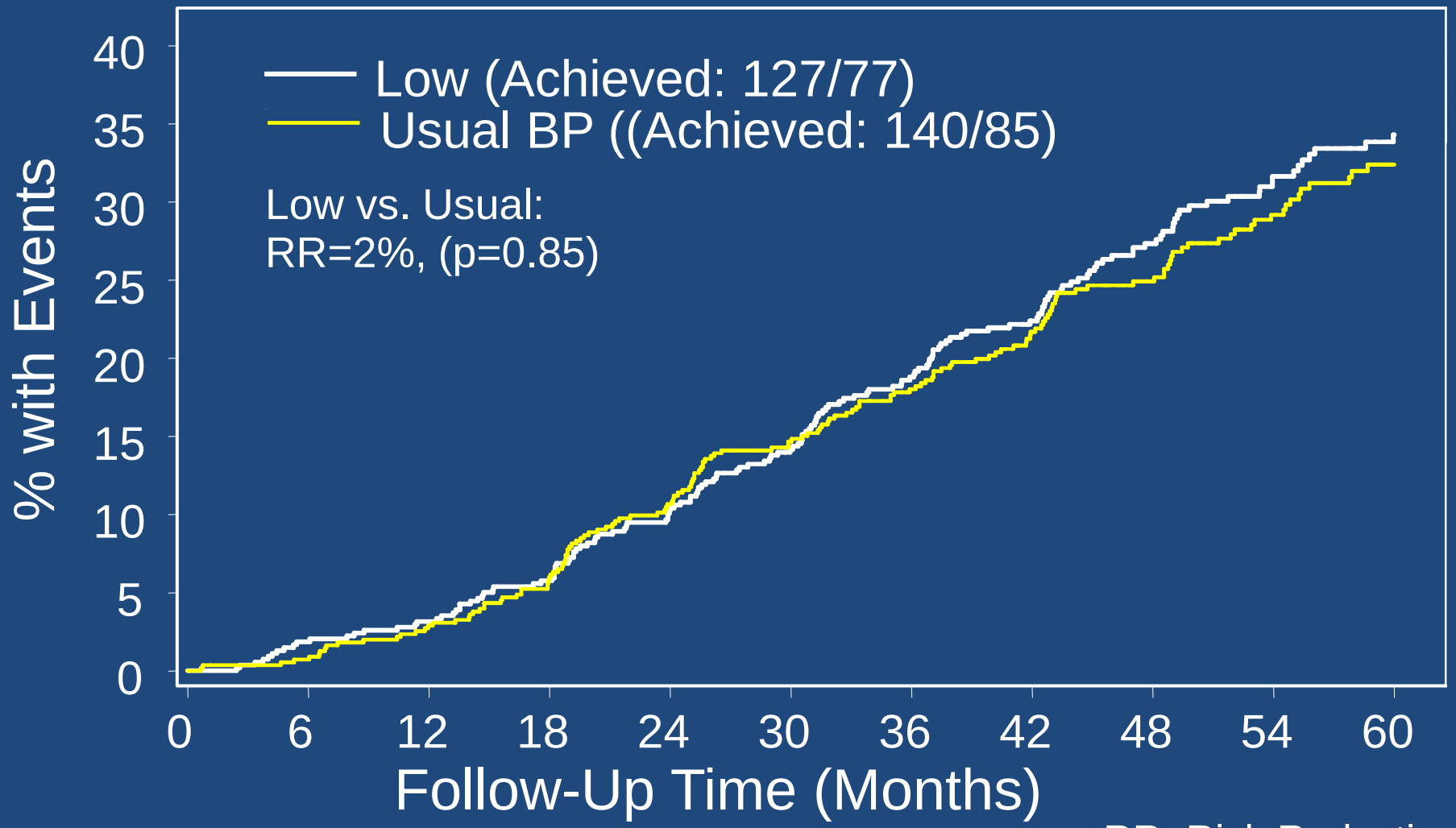
	Initial therapy with:		
	Ramipril	Amlodipine	Metoprolol
Low BP Goal: MAP < 92	A	B	C
Usual BP Goal: MAP 102-7	D	E	F

- *Cohort phase (completed June 2007)*
  - All participants received recommended BP therapy:
    - ACEI (or ARB)
    - BP goal < 130/80 mmHg
  - 1^0 outcome: composite 2X sCreatinine, ESRD, or death

Mean Arterial Pressure During Follow-up



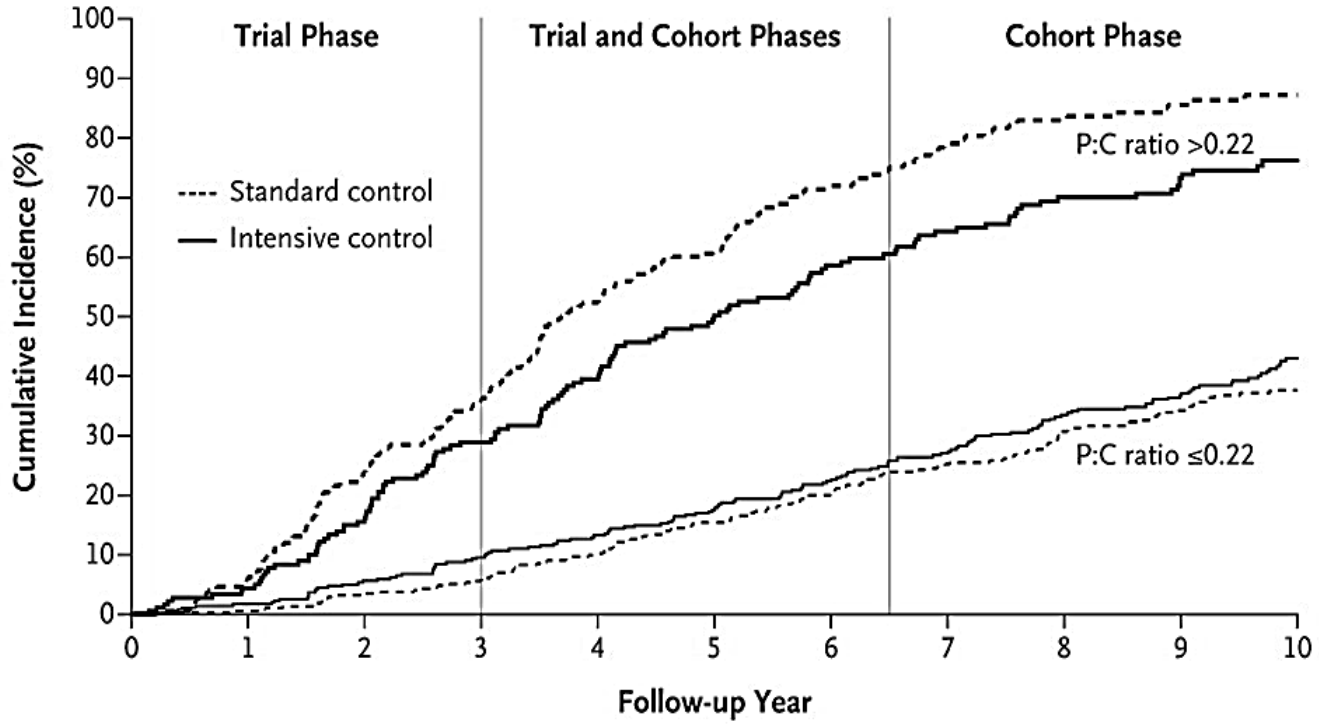
Composite Clinical Events: Declining GFR Event, ESRD or Death by BP Goal



RR=Risk Reduction

Wright JT Jr. et.al. JAMA 2002

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

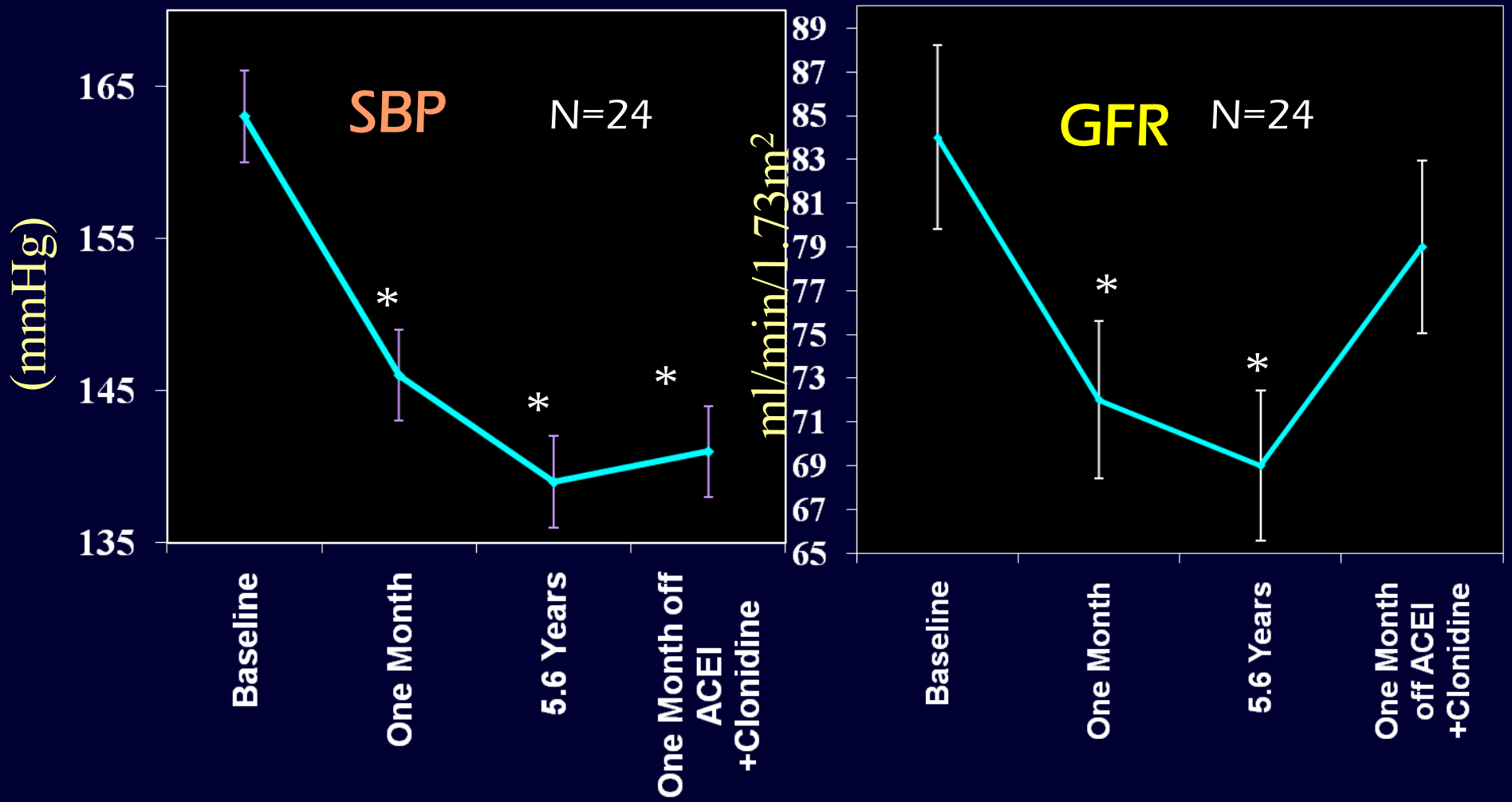
Appel LJ et al. N Engl J Med 2010;363:918-929.

What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

Group	Goal BP (mmHg)	Initial Therapy
Canadian HTN Soc (2010)	<130/80	ACE Inhibitor/ARB*
ADA (2010)	<130/80	ACE Inhibitor/ARB*
ASH (2008)	<130/80	ACE Inhibitor/ARB*^
KDOQI (NKF) (2007)	<130/80	ACE Inhibitor/ARB*
ESH (2007)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2002)	<130/80	ACE Inhibitor/ARB*
Natl. Kidney Foundation (2000)	<130/80	ACE Inhibitor*
British HTN Soc. (1999)	<140/80	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

* Indicates use with diuretic

Impact of ACE Inhibition on Blood Pressure and GFR: Acute vs. Chronic Effects



*P<0.05 compared to baseline

Complications Associated with CKD

- Hypertension: CKD and CV disease
- Dyslipidemia: CKD progression and CV disease
- Anemia: CKD progression and CV disease
- Cardiovascular disease and mortality
- Diabetes: CKD progression and CV disease
- Osteodystrophy
- Malnutrition
- Metabolic Acidosis

Summary

- Advanced CKD is growing by an alarming degree
- Ideal steps for prevention include a program of CV risk reduction, i.e. glycemic, lipid and BP control. Additionally, avoid dehydration, routine NSAID or Tylenol use.
- In those with established CKD-<3 grams sodium daily, BP <140/90, HbA 1 c <7% and LDL <70

If Blood Pressure >130/80 mm Hg in Diabetes (*eGFR ≥ 50 ml/min^*)

(*if systolic BP< 20 mmHg above goal*)
Start ARB or ACE Inhibitor titrate upwards

(*if systolic BP ≥20 mmHg above goal*)
START with ACEI or ARB + thiazide diuretic* or CCB

Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)

Add Long Acting Thiazide Diuretic* or CCB

Add CCB or β blocker**

Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)

Consider and Aldosterone Receptor Blocker
If CCB used, Add Other Subgroup of CCB
(ie, amlodipine-like agent if verapamil or diltiazem already being used and the converse)
OR could add alpha blocker is not using vasodilating β blocker with alpha effects

Recheck within 4 weeks

If BP Still Not at Goal (130/80 mm Hg)

Refer to a Clinical Hypertension Specialist#

Bakris GL and Sowers JR, J AM Soc Hypertens, 2010