

Answers to the Most Common Questions about Kidney Disease

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and Human Services
National Institute of Health

NIDDK | NATIONAL INSTITUTE OF
DIABETES AND DIGESTIVE
AND KIDNEY DISEASES



Objective

To enhance the ability of primary care clinicians to manage chronic kidney disease (CKD) in the primary care setting by addressing the most common questions asked at meetings, including:

- Lab assessment of CKD
- Benefits and risks of ACEi and ARB
- Individualizing the BP goal in CKD
- How to initiate discussions with patients about progressive kidney disease and its treatment (Gayle Romancito)

Questions: Lab Assessment: UACR

- Should a trace of protein on a dipstick be investigated? **Yes**
- Is a UA adequate for screening and monitoring? **No**
- Does UACR replace the need for 24-hour urine collection? **Yes**
- Because UACR is a “continuous variable” is the evidence of CKD based on a single result or a continuous upward trend? **> 3 months**
- How often should you monitor GFR/urine albumin in a person with kidney disease in primary care? **Depends on clinical status**
- What is the first sign (lab values) of decreased renal function and when should we refer to nephrology? **DM often increased UACR**

CKD is Reduced Kidney Function and/or Kidney Damage

- Chronic kidney disease
 - Kidney function
 - GFR < 60 mL/min/1.73 m² for > 3 months with or without kidney damage
 - AND/OR***
 - Kidney damage
 - > 3 months, with or without decreased GFR, manifested by either
 - Pathological abnormalities
 - Markers of kidney damage, e.g., albuminuria
 - Urine albumin-to-creatinine ratio (UACR) > 30 mg/g

Reference: National Kidney Foundation, 2002

Urine Albumin Results are Used for Screening, Diagnosing, and Treating CKD

- An abnormal urine albumin level is often the earliest marker for kidney disease complicating diabetes
- Important prognostic marker, especially in diabetes
- Used to monitor and guide therapy
- Tool for patient education and self-management (such as A1C or eGFR)

Very Little Albumin or Protein Normally is Excreted into Urine

- Currently accepted “normal” level ≤ 30 mg/g
 - Albumin is a medium-size molecular-weight protein with a negative charge.
 - Most is reabsorbed by the tubules.
- Normal urine protein is < 150 mg/day
 - Includes albumin and other proteins.

Reference: Danziger J. *Mayo Clinical Proceedings*, 2008

Use Urine Albumin-to-creatinine Ratio (UACR) for Urine Albumin Assessment

- UACR uses a spot urine sample.
- In adults, the ratio of urine albumin to creatinine correlates closely to total albumin excretion.
- Ratio is between two measured substances (not dipstick).

Urine albumin (mg/dL) / Urine creatinine (g/dL) = UACR (mg/g) \cong Albumin excretion in mg/day

- UACR of 30 mg/g is generally the most widely used cutoff for “normal.”

Reference: <https://www.niddk.nih.gov/health-information/professionals/advanced-search/quick-reference-uacr-gfr>

Questions: Lab Assessment: eGFR

- Why is the eGFR different for African Americans? **Cr reflects muscle mass**
- Is there a different eGFR for Native Americans? **No**
- How do I explain to my lab the importance for the need of the “actual” numerical value of GFR and not just >60 ml/min. **Generally don’t.** I treat HIV patients and feel it is important to know the actual #. **caveat**
- At what point (eGFR) do you need to get actual GFR and how is actual GFR measured? **Rarely need measured GFR**
- Is eGFR part of routine/annual screening in health population? **No** How about spot urine for albumin? **No** Is it a routine screen at annual exam? **No but hard to avoid**
- How often should you monitor GFR/urine albumin in a person with kidney disease in primary care? **Depends on clinical status**
- The practice I work in has begun using Cystatin-C. Has this measure become a standard of care for measuring CKD? **Useful but no**

CKD is Reduced Kidney Function and/or Kidney Damage

- Chronic Kidney Disease

- Kidney function

- Glomerular Filtration Rate (GFR) $< 60 \text{ mL/min/1.73 m}^2$ for > 3 months with or without kidney damage

And/or

- Kidney damage

- > 3 months, with or without decreased GFR, manifested by either
 - Pathological abnormalities
 - Markers of kidney damage, e.g., albuminuria
 - Urine albumin-to-creatinine ratio (UACR) $> 30 \text{ mg/g}$

Reference: National Kidney Foundation, 2002

Estimating Equations for eGFR

- The Modification of Diet in Renal Disease (MDRD) and CKD Epi study equations are most widely used for estimating GFR.
- The variables are serum creatinine, age, race, and gender.
- MDRD eGFR = $175 \times (\text{Standardized } \mathbf{Scr})^{-1.154} \times (\mathbf{age})^{-0.203} \times (0.742 \text{ if } \mathbf{female}) \times (1.212 \text{ if } \mathbf{African American})$
 - CKD-EPI eGFR = $141 \times \min(\text{Scr} / \kappa, 1)^\alpha \times \max(\mathbf{Scr} / \kappa, 1) - 1.209 \times 0.993 \mathbf{Age} \times 1.018 \text{ [if } \mathbf{female}] \times 1.159 \text{ [if } \mathbf{African American}]$
 - The estimate is normalized to body surface area.

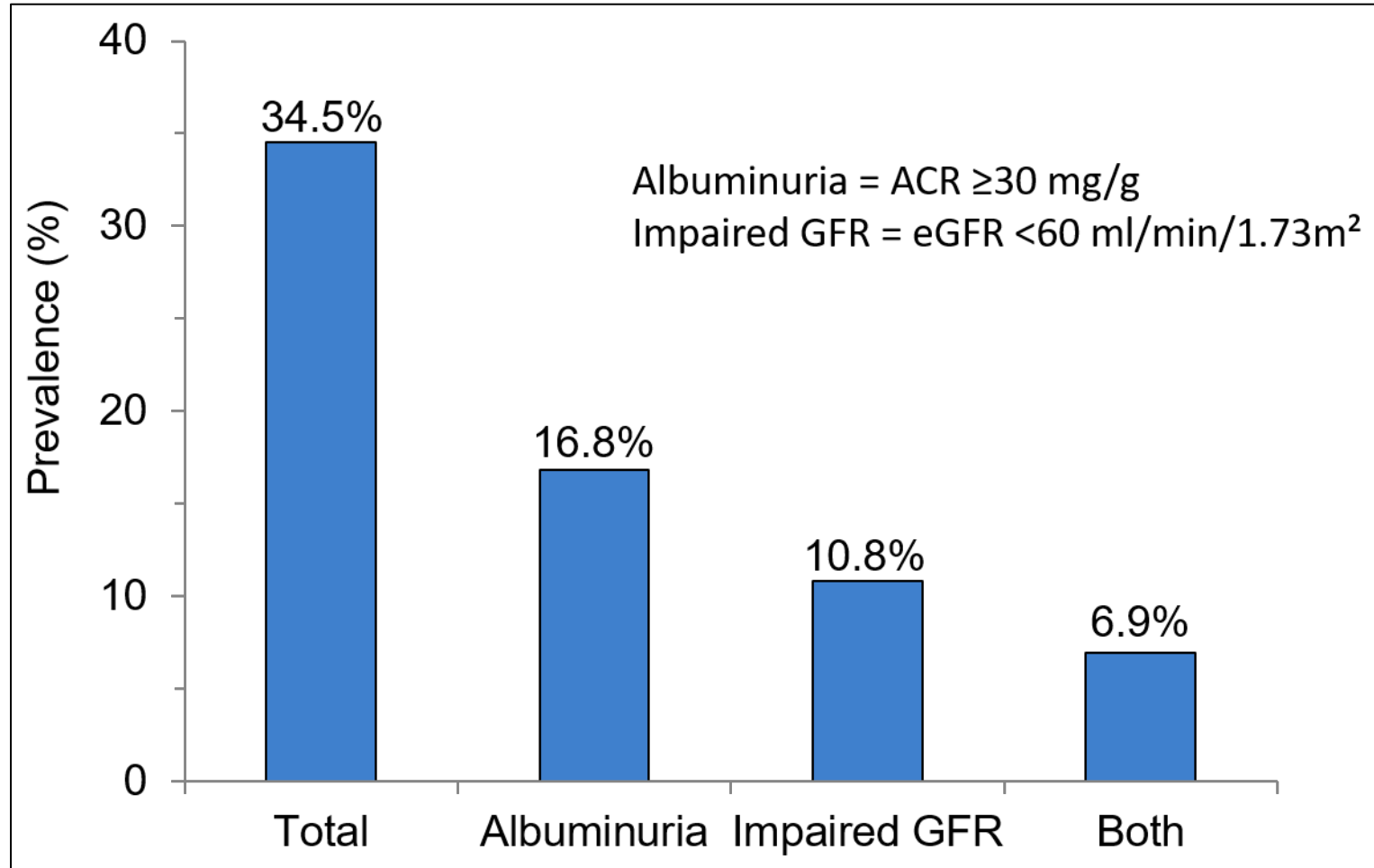
eGFR Estimates the Measured GFR

- eGFR is **not** the measured GFR.
- **eGFR estimates the measured GFR.**
- Estimating equations are derived from population-based studies.
- The performance measurement of the estimating equation is the **P30**.
- **P30** refers to the percent of GFR estimates that are ***within 30% of mGFR***.
- Example: a patient with an eGFR of 59 has an **79.9%** chance of having a measured GFR **between 42 and 78**.

Questions: Diagnosis

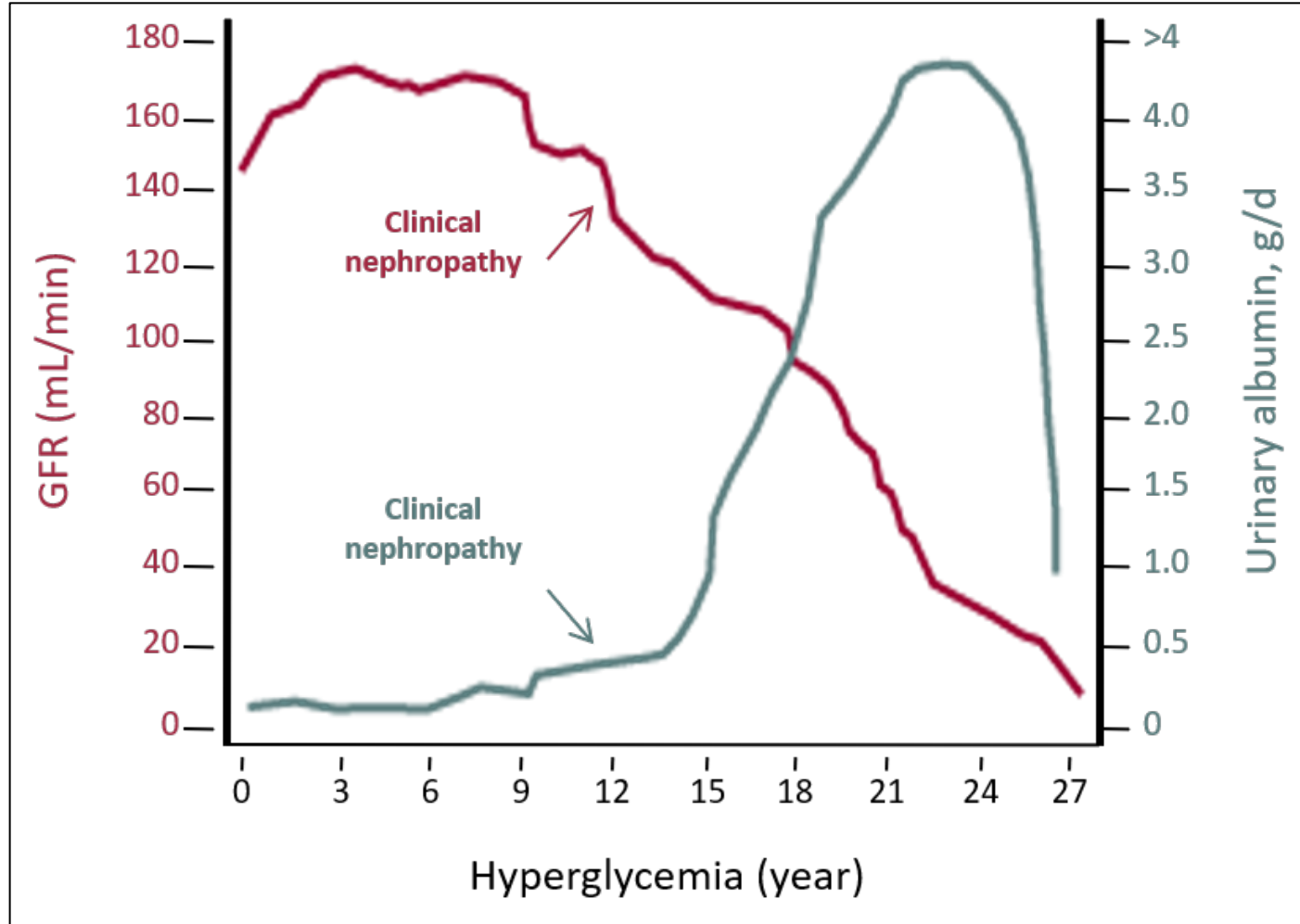
- Is there a way to know if CKD is caused by the diabetes or hypertension that a patient already has? **Predict only**
- How can you differentiate diabetic kidney disease from another CKD? **Clinical, bx if needed**
- Can one say kidney disease is caused by diabetes if the patient also has hypertension along with diabetes? **No**
- If a diabetic patient is controlled (A1c of 6.5), but has a microalbumin of 730 mg/g, does this mean they are currently having acute renal damage, or is this damage that occurred when they were uncontrolled? **AKI dx based on Cr/eGFR**

Prevalence of Diabetic Kidney Disease (DKD) Among Adults with Diabetes; United States, 2005–2008



JAMA 305:2532-2539, 2011

Natural History of Diabetic Nephropathy: Hyperglycemia Causes Hyperfiltration, May Be Followed by Albuminuria

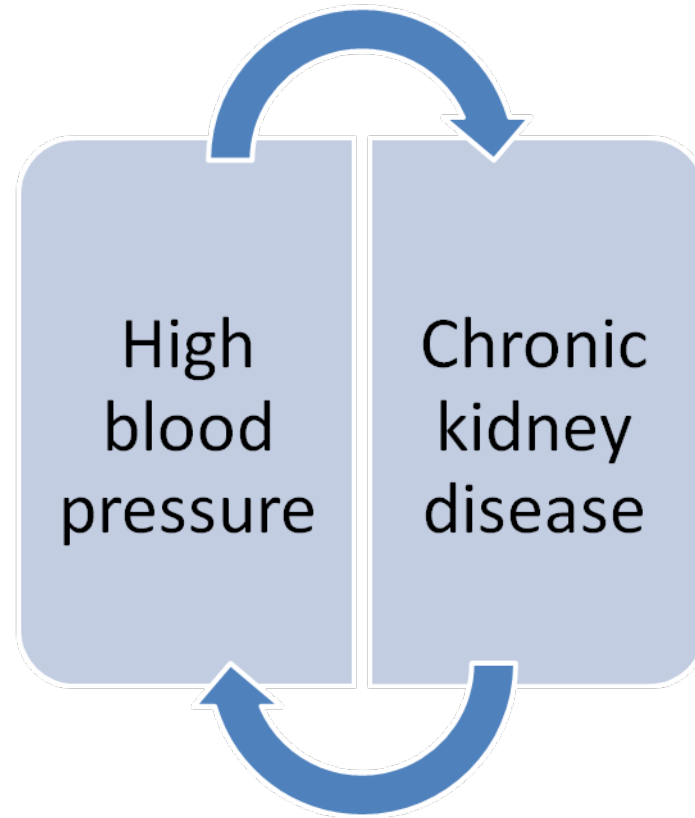


Reference: Adapted from Friedman, 1999

However

- Microalbuminuria can regress
 - de Boer IH et al, *Arch Int Med*, 2011
- Impaired GFR can develop without albuminuria
 - Molitch M et al, *Diabetes Care*, 2010
- Disease heterogeneity often not reflected by GFR
 - Bohle et al. *American Journal of Nephrology*, 1987

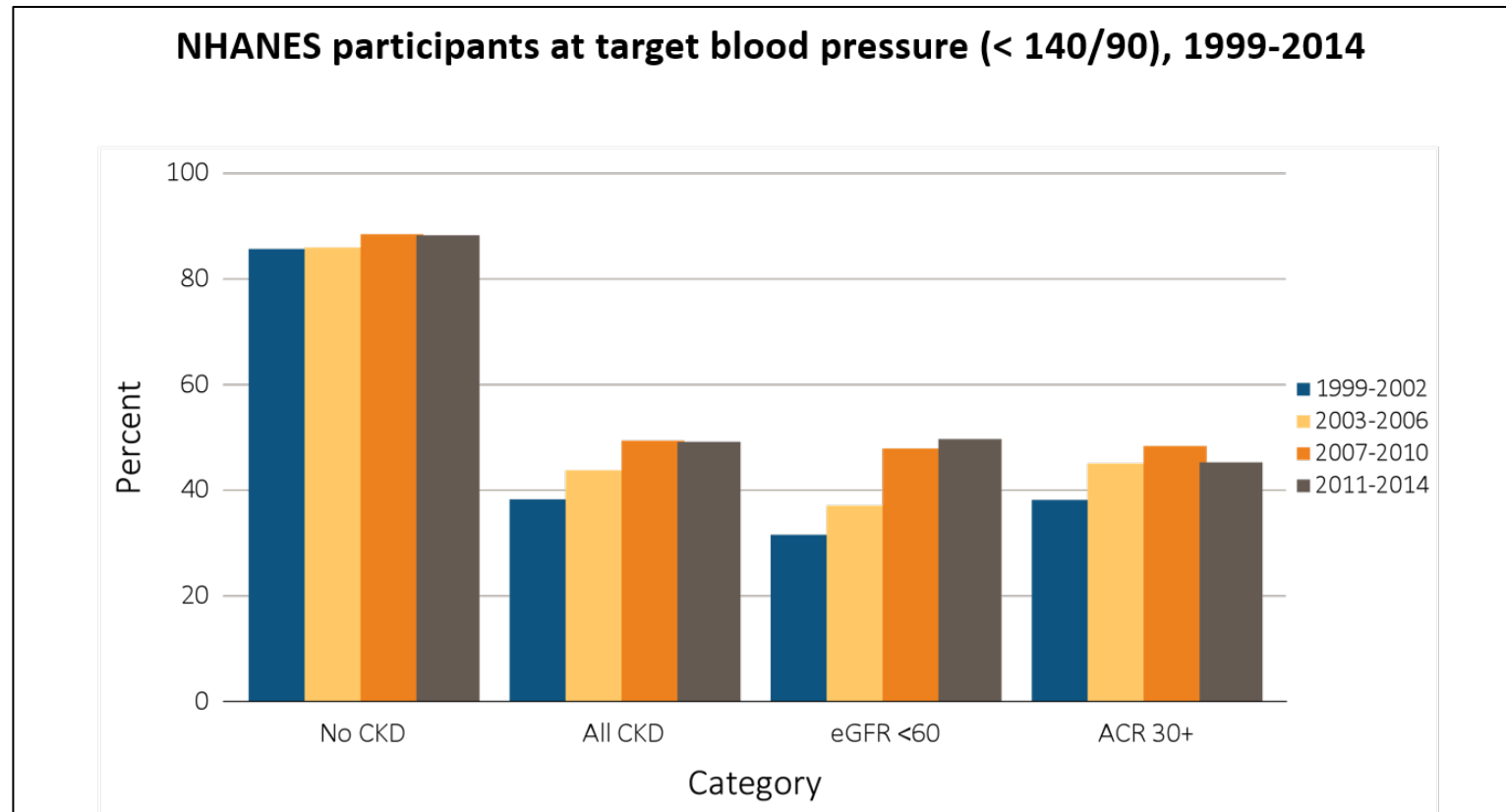
Hypertension May Cause CKD, and CKD May Cause Worsening Hypertension



Questions: Treatment of HTN

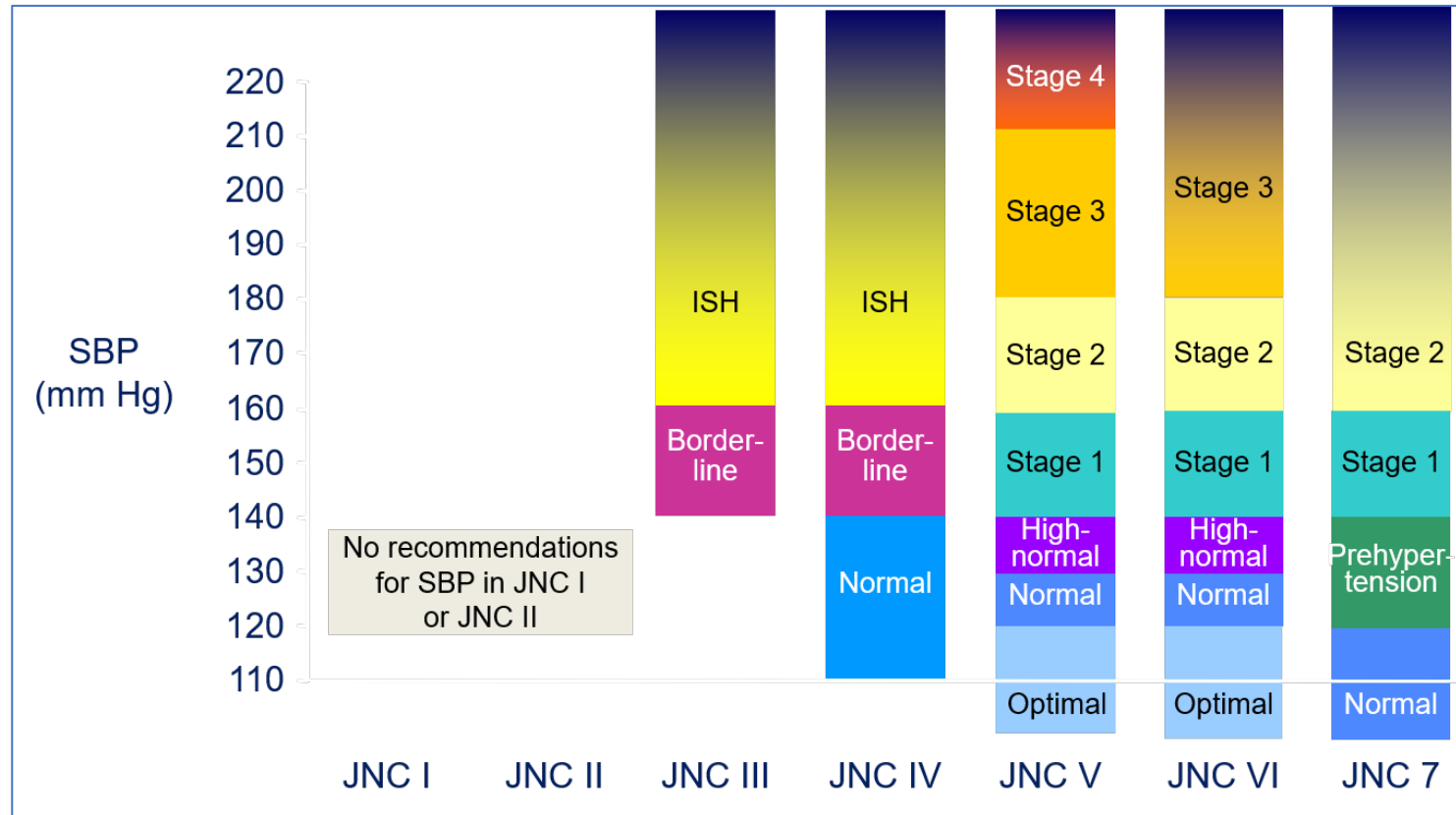
- Should patients with CKD ideally have blood pressure $> 120/80$ and $< 140/90$? **Good question**
- Is there a risk of hypo-perfusion with controlling blood pressure to $< 120/80$? **Yes**
- Can you briefly discuss the use of diuretics to treat HTN in patients with CKD?

Blood Pressure Is Poorly Controlled in People with CKD



Reference: *USRDS 2017 Annual Data Report*

Hypertension: A Moving Target JNC Classifications: Systolic Blood Pressure



JNC I. *JAMA*. 1977;237:255-261.

JNC II. *Arch Intern Med*. 1980;140:1280-1285.

JNC III. *Arch Intern Med*. 1984;144:1045-1057.

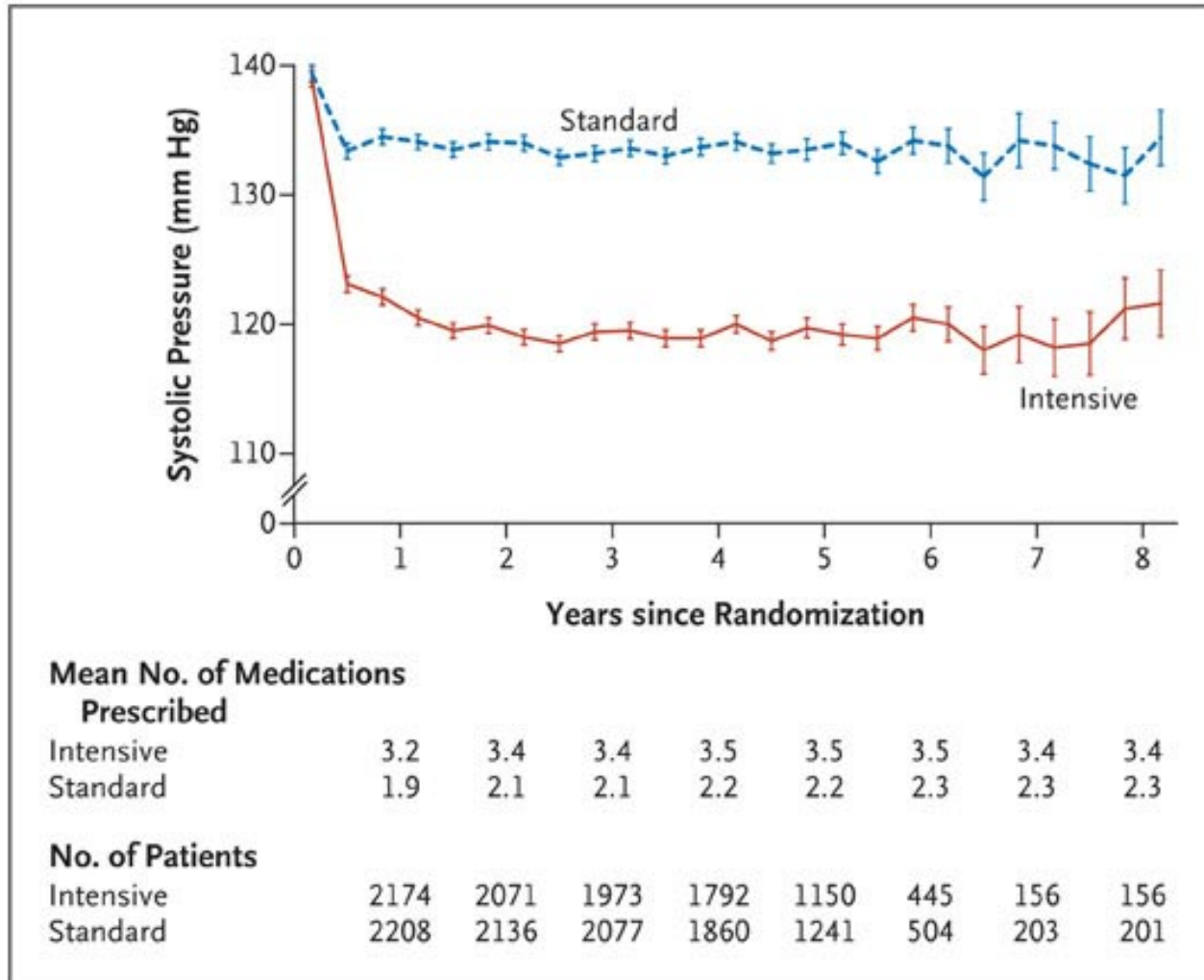
JNC IV. *Arch Intern Med*. 1988;148:1023-1038.

JNC V. *Arch Intern Med*. 1993;153:154-183.

JNC VI. *Arch Intern Med*. 1997;157:2413-2446.

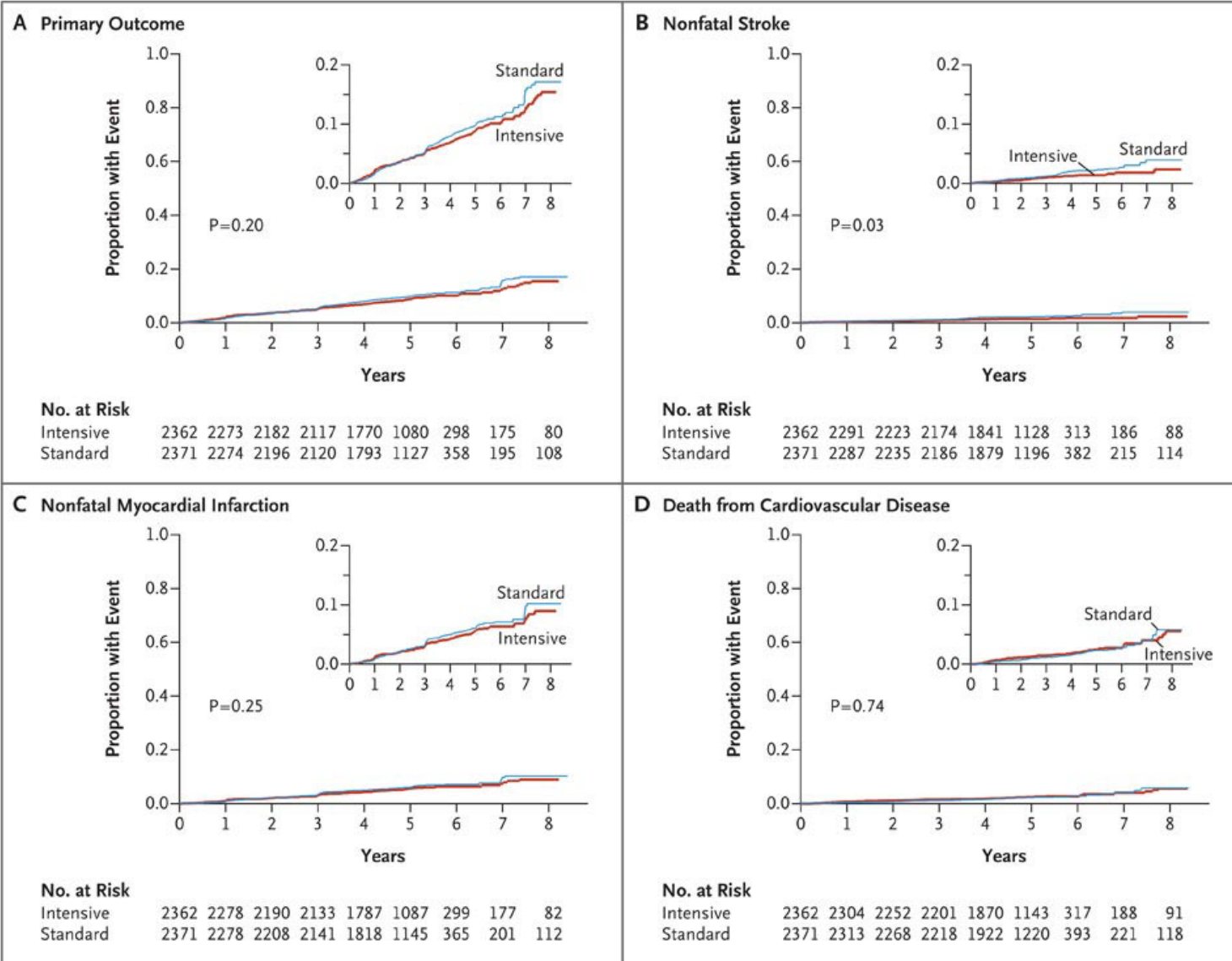
Chobanian AV et al. *JAMA*. 2003;289:2560-2572.

ACCORD: Mean Systolic Blood-Pressure Levels



NEJM 362(17):1575-1585

ACCORD: Kaplan-Meier Analyses of Selected Outcomes



NEJM

362(17):1575-1585

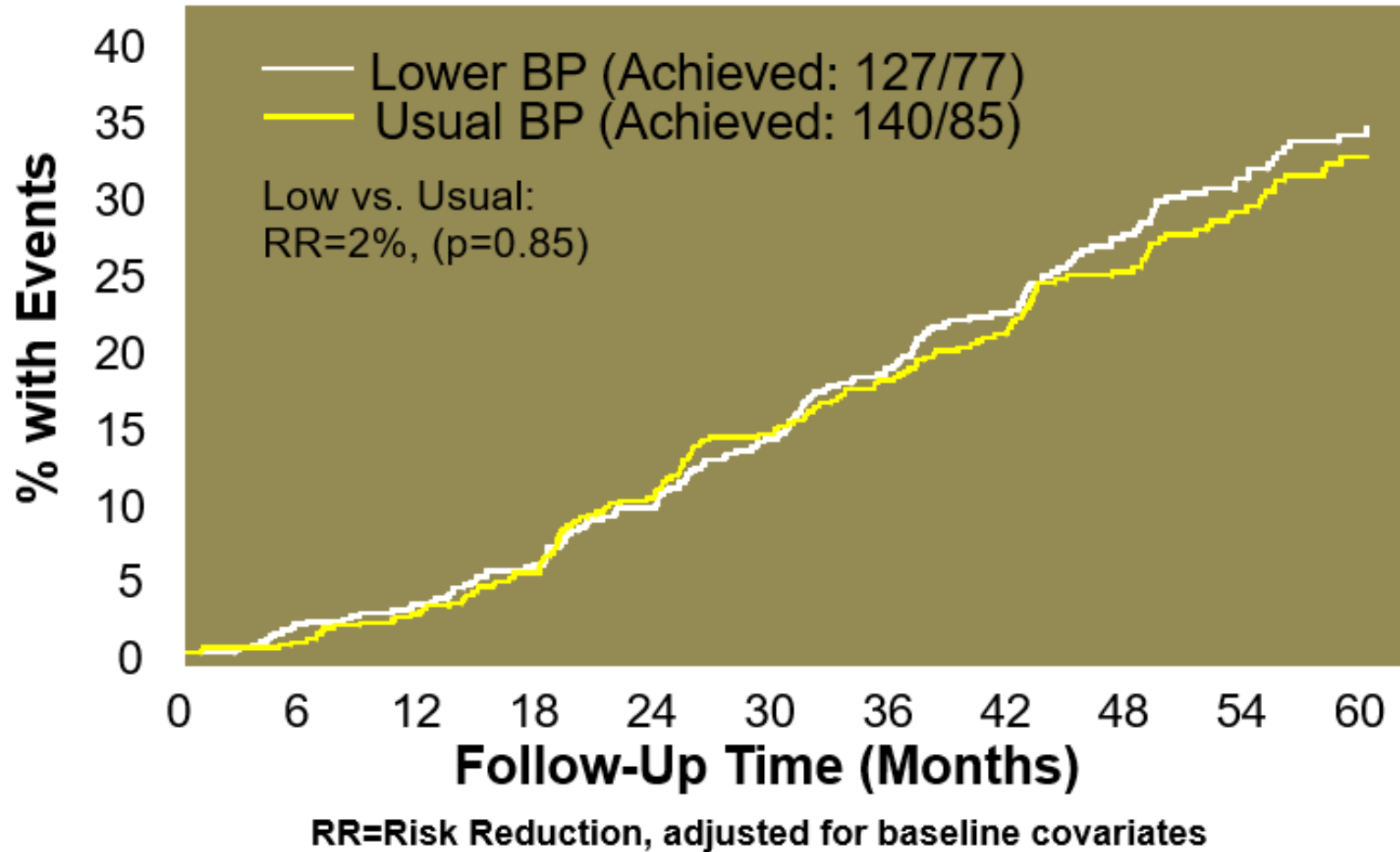
ACCORD: Conclusion

Targeting a systolic BP of < 120 versus < 140 mm Hg did not reduce the rate of fatal and nonfatal major cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events.

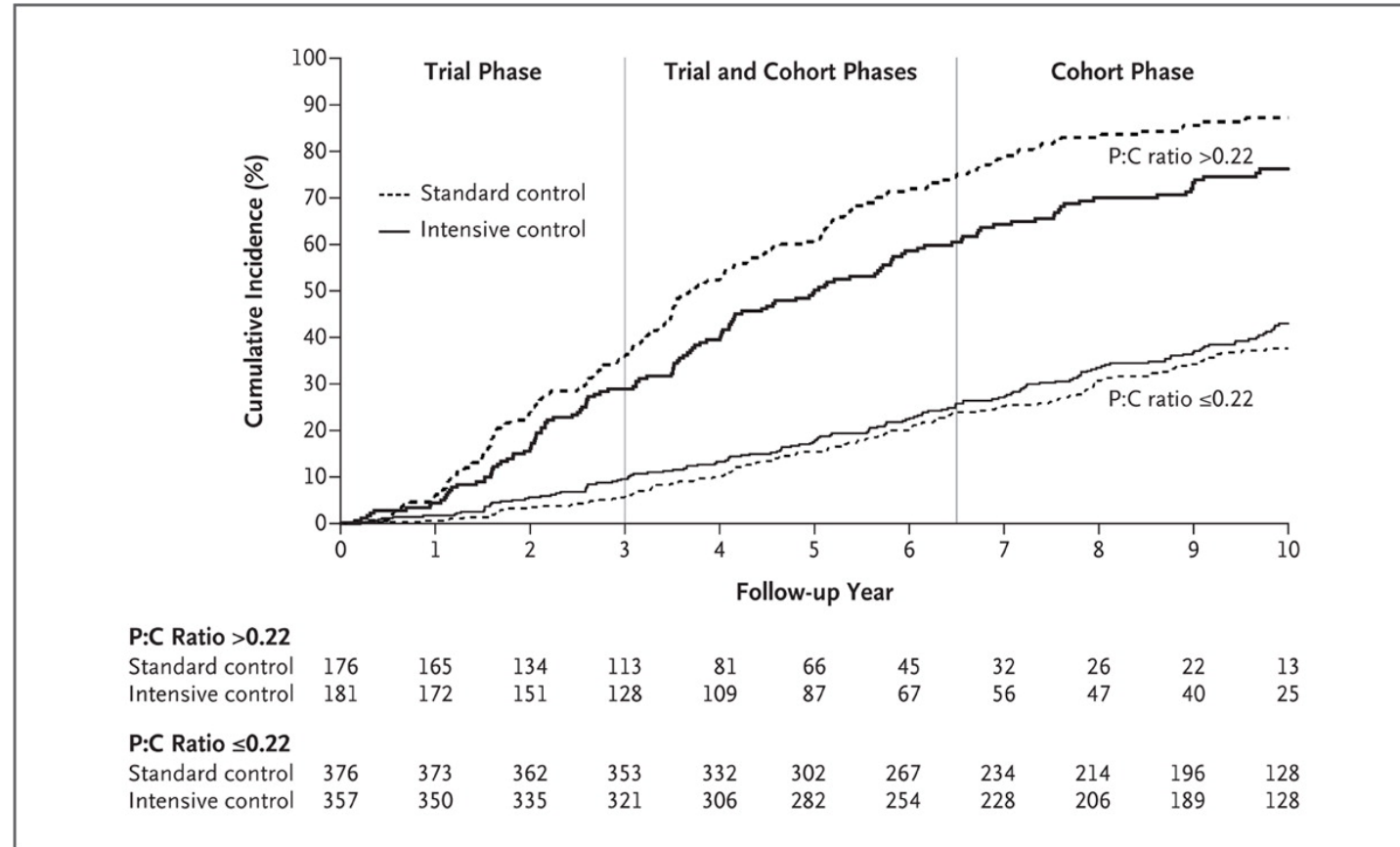
Compared with the standard-therapy group, the intensive-therapy group had significantly higher rates of serious adverse events attributed to antihypertensive treatment, as well as higher rates of hypokalemia and elevations in serum creatinine level.

NEJM 362(17): 1575–1585

AASK Trial: Composite Clinical Outcome Declining GFR Event, ESRD, or Death



AASK Trial and Cohort: Composite Primary Outcome, According to Baseline Proteinuria Status



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

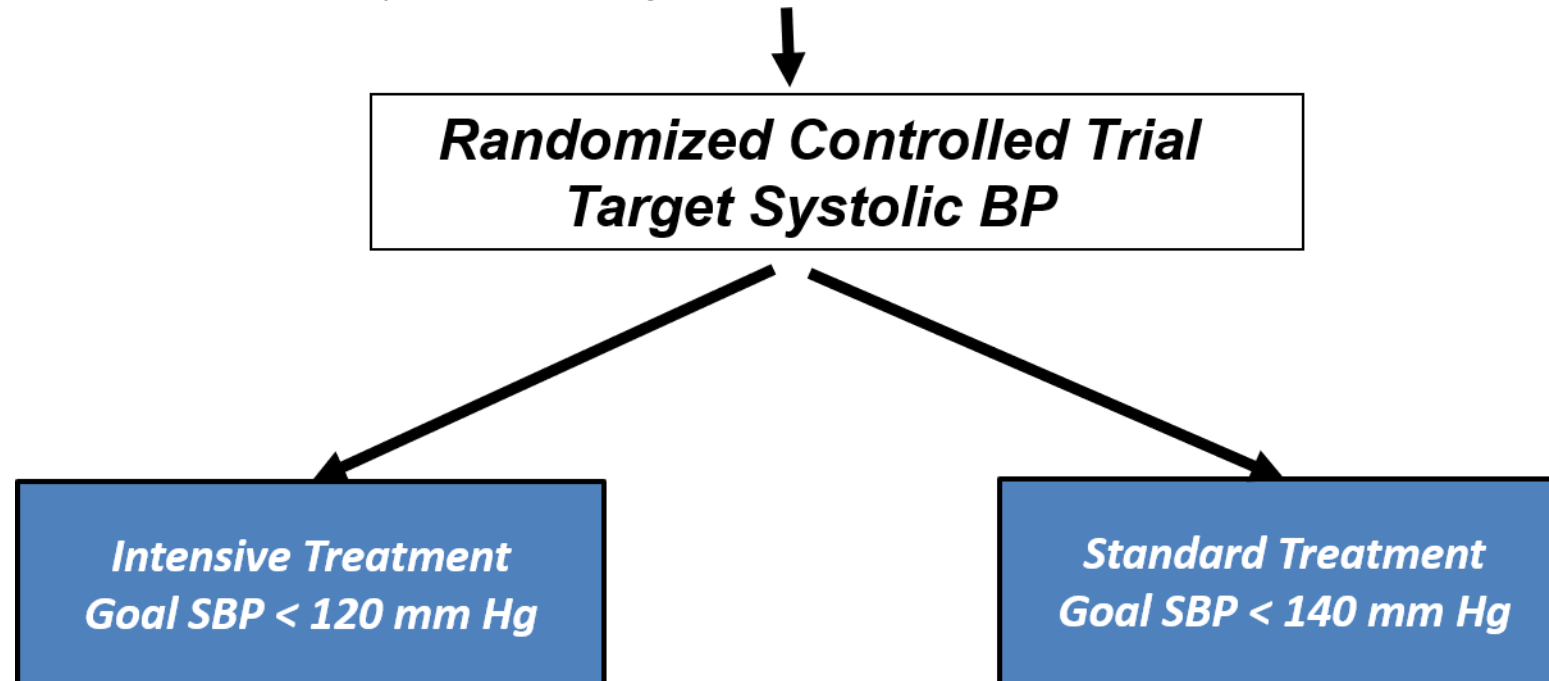
JNC 8 Blood Pressure Goals

- For people ages 60+ years without diabetes or kidney disease, strong evidence to support Goal BP < 150/90 based on Grade A level evidence
- For all others, we recommend Goal BP < 140/90 based on expert opinion
- Randomized controlled trials target <130/80 vs < 140/90: MDRD, AASK, REIN-2: all negative in decreasing CV or renal events

SPRINT Research Question

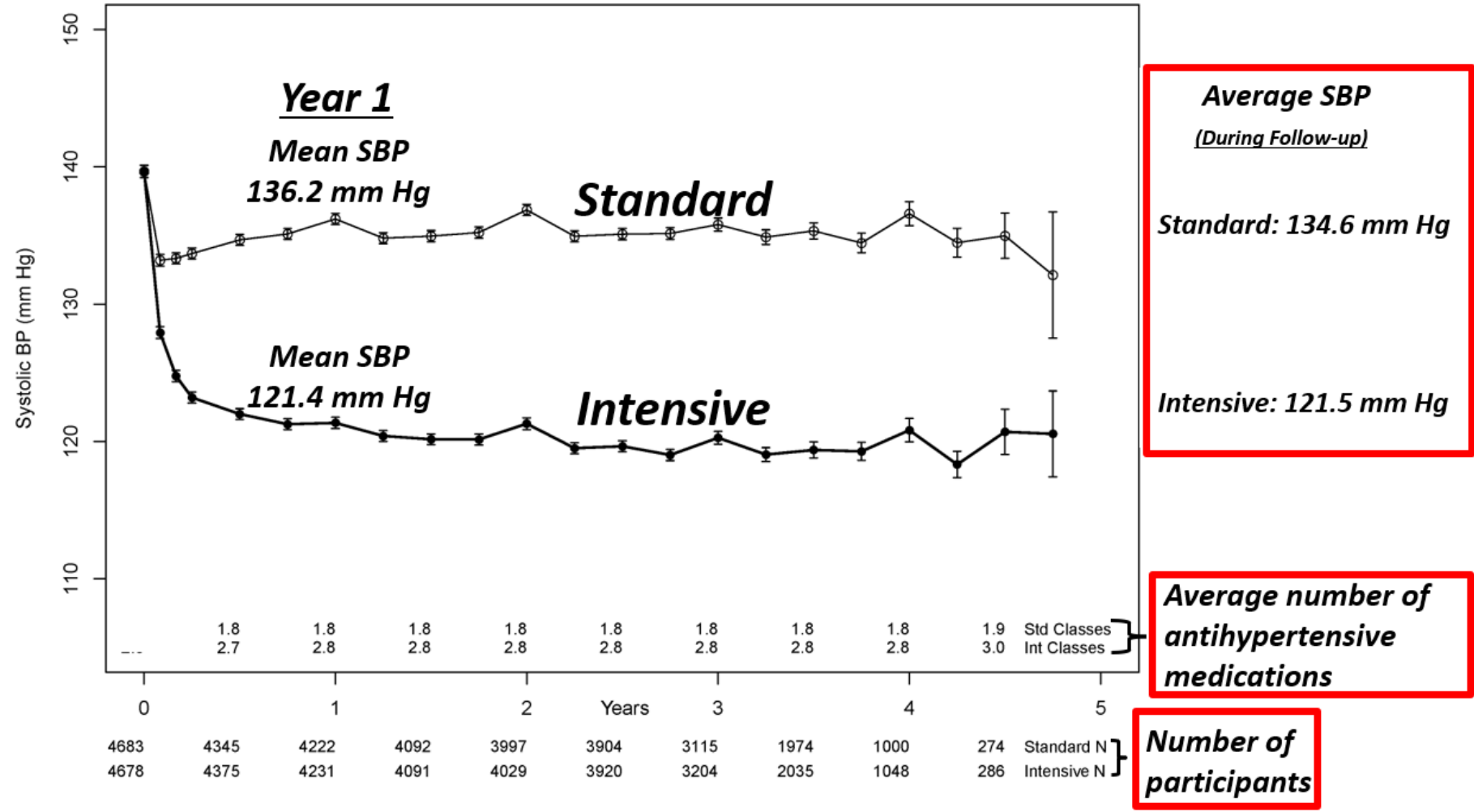
Examine the effect of more intensive high blood pressure treatment than is currently recommended

Sprint Study Group N Engl. J. Med. vol. 373 no. 22:2103-2116

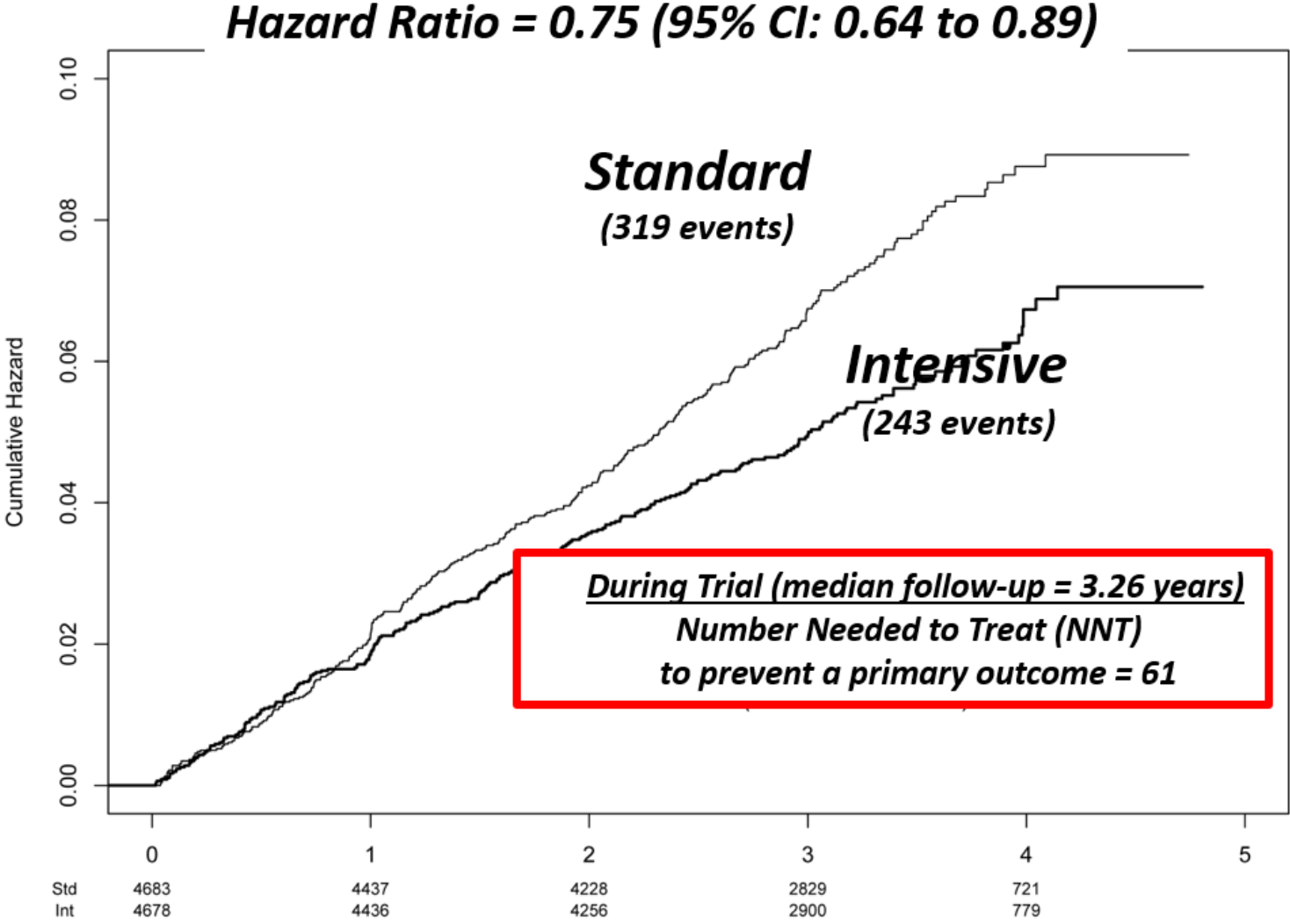


Systolic BP During Follow-up

Figure 1: Mean Systolic BP (95% CI)



SPRINT Primary Outcome Cumulative Hazard



AHA ACC: Summary

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk $\geq 10\%$	$\geq 130/80$	$< 130/80$
Clinical CVD or 10-year ASCVD risk $\geq 10\%$	$\geq 130/80$	$< 130/80$
Older persons (≥ 65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific comorbidities		
Diabetes mellitus	$\geq 130/80$	$< 130/80$
Chronic kidney disease	$\geq 130/80$	$< 130/80$
Chronic kidney disease after renal transplantation	$\geq 130/80$	$< 130/80$
Heart failure	$\geq 130/80$	$< 130/80$
Stable ischemic heart disease	$\geq 130/80$	$< 130/80$
Secondary stroke prevention	$\geq 140/90$	$< 130/80$
Secondary stroke prevention (lacunar)	$\geq 130/80$	$< 130/80$
Peripheral arterial disease	$\geq 130/80$	$< 130/80$

Uncertainty Persists

Annals of Internal Medicine

IDEAS AND OPINIONS

Let's Not SPRINT to Judgment About New Blood Pressure Goals

Eduardo Ortiz, MD, MPH, and Paul A. James, MD

SPRINT (Systolic Blood Pressure Intervention Trial), a randomized, controlled trial that compared aggressive treatment to a target systolic blood pressure (BP) less than 120 mm Hg with a target less than 140 mm Hg in patients at increased cardiovascular risk, was stopped early and its results were promoted widely months before publication (1). Participants were mostly men (64%) with a mean age of 68 years and comorbidities that increased their cardiovascular risk, but patients with diabetes were excluded. With the lower treatment target, the trial found a 25% relative risk reduction in the primary composite outcome. Although a 25% re-

cluded significant increases in hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure. Emergency department visits also occurred more frequently for each of these events, as well as for bradycardia and injurious falls (4). These adverse drug events underscore a concern about potential overtreatment in both groups, given that previous evidence from randomized trials has not demonstrated a benefit in important health outcomes of drug treatment to a BP goal less than 140/90 mm Hg compared with less than 150/90 mm Hg, especially in those without underlying cardiovascular disease (5).

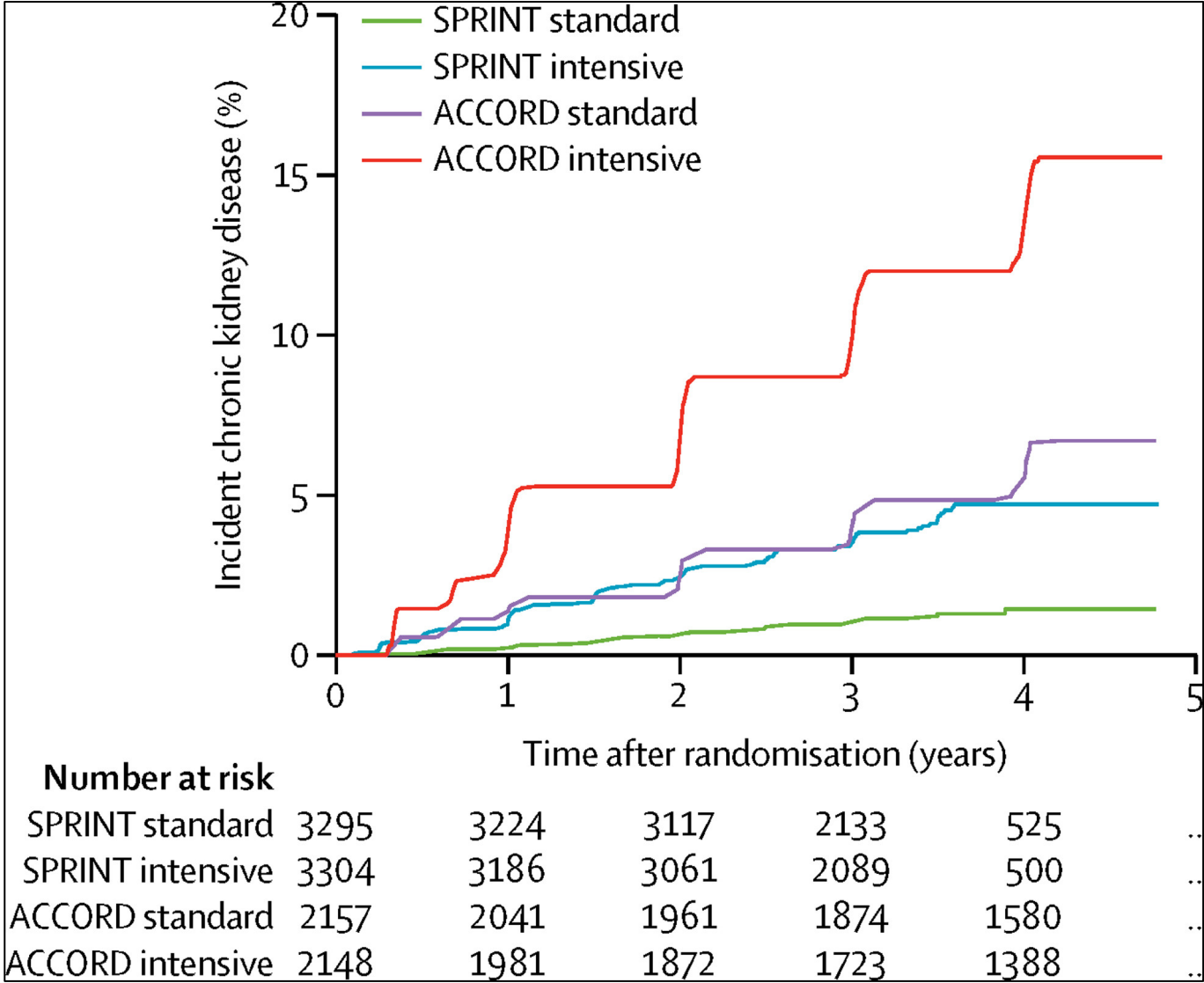
ADA Hypertension Control Recommendations

Treatment Goals

- Most people with diabetes and hypertension should be treated to a systolic BP goal of < 140 mmHg and a diastolic BP goal of < 90 mmHg. **A (strong)**
- Lower systolic and diastolic BP targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of CVD, if they can be achieved without undue treatment burden. **C (weak)**

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes – 2018. Diabetes Care 2018; 41 (Suppl. 1): S86–S104

Cumulative Incidence of CKD in SPRINT and ACCORD



Number at risk		0	1	2	3	4	5
SPRINT standard		3295	3224	3117	2133	525	..
SPRINT intensive		3304	3186	3061	2089	500	..
ACCORD standard		2157	2041	1961	1874	1580	..
ACCORD intensive		2148	1981	1872	1723	1388	..

Lancet, July 2018

CKD vs. CVD

- The risk of incident chronic kidney disease is higher in people with type 2 diabetes than in those without this disease with intensive systolic blood pressure lowering.
- Chronic kidney disease is known to be a risk factor for future cardiovascular events.
- However, it is unclear whether incident chronic kidney disease due to intensive lowering of systolic blood pressure increases the risk of future cardiovascular events.
- Further studies are warranted to ascertain whether the higher risk of incident chronic kidney disease with intensive lowering of systolic blood pressure is outweighed by the expected reductions in cardiovascular disease and all-cause mortality in type 2 diabetes in the long term.

Individualized BP Goal and Medication in CKD

- Target < 140/90 mmHg was endorsed by JNC 8 in 2014.
- Target < 130/80 mmHg was recommended by the American College of Cardiology and American Heart Association in 2017.
- SPRINT trial showed intensive lowering (SBP < 120 mmHg) reduced fatal and nonfatal CVD events.
- Excluded people with diabetes or > 1g/day proteinuria, among others
- Uncontrolled hypertension (systolic blood pressure > 160) is a major challenge.
- **A guideline is not a substitute for clinical judgment**

Addressing “Resistant” Hypertension

Before adding additional anti-hypertensives consider these potential issues:

- Adherence-barriers to taking medications as prescribed
 - Side effects
 - Fatigue, headache, dizziness, sexual dysfunction
 - High pill burden
- Sodium restriction
 - Re-education should be part of medication management
 - Consider dietician referral
 - Consider whether the dose of diuretic is adequate; may require higher doses for natriuresis

Xie et al. *Curr Med Res Opin.* 2014 Dec; 30 (12): 2415–22.;
Brater DC. *N Engl J Med.* 1998 Aug 6; 339(6): 387–95.

Questions: Use of RAAS Antagonists

- Is there a lowest effective dose of ACEi or ARB that will give benefit the kidney? **Not tested**
- At what point with creatinine elevation/eGFR does ACE/ARB become less beneficial and should be discontinued? **30% increase empiric**
- When you stop ACE or ARB, what should we use? **Bblocker, CCB, diuretic**
- If a diabetic patient on losartan or linsinopril has hyperkalemia (5.1-5.3) do you decrease the ACE/ARB? **Not necessarily**
- Risks/benefits of treating concomitantly with ARBs/ACE? When do they have to be stopped? **Don't do this**
- Recommendation when you have increased ACE/ARB to max and still have elevated albuminuria? **SGLT2 inhibitor**
- Does the myalgia associated with ARBs/ACE decrease with lower does medications? **statins**

Considerations for ACE-I and ARB Therapy in CKD

- Common adverse effects
 - Hyperkalemia
 - Increased risk of hyperkalemia with higher dose and reduced kidney function
 - Potassium-sparing diuretics, aliskiren, dual ACE-I/ARB Treatment
>>> hyperkalemia
 - Cough with ACE-I
 - Angioedema
 - Increase of serum creatinine (Scr) up to 30%
 - SCr <30% change reflects decrease in glomerular capillary pressure (renoprotective effect)
 - SCr > 30% change may require dose modification

St. Peter WL, et al. Pharmacotherapy 2013;33:496-514

Considerations for ACE-I and ARB Therapy in CKD (2)

- With renin dependent disease states >>> risk of acute kidney injury
 - Congestive heart failure
 - Volume depletion/overdiuresis
 - cirrhosis
- NSAID treatment >>> Further increases risk of acute kidney injury

VA NEPHRON-D Investigators. *N Engl J Med* 2013; 369:1892–1903

The ONTARGET Investigators. *N Engl J Med* 2008;358:1547–1559

Who Is at High Risk for AKI?

- Patients with diabetes and/or hypertension because both cause kidney damage over time
- Multiple co-morbid conditions which are acquired with age (e.g., congestive heart failure, renal artery disease, severe liver disease)
- Patients with multiple co-morbid conditions who were recently discharged from the hospital
- Patients with co-morbid conditions that require the use of drugs that affect renal hemodynamics (e.g., ACE Inhibitors, ARBs, diuretics, NSAIDs)

Counseling Patients on NSAID Use to Prevent Kidney Injury

Video on Counseling Patients on NSAID Use to Prevent Kidney Injury:

<https://www.niddk.nih.gov/health-information/professionals/education-cme/counseling-patients-nsaid-use>

Should ACE-I and ARBs Be Used in Combination?

ONTARGET Trial

- A randomized controlled trial comparing telmisartan + ramipril or ramipril alone
- 25,620 patients
- **No difference in cardiovascular endpoints among two treatment groups**
- **More adverse effects** in combination group:
 - Hyperkalemia
 - Syncope
 - Hypotension
 - Higher risk of renal dysfunction requiring dialysis

The ONTARGET Investigators. *N Engl J Med* 2008; 358: 1547–1559.

Can We Use ACE-I and ARB Together?

VA-NEPHRON D Trial

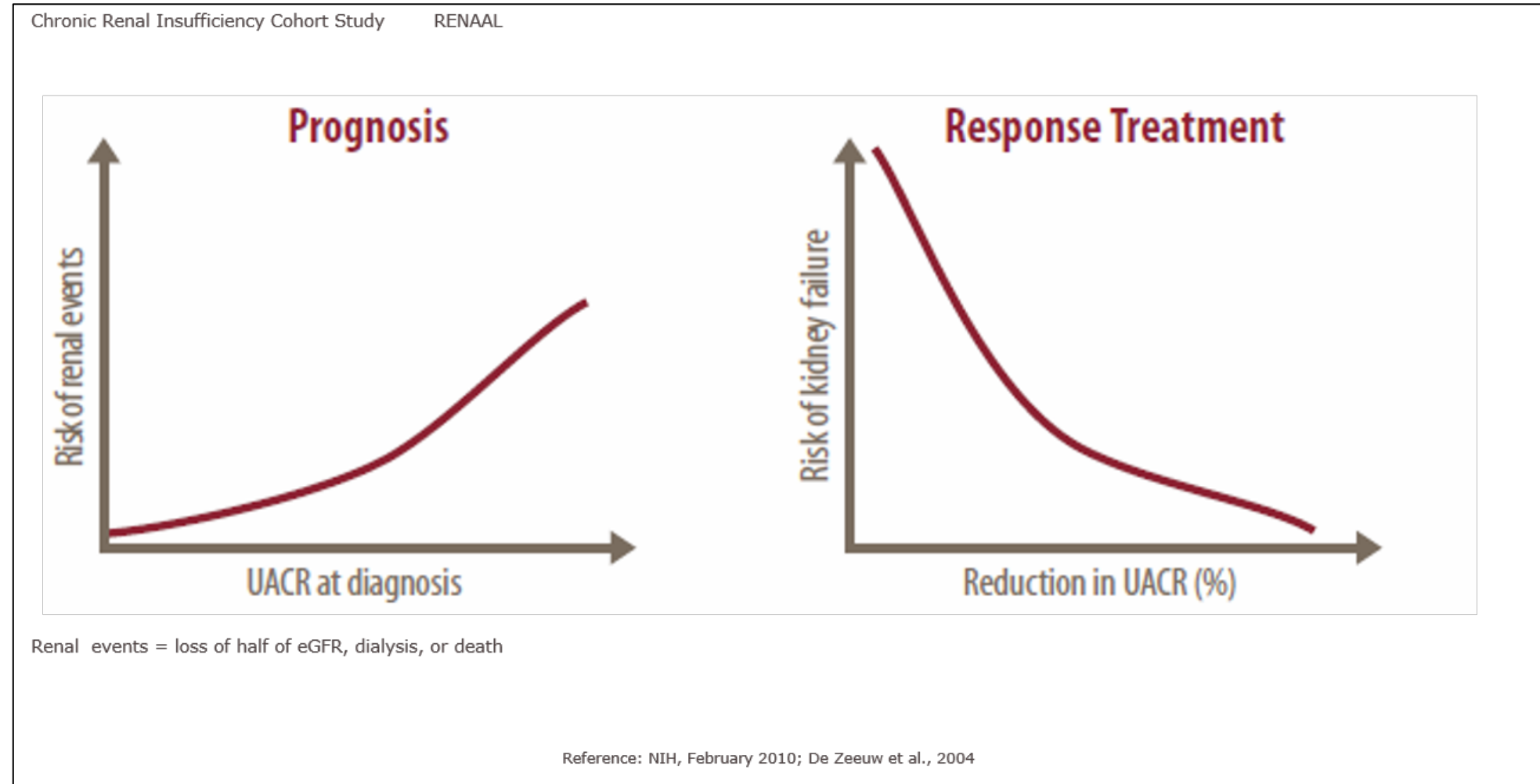
- A randomized controlled trial comparing losartan + lisinopril or losartan alone in slowing progression of proteinuric diabetic nephropathy
- Study was terminated early.
- **No benefit with respect to mortality, cardiovascular events between two groups**
- More adverse effects in combination group:
 - Hyperkalemia
 - Increased rates of acute kidney injury

Fried LF, et al. *N Engl J Med* 2013; 369: 1892–1903

Questions: Prognosis/Referral

- Should a person who has one kidney, due to being a donor:
 - Be on a low-dose ACEI for renal protection?
 - Be screened annually for UACR?
- In light of nephrectomy, for whatever reason, would you expect decreased GFR or does the other kidney compensate?
- Do you recommend ace/arb prior to elevated protein in urine? (As in all diabetics)?
- As a primary care provider, at which eGFR should I initiate a referral to Renal?
- If we have high urine microalbumin and normal BUN and creatinine, what should be ordered?

Elevated UACR Is Associated with Risk of Renal Events; Lowering UACR May Lower Risk of Progression



Interventions for Reducing Urine Albumin

- Control blood pressure
- Reduce sodium intake
- Achieve good control of diabetes early; may help prevent albuminuria
- Reduce weight (if obese)
- Reduce protein intake (if excessive)
- Achieve tobacco cessation

Considerations for Nephrology Referral

- Treat primary kidney diseases such as glomerulonephritis.
- Prepare for renal replacement therapy, especially when eGFR is less than 30.
- Assist with diagnostic challenges.
- Rapid decrease of eGFR.
- Assist with therapeutic challenges related to CKD complications such as blood pressure, anemia, abnormal mineral metabolism and bone disorders, hyperkalemia, hyperphosphatemia, malnutrition, and secondary hyperparathyroidism.
- Assist with acute kidney injury.

Nephrology Referral Form

Nephrology Referral

NAME _____ DATE OF BIRTH _____ FACILITY/PRACTICE AND RECORD NUMBER _____

REASON FOR REFERRAL

FOR DIABETICS YEAR OF DIAGNOSIS _____ RECENT A1C _____ MONTH/YEAR _____

COMPLICATIONS RETINOPATHY: BDR PDR NOT PRESENT NO DILATED EXAM
 NEUROPATHY PVD OTHER _____

ALBUMINURIA NOT PRESENT IF PRESENT, SINCE _____ MONTH/YEAR
 MOST RECENT UACR _____

HEMATURIA NOT PRESENT IF PRESENT, SINCE _____ MONTH/YEAR

URINE SEDIMENT _____

eGFR MOST RECENT eGFR _____ MONTH/YEAR _____

BLOOD PRESSURE AT LAST VISIT _____ USUAL RANGE _____

ADDITIONAL EVALUATION ANA _____ RF _____ C3 _____ C4 _____ HBsAg _____ AntiHCV _____
 SPEP _____ UPEP _____ RENAL U/S _____
 OTHER _____

FAMILY HISTORY KIDNEY DISEASE NO YES IF YES, HOW RELATED _____
 OTHER CONDITION(S) AND HOW RELATED _____


CURRENT MEDICATIONS (or attach list)

KNOWLEDGE DOES THE PATIENT KNOW HE/SHE HAS KIDNEY DISEASE? YES NO DON'T KNOW
 DOES THE PATIENT KNOW THE SEVERITY? YES NO DON'T KNOW
 IS THE PATIENT AWARE THAT HE/SHE MAY NEED DIALYSIS? YES NO DON'T KNOW

ADDITIONAL INFORMATION

REFERRED BY _____ DATE _____
 CONTACT TELEPHONE _____ EMAIL _____

For more information about why these data are important to share with the nephrologist, visit www.nkdep.nih.gov.



Goals for Population Management Delay the Need for Renal Replacement Therapy (Dialysis or Transplant)

- Identify patients with kidney disease and monitor progression: eGFR (kidney function) and UACR (kidney damage)
- Implement appropriate therapy to slow progression
- Screen for complications: anemia, malnutrition, metabolic bone disease
- Treat cardiovascular risk, especially with smokers and hypercholesterolemia
- Refer to dietitian for nutritional guidance
- Avoid acute injury to the kidney (NSAIDs)
- Educate patients about kidney disease and treatment

NKDEP Resources

