



# Justification for Chronic Kidney Disease Subgroup in SPRINT

American Society of Hypertension  
27<sup>th</sup> Annual Meeting, May 20, 2012

Alfred K. Cheung, M.D.  
University of Utah



American Society of Hypertension, Inc. (ASH)

# **Disclosure of Relationships**

Over the past 12 months

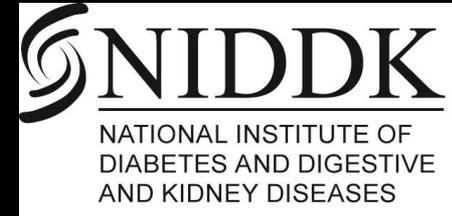
**No relevant conflict of interest**

# Outline

- High CV events in CKD
- Association of BP with CV outcomes in CKD
- Association of BP with kidney outcomes in CKD
- CKD in SPRINT protocol
- Considerations for proteinuria in SPRINT
- Take-home message



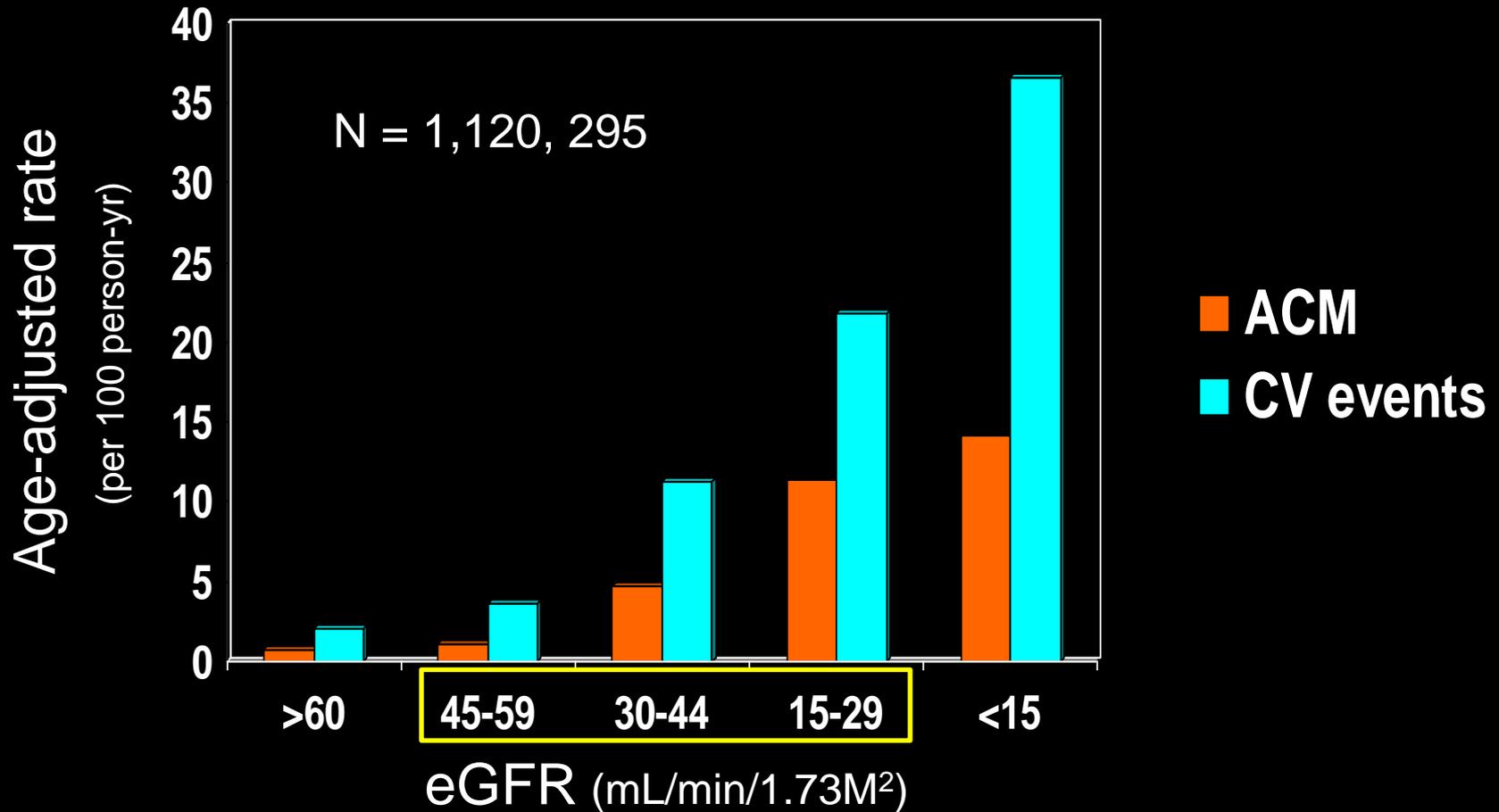
# Mutual Interests to NHLBI and NIDDK



- SPRINT targets individuals with high CV risks; CKD confers very high CV risks
- The optimal BP target for CKD population is unclear

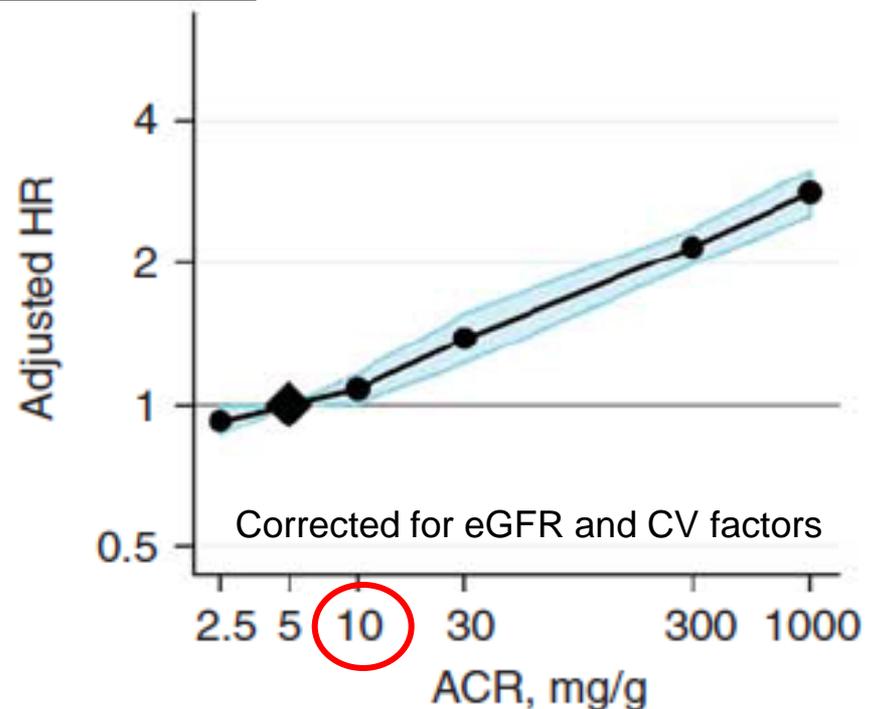
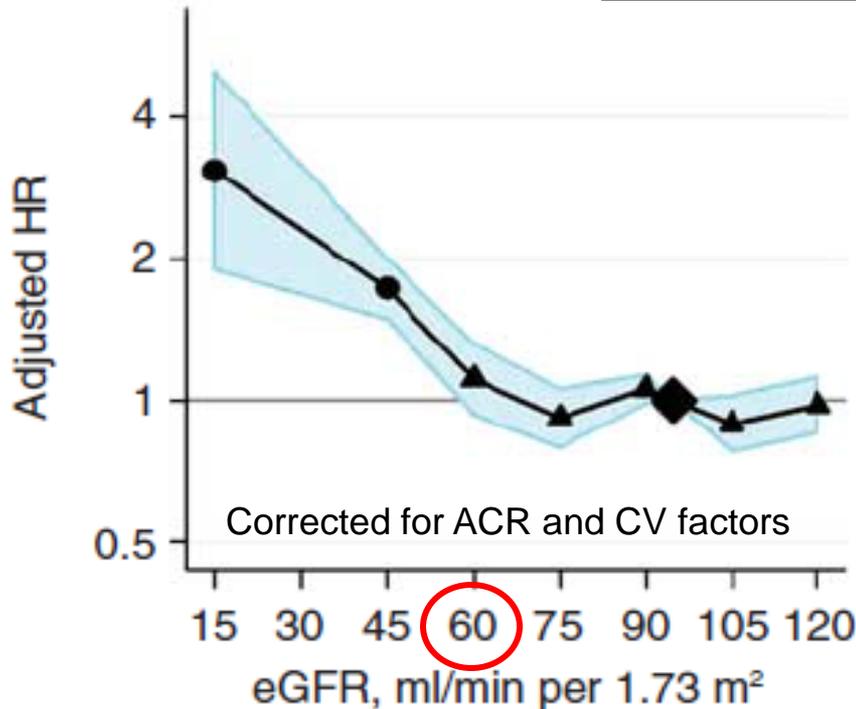


# Adjusted Rate of Death or CV Events



# Association of eGFR and Albuminuria with CV Mortality

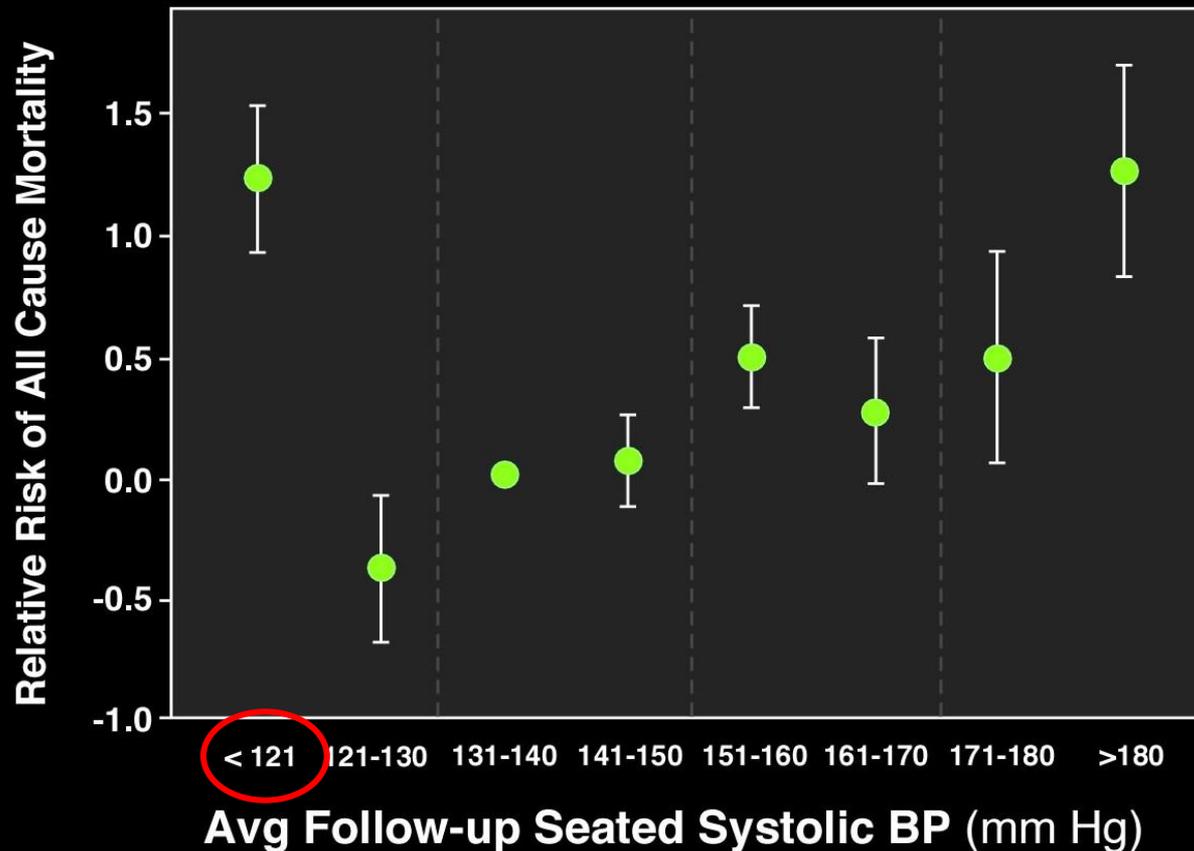
Multiplicative effects



- CKD Prognosis Consortium
- 266,975 community-based high-risk (HTN, DM, CVD) individuals

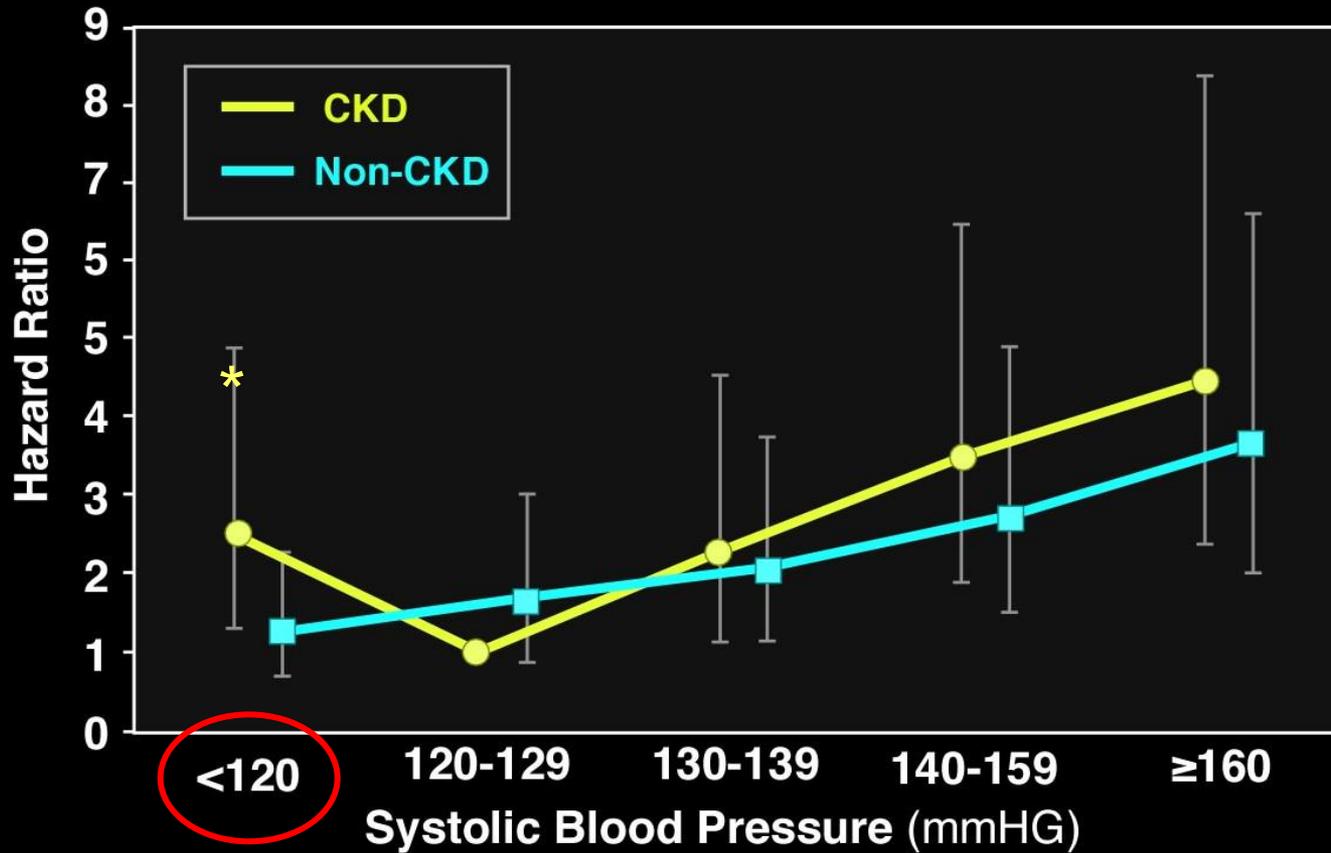
**Observational** Studies of  
Association between SBP  
and **Non-Renal** Outcomes in **CKD**

# Observational Studies of SBP and Death



- IDNT (Irbesartan **Diabetic** Nephropathy Trial)
- 1,590 T2DM; mean **Screat** ~1.67 mg/dL; **Upr** > 0.9 g/d
- BP goal <135/85

# Observational Studies of SBP and Stroke



- Atherosclerosis Risk in Community Study + Cardiovascular Health Study
- 1,549 CKD (eGFR <60 mL/min/1.73m<sup>2</sup>) + 18,809 non-CKD

RCT of BP Level  
on CV Outcomes in CKD

# Effect of BP on CV Events in CKD

## Post-hoc Analysis of RCT (AASK)

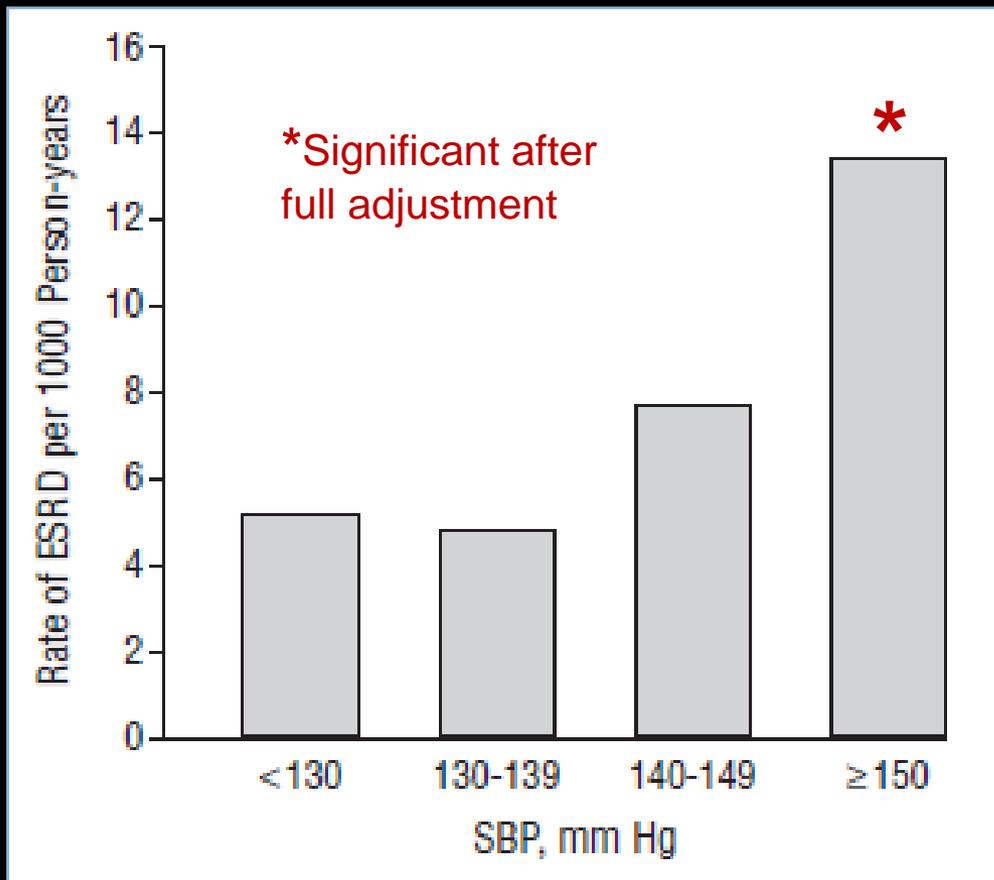
(African-American Study of Kidney Disease & HTN; eGFR 20-65 mL/min)

CV Composite (hospitalization + death)	Event number (per patient-year)
Target MAP 102-107 mm Hg	78 (0.035)
Target MAP 92 mm Hg	71 (0.032)
<b>HR = 0.84</b> (0.61-1.16); p = 0.29	

- No BP effect on CV events
- **No interaction of BP with proteinuria on CV events**

**Observational** Study of  
Association between SBP  
and **Kidney Outcomes** in **CKD**

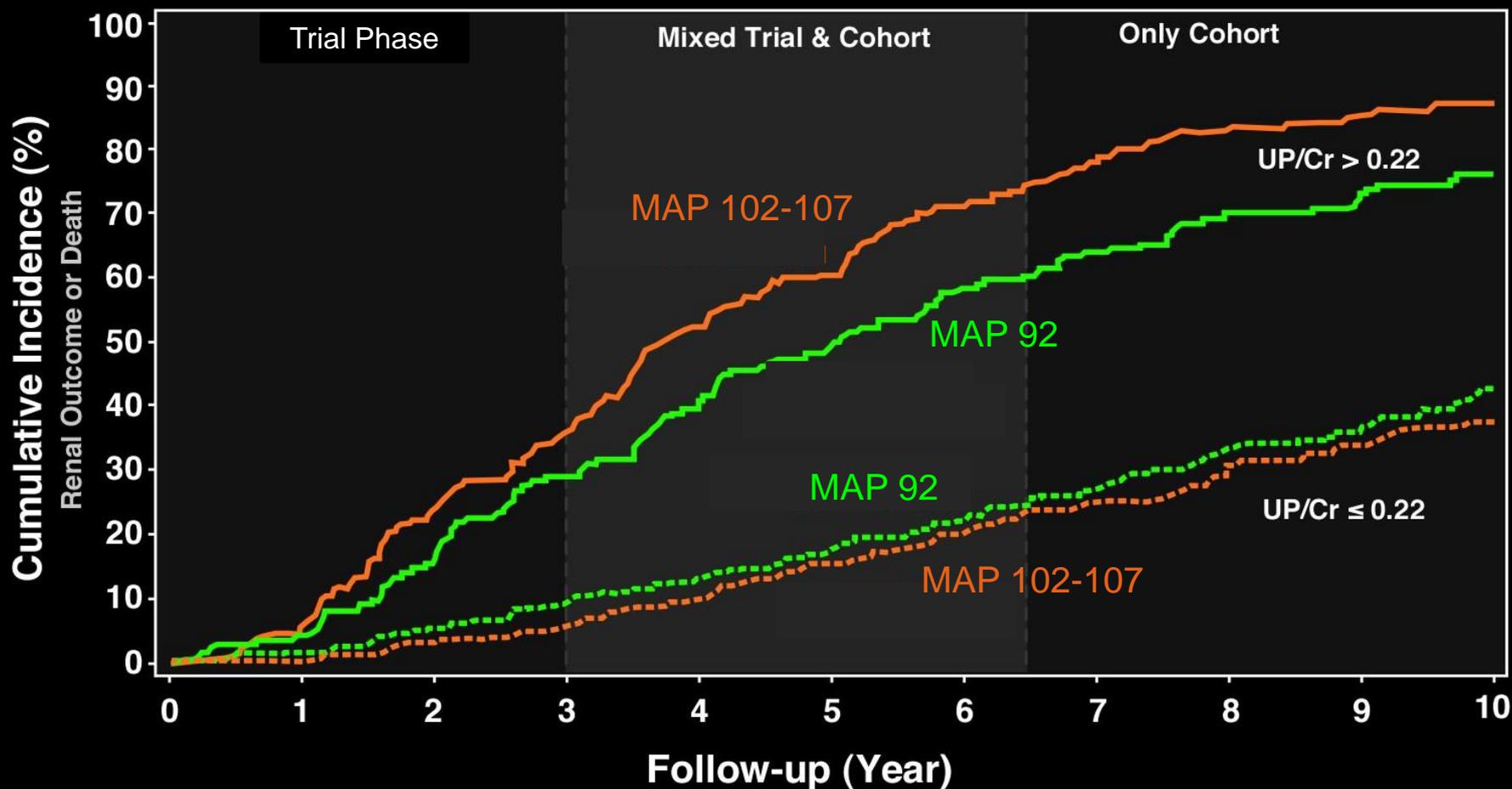
# Observational Studies of SBP in CKD



- N = 16,129 in KEEP (Kidney Early Evaluation Program)
- Mean age = 69 yrs
- eGFR < 60 mL/min/1.73m<sup>2</sup>
- 43% DM
- 320 ESRD events in 2.87 yr

RCT of BP Level  
on **Renal** Outcomes in **CKD**

# Apparent Renoprotection Associated with Lower BP (post-trial long-term follow-up in AASK)

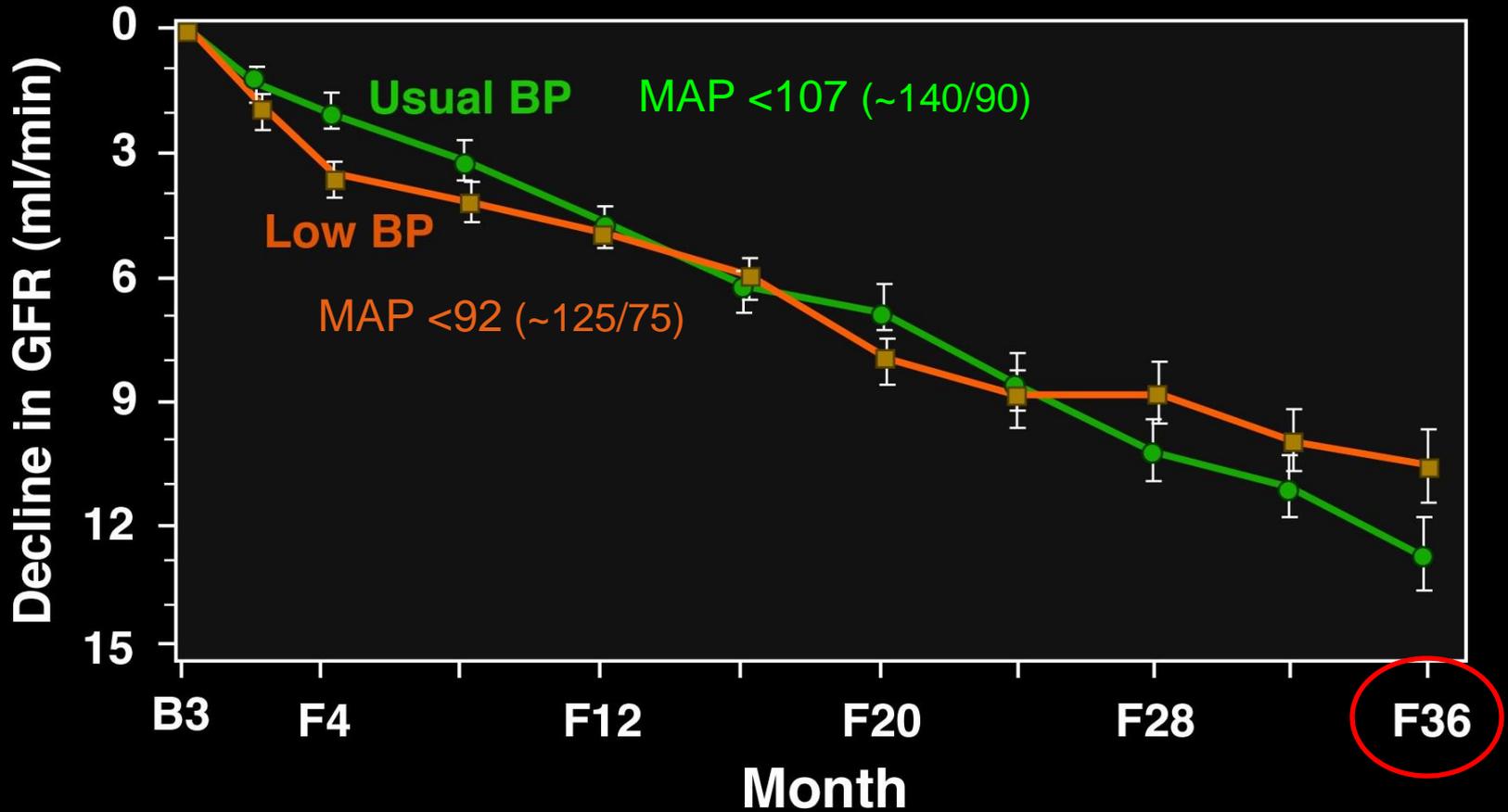


N=1,094 (iGFR 20-65 mL/min)

Appel, NEJM, 2010

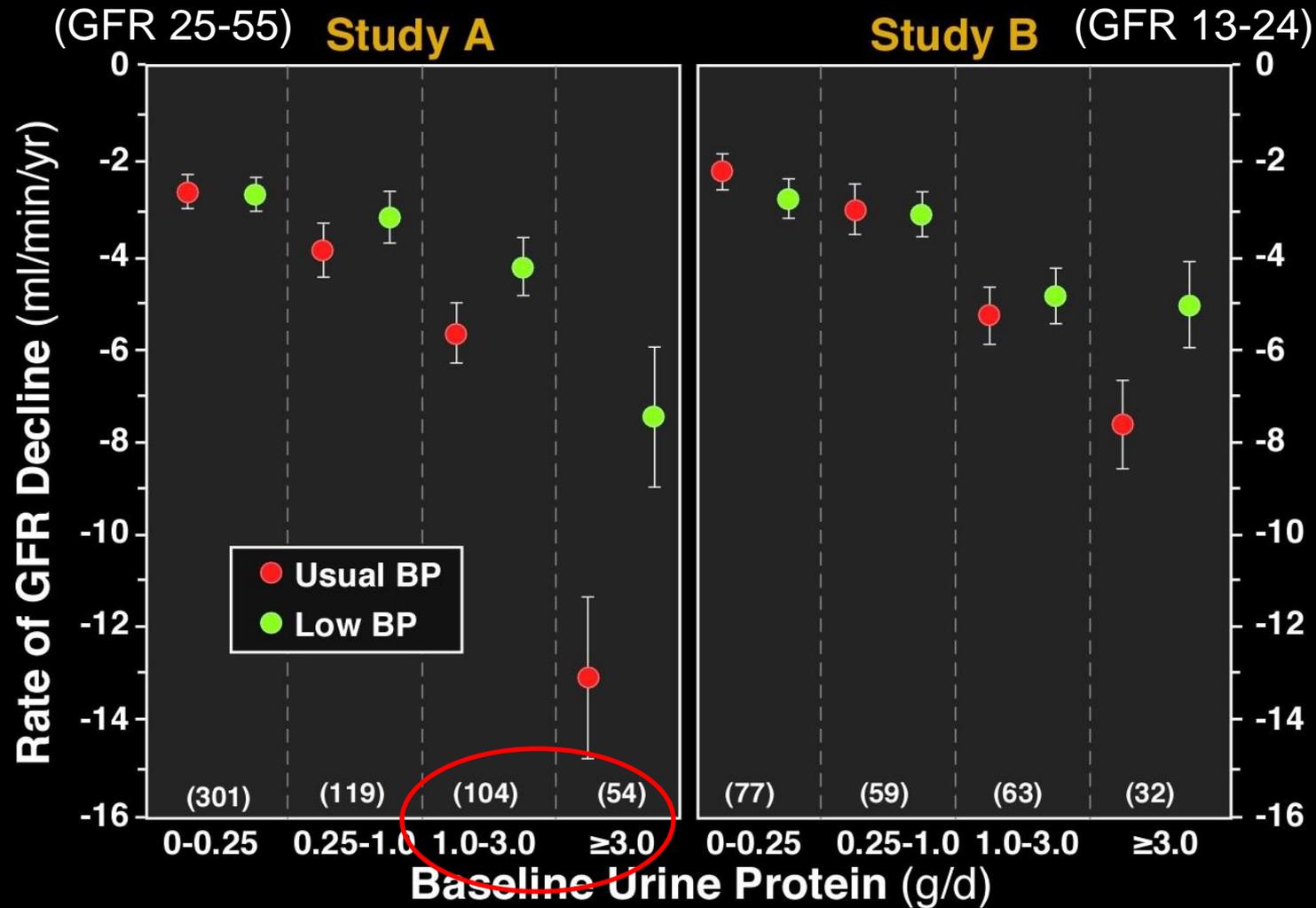
# Effect of BP on GFR Decline in non-IDDM CKD

## Modification Diet in Renal Disease (RCT)



No renal benefits in low BP arm

# Renprotection of MAP <92 mm Hg in Proteinuria?



Limited **subgroup** data on **proteinuric** individuals suggest benefits with BP  
~**125/75**

Practice guideline BP target  
for **all** CKD < **130/80**

# BP Targets in MDRD Study

	18-60 yrs old	61-70 yrs old
Usual MAP target	$\leq 107$ mm Hg (~ 140/90 mm Hg)	$\leq 113$ mm Hg (~ <b>160</b> /90 mm Hg)
Low MAP target	$\leq 92$ mm Hg (~ 125/75 mm Hg)	$\leq 98$ mm Hg (~ <b>145</b> /75 mm Hg)

# What stage of CKD should be included in SPRINT?

- CKD stage 3 (GFR 30-59 mL/min/1.73m<sup>2</sup>) is common and associated with high CV risks
- Including more advanced CKD
  - Pro: Higher CV event rate  
Understand how to treat CKD subpopulation (more than modest age-related GFR decline)
  - Cons: More likely to have effect modification  
Too close to dialysis (difficulty with BP target)
- Inclusion criterion: eGFR 20-59 mL/min/1.73m<sup>2</sup> (not defined by proteinuria)
- Kidney exclusion criteria: DM or PKD

## Justification for Equipoise to Study BP Effect in Pts with CKD and Baseline UP < 1 g/day

- MDRD and AASK evidence for BP x proteinuria interaction based on secondary analyses
- MDRD
  - small number of patients
  - short BP exposure
  - confounded with ACEI
  - based primarily on patients with baseline UP > 3 g/d
- AASK evidence depends on post-hoc analysis after intervention termination
- Evidence limited to kidney outcomes; little data on CVD events or mortality and no trends for interaction

# Considerations for Proteinuria as Exclusion Criteria

- Significant proteinuria is risk factor for rapid decline in eGFR; this association may be dependent on BP level
- Therefore, questionable equipoise for proteinuria  $>1$  g/d (~1 g/g creatinine)



# Renal Outcomes in SPRINT

- Main renal outcome: Composite of initiation of ESRD therapy or a confirmed 50% decline in eGFR (CKD subgroup only)
- Other renal outcome: initiation of ESRD therapy or a 30% decline in eGFR to  $<60$  mL/min/1.73m<sup>2</sup> (non-CKD subgroup only)
- Incident proteinuria: doubling of urinary albumin-to-creatinine ratio from  $<10$  mg/g to  $>10$  mg/g (entire cohort)

# Take-Home Message

- Optimum SBP target in CKD Is uncertain
- At high CV risks, CKD subpopulation contributes to CV events in SPRINT





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