Justification for Chronic Kidney Disease Subgroup in SPRINT

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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

Age-adjusted rate (per 100 person-yr)

N = 1,120, 295

Go, NEJM, 2004
Association of eGFR and Albuminuria with CV Mortality

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

Van der Velde, KI, 2011
Observational Studies of Association between SBP and Non-Renal Outcomes in CKD
• 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/1.73m²) + 18,809 non-CKD

Weiner, JASN, 2007
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)

<table>
<thead>
<tr>
<th>CV Composite (hospitalization + death)</th>
<th>Event number (per patient-year)</th>
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<tbody>
<tr>
<td>Target MAP 102-107 mm Hg</td>
<td>78 (0.035)</td>
</tr>
<tr>
<td>Target MAP 92 mm Hg</td>
<td>71 (0.032)</td>
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</table>

\[ HR = 0.84 \ (0.61-1.16); \ p = 0.29 \]

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

Greene, unpublished
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/1.73m²
- 43% DM
- 320 ESRD events in 2.87 yr

*Significant after full adjustment

Peralta, Arch Int Med, 2012
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

Klahr, NEJM, 1994
Renprotection of MAP <92 mm Hg in Proteinuria?

(Klahr, NEJM, 1994)
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

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<th>18-60 yrs old</th>
<th>61-70 yrs old</th>
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<tbody>
<tr>
<td><strong>Usual MAP target</strong></td>
<td>$\leq 107 \text{ mm Hg}$ ($\sim 140/90 \text{ mm Hg}$)</td>
<td>$\leq 113 \text{ mm Hg}$ ($\sim 160/90 \text{ mm Hg}$)</td>
</tr>
<tr>
<td><strong>Low MAP target</strong></td>
<td>$\leq 92 \text{ mm Hg}$ ($\sim 125/75 \text{ mm Hg}$)</td>
<td>$\leq 98 \text{ mm Hg}$ ($\sim 145/75 \text{ mm Hg}$)</td>
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*Beck, CCT, 1991*
What stage of CKD should be included in SPRINT?

• CKD stage 3 (GFR 30-59 mL/min/1.73m²) 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/1.73m²
  (not defined by proteinurias)

• 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/1.73m² (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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