Hong Kong Society of Nephrology

The Asian Pacific Society of Nephrology

Blood Pressure Targets in CKD Patients in the post SPRINT era

Carmine Zoccali
Risk factors ⇒ modifiable risk factors

Risk amplifiers

Blood Pressure

Albuminuria / Proteinuria

CKD

Diabetes
GRADE 1

NON DIABETIC

- Without albuminuria (<30 mg/d) 140/90
- With albuminuria 30-300 mg/d 130/80
- With albuminuria >300 mg/d 130/80

GRADE 2  Substantial debate. Different choices will be appropriate for different patients

DIABETIC

- Without albuminuria (<30 mg/d) 140/90
- With albuminuria 30-300 mg/d 130/80
- With albuminuria >300 mg/d 130/80

Meta-analysis of death and renal outcomes trials: MDRD, AASK, ESCAPE
renal outcomes trials: 130/80
A randomized trial of intensive versus standard blood-pressure control

November 9, 2015,
A Randomized Trial of Intensive versus Standard Blood-Pressure Control
The SPRINT Research Group

Designated by the National Heart, Lung, and Blood Institute (NHLBI) expert panel in 2007

- A strategy trial, i.e., a trial comparing two BP targets rather than two drugs

**N=9361** (age >50 years, non-diabetic)

- Syst BP >130 mmHg and at higher CV risk

- With clinical or subclinical CV disease other than stroke
- CKD (no ADPKD); eGFR 20 to 60 ml per minute per 1.73 m² and proteinuria <1g/24h) (n=2646)
- 10 year CV risk by Framingham >15%
- >75 years

**Primary End Point (Cardiovascular)**
MI, other acute coronary syndromes, stroke, HF, or death from CV causes

3 unattended BP measurements at an office visit while the patient was seated and after 5 min. of quiet rest.
Primary END POINT, a Cardiovascular Outcome (composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular causes)

- with clinical or subclinical CV disease other than stroke
- CKD (no ADPKD) (eGFR 20 to 60 ml per minute per 1.73 m² and proteinuria <1g/24h) (n=2646)
- 10 year CV risk by Framingham >15%
- >75 years
<120 mmHg  N=1330
72±9 years  >75 years 44%
eGFR= 47±9 ml/min/1.73m²
anti hypertensive drugs = 2.1 ±1
Alb/cr (median) 13 mg/g (6-43 mg/g)
<140 mmHg  N=1316
..comparable for gender and ethnicity and a large series of clinical variables

SPRINT study protocol

Recruitment of a subgroup of 4300 participants with CKD provides 80% power to detect a 20% effect on the CVD composite endpoint.

- CKD (no ADPKD) (eGFR 20 to 60 ml per minute per 1.73 m² and proteinuria <1g/24h) (n=2646)
Effects of Intensive BP Control in CKD


Systolic BP
mmHg

SERIOUS ADVERSE EVENTS N=640
<140 mmHg anti hypertensive drugs = 2.0 ±1

SERious ADVERSE EVENTS N=627
<120 mmHg anti hypertensive drugs = 2.9 ±1

years
**Effects of Intensive BP Control in CKD**

Alfred K. Cheung,*† Mahboob Rahman,*‡ David M. Reboussin,*§ Timothy E. Craven,‡
Tom Greene,§ Paul L. Kimmel,** William C. Cushman,** Amret T. Hawfield,‡
Karen C. Johnson,‡* Cora E. Lewis,* Suzanne Oparil,** Michael V. Rocco,**
Kaycee M. Sink,** Paul K. Whelton,** Jackson T. Wright Jr.,§ Jan Basile,*§§§§
Srinivasan Beddhu,*§ Udayan Bhatt,*§ Tara I. Chang,**§ Glenn M. Chertow,**§
Michel Chonchol,**§ Barry J. Freedman,**§ William Haley,**§§§ Joachim H. Ix,**§§
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Ana C. Ricardo,**§§§ Karen Servilla,**§§§ Barry Wall,**§§§§ Dawn Wolfgram,**§§§ and
Jerry Yee,**§§§§ for the SPRINT Research Group

Primary END POINT, a Cardiovascular Outcome (composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular causes)

Results substantially similar to those in the whole study population (i.e., no effect modification by CKD on the study main end-point) where the difference was instead highly significant. Statistical significance not achieved for insufficient power.
Effects of Intensive BP Control in CKD

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Ana C. Ricardo,††††† Karen Servilla,††††† Barry Wall,†††††††† Dawn Wolfgram,†††† and
Jerry Yee,****** for the SPRINT Research Group

Cumulative Hazard

0.15

0.12

0.09

0.06

0.03

0
1
2
3
4
5

years

all cause death
(secondary end-point)

HR=0.72  (95%CI 0.53-0.99)

<120 mmHg

<140 mmHg

70 deaths

90 deaths
Effects of Intensive BP Control in CKD

Alfred K. Cheung,*1 Mahboob Rahman,1* David M. Reboussin,2 Timothy E. Craven,1 Tom Greene,1 Paul L. Kimmel,2* William C. Cushman,1† Amret T. Hawfield,1‡

*main kidney outcome (secondary end point) a ↓ in eGFR of 50% from baseline, confirmed by repeat testing 90 days later, or ESRD

Cumulative Hazard

HR=0.90 (95%CI 0.44-1.13)
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**eGFR**
ml/min/1.73 m²

![Graph showing the relationship between eGFR and confirmed events over months](image)
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alb/Cr U
mean ratio to baseline

months
6 12 24 36 48
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Episodes
0.4% per year

serum K >5.5 mMol/L
0.7% per year

Serum K <3.0 mMol/L
2.7% per year

anti hypertensive drugs = 2.0 ±1

anti hypertensive drugs = 2.9 ±1

Systolic BP
mmHg

150
140
130
120
110

0             1             2             3             4             5
years

SERIOUS ADVERSE EVENTS N=640

SERIOUS ADVERSE EVENTS N=627
The SPRINT CKD substudy message

In patients with mild to moderate CKD and hypertension, intensive reduction in SBP resulted in substantial reductions in CV events and all-cause death without an effect on the incidence of 50% eGFR loss or ESRD.

In exploratory analyses, intensive SBP lowering caused a slightly higher rate of eGFR decline of degree less than 50% and a modest risk excess for hypokaliemia and hyperkaliemia.

The balance of benefits and harms seems to favor intensive SBP lowering in this population.

This is not standard Office BP (the measure we apply in clinical practice) but a «research grade» BP measurement

3 unattended BP measurements at an office visit while the patient was seated and after 5 min. of quiet rest.
BP measured as in the SPRINT study and routinely measured BP in the office in 275 CKD patients with BP <140/90

For high-risk patients (including CKD) intensive management to target a systolic BP ≤120 mm Hg should be considered.

Intensive management should be guided by automated office BP measurements

The 95% CI is too wide for office systolic BP 130 mmHg be adopted as the target BP

For establishing the target to apply in clinical practice can we pragmatically add 10 mmHg to the SPRINT systolic BP target (120 mmHg) and set the threshold at 130 mmHg?
How representative is the SPRINT study CKD sub-population of CKD patients normally seen in Nephrology clinics?

602 (80%) were not eligible for SPRINT.

SPRINT is not a typical CKD trial. Findings in SPRINT apply to a minority of the CKD population seen by nephrologists.

A series of 753 incident CKD patients in 12 Nephrology clinics in a 2 million population Southern Italy area.

- Age <50 years (17%)
- Diabetes (38%)
- eGFR >59 <20 ml/min/1.73m² (37%)
- Proteinuria (32%)
- ADPKD (5.3%)
- Syst BP>150-180 (15%)
- BP already on target (33%)
- Symptomatic HF (5.6%)
- on immunosuppressive drugs (2.2%)

Trials profiled to the characteristics of the CKD population remain a priority to set treatment targets in CKD.
Guidelines Debate
Hypertension, 2016;68:3-5.
Recommendations for Intensive Blood Pressure Lowering in High-Risk Patients, the Canadian Viewpoint

Raj Fulbright, Doreen M. Rob, Ernest L. Schirin

Clinical Practice Guideline: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Treatment of Hypertension in Patients With CKD

References that support recommendations are summarized in Online Data Supplements 37 and 38 and Systematic Review Report.

<table>
<thead>
<tr>
<th>LEVEL B-R</th>
<th>(Randomized)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Moderate-quality evidence‡ from 1 or more RCTs</td>
<td></td>
</tr>
<tr>
<td>Meta-analyses of moderate-quality RCTs</td>
<td></td>
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</tbody>
</table>

DBP: C-EO mm Hg

With albuminuria ≤300 mg/d:
- 140/90
- 130/80
- 130/80

With albuminuria >30 mg/d:
- 140/90
- 130/80
- 130/80

December 2012

No interaction between alb/cr and the composite end-point in patients with 24h proteinuria <1g

Hypertension. 2016;68:3-5.
Hypertension is a risk factor too important for BP to be suboptimally measured.

Major efforts should be made for measuring BP by adopting «research grade» BP measurements, like in the SPRINT study.

The adoption of this metric is essential for making sound decisions considering the novel information generated in the SPRINT trial.

Office BP is an overtly inadequate means for estimating BP in CKD and in the general population as well.
### Cardiovascular Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOT, 1998</td>
<td>1.069</td>
<td>[0.890; 1.378]</td>
</tr>
<tr>
<td>Adding UKPDS–38, 1998</td>
<td>0.861</td>
<td>[0.542; 1.369]</td>
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<tr>
<td>Adding ABCD (H), 2000</td>
<td>0.807</td>
<td>[0.534; 1.221]</td>
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<tr>
<td>Adding AASK, 2002</td>
<td>0.861</td>
<td>[0.620; 1.195]</td>
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<tr>
<td>Adding ABCD (N), 2002</td>
<td>0.912</td>
<td>[0.671; 1.240]</td>
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<tr>
<td>Adding Schrier et al., 2002</td>
<td>0.914</td>
<td>[0.693; 1.206]</td>
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<tr>
<td>Adding REIN–2, 2005</td>
<td>0.911</td>
<td>[0.711; 1.168]</td>
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<tr>
<td>Adding JATOS, 2008</td>
<td>0.933</td>
<td>[0.753; 1.158]</td>
</tr>
<tr>
<td>Adding Cardio–Sis, 2009</td>
<td>0.925</td>
<td>[0.750; 1.140]</td>
</tr>
<tr>
<td>Adding ACCORD BP, 2010</td>
<td>0.956</td>
<td>[0.809; 1.129]</td>
</tr>
<tr>
<td>Adding VALISH, 2010</td>
<td>0.957</td>
<td>[0.813; 1.127]</td>
</tr>
<tr>
<td>Adding HOMED–BP, 2012</td>
<td>0.951</td>
<td>[0.809; 1.119]</td>
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<tr>
<td>Adding SP3S, 2013</td>
<td>0.944</td>
<td>[0.810; 1.099]</td>
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<tr>
<td>Adding Wei et al., 2013</td>
<td>0.862</td>
<td>[0.715; 1.038]</td>
</tr>
<tr>
<td><strong>Adding SPRINT, 2015</strong></td>
<td><strong>0.816</strong></td>
<td><strong>[0.674; 0.988]</strong></td>
</tr>
</tbody>
</table>

Cumulative estimate

- Random effects model
  - $z = 2.083; p = 0.037$
  - $95\% CI: [0.816; 0.988]$
  - $I^2 = 32.1\%; p = 0.112$

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### All-cause Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>MDRD, 1995</td>
<td>1.637</td>
<td>[0.638; 4.199]</td>
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<tr>
<td>Adding Toto et al., 1995</td>
<td>1.695</td>
<td>[0.686; 4.189]</td>
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<tr>
<td>Adding HOT, 1998</td>
<td>1.087</td>
<td>[0.915; 1.292]</td>
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<tr>
<td>Adding UKPDS–38, 1998</td>
<td>0.992</td>
<td>[0.786; 1.251]</td>
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<td>Adding ABCD (H), 2000</td>
<td>0.899</td>
<td>[0.644; 1.253]</td>
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<td>Adding AASK, 2002</td>
<td>0.902</td>
<td>[0.698; 1.166]</td>
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<tr>
<td>Adding ABCD (N), 2002</td>
<td>0.911</td>
<td>[0.731; 1.135]</td>
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<tr>
<td>Adding Schrier et al., 2002</td>
<td>0.918</td>
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<td>Adding REIN–2, 2005</td>
<td>0.927</td>
<td>[0.775; 1.107]</td>
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<td>Adding JATOS, 2008</td>
<td>0.941</td>
<td>[0.600; 1.107]</td>
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<td>Adding ACCORD BP, 2010</td>
<td>0.972</td>
<td>[0.625; 1.464]</td>
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<tr>
<td>Adding Cardio–Sis, 2009</td>
<td>0.980</td>
<td>[0.849; 1.131]</td>
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<tr>
<td>Adding ACCORD BP, 2010</td>
<td>1.003</td>
<td>[0.896; 1.123]</td>
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<tr>
<td>Adding VALIDISH, 2010</td>
<td>0.993</td>
<td>[0.889; 1.110]</td>
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<tr>
<td>Adding HOMED–BP, 2012</td>
<td>0.987</td>
<td>[0.886; 1.100]</td>
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<tr>
<td>Adding SP3S, 2013</td>
<td>0.997</td>
<td>[0.901; 1.103]</td>
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<tr>
<td>Adding Wei et al., 2013</td>
<td>0.917</td>
<td>[0.706; 1.197]</td>
</tr>
<tr>
<td><strong>Adding SPRINT, 2015</strong></td>
<td><strong>0.888</strong></td>
<td><strong>[0.772; 1.021]</strong></td>
</tr>
</tbody>
</table>

Cumulative estimate

- Random effects model
  - $z = 1.674; p = 0.094$
  - $95\% CI: [0.888; 1.021]$
  - $I^2 = 40.9\%; p = 0.037$
Composite Ranking for Relative Risks by GFR and Albuminuria (KDIGO 2009)

GFR Stages
(mL/min/ 1.73m²)

Albuminuria (mg/g)

<table>
<thead>
<tr>
<th>Albuminuria (mg/g)</th>
<th>&lt;10</th>
<th>11-29</th>
<th>30-300</th>
<th>300-2000</th>
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<td>90-104</td>
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