Management of Hypertension in Chronic Kidney Disease

UCSF Advances in Internal Medicine CME Series

Christopher Carlos, MD MAS
Division of Nephrology

6/18/2020
Disclosures

I have no relevant financial relationships with any companies related to the content of this course.
Outline

Pathophysiology of hypertension in chronic kidney disease

Methods of blood pressure measurement

Treatment options

Effect of therapy on outcomes
Consequences of uncontrolled hypertension

Premature death
Generalized arteriosclerosis and atherosclerosis
Heart disease
Stroke
Malignant Hypertension with kidney failure

Hypertension remains a leading attributed cause of end-stage kidney disease in the United States
Stroke risk rises exponentially with BP

61 prospective studies: > 1 million subjects: Lancet 2002
Pathophysiologic mechanisms of hypertension in CKD

Ku AJKD 2019 Core Curriculum 2019
CKD can worsen hypertension

Reduced nephron mass decreases GFR, which increases renin

Ang II increase, which causes proximal tubular sodium reabsorption

Chronic sodium retention stimulates vasoconstriction and leads to arterial stiffness
Outline

Pathophysiology of hypertension in chronic kidney disease

Methods of blood pressure measurement

Treatment options

Effect of therapy on outcomes
Blood pressure measurements

Importance of standardized protocol
- Abstinence from caffeine, exercise and smoking for > 30 minutes
- Feet on floor; arm and back supported
- Keep quiet (and not talked to) and relaxed for > 5 minutes
- Use correct cuff size and position

## Comparison of BP measurement methods

<table>
<thead>
<tr>
<th></th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinic</strong></td>
<td>Routine / easy</td>
<td>Poor reproducibility</td>
</tr>
<tr>
<td></td>
<td>Use in clinical trials</td>
<td>White coat effect</td>
</tr>
<tr>
<td></td>
<td>Outcome data</td>
<td>Staff training / time when done right</td>
</tr>
<tr>
<td><strong>Home BP</strong></td>
<td>Inexpensive</td>
<td>?Outcome data (TBD)</td>
</tr>
<tr>
<td></td>
<td>Empowers patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adherence</td>
<td></td>
</tr>
<tr>
<td><strong>ABPM</strong></td>
<td>Many values</td>
<td>?Expensive</td>
</tr>
<tr>
<td></td>
<td>Sleep data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rx entire dose interval</td>
<td></td>
</tr>
</tbody>
</table>
Automated office BP devices

Multiple consecutive BP readings in the office with the patient sitting and resting *alone*

Decreased white coat response

CAMBO trial (with BPM-100 Monitor device)
  - BPM-100 Monitor readings significantly closer to daytime ambulatory blood pressure (ABPM) readings than conventional manual readings

Self-Measured Blood Pressure Monitoring (SMBP)

NICE guidelines for confirmation of HTN
- Take 2 consecutive readings 1 minute apart
- Seated position
- Record BP twice daily (AM and PM)
- 4 to 7 days of recording

Provides out of office readings, BP variability, identification of white coat HTN and masked HTN

Lower cost, high availability, easy application, useful over long periods of time
Self measured blood pressure monitoring (SMBP) improves BP at 6 months

SBMP, with ancillary support, more effective than usual care 12 months

Some studies found more medication changes and greater adherence with SBMP monitoring
Ambulatory Blood Pressure Monitoring
Normal readings

Awake: 121/77 mm Hg
Nocturnal: 95/53 mm Hg
ABPM outperforms clinic BP in predicting mortality
Dolan E et al: Hypertension 46:156, 2005
Poor Correlation Between Routine and Standardized Office BP
Agarwal JAHA 2017

- N = 275 CKD
- eGFR 29 +/- 10 ml/min/1.73m²
- Bland-Altman plot with limits of agreement

Though standardized BP is generally lower than routine office BP, not a strong enough correlation to "convert" one reading to another.
Classification of BP for Adults
2017 High Blood Pressure Clinical Practice Guideline : AHA/ACC

Table 1. Definitions of Normal and Abnormal BP Based on the 2017 AHA/ACC Guideline in Patients With CKD

<table>
<thead>
<tr>
<th>BP Classificationa</th>
<th>Office BP</th>
<th>Daytime ABPM or Home BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or elevated BP</td>
<td>&lt;130/80 mm Hg</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>≥130/80 mm Hg</td>
<td>≥130/80 mm Hg</td>
</tr>
<tr>
<td>White coat hypertension</td>
<td>≥130/80 mm Hg</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>&lt;130/80 mm Hg</td>
<td>≥130/80 mm Hg</td>
</tr>
</tbody>
</table>
Outline

Pathophysiology of hypertension in chronic kidney disease

Methods of blood pressure measurement

Treatment options

Effect of therapy on outcomes
Lifestyle modification remains first step

Target salt intake to < 2 g per day among CKD patients with high BP

DASH diet can lead to moderate declines in BP by ~ 10 mm Hg
(though high potassium diets despite evidence of benefit may place patients with advanced CKD at risk of hyperkalemia)

Weight loss can reduce BP by ~5 mm Hg for every 5-kg weight loss

Limiting alcohol intake
ACE-inhibitors delay progression of kidney disease in CKD
Hou NEJM 2006;354:131-40

Group 1: Baseline Cr 1.5 – 3.0, given benazepril 20mg
Group 2: Baseline Cr 3.1 – 5.0, given benazepril 20mg
Group 3: Baseline Cr 3.1 – 5.0, given placebo

Effect is independent of blood pressure control
Perhaps we should never stop ACE inhibitors?
Ruggenenti JASN 2001; 12: 2832-2837

Across all starting baseline GFR, there seemed to be a benefit to ACE/ARB use
Perhaps we should never stop ACE inhibitors?

Ruggenenti JASN 2001; 12: 2832-2837

Table 3. Serious adverse events leading to patient withdrawal

<table>
<thead>
<tr>
<th>Event</th>
<th>Lowest Tertile</th>
<th>Middle Tertile</th>
<th>Highest Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
<td>Ramipril</td>
<td>Conventional</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Worsening of renal function</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Uncontrolled BP</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

Events of hyperkalemia and AKI were quite low
(caveat: clinical trial population under close surveillance?)
Even among predialysis CKD5, ACEI/ARB was beneficial
Hsu, Ta-Wei. JAMA IM 2014;174(3):347-354

HR 0.93 (0.91-0.96) of dialysis initiation or death

Also higher rates of hyperkalemia-associated hospitalizations
RR = 1.31 (1.21-1.43)
Anecdotally, we stop ACE/ARB frequently to delay dialysis
Ahmed NDT 2010; 25: 39277-3982
Other pharmacologic agents use in CKD

Diuretics:
- Helps with fluid overload, may prevent hyperkalemia with RAS inhibitors
- Classic teaching states loop diuretics more effective than thiazides when eGFR < 30 (though some studies refute this)

Calcium Channel Blockers:
- Nondihydropyridine (diltiazem, verapamil) can also have proteinuria reduction

Beta blockers:
- Best in patients with concomitant heart failure or atrial fibrillation
Outline

Pathophysiology of hypertension in chronic kidney disease

Methods of blood pressure measurement

Treatment options

Effect of therapy on outcomes
SPRINT Trial: CKD subgroup analysis
Cheung et al. SPRINT research group. JASN 2017; 28:2812-2823

- Of the total SPRINT cohort (n=9361), 2646 (28.3%) had CKD at baseline
- Intensive group used an average of 2.9 (vs 2.0, control group) medications to lower SBP to 123 mm Hg (vs 136 mm Hg) at one year.
Targeting BP < 120 lowers all-cause death in CKD patients
Cheung et al. SPRINT research group. JASN 2017; 28:2812-2823
Targeting BP < 120 lowers all-cause death in CKD patients
Cheung et al. SPRINT research group. JASN 2017; 28:2812-2823

Death rates were low (70 / 1330 vs 95 / 1336)
Excluded diabetes and proteinuria > 1000mg/g
Meta-Analysis: Intensive BP lowering reduces mortality in patients with CKD 3-5
Malhotra JAMA IM 2017

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
<th>Score</th>
<th>No. of Deaths/Total No.</th>
<th>Favors More Intensive BP</th>
<th>Favors Less Intensive BP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al, 2002</td>
<td>0.874 (0.554-1.380)</td>
<td>-0.578</td>
<td>37/540</td>
<td>43/554</td>
<td></td>
<td>.56</td>
</tr>
<tr>
<td>Estacio et al, 2000</td>
<td>0.575 (0.182-1.820)</td>
<td>-0.941</td>
<td>5/62</td>
<td>9/68</td>
<td></td>
<td>.35</td>
</tr>
<tr>
<td>Schrier et al, 2002</td>
<td>1.227 (0.398-3.865)</td>
<td>0.349</td>
<td>6/57</td>
<td>7/80</td>
<td></td>
<td>.73</td>
</tr>
<tr>
<td>Cushman et al, 2010</td>
<td>1.271 (0.685-2.360)</td>
<td>0.761</td>
<td>26/208</td>
<td>20/198</td>
<td></td>
<td>.45</td>
</tr>
<tr>
<td>Heerspink et al, 2010</td>
<td>0.862 (0.662-1.123)</td>
<td>-1.102</td>
<td>117/1010</td>
<td>135/1023</td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>Lonn et al, 2016</td>
<td>0.993 (0.699-1.410)</td>
<td>-0.039</td>
<td>49/1220</td>
<td>97/2399</td>
<td></td>
<td>.97</td>
</tr>
<tr>
<td>Beckett et al, 2008</td>
<td>0.676 (0.502-0.911)</td>
<td>-2.570</td>
<td>83/788</td>
<td>121/816</td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Klahr et al, 1994</td>
<td>1.366 (0.681-2.742)</td>
<td>0.878</td>
<td>20/432</td>
<td>14/408</td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Mant et al, 2016</td>
<td>3.588 (0.140-9145)</td>
<td>0.772</td>
<td>1/26</td>
<td>0/30</td>
<td></td>
<td>.44</td>
</tr>
<tr>
<td>Ruggenenti et al, 2005</td>
<td>0.667 (0.110-4.042)</td>
<td>-0.441</td>
<td>2/167</td>
<td>3/168</td>
<td></td>
<td>.66</td>
</tr>
<tr>
<td>Schrier et al, 2002</td>
<td>0.825 (0.050-13.701)</td>
<td>-0.134</td>
<td>1/41</td>
<td>1/34</td>
<td></td>
<td>.89</td>
</tr>
<tr>
<td>SHEP Cooperative Research Group, 1991</td>
<td>0.900 (0.670-1.209)</td>
<td>-0.700</td>
<td>96/879</td>
<td>103/859</td>
<td></td>
<td>.48</td>
</tr>
<tr>
<td>Wright et al, 2015</td>
<td>0.714 (0.519-0.982)</td>
<td>-2.072</td>
<td>70/1330</td>
<td>95/1316</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Benavente et al, 2013</td>
<td>0.850 (0.468-1.544)</td>
<td>-0.534</td>
<td>24/216</td>
<td>25/195</td>
<td></td>
<td>.59</td>
</tr>
<tr>
<td>Staessen et al, 1997</td>
<td>0.826 (0.470-1.451)</td>
<td>-0.665</td>
<td>26/242</td>
<td>29/228</td>
<td></td>
<td>.51</td>
</tr>
<tr>
<td>Toto et al, 1995</td>
<td>2.566 (1.011-6.993)</td>
<td>0.572</td>
<td>1/42</td>
<td>0/35</td>
<td></td>
<td>.57</td>
</tr>
<tr>
<td>UK Prospective Diabetes Study Group, 1998</td>
<td>1.667 (0.626-4.435)</td>
<td>1.023</td>
<td>20/68</td>
<td>7/35</td>
<td></td>
<td>.31</td>
</tr>
<tr>
<td>Overall</td>
<td>0.859 (0.764-0.965)</td>
<td>-2.560</td>
<td>584/7451</td>
<td>709/8473</td>
<td></td>
<td>.01</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0\%; P = .77; I^2 = 0\%$

1293 deaths / 15924

OR = 0.86
## Can intensive BP control increase ESRD progression risk?

Ku. JASN 2017

Table 2. Association between percentage decline in renal function in the AASK participants (n=899) from time of randomization until month 3 and risk of ESRD

| Renal Function Decline, % | Strict BP Arm | | | Usual BP Arm | |
|----------------------------|---------------|-------------------------|-------------------------|-------------------------|
|                           | N             | ESRD Incidencea (95% CI) | Unadjusted HR (95% CI) | Adjusted HRb (95% CI) | N | ESRD Incidencea (95% CI) | Unadjusted HR (95% CI) | Adjusted HRb (95% CI) |
| AASK                      | 448           | 2.9 (2.4 to 3.6)         | 1.00 (0.75 to 1.34)     | 0.94 (0.70 to 1.25)   | 451 | 2.9 (2.4 to 3.5)         | 1.0 (Reference)         | 1.0 (Reference)         |
| <5                        | 271           | 3.6 (2.7 to 4.7)         | 1.26 (0.90 to 1.76)     | 1.19 (0.84 to 1.68)   | 319 | 6.3 (4.8 to 8.1)         | 2.22 (1.60 to 3.09)     | 1.83 (1.30 to 2.57)     |
| 5 to <20                  | 139           | 9.8 (6.7 to 14.4)        | 3.58 (2.32 to 5.52)     | 3.04 (1.95 to 4.77)   | 98  | 10.4 (6.9 to 15.7)       | 3.83 (2.43 to 6.04)     | 2.56 (1.60 to 4.11)     |
| ≥20                       | 38            | 15.5 (11.5 to 20.9)      | 2.03 (1.44 to 2.87)     | 1.57 (1.09 to 2.24)   | 34  | 17.3 (13.0 to 23.7)      | 2.39 (1.71 to 3.35)     | 1.48 (1.04 to 2.1)      |
| MDRD                      | 388           | 7.1 (6.0 to 8.5)         | 0.93 (0.73 to 1.19)     | 0.88 (0.68 to 1.13)   | 373 | 7.6 (6.4 to 9.0)         | 1.0 (Reference)         | 1.0 (Reference)         |
| <5                        | 190           | 9.7 (8.1 to 11.7)        | 1.28 (0.99 to 1.64)     | 1.08 (0.84 to 1.40)   | 182 | 12.6 (10.5 to 15.1)      | 1.66 (1.29 to 2.13)     | 1.62 (1.25 to 2.11)     |
| 5 to <20                  | 150           | 15.5 (11.5 to 20.9)      | 2.03 (1.44 to 2.87)     | 1.57 (1.09 to 2.24)   | 136 | 17.3 (13.0 to 23.7)      | 2.39 (1.71 to 3.35)     | 1.48 (1.04 to 2.1)      |

- **a**Per 100 person-years.
- **b**Adjusted for age, sex, baseline heart disease, antihypertensive drug assignment (ACE inhibition versus other agents), baseline eGFR category, baseline proteinuria category, and baseline MAP. Model is additionally adjusted for race for MDRD participants.
- **c**HRs are statistically significantly different comparing strict with usual BP arms (P<0.05).

Lowering eGFR < 20% within 3-4 months with strict BP control not associated with development of ESRD
Take home points

Automated office blood pressure measurements are supported in clinical trials, though standardized protocols should be employed.

Use of RAAS inhibitors remains first line, particularly among patients with proteinuric CKD. Diuretics are often 2nd line for management of sodium retention and hyperkalemia.

Targeting a systolic BP of less than 120 has favorable survival benefits among patients with prevalent nonproteinuric CKD patients.

Individualization is key: High level data remains uncertain in patients with diabetic CKD, proteinuria > 1g/g and the very old / frail.