Blood Pressure Measurement, Targets, and Pharmacologic Management

KDIGO Controversy Conference
Lisbon, 2019

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Conflict of Interest

- Boehringer-Ingelheim (consultant)
- NIH (awardee including SPRINT)
- KDIGO (co-chair, BP in CKD)
- UptoDate (contributor)
Objectives of This Presentation

• Unsettled or controversial topics
• Not comprehensive literature review
• Focus on BP instead of fluid volume
• HD and PD
What Are Controversial in BP Management in Maintenance Dialysis Patients?

Almost everything

Yet, we all measure BP in dialysis patients
KDIGO Controversy Conference in New York in March, 2009

• What is the optimal BP treatment target in relation to end-organ damage and outcomes?
  (AKC: Requires large RCT)

• How should anti-hypertensive drugs be used?
  (AKC: Requires large RCT)

• What non-pharmacological therapies can be considered in achieving BP targets?
BP Measurements
BP Measurements in Non-Dialysis Patients

- Equipment (manual vs. automated)
- Location (office vs. home)
- Preparations (abstinence from stimulants, rest, body position, ambient temperature)
- Number of readings (random, diurnal, nocturnal dip, 24-hr)
- Reasonable standardizations

Additional considerations in dialysis patients

- Fluctuations in fluid status (HD > PD)
- Vascular access
- Convenience of geographical location
- Withholding anti-hypertensive medications pre-HD
Increase in Inter-dialytic BP

Unique problem in HD patients

Heart rate or Blood Pressure

Systolic BP

Diastolic BP

Pulse Pressure

Time elapsed since end of dialysis (h)

Agarwal, AJKD, 2009
High Variability in Pre-HD SBP

Magnitude of within-patient SD > between-patient SD

25 Random HD Patient ID
Prediction of Mortality Using Various BP Measurements in HD Patients

N=150
26 CV deaths

Alborzi, CJASN 2007
Pre-HD vs. Inter-dialytic Clinic SBP Association with Mortality in HD Patients

- CRIC Study

Hazard ratio

Frequency

SBP (mm Hg)

1.26 [1.14-1.40] per 10 mm Hg increase

Bansal, Hypertens, 2015
What Do We Need?

• “Accuracy”
  – What is gold standard?
  – Is it important?

• “Reliability” (reproducibility)

• Association of various BP measurement methods with various clinical outcomes

• Large sample sizes
Fuzzy Terms in Dialysis Patients

• Prevalence of hypertension (definition?)
• Optimization of BP (and fluid status) (target?)
• Better control of BP (target?)
Definition of HTN in HD Patients

- Normative in general population?
- Normative in dialysis population?
- Prognosticative?
- Benefits from BP lowering?

Harm of “low” BP
- Impaired intradialytic and interdialytic organ perfusion
- Special consideration – loss of residual kidney function
BP Target

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2005 K/DOQI Guideline for CVD in Dialysis

• 12.2. Predialysis and postdialysis blood pressure goals should be <140/90 mmHg and <130/80 mmHg, respectively. (C)
Association of Pre-HD SBP with Mortality in HD Patients

(N=4499)

- Misclassification
- Confounding
- Non-steady state
- Duration of F/U

Should we increase BP?

Average
~140-159 mm Hg in 2015 U.S. DOPP Monitor

Port, USRDS, AJKD, 1999
Association between SBP and Mortality Risk in HD and PD Patients

South Korea registry

Jhee, Sci Rep, 2018
Association between SBP and \textbf{Mortality} Risk May Varies with \textbf{Age} in Dialysis (HD+PD) Patients

\textbf{N} = 2299
Median FU = 4.5 yr
Paradoxical Association Not Seen in HD Patients Without Heart Disease

Port, AJKD, 1999

USRDS N=4499
Association of Predialysis SBP with Mortality Risk Depends on HD Vintage

HR for Mortality

16,959 incident HD patients

Predialysis SBP (mm Hg)
Association of BP with Death in PD Patients
Effect of F/U Duration and Cardiac Function

- RR for death = 7.3 [1.5-35.7] for SBP <120 mm Hg (vs. SBP 140-159 mm Hg)
- RR = 3.4 [0.7-17.7] after adjustment for ejection fraction

Afshinnia, PDI, 2016
Never Consistently Euvolemic

Continuous (or frequent and long) HD treatment is best way to minimize fluctuation

Frequency and total duration of HD modify association between pre-HD BP and clinical outcomes

KDIGO
Effect of Intensive vs. Standard SBP on Clinical Outcomes by Baseline DBP Quintiles in SPRINT

We need large RCTs to determine BP targets in dialysis patients

Beddhu, Circ, 2018
BP in Dialysis (BID) Pilot Trial

- 126 HD patients randomized to Pre-HD SBP 110-140 mm Hg vs. 155-165 mm Hg
- More intradialytic hypotensive symptoms in intensive SBP arm
- Not powered for clinical outcomes, but risks were numerically higher in intensive SBP arm for MACE, hospitalization and (3x higher) vascular access thrombosis

\[ \Delta = 12.9 \text{ mm Hg at months 4-12} \]

\[ \Delta = 6.1 \text{ mm Hg at months 4-12} \]

Miskulin, JASN, 2018
Pharmacotherapy
Lowering BP in dialysis patients is beneficial

Combined N=1,679 in 8 trials

Caveats:

- Heterogeneous study design
- Pre-dialysis BP
- None was BP trial
- Interventions were specific agents (RAAS blocker, BB, CCB), not targeting BP

Heerspink, Lancet, 2009
Effect of ACEI/ARB on CHF in HD/PD Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/patients</th>
<th>Relative ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI/ARBs</td>
<td>control</td>
</tr>
<tr>
<td></td>
<td>15/100</td>
<td>5/100</td>
</tr>
<tr>
<td>HDPAL 2014</td>
<td>21/183</td>
<td>42/183</td>
</tr>
<tr>
<td>Suzuki 2008</td>
<td>5/43</td>
<td>11/37</td>
</tr>
<tr>
<td>Takahashi 2006</td>
<td>14/235</td>
<td>19/234</td>
</tr>
<tr>
<td>OCTOPUS 2013</td>
<td>55/561</td>
<td>77/554</td>
</tr>
<tr>
<td>Overall</td>
<td>55/561</td>
<td>77/554</td>
</tr>
</tbody>
</table>

(I-squared = 74.6%, p = 0.008)

NOTE: Weights are from random effects analysis

• Meta-analysis of 11 RCTs and 1856 patients

Liu, BMC Nephrol, 2017
## Removal of Antihypertensive Drugs by HD

<table>
<thead>
<tr>
<th>ACE-I</th>
<th></th>
<th>ARB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>&lt;30%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Enalapril</td>
<td>35%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>2%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lisinopril*</td>
<td>50%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ramipril</td>
<td>30%</td>
<td>None</td>
<td>None</td>
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<tr>
<td><strong>β-Blockers</strong></td>
<td></td>
<td><strong>ARB</strong></td>
<td></td>
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<tr>
<td>Atenolol*</td>
<td>75%</td>
<td>None</td>
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<tr>
<td>Carvedilol</td>
<td>None</td>
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<td>None</td>
</tr>
<tr>
<td>Labetalol</td>
<td>&lt;1</td>
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<td>None</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>High</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td><strong>CCB</strong></td>
<td></td>
</tr>
<tr>
<td>Clonidene</td>
<td>5%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>None</td>
<td>Low</td>
<td>30%</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
</tr>
</tbody>
</table>

**KDIGO**
β-Blocker Dialyzability and Mortality in HD Patients

- Propensity-matched retrospective cohort study using administrative database in Canada
- Highly-dialyzable β-blockers (atenolol, metoprolol, acebutolol; N=3294) vs. lowly-dialyzable β-blockers (propanolol, bisoprolol; N=3294)
- Initiating highly-dialyzable β-blockers were associated with higher risk of death in 180 days (RR 1.4 [1.1-1.8])

Weir, JASN, 2015
Carvedilol vs. Metoprolol with 1-Year Mortality in HD Patients

- 9558 carvedilol (low dialyzability) + 17506 metoprolol (high dialyzability)
- Inverse-probability weighting
- Carvedilol had higher rate of IDH (IRR 1.10 [1.09-1.11])

Assimon, AJKD, 2018
How much of HTN in Dialysis Patients is volume-dependent?

- Do not know (not in CKD or non-CKD either)
- Probably quite a bit
- Probably varies among individuals
Volume-Independent Blood Pressure Increase in HD Patients

- Arterial stiffness (e.g., calcification)
- Sympathetic over-activity (kidney ischemia, CHF, decreased renalase)
- Other mediators (RAAS, ET-1/NO ratio)
- ESA (increases sensitivity to AII and NE and increases ET-1)
- Sleep apnea (contributes to impaired nocturnal dipping)
Circulation: Overall Regulation

Guyton, Annu Rev Physiol, 1972
Endocrine and Paracrine Ang II and Aldosterone in CNS Modulate Sympathetic Outflow

Leenen, Endocrin Connect, 2017
Effects of Spironolactone on BP in Dialysis Patients

- Double-blinded RCT of 76 patients on HD or PD x 56 mos
- ~78% had urine volume <100 ml/24 hr
- ABP ~146/90 on 5 drugs
- Spironolactone 25 mg vs. placebo as add-on
- No Δ in BW and serum K⁺

Ni, AJH, 2014
How do we decide what to do with BP in dialysis patients?

- **Limited hard data**
- Inference from other populations
- Clinical decisions + ?? guidelines
- Known physiology + pathophysiology
- Common sense + intuition
Conclusions

• **BP Measurements for dialysis patients**
  – Peri-HD measurements are convenient, but not reliable
  – Should move towards home or clinic measurements for clinical use and research

• **BP Target for dialysis patients**
  – Unknown, but be leery of U-shape curve in observational studies
  – Needs large RCTs

• **Pharmacotherapy for dialysis patients**
  – No clear winner among anti-hypertensive agents
  – CV outcomes and preservation of residual kidney function should be considered