Hypertension in patients on chronic dialysis

Csaba Ambrus

Szent Imre Teaching Hospital, Div. of Nephrology-Hypertension
Semmelweis University, Div.Sect. of Geriatric Medicine
B.Braun Avitum Hungary, Budapest
Global prevalence of dialysis patients

3 000 000 patients on dialysis

89% hemodialysis (HD)

11% peritoneal dialysis (PD)
Prevalence of hypertension in dialysis patients

Prevalence of hypertension in dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>Definition of hypertension</th>
<th>Prevalence of hypertension (%)</th>
<th>BP treatment among hypertensive patients (%)</th>
<th>BP control among hypertensive patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem [55]</td>
<td>1995</td>
<td>649</td>
<td>Prehemodialysis MAP $\geq$ 114 mmHg or use of antihypertensive agents</td>
<td>71.9</td>
<td>81.5</td>
<td>48.6</td>
</tr>
<tr>
<td>Rahman et al. [60]</td>
<td>1999</td>
<td>489</td>
<td>Prehemodialysis SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mm</td>
<td>87.7</td>
<td>93.2</td>
<td>71.1</td>
</tr>
<tr>
<td>Agarwal et al. [1]</td>
<td>2003</td>
<td>2535</td>
<td>1-week average prehemodialysis SBP $\geq$ 150 mmHg and/or DBP $\geq$ 85 mmHg, or use of antihypertensive agents</td>
<td>85.8</td>
<td>88.4</td>
<td>30.3</td>
</tr>
<tr>
<td>Agarwal [56]</td>
<td>2011</td>
<td>369</td>
<td>44-h interdialytic ambulatory SBP $\geq$ 135 mmHg and/or DBP $\geq$ 85 mmHg or use of antihypertensive medications</td>
<td>82</td>
<td>89</td>
<td>38</td>
</tr>
<tr>
<td>Cocchi</td>
<td>1999</td>
<td>444</td>
<td>24h ABPM: SBP $&gt;140$, DBP $&gt;90$, or antihypertensive medication</td>
<td>88.1</td>
<td>81.5</td>
<td>22.7</td>
</tr>
<tr>
<td>Inal</td>
<td>2012</td>
<td>37</td>
<td>office BP $&gt;140/90$ mmHg</td>
<td>73</td>
<td>-</td>
<td>37</td>
</tr>
</tbody>
</table>

The most common cause, consequence, co-morbidity: 70-80-90%?
Prevalence of hypertension in dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>Definition of hypertension</th>
<th>Prevalence of hypertension (%)</th>
<th>BP treatment among hypertensive patients (%)</th>
<th>BP control among hypertensive patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem [55]</td>
<td>1995</td>
<td>649</td>
<td>Prehemodialysis MAP $\geq$ 114 mmHg or use of antihypertensive agents</td>
<td>71.9</td>
<td>81.5</td>
<td>48.6</td>
</tr>
<tr>
<td>Rahman et al. [60]</td>
<td>1999</td>
<td>489</td>
<td>Prehemodialysis SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mm</td>
<td>87.7</td>
<td>93.2</td>
<td>71.1</td>
</tr>
<tr>
<td>Agarwal et al. [1]</td>
<td>2003</td>
<td>2535</td>
<td>1-week average prehemodialysis SBP $\geq$ 150 mmHg and/or DBP $\geq$ 85 mm or use of antihypertensive agents</td>
<td>85.8</td>
<td>88.4</td>
<td>30.3</td>
</tr>
<tr>
<td>Agarwal [56]</td>
<td>2011</td>
<td>369</td>
<td>44-h interdialytic antimicroorganism SBP $\geq$ 135 mmHg and/or DBP $\geq$ 85 mm or use of antihypertensive agents</td>
<td>82</td>
<td>89</td>
<td>38</td>
</tr>
<tr>
<td>Cocchi</td>
<td>1999</td>
<td>444</td>
<td>24h ABPM, SBP $\geq$ 140, DBP$\geq$90, or antihypertensive medication</td>
<td>88.1</td>
<td>81.5</td>
<td>22.7</td>
</tr>
</tbody>
</table>
| Inal          | 2012 | 37  | Office BP $>140/90$ mmHg                                                                  | 73                              | -                                           | 37                                         

High prevalence of hypertension and Poor BP control among both HD and PD patients!

Prevalence of hypertension in dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>Definition of hypertension</th>
<th>Prevalence of hypertension (%)</th>
<th>BP treatment among hypertensive patients (%)</th>
<th>BP control among hypertensive patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem [55]</td>
<td>1995</td>
<td>649</td>
<td>Prehemodialysis MAP $\geq$ 114 mmHg or use of antihypertensive agents</td>
<td>71.9</td>
<td>81%</td>
<td>89%</td>
</tr>
<tr>
<td>Rahman et al. [60]</td>
<td>1999</td>
<td>489</td>
<td>Prehemodialysis SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mm</td>
<td>87.7</td>
<td>76%</td>
<td>75%</td>
</tr>
<tr>
<td>Agarwal et al. [1]</td>
<td>2003</td>
<td>2535</td>
<td>1-week average prehemodialysis SBP $\geq$ 150 mmHg and/or DBP $\geq$ 90 mm, or use of antihypertensive agents</td>
<td>85.8</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>Agarwal [56]</td>
<td>2011</td>
<td>369</td>
<td>44-h interdialytic ambulatory SBP $\geq$ 135 mmHg and/or DBP $\geq$ 85 mmHg or use of antihypertensive medications</td>
<td>82</td>
<td>92%</td>
<td>75%</td>
</tr>
<tr>
<td>Cocchi</td>
<td>1999</td>
<td>444</td>
<td>24h ABPM: SBP$&gt;140$, DBP$&gt;90$, or antihypertensive medication</td>
<td>88.1</td>
<td>81.5</td>
<td></td>
</tr>
<tr>
<td>Inal</td>
<td>2012</td>
<td>37</td>
<td>office BP $&gt;140/90$ mmHg</td>
<td>73</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

High prevalence of hypertension and Poor BP control among both HD and PD patients!

Hypertension guidelines in kidney disease

**Therapeutic strategies for treatment of hypertension in CKD**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>In patients with diabetic or non-diabetic CKD:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- It is recommended to lower SBP to a range of 130–139 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>- Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of a RAS blocker with a CCB or a diuretic is recommended as initial therapy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of two RAS blockers is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

**Blood pressure targets recommendations in CKD**

<table>
<thead>
<tr>
<th>Blood pressure target in CKD without proteinuria*</th>
<th>Blood pressure target in CKD with proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA JNC8</td>
<td>&lt;140/&lt;90 mmHg</td>
</tr>
<tr>
<td>KDIGO</td>
<td>&lt;140/&lt;90 mmHg</td>
</tr>
<tr>
<td>NICE</td>
<td>&lt;140/&lt;90 mmHg</td>
</tr>
<tr>
<td>CHEP</td>
<td>&lt;140/&lt;90 mmHg</td>
</tr>
<tr>
<td>ESC/ESH</td>
<td>&lt;140 mmHg</td>
</tr>
<tr>
<td>ASH/ISH</td>
<td>&lt;140/&lt;90 mmHg</td>
</tr>
<tr>
<td>ISHIB</td>
<td>&lt;130/&lt;80 mmHg</td>
</tr>
</tbody>
</table>

* Blood pressure target in CKD with proteinuria: <130/80 mmHg
Hypertension guidelines in kidney disease ...

### Therapeutic strategies for treatment of hypertension in CKD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with diabetic or non-diabetic CKD:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- It is recommended to lower SBP to a range of 130–139 mmHg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinauria.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of a RAS blocker with a CCB or a diuretic is recommended as initial therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of two RAS blockers is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

and in Hemodialysis & Peritoneal dialysis?
Blood pressure and mortality in dialysis

- Is “esreveR” epidemiology a unique feature in dialysis patients?
  paradoxical relationship between traditional risk factors and mortality

- blood pressure
- body weight
- cholesterol
- creatinine
- homocystein
- osteoprotegerin
Blood pressure and mortality in dialysis

65338 incident and 69590 prevalent HD patients, 1 year survival

Zhensheng et al, AJKD 2006; 48:606-615
Blood pressure and mortality in dialysis

Zhensheng et al, AJKD 2006; 48:606-615

65338 incident and 69590 prevalent HD patients, 3 year survival
Incident sample, CV events: 59.2%
Blood pressure and mortality in dialysis

65338 incident and 69590 prevalent HD patients, 3 year survival
Prevalent sample, CV events: 60.2%

Zhensheng et al, AJKD 2006; 48:606-615
Blood pressure and mortality in dialysis

2299 prevalent HD & PD patients, 4.5 year follow-up

Jhee et al, Sci Rep 2018; 8:14123
How should we define hypertension on dialysis?

**Diagnosis based on:**
- pre-dialysis blood pressure
- post-dialysis blood pressure
- myriad of measurements available
- convenient and tempting method
- but only useful to ensure hemodynamic stability during HD

*Not suitable for diagnosing hypertension!*
Problems with peri-dialysis BP

*Peri-dialysis BP is not suitable for diagnosing hypertension!*

Many factors affecting pre-dialysis BP

- impatient patient
  (early start, early escape from unit)
- needle-effect
- white-coat effect (30% of dialysis patient!)
- pre-dialysis BP highly depends on volume status
  (interdialysis weight gain)

Post-dialysis BP depends on ultrafiltration rate, ...

Technique not standardized
Problems with peri-dialysis BP

Peri-dialysis BP is not suitable for diagnosing hypertension!

Many factors affecting pre-dialysis BP
• impatient patient
  (early start, early escape from unit)
• needle-effect
• white-coat effect (30% of dialysis patient!)
• pre-dialysis BP highly depends on volume status
  (interdialysis weight gain)

Post-dialysis BP depends on ultrafiltration rate, ...
Technique not standardized
Problems with peri-dialysis BP

Failure of normal stress response?

Jhee et al, Sci Rep 2018; 8:14123
Problems with peri-dialysis BP

*Peri-dialysis BP is not suitable for diagnosing hypertension!*

Many factors affecting pre-dialysis BP

• impatient patient
  (early start, early escape from unit)
• needle-effect
• white-coat effect (30% of dialysis patient!)
• pre-dialysis BP highly depends on volume status
  (interdialysis weight gain)

Post-dialysis BP depends on ultrafiltration rate, ... 
Technique not standardized
Problems with peri-dialysis BP

BP measurement technique not standardized
multi-center survey - proportion of physicians adhering to recommendations

BP taken before dialysis
back supported
arm supported
correct cuff position
no talking
same body position
taken after 5 min rest
cuff direct to skin
calm room
explanation of procedure
>1 measurements
both arms
arm circumferenc measurement

Pappaccogli et al, Nephrol Dial Transplant (2019) 1–4
Problems with peri-dialysis BP

BP measurement technique not standardized
multi-center, cross sectional survey - proportion of physicians adhering to recommendations

BP taken before dialysis
back supported
arm supported
**correct cuff position**
**no talking**
same body position
**taken after 5 min rest**
**cuff direct to skin**
**calm room**
explanation of procedure
>1 measurements
both arms
**arm circumferenc measurement**
Hypertension and mortality in patients on PD

- NECOSAD study, 118 incident PD patients
  +42% relative risk for each 10mmHg SBP

- England and Wales, 3086 incident PD patients
  association btw BP and survival varies over time:
  • in 1st year: higher SBP, DBP - lower mortality (= contraselection of sic patients)
  • >5 year survivors: higher SBP - higher mortality

---

**Table 5.** Multivariate Cox proportional hazards model for patient survival using urinary and dialysate creatinine appearance

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 1 year</td>
<td>1.05</td>
<td>1.01–1.09</td>
</tr>
<tr>
<td>Systolic blood pressure 10 mm Hg</td>
<td>1.42</td>
<td>1.17–1.73</td>
</tr>
<tr>
<td>Urinary creatinine appearance 1 mmol/week/1.73 m²</td>
<td>0.95</td>
<td>0.92–0.98</td>
</tr>
<tr>
<td>Dialysate creatinine appearance 1 mmol/week/1.73 m²</td>
<td>0.93</td>
<td>0.89–0.98</td>
</tr>
</tbody>
</table>

^a P < 0.001; ^b P < 0.01

---

Hypertension and mortality in patients on PD

• USRDS, 1053 incident PD patients
Higher CV & all-cause mortality if SBP < 110mmHg
only in patients with heart failure or diabetes or antihypertensive medication

What is the useful definition for hypertension?

**Diagnosis based on:**
- pre-dialysis blood pressure (**x**)
- post-dialysis blood pressure (**x**)
- interdialytic BP outside dialysis unit
  - office BP on non-dialysis days
  - home BP measurements
  - 24/44 hour ABPM
- Home or office BP measurements for PD patients

Hypertension and mortality: peri-dial vs H/ABPM

• Pre-dialysis BP and mortality:
  • U-shaped association - a "reverse epidemiology"?
    higher mortality with SBP < 130 or SBP > 160 mmHg
  • lack on normal response to stress @ dialysis start (background cardiovascular disease?)
  • associations not adjusted for cardiac function, co-morbidities, medication

• Home BP or ABPM
  • linear associations, more reliable and reproducible

Nisha Bansal et al. Hypertension. 2015;65:93-100
Hypertension and mortality: peri-dial vs H/ABPM

No associations when using pre-, or post-dialysis measurements.

<table>
<thead>
<tr>
<th>Home BP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q1:</strong> &lt; 125.7</td>
<td><strong>P = 0.999</strong></td>
</tr>
<tr>
<td><strong>Q2:</strong> 125.7 - 143.6</td>
<td><strong>P = 0.182</strong></td>
</tr>
<tr>
<td><strong>Q3:</strong> 143.6 - 157.9</td>
<td><strong>P = 0.228</strong></td>
</tr>
<tr>
<td><strong>Q4:</strong> &gt; 157.9</td>
<td><strong>P = 0.339</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABPM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q1:</strong> &lt; 113.5</td>
<td><strong>P = 0.05</strong></td>
</tr>
<tr>
<td><strong>Q2:</strong> 113.5 - 125</td>
<td><strong>P = 0.011</strong></td>
</tr>
<tr>
<td><strong>Q3:</strong> 125 - 145</td>
<td></td>
</tr>
<tr>
<td><strong>Q4:</strong> &gt; 145</td>
<td></td>
</tr>
</tbody>
</table>

Pooneh Alborzi et al. CJASN 2007;2:1228-1234
Hypertension and mortality: ABPM

ABPM SBP
Q1: < 119.2
Q2: 119.2 - 134.6
Q3: 134.6 - 146.1
Q4: > 146.1

Agarwal et al, Hypertension. 2010;55:762-768
Hypertension and mortality: HBPM

**Home SBP**
- Q1: < 133
- Q2: 133 - 149
- Q3: 150 - 164
- Q4: > 164

**Number at risk**

<table>
<thead>
<tr>
<th>Quartile</th>
<th>1</th>
<th>81</th>
<th>78</th>
<th>73</th>
<th>64</th>
<th>53</th>
<th>45</th>
<th>42</th>
<th>38</th>
<th>37</th>
<th>33</th>
<th>18</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile</td>
<td>2</td>
<td>81</td>
<td>69</td>
<td>60</td>
<td>50</td>
<td>42</td>
<td>35</td>
<td>24</td>
<td>20</td>
<td>17</td>
<td>12</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Quartile</td>
<td>3</td>
<td>81</td>
<td>72</td>
<td>63</td>
<td>59</td>
<td>51</td>
<td>36</td>
<td>25</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Quartile</td>
<td>4</td>
<td>80</td>
<td>72</td>
<td>64</td>
<td>60</td>
<td>49</td>
<td>37</td>
<td>24</td>
<td>18</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
Diagnosis of hypertension in dialysis patients

EURECA Consensus 2017

• ABPM BP average ≥ 135/85 mmHg over 24 hours
  • HD: during mid-week, non-dialysis day
  • HD: extended to 44 hours if feasible, covering whole interdialysis

• Home BP average ≥ 135/85 mmHg
  • HD: over 6 non-dialysis days, in the morning and evening
  • PD: over 7 consecutive days, in the morning and evening

• Office BP ≥ 140/90 mmHg
  • if home BP or ABPM not available
  • HD: on mid-week, non-dialysis day
  quiet room, seated position, after 5 min rest, back & arm supported, 2 measurements 1-2 min apart

BP outside the dialysis unit: ABPM

ABPM
- gold standard in the general population
- strong association with mortality and morbidity (both HD & PD)
- can detect masked or white-coat hypertension
- 44 hour interdialytic period covered
- additional night-time measurement
  non-dipping pattern is very common (50-60%) and linked to mortality

Feasibility?
- inconvenient for patients over 24-44 hours
- challenging in patients with (multiple, previous) AV fistulas
- limited availability, organizational barriers
- multiple assessment needed for follow-up of treatment
BP outside the dialysis unit: HBPM

HBPM: home BP monitoring
  • measured on non-dialysis days
  • good correlation to target-organ damage
  • predictor of cardiovascular events and mortality
  • best agreement with ABPM results (compared to peri-dial BP)
BP outside the dialysis unit: HBPM

HBPM: home BP monitoring

- measured on non-dialysis days
- good correlation to target-organ damage
- predictor of cardiovascular events and mortality
- best agreement with ABPM results (compared to peri-dial BP)
- helps patient education, improves adherence
- ideal for treatment follow-up
BP outside the dialysis unit: HBPM

- Many patients have BP device at home
- and measure BP on a regular basis

Why are we not using these data?

Patient's own device and technique need to be checked and validated!

- 7% no device
- 69% BP measured daily
- 31% no regular measurements
Is it worth lowering BP in dialysis patients?

• Definition of HTN changing - Treatment target changed?

• Can we still rely on old studies using peri-dialysis BP measurements?
Is it worth lowering BP in dialysis patients?

**Randomized trials**
*various drugs to placebo*

BP lowering associated with

20% reduction in all-cause mortality
29% reduction in CV-mortality

<table>
<thead>
<tr>
<th></th>
<th>Numbers of events/patients</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active treatment</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (2003)97</td>
<td>3/30</td>
<td>2/30</td>
<td>1.40 (0.30–6.55)</td>
</tr>
<tr>
<td>Takahashi et al (2006)99</td>
<td>0/43</td>
<td>7/37</td>
<td>0.06 (0.00–0.97)</td>
</tr>
<tr>
<td>Tepel et al (2008)21</td>
<td>15/123</td>
<td>20/128</td>
<td>0.72 (0.39–1.30)</td>
</tr>
<tr>
<td>Suzuki et al (2008)20</td>
<td>30/58</td>
<td>41/56</td>
<td>0.71 (0.53–0.95)</td>
</tr>
<tr>
<td>Nakao et al (2007)22</td>
<td>NR</td>
<td>NR</td>
<td>0.66 (0.41–1.04)</td>
</tr>
<tr>
<td>Cice et al (2006)28</td>
<td>88/151</td>
<td>111/152</td>
<td>1.09 (0.78–1.52)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>213/784</td>
<td>268/787</td>
<td>0.80 (0.66–0.96)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\hat{\lambda}^{2}$=30.0%, $Q$=8.57, $p$=0.20

<table>
<thead>
<tr>
<th></th>
<th>Numbers of events/patients</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active treatment</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (2003)97</td>
<td>2/30</td>
<td>2/30</td>
<td>1.00 (0.15–6.64)</td>
</tr>
<tr>
<td>Suzuki et al (2008)20</td>
<td>17/58</td>
<td>38/56</td>
<td>0.48 (0.28–0.67)</td>
</tr>
<tr>
<td>Nakao et al (2007)22</td>
<td>NR</td>
<td>NR</td>
<td>0.60 (0.30–1.15)</td>
</tr>
<tr>
<td>Zannad et al (2006)11</td>
<td>31/196</td>
<td>30/201</td>
<td>1.05 (0.67–1.68)</td>
</tr>
<tr>
<td>Cice et al (2006)28</td>
<td>59/151</td>
<td>75/152</td>
<td>0.80 (0.61–1.02)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>121/618</td>
<td>165/622</td>
<td>0.71 (0.50–0.99)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\hat{\lambda}^{2}$=54.6%, $Q$=8.8, $p$=0.07

Is it worth lowering BP in dialysis patients?

Blood pressure In Dialysis pilot study (safety & feasibility)

- prevalent chronic HD patients, predial SBP>155mmHg
- randomized: intensive (110-140mmHg) vs standard (155-165mmHg)
- 126 patients randomized

- more patients (4 vs 1) died in the intensive arm

Is it worth lowering BP in dialysis patients?

• Definition of HTN changing -> Treatment target changed?

• Can we still rely on old studies using peri-dialysis BP measurements?

• *Maybe, not yet clear, we need more ABPM / HBPM targeted studies.*
Pathophysiology of hypertension in dialysis

- Volume overload
- Sodium retention
- RAAS activation
- Sympathetic overactivity
- Sleep apnea
- Other secondary causes
- Erythropoetin use
- Vascular calcification
- Increased vascular stiffness
- Endothelial dysfunction
- Hyperparathyroidism

Hypertension in dialysis patient
Interdialytic weight gain and blood pressure

Continuous water and sodium accumulation between dialysis sessions.

weight gain percentiles
10: + 0.9kg
50: + 2.4kg
90: + 4.6kg

This changing volume status also *influences the effect of some antihypertensive agents*.

*Sources of salt: dietary and dialysis!*

Agarwal et al, Am J Physiol Renal Physiol 2008;294:F303-F308
Sodium retention and blood pressure

- Dialysate sodium is often not set to patient pre-dialysis Na level
  - many patients are dialyzed against a high Na bath

Dialysate Na 136mmol/l

33.5%
Sodium retention and blood pressure

- Dialysate sodium is often not set to patient pre-dialysis Na level
  - many patients are dialyzed against a high Na bath
- Sodium gain during dialysis → increases thirst after dialysis
  - greater interdialytic weight gain
  - increased blood pressure - *also independent of water retention*
  - more ultrafiltration on next HD
    - higher risk of hypotensive episodes
Sodium retention and blood pressure

- Dialysate sodium is often not set to patient pre-dialysis Na level
  - many patients are dialyzed against a high Na bath
- Sodium gain during dialysis → increases thirst after dialysis
  - greater interdialytic weight gain
  - increased blood pressure - also independent of water retention
  - more ultrafiltration on next HD
  - higher risk of hypotensive episodes

(Dialysis) people like Camel
Sodium retention and blood pressure

• Dialysate sodium is often not set to patient pre-dialysis Na level
  • many patients are dialyzed against a high Na bath
• Sodium gain during dialysis → increases thirst after dialysis
  • greater interdialytic weight gain
  • increased blood pressure - also independent of water retention
  • more ultrafiltration on next HD
    • higher risk of hypotensive episodes

(Dialysis) people like Camel
Dialysis machines like Salt-shaker
Sodium retention and blood pressure

• Dialysate sodium is often not set to patient pre-dialysis Na level
  • many patients are dialyzed against a high Na bath
• Sodium gain during dialysis → increases thirst after dialysis
  • greater interdialytic weight gain
  • increased blood pressure - *also independent of water retention*
  • more ultrafiltration on next HD
    • higher risk of hypotensive episodes

• Lowering dialysate sodium + *low sodium diet*
  • improve blood pressure control
  • reduce interdialytic weight gain
# The effect of low sodium dialysate

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>BP</th>
<th>IDWG</th>
<th>Thirst</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecking 2012 (110)</td>
<td>Observational data (DOPPS)</td>
<td>Variable: facility dependent change in predialysis SBP seen</td>
<td>Higher with higher DNA</td>
<td>NA</td>
<td>Less hospitalizations with higher DNA</td>
<td>Lower in facilities using standardized DNA</td>
</tr>
<tr>
<td>Shah 2012 (106)</td>
<td>Lowered facility DNA followed by reaudit of clinical practice</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NA</td>
<td>Less IDH seen</td>
<td>NA</td>
</tr>
<tr>
<td>McCausland 2011 (143)</td>
<td>Observational data</td>
<td>No association</td>
<td>Decreased with lower DNA</td>
<td>NA</td>
<td>NA</td>
<td>Increased if high DNA and SNA</td>
</tr>
<tr>
<td>Munoz-Mendoza 2011 (100)</td>
<td>Intra-individual period of lowered DNA compared to periods of standard DNA</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NA</td>
<td>No difference IDH seen</td>
<td>NA</td>
</tr>
<tr>
<td>Sayarlioglu 2007 (144)</td>
<td>Lowered DNA with echo pre and post</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NA</td>
<td>Improved echo parameters at 8 weeks</td>
<td>NA</td>
</tr>
<tr>
<td>Thein 2007 (95)</td>
<td>Facility level decrease in dialysate sodium</td>
<td>Decreased</td>
<td>No change</td>
<td>NA</td>
<td>No difference IDH seen</td>
<td>NA</td>
</tr>
<tr>
<td>Lambie 2005 (92)</td>
<td>Effective lowering DNA</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Trend to decrease</td>
<td>Increased IDH in treatment group</td>
<td>NA</td>
</tr>
<tr>
<td>De-Paula 2004 (102)</td>
<td>Individualized DNA</td>
<td>Decreased (if HPT at baseline)</td>
<td>Decreased</td>
<td>Decreased</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

DNa, dialysate sodium; SNa, serum sodium; HPT, hypertensive; IDH, intradialytic hypotension; NA, not assessed.
The effect of low sodium dialysate

DOPPS analysis
n=29593

higher mortality with
low se Na + low dial Na !!

adjusted for age, sex, body mass index, diabetes and 13 other comorbid conditions, residual renal function, vascular access, serum albumin, hemoglobin, ferritin, serum creatinine, white blood cell count, and facility clustering.
The effect of low sodium dialysate

Systematic review of 23 studies (n=76635)

- heterogenous studies
- inconclusive results
- low quality evidence

The effect of low sodium dialysate

Observational study, 125 patients on PD, follow-up: 3 years

Low sodium dialysate?

Risk of lowering

• muscle cramps
• intradialytic hypotension -> inferior outcome?

• careful and slow adjustment of dialysate Na close to serum Na?
  in hypertensive dialysis patients

• More evidence is needed.

Control of volume overload and hypertension

The importance of dry-weight reduction to control hypertension

DRIP Trial: HD patients with hypertension
- RCT: additional ultrafiltration (n=100) vs control (n=50)
- 44h ABPM for blood pressure evaluation

Volume overload is very common in PD patients linked to

- loss of residual kidney function
- number of antihypertensive medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>r value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW (L)</td>
<td>-0.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECW (L)</td>
<td>0.153</td>
<td>0.0002</td>
</tr>
<tr>
<td>Number of different BP meds prescribed</td>
<td>0.249</td>
<td>0.0003</td>
</tr>
<tr>
<td>Prescription of ≥22.7 g/L glucose dialysate</td>
<td>0.13</td>
<td>0.0014</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.119</td>
<td>0.0036</td>
</tr>
<tr>
<td>Intracellular water (L)</td>
<td>-0.098</td>
<td>0.0158</td>
</tr>
<tr>
<td>Daily urine volume (L)</td>
<td>-0.1022</td>
<td>0.0149</td>
</tr>
<tr>
<td>Fat weight (kg)</td>
<td>0.085</td>
<td>0.037</td>
</tr>
<tr>
<td>Log CRP (mg/L)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Volume overload is very common in PD patients linked to

- hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive?</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>77.3±20.3</td>
<td>0.05</td>
</tr>
<tr>
<td>ECW (L)</td>
<td>19.4±4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>ICW (L)</td>
<td>23.5±6.6</td>
<td>0.12</td>
</tr>
<tr>
<td>TBW (L)</td>
<td>43.8±11.5</td>
<td>0.05</td>
</tr>
<tr>
<td>nECW (L/m)</td>
<td>11.6±1.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ECW = extracellular water; ICW = intracellular water; TBW = total body water; nECW = extracellular water normalized to height in meters.
The Secrets of Tassin
The Secrets of Tassin

The effect of long dialysis, sodium restriction and ultrafiltration

• 692 HD patients in Tassin, France
• long dialysis sessions: 3x8h
• dialysate sodium: 138 mmol/l
• sodium restriction: 4-5g/day!
  • low sodium bread from dialysis unit
• aggressive dry-weight reduction within 2-3 months

The Secrets of Tassin

The effect of long dialysis, sodium restriction and ultrafiltration

- 692 HD patients in Tassin, France
- long dialysis sessions: 3x8h
- dialysate sodium: 138 mmol/l
- sodium restriction: 4-5g/day!
  - low sodium bread from dialysis unit
- aggressive dry-weight reduction within 2-3 months
- 98.4% of patients do not require antihypertensive medication

Aggressive ultrafiltration for all patients?

- Aggressive ultrafiltration → early loss of residual kidney function
- Residual renal function is of paramount importance!
  - survival advantage
  - better blood pressure control
  - better control of renal anemia and bone-mineral disorder
  - lower inflammation
  - greater quality of life
Aggressive ultrafiltration for all patients?

- Aggressive ultrafiltration → early loss of residual kidney function
- Residual renal function is of paramount importance!
  - survival advantage
  - better blood pressure control

Oh, my patient has volume overload!

Easy, ultrafiltration will take care of it!
Aggressive ultrafiltration for all patients?

• Aggressive ultrafiltration → early loss of residual kidney function
• Residual renal function is of paramount importance!
  • survival advantage
  • better blood pressure control
  • better control of renal anemia and bone-mineral disorder
  • lower inflammation
  • greater quality of life

• Methods for controlling hypervolemia, lowering dry-weight
  • aggressive ultrafiltration - for anuric patients
  • non-anuric patients: use more diuretics!
Antihypertensive therapy in real-world
multicenter cross-sectional survey, n=323

Ambrus, unpublished
Diuretics in dialysis patients

Ineffective for blood pressure control, per se.

- useful for
  - reaching euvoletic state / dry weight
  - preservation of residual kidney function
    - better control of CKD-MBD
    - better outcome

- loop diuretics: furosemid
  - administer high enough single dose \((160-250 \, ? \, 500\,\text{mg})\)

- thiazides
  - ineffective alone
  - can enhance the effect of furosemid even in patients on dialysis
Diuretics in dialysis patients

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Usual dose</th>
<th>Excretion</th>
<th>GFR &lt; 10 ml/min</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Supplement for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>250 mg q6-8 h</td>
<td>K</td>
<td>Avoid</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Amiloride</td>
<td>5-10 mg q.d.</td>
<td>K</td>
<td>Avoid</td>
<td>N/A</td>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Bumantanide</td>
<td>0.5-2 mg q8-12 h</td>
<td>K</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>30-60 mg q.d.</td>
<td>K</td>
<td>Avoid</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>50-100 mg b.i.d.</td>
<td>L (K)</td>
<td>Avoid</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40-80 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25-50 mg q.d.</td>
<td>K</td>
<td>Avoid</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 mg q.d.</td>
<td>K</td>
<td>Avoid</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Metolazone</td>
<td>5-10 mg q.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>50-100 mg q.d./b.i.d.</td>
<td>K (L)</td>
<td>Avoid</td>
<td>N/A</td>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Torsemide</td>
<td>5-10 mg b.i.d.</td>
<td>L (K)</td>
<td>100%</td>
<td>Avoid</td>
<td>Avoid</td>
<td>None</td>
</tr>
<tr>
<td>Trimaterene</td>
<td>25-50 mg b.i.d.</td>
<td>K</td>
<td>Avoid</td>
<td>N/A</td>
<td>N/A</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Should we really avoid using: thiazide / spironolactone?

Antihypertensive therapy in real-world multicenter cross-sectional survey, n=323

Ambrus, unpublished
Ideal antihypertensive drugs in dialysis patients.
Unchanged pharmacokinetics in ESRD.
Effective in patients with volume overload.

**Calcium channel blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Excretion</th>
<th>GFR &lt; 10 ml/min</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Supplement for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>2.5–10 mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Diltiazem CD</td>
<td>180–360 mg</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5–10 mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Isradipine</td>
<td>2.5–10 mg b.i.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lacidipine</td>
<td>2–6 mg/day</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Manidipine</td>
<td>10–20 mg/day</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20–40 mg t.i.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nifedipine XL</td>
<td>30–90 mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>30 mg q8h</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>10 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>20 mg b.i.d.</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Verapamil CD</td>
<td>180–360 mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Calcium channel blockers

Do they also lower mortality?

- randomized trial, 251 HD patients with hypertension
  - amlodipine 10mg daily vs placebo
  - follow-up: 30 months
  - **no effect on mortality**, but reduced CV events (due to antihypertensive effect?)

# Beta-blockers in dialysis patients

First or second line therapy in dialysis patients partly due to cardiovascular co-morbidity


<table>
<thead>
<tr>
<th>β-blockers</th>
<th>Usual dose</th>
<th>Excretion</th>
<th>GFR &lt; 10 ml/min</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Supplement for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>400-600 mg q.d./b.i.d.</td>
<td>L (K)</td>
<td>30-50%</td>
<td>30%</td>
<td>None</td>
<td>150 mg</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50–100 mg q.d.</td>
<td>K (L)</td>
<td>25-50%</td>
<td>50%</td>
<td>None</td>
<td>25-50 mg</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>10–20 mg q.d.</td>
<td>L</td>
<td>50%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.5–20 mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>25 mg b.i.d.</td>
<td>L (K)</td>
<td>50%</td>
<td>None</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Esmolol</td>
<td>50–150 μg/kg/min i.v.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Labetalol</td>
<td>200–600 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50–100 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nadolol</td>
<td>80–100 mg b.i.d.</td>
<td>K</td>
<td>25%</td>
<td>50%</td>
<td>None</td>
<td>80 mg</td>
</tr>
<tr>
<td>Pindolol</td>
<td>10–40 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Propanolol</td>
<td>80–160 mg b.i.d.</td>
<td>K</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sotalol</td>
<td>160 mg q.d.</td>
<td>K</td>
<td>15–30%</td>
<td>50%</td>
<td>None</td>
<td>50 mg</td>
</tr>
<tr>
<td>Timolol</td>
<td>10–20 mg b.i.d.</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Beta-blockers in dialysis patients

Reduction in mortality, CV morbidity and risk of sudden death

- DOPPS, observational, 37765 patients, 12 countries lower risk of sudden death in patients using beta-blockers: HR 0.88 (95% CI: 0.78-0.99, p=0.03)

- randomized trial, 114 HD patients with DCM: carvedilol vs placebo

Table 3. Secondary End Points and Exploratory Analyses

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Placebo (n = 56)</th>
<th>Carvedilol (n = 58)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>41 (73.2%)</td>
<td>30 (51.7%)</td>
<td>0.51 (0.32–0.82)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>33 (58.9%)</td>
<td>20 (34.5%)</td>
<td>0.44 (0.25–0.77)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>All cardiovascular deaths</td>
<td>38 (67.9%)</td>
<td>17 (29.3%)</td>
<td>0.32 (0.18–0.57)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>1 (1.8%)</td>
<td>0 (0%)</td>
<td>0.81 (0.61–1.34)</td>
<td>0.31</td>
</tr>
<tr>
<td>Combined end point</td>
<td>39 (69.6%)</td>
<td>17 (29.3%)</td>
<td>0.76 (0.47–1.22)</td>
<td>0.22</td>
</tr>
<tr>
<td>Permanent treatment withdrawals</td>
<td>15 (26.8%)</td>
<td>17 (29.3%)</td>
<td>1.12 (0.84–1.24)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Beta-blockers in dialysis patients

Are they also good antihypertensives?

- randomized trial (pilot), 25 HD patients with intradial hypertension
  - carvedilol titrated to 50mg bid vs placebo, follow-up: 12 weeks
  - decreased SBP on ABPM by 7.5mmHg
  - improved endothel dependent flow-mediated vasodilation
  - reduced occurrence of intradialytic hypertension

Are they also good antihypertensives?

- HDPAL, randomized trial, 200 HD patients with HTN and LVH
  - atenolol 25-100mg vs lisinopril 10-40mg three times weekly
  - no difference in SBP and DBP on ABPM or home BP control
  - lisinopril group needed dry-weight reduction and "rescue" therapy
  - higher incidence of CV events with lisinopril

Beta-blockers in dialysis patients

<table>
<thead>
<tr>
<th>β-blockers</th>
<th>Usual dose</th>
<th>Excretion</th>
<th>GFR &lt; 10 ml/min</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Supplement for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>400-600 mg q.d./b.i.d.</td>
<td>L (K)</td>
<td>30-50%</td>
<td>30%</td>
<td>None</td>
<td>150mg</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-100 mg q.d.</td>
<td>K (L)</td>
<td>25-50%</td>
<td>50%</td>
<td>None</td>
<td>25-50mg</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>10-20 mg q.d.</td>
<td>L</td>
<td>50%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2.5-20mg q.d.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>25 mg b.i.d.</td>
<td>L (K)</td>
<td>50%</td>
<td>None</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Esmolol</td>
<td>50–150 μg/kg/min i.v.</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Labetalol</td>
<td>200-600 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50-100 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nadolol</td>
<td>80-100 mg b.i.d.</td>
<td>K</td>
<td>25%</td>
<td>50%</td>
<td>None</td>
<td>80 mg</td>
</tr>
<tr>
<td>Pindolol</td>
<td>10-40 mg b.i.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Propanolol</td>
<td>80-160 mg b.i.d.</td>
<td>K</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sotalol</td>
<td>160 mg q.d.</td>
<td>K</td>
<td>15-30%</td>
<td>50%</td>
<td>None</td>
<td>50 mg</td>
</tr>
<tr>
<td>Timolol</td>
<td>10-20 mg b.i.d.</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Differences in removal with hemodialysis: atenolol, sotalol can be dialyzed. **The use non-dialysable beta-blockers is advised.**

Antihypertensive therapy in real-world
multicenter cross-sectional survey, n=323

Ambrus, unpublished
ACE inhibitors and ARBs

- first-line therapy in non CKD, also in patients with CKD
- in patients on dialysis: not convincing benefit, conflicting results

<table>
<thead>
<tr>
<th>author</th>
<th>year</th>
<th>n</th>
<th>ACEI/ARB</th>
<th>design</th>
<th>f/u</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zannad</td>
<td>2006</td>
<td>397</td>
<td>fosinopril</td>
<td>pts with LVH, HTN was not criteria</td>
<td>24</td>
<td>CV events: no difference</td>
</tr>
<tr>
<td>Takahashi</td>
<td>2006</td>
<td>80</td>
<td>candesartan</td>
<td>not hypervolemic patients! HTN was not criteria</td>
<td>36</td>
<td>lower CV event rate</td>
</tr>
<tr>
<td>Suzuki</td>
<td>2008</td>
<td>360</td>
<td>losartan, valsartan, candesartan</td>
<td>pts <strong>with hypertension</strong></td>
<td>36</td>
<td>lower CV death &amp; event rate</td>
</tr>
<tr>
<td>Iseki</td>
<td>2013</td>
<td>469</td>
<td>olmesartan</td>
<td>pts <strong>with hypertension</strong></td>
<td>42</td>
<td>CV events: no difference</td>
</tr>
<tr>
<td>Cice</td>
<td>2010</td>
<td>332</td>
<td>telmisartan</td>
<td>pts with CHF, LVEF &lt;40% telmisartan ADDED to ACEI</td>
<td>36</td>
<td>lower CV death &amp; CV event rate</td>
</tr>
</tbody>
</table>
ACE inhibitors and ARBs vs beta-blocker

- USRDS & Dialysis Clinic Inc. (DCI) cohort study
- n=33005 & 11291
- beta-blocker monotherapy vs
  - ACEI/ARB
  - beta-blocker+ACEI/ARB
  - other medication
- better survival with addition of ACE / ARB

ACE inhibitors and ARBs in patients on PD

• USRDS cohort study, n=4879
• ACEI/ARB use (42%) vs non-use
• all-cause mortality: 17% relative risk reduction
• CV death: 26% relative risk reduction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis</th>
<th>Exposure group</th>
<th>Follow-up time (years)</th>
<th>Incidence rate (per 100 person-years)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>ITT</td>
<td>ACEI/ARB</td>
<td>1.61 ± 1.20</td>
<td>1.33</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuser</td>
<td>1.54 ± 1.18</td>
<td>1.27</td>
<td>22.6</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>ACEI/ARB</td>
<td>0.74 ± 0.82</td>
<td>0.46</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuser</td>
<td>1.07 ± 1.02</td>
<td>0.75</td>
<td>22.6</td>
</tr>
<tr>
<td>CV death</td>
<td>ITT</td>
<td>ACEI/ARB</td>
<td>1.61 ± 1.20</td>
<td>1.33</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuser</td>
<td>1.54 ± 1.18</td>
<td>1.27</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>ACEI/ARB</td>
<td>0.74 ± 0.82</td>
<td>0.46</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuser</td>
<td>1.07 ± 1.02</td>
<td>0.75</td>
<td>8.1</td>
</tr>
</tbody>
</table>
ACE inhibitors and ARBs

• randomized trial, 397 patients with left ventricular hypertrophy (hypertension was not inclusion criteria)
• fosinopril (up to 20mg/d) vs placebo, follow-up: 48 months
• fosinopril lowered SBP
• cardiovascular events: no difference

Zannad et al, Kidney Int. 2006;70(7):1318-1324.
ACE inhibitors and ARBs

- randomized trial, 360 patients with hypertension
- ARBs (candesartan, losartan, valsartan) vs other non RAAS blocker
  - follow-up: 36 months
- lower incidence of cardiovascular death and events with ARBs
- 49% relative risk reduction (0.33-0.79)
  - adjusted for: age, gender, diabetes, SBP, and center
- no difference in blood pressure

ACE inhibitors versus ARBs in patients on HD

- USRDS cohort study, using "new user paradigm", n=4997 / 4635
- survival advantage with ARBs
- no difference in CV event rate

ACE inhibitors and ARBs

- ARBs might be better in prevention of cardiovascular events and death
- **ACE inhibitors are dialysable** and require additional dosing after HD!
- these medications have better effect in volume contracted state

<table>
<thead>
<tr>
<th></th>
<th>Usual dose</th>
<th>Excretion</th>
<th>GFR &lt; 10 ml/min</th>
<th>Removal with dialysis</th>
<th>Supplement for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazapril</td>
<td>5-40 mg q.d.</td>
<td>K (L)</td>
<td>50-75%</td>
<td>Negligible</td>
<td>None</td>
</tr>
<tr>
<td>Captopril</td>
<td>12.5-50 mg t.i.d.</td>
<td>K</td>
<td>50%</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5-10 mg q12 h</td>
<td>K (L)</td>
<td>50%</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10 mg q.d.</td>
<td>K (L)</td>
<td>75%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-10 mg q.d.</td>
<td>K</td>
<td>25-50%</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2-8 mg/day</td>
<td>K (L)</td>
<td>25-50%</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10-20 mg q.d.</td>
<td>K (L)</td>
<td>50%</td>
<td>25%</td>
<td>None</td>
</tr>
<tr>
<td>Ramipril</td>
<td>5-10 mg q.d.</td>
<td>K (L)</td>
<td>25-50%</td>
<td>20%</td>
<td>None</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5-4 mg/day</td>
<td>K (L)</td>
<td>25-50%</td>
<td>30%</td>
<td>None</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>8-35 mg/day</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>600-1200 mg/day</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ibersartan</td>
<td>75-300 mg/day</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Losartan</td>
<td>50-100 mg q.d.</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>10-40 mg/day</td>
<td>K (L)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40-80 mg/day</td>
<td>L</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80-320 mg q.d.</td>
<td>L (K)</td>
<td>100%</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

- Clear benefit of preserving residual kidney function (both HD & PD)
earlier suggestion: avoidance regarding risk of hyperkalemia

- randomized trial, 309 oligo-anuric patients on hemodialysis
- spironolactone 25mg vs control, follow-up: 3 year
- lower CV death and all-cause mortality
  - hyperkalemia: 3%
  - gynecomastia: 10%

Mineralocorticoid receptor antagonists

earlier suggestion: avidance regarding risk of hyperkalemia

• randomized trial, 253 HD patients without heart failure
• spironolactone 25mg vs control, follow-up: 2 year
• lower CV death and all-cause mortality

CV death or CV events
HR: 0.40 (95%CI: 0.21-0.84) p=0.014

all-cause mortality
HR:0.49 (95%CI: 0.26-0.95) p=0.036

Lin et al, J Clin Hypertens. 2015;18(2):
Other agents

Alpha-adrenergic blocking agents
- safe in dialysis patients, avoid if intradialytic hypotension
- no additional dosing after HD required
- risks: orthostatic hypotension

Direct vasodilators
- effective and safe in dialysis
- hydralazin and minoxidil are not dialysable

Central acting sympatholytics
- rarely used due to side effects
Fears, Beliefs and Facts

- 57% of patients are advised not to take medication before dialysis

  - "Meds are removed during HD - useless to take"
    - very few meds are removed (ACE inhibitors, few beta blockers)

  - "Intradialytic hypotension caused by antihypertensives"
    - not proven
    - mainly if antihypertensive therapy is driven by pre-dial BP!

Antihypertensives and intradialytic hypotension

- 2630 prevalent HD patients in Greater London area
- Incidence of intradialytic hypotension
  - without antihypertensive therapy: 21%
  - with antihypertensive therapy: 13%!! (p<0.001)

no significant association between drug prescription and hypotensive events

Fears, Beliefs and Facts

- 57% of patients are advised not to take medication before dialysis
  - "Meds are removed during HD - useless to take"
    - very few meds are removed (ACE inhibitors, few beta blockers)
  - "Intradialytic hypotension caused by antihypertensives"
    - not proven
    - mainly if antihypertensive therapy is driven by pre-dial BP!

- orthostatic hypotension
  - falls and fractures, cognitive decline
    if therapy prescribed for normotensive patients
  
  *Don't treat pre-dialysis blood pressure!*

Summary & recommendations

1. Encourage patients to measure BP at home (BP diary)
2. Diagnose hypertension based on home BP monitoring / ABPM
3. Start with optimal dry-weight reduction and salt restriction
   • carefully lower dialysate Na?
4. Combination medical therapy with
   • beta-blockers, Ca-channel blockers, RAAS inhibitors
5. Do not forget about secondary causes of hypertension!

What is the optimal blood pressure target in dialysis patients?
Sympathetic overactivity in dialysis

- Patients on hemodialysis, before and after bilateral nephrectomy

Sympathetic overactivity in dialysis

- Surgical sympathectomy was a very effective treatment

Sympathetic overactivity and the kidney

- The kidney is source of sympathetic overactivity
- Destroying perivascular renal nerves can decrease sympathetic activity and blood pressure

Chemoreceptors - interstitial ischaemia + markedly decreased renalase activity
Renal denervation in dialysis

- Increasing number of case reports in dialysis patients
- Case series of 12 anuric patients on HD

Renal denervation in dialysis

- Increasing number of case reports in dialysis patients
- Case series of 12 anuric patients on HD