Managing Hypertension in CKD5HD Patient by Volume Control and/or Medications: Best Practices

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Speaker name: Prof. Bernard Canaud

- I have the following potential conflicts of interest to report:
  - Consulting in industry (FMC)
  - Employment in industry
  - Shareholder in a healthcare company
  - Owner of a healthcare company
  - Other(s)

- I do not have any potential conflict of interest
Managing Hypertension in CKD5HD Patient
Outline of the Presentation

1. Unmet needs in CKD5 hemodialysis patients
   • Hypertension and chronic fluid overload
   • Cause of poor cardiac outcomes

2. Diagnosis hypertension
   • Epidemiologic versus cardiac risk

3. Epidemiology of hypertension in CKD5D patients

4. Factors contributing to hypertension in CKD5D patients

5. Managing hypertension in CKD5D patients
   • Volume control first
   • Medication control second
   • Combined approach third

6. Take home message
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6. Take home message
Hypertension and Chronic Fluid Overload Are Partners in Crime

Outcome
Morbidity
COST
Inflammation
Protein Energy Malnutrition

Hypertension
Fluid Overload Na Excess

Stroke
Anemia
Arteriosclerosis
Lung HT
Left Ventricular Hypertrophy

Cause-Specific Mortality in Dialysis Patients
Percentages of Deaths by Cause in Dialysis Patients USA

Unadjusted Causes of Death in Dialysis Patients (2014)

https://www.usrds.org/2017/download/v2_c05_Mortality_17.pdf
Pulmonary Edema
A Major Cause of Hospital Readmission

Retrospective cohort study
Medicare coverage 2011-2013
215251 US HD patients
Readmission causes - Index hospital.
Overall - Pulmonary edema

High Prevalence of Pulmonary Hypertension in CKD5 HD Patients

Predialysis Systolic Blood Pressure and Patient Outcomes in Incident ESRD

Chronic EC Fluid Overload Is An Additive Risk Factor of Mortality In Incident ESRD Patients

Blood Pressure Control – Hemodynamic Stability
Interaction Patient/Hemodialysis Treatment

- Diet Intake (Na & Fluid Intake) & Lifestyle
- Cardiac Medication
- Diet & Treatment Observance
- Residual Kidney Function
- Age - Gender
- Anthropometric Medical Condition
- Cardiac Function
- Treatment Time & Frequency
- Dialysis Modality (e.g., HDF, Nocturnal HD)
- Dialysate Sodium Concentration
- Ultrafiltration Rate
- Feedback Controlled HD (e.g., thermal, volemic, sodium)
- Electrolytes (e.g., Ca, Mg, HCO3, Acidifier)
‘Unphysiologic Profile’ of Intermittent Hemodialysis
Main Challenge for Hemodynamic Stability & Tolerance

- Weight (Kg)
  - HD: 80
  - HD: 75
  - HD: 70
- Blood Pressure (mmHg)
  - HD: 14
  - HD: 13
- Mean Blood Pressure
  - HD: 14
- Mean Serum Na (mmol/l)
  - HD: 14

Graphs showing the effects of intermittent hemodialysis on weight, blood pressure, and serum sodium levels over time.
Changes in right heart pressures over 8 days in patients undergoing hemodialysis

Volume loading creates markedly abnormal cardiac pressure, wall stress, LVH and systolic/diastolic dysfunction

Blood Pressure Control From a Mechanistic View in HD Patient

Effective Volemia
- Extracellular volume
- Na pool
- Oncotic Pressure
- Vascular permeability...

Cardiac Output
- Heart Rate
- Stroke Volume

Blood Pressure Control

Peripheral Vascular Resistance
- Vascular Stiffness
- Vasoactive mediators: Constricting vs Dilating
- Electrolytes (Na, Ca, Mg...)

HD prescription (e.g., Time/Frequency/dNa) & Ultrafiltration Rate
Blood Pressure & EC Fluid Management
Nephrologist as a Tightrope Walker

- EC Fluid Control
- Blood Pressure Control
- Cardiac Protection

- Hypovolemia
- Intradialytic Hypotension
- Ischemic Injury
  (cardiac stunning, leukoaraiosis, gut translocation...)

RISK

REWARD
Ultrafiltration Rate and CV Mortality

UFR over 10-13ml/h/kg is Associated with Poor Outcome

Intra-Dialytic Hypotension and Mortality
Intensity and Frequency of IDH >90 mmHg are Associated with Poor Outcome

**HEMO Cohort**
- 1409 patients
- 12,561 treatments

**LDO Cohort**
- 10,392 patients
- 136,754 treatments

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   • Epidemiologic versus cardiac risk

3. Epidemiology of hypertension in CKD5D patients

4. Factors contributing to hypertension in CKD5D patients

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Hypertension Control
Population-Based Versus Individual-Based Risk Approach
Predictive Value of Systolic Blood Pressure
Predialysis Value Measured at Dialysis Unit

Association Predialysis Blood Pressure (Systolic & Diastolic) & HR of CV Mortality in HD Patients


Multicenter Prospective Observational Study France 9333 prevalent HD Associations BP & all-cause, CV mortality Median follow-up 548 days.
Association Predialysis Systolic Blood Pressure and CV Mortality in HD Patients With & Without Medication

Association Predialysis Systolic Blood Pressure and CV Mortality in HD Patients With & Without History of CVD

Association Systolic Blood Pressure and CV Mortality
Dialysis-Unit versus Ambulatory BPM

CRIC Study
Chronic Renal Insufficiency Cohort
Prospective Observational cohort
3939 CKD pts FU 2003-2008,
377 pts initiated HD in 2013

Hypertension Control Target
Population-wide versus individual-based cardiac risk approach

pressure
One Size Does Not Fit All
Cardiac Risk of Systolic Blood Pressure

- **Original Distribution**
- **Population-Based Approach**
- **Individual-Based Approach**

Systolic Blood Pressure
Extracellular Fluid Management: New Technology Provides More Appropriate Tools

Unit Blood Pressure

Ambulatory or Home Blood Pressure
Ambulatory Blood Pressure Monitoring (48hrs)
Unit BP Values vs. ABPM

What is the Blood Pressure Value Collected During Dialysis that Fits Best With Average 48hr. ABPM?


**Abbreviations:**
Con av: Conceptual average BP 5 last HD
PreC0: predialysis BP on arrival
PreC10: 10 min predialysis BP
onC: onset of dialysis
EnC: BP end of dialysis
P0C20: 20 min postdialysis BP
AvC: Average pre and postdialysis BP
MBP: mean blood pressure

40 Prevalent HD Pts
BP Measurement:
Dialysis Unit BP vs 48h Ambulatory BP Monit.
Dinamap vs Tm2421 (ABPM)

*Systolic BP Difference: Dialysis Unit BP – Average Ambulatory BP Monitoring
Blood Pressure in Hemodialysis Patient
What is the BP of Interest? ABP, Home, Pre or PostHD?

**Control Group**

**Ultrafiltration Group**

**DRIP Study - RCT**
Dry weight Reduction in Hypertensive HD Patients
91 (UF) vs 43 (C)

Diagnose Hypertension in Hemodialysis Patients

Hypertension in hemodialysis patients should be based on home BP or ABPM evaluation.

- **Home BP** in HD, an average \( BP \geq 135/85 \) mmHg obtained over 6 non-dialysis days, during a **two-week period**
  with the measurements made in a quiet room, with the patient in seated position, back and arms supported, after 5 minutes of rest and with 2 measurements taken 1-2 minutes apart.

- **ABPM** in HD patients, an average \( BP \geq 130/80 \) mmHg over **24-hour** monitoring during a **mid-week non-dialysis** day and, if possible, extended to 44 hours.

- For HD patients: when **neither ABPM** nor **home BP** measurements are **available**, the diagnosis can be made based on **office BP measurements** taken in a **mid-week non-dialysis day**, with the standard technique described above

Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH).

Diagnose Hypertension in Peritoneal Dialysis Patients

Hypertension in peritoneal dialysis patients should be based on home BP or ABPM evaluation.

- **Home BP** in peritoneal dialysis: an average $\text{BP} \geq 135/85 \text{ mmHg}$ over 7 consecutive days with the above described conditions.

- **ABPM** in peritoneal dialysis: an average $\text{BP} \geq 130/80 \text{ mmHg}$ over 24-hour monitoring.

- For peritoneal dialysis patients: **office BP** $\geq 140/90 \text{ mmHg}$ obtained with the standard technique as described above.

Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH).

### Blood Pressure Targets

**Individual Targets**

<table>
<thead>
<tr>
<th>Type</th>
<th>Target</th>
<th>Measurement Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home BP</td>
<td>135/85 mmHg</td>
<td>over 6 non-dialysis days, during a two-week period</td>
</tr>
<tr>
<td>ABPM</td>
<td>130/80 mmHg</td>
<td>24-hour monitoring during a mid-week non-dialysis day</td>
</tr>
<tr>
<td>Office BP</td>
<td>135/85 mmHg</td>
<td>mid-week non-dialysis day</td>
</tr>
</tbody>
</table>

Survival Life Expectancy in HD Patients According to Quartiles of Ambulatory Systolic BP

Agarwal R et al, Hypertension 2010;55:762-768

Prospective NR Monocentric Study
326 Prevalent HD patients
BP Assessment:
HD Unit BP (pre/post) 2wk- Home BP (1wk) – Amb. BP (48hr)
Follow-up: 29mo [16-48mo] Max 6yr
74% Anti-HT medications
Crude mortality 118/1000 patient years

Q1 79.2-119.2
Q2 119.4-134.6
Q3 134.6-146.1
Q4 146.3-199.7
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6. Take home message
Prevalence of Hypertension 2002-2011
Cross-Section & Country

# Prevalence of Hypertension in Hemodialysis Patients


<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem [55]</td>
<td>1995</td>
<td>649</td>
</tr>
<tr>
<td>Rahman et al. [60]</td>
<td>1999</td>
<td>489</td>
</tr>
<tr>
<td>Agarwal et al. [1]</td>
<td>2003</td>
<td>253</td>
</tr>
<tr>
<td>Agarwal [56]</td>
<td>2011</td>
<td>369</td>
</tr>
</tbody>
</table>

![Graph showing the proportion of patients with hypertension (HTN), blood pressure treatment (BP Treatment), and blood pressure control (BP Control).]

- **Proportion of Patients (%)**
  - **HTN**: 83.9%
  - **BP Treatment**: 90.8%
  - **BP Control**: 43.3%

*BP, MAP, blood pressure; MAP, mean arterial pressure.*
Quartiles of Systolic Blood Pressure (SBP) and Conditions of Measurement: Home BP, Ambulatory BP, Dialysis Unit & Standardized BP

HR For All-Cause Mortality for Quartiles of Systolic Blood Pressure (SBP) – pre HD, post HD, home, ambulatory

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3. Epidemiology of hypertension in CKD5D patients
4. **Factors contributing to hypertension in CKD5HD patients**
5. Managing hypertension in CKD5D patients
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6. Take home message
Factors Implicated in Genesis of Hypertension in HD Patients

Sodium Excess & Fluid Overload

Volo-Dependent

Activation Sympathetic Nerve Activity

Endothelial Dysfunction

Activation RAA System

Erythropoietin Hyperviscosity

Sleep Apnea

Native Kidney
Kidney Transplant
Pheochromocytoma
Renin Tumor
Thyroid Disorders

Vaso-Dependent

Mixed Causes
Main Pathogenic Mechanism of Hypertension in Dialysis

• Sodium and volume overload.
• Increased arterial stiffness.
• Activation of the sympathetic nervous system.
• Activation of the renin–angiotensin–aldosterone system.
• Endothelial dysfunction (i.e. imbalance between endothelium-derived vasodilators and vasoconstrictors).
• High prevalence of sleep apnea.
• Use of recombinant erythropoietin.
Main Non-Pharmacological Measures To Reduce Sodium and Volume Overload In HD Patients

• Achievement of individual patients’ dry-weight
• Minimization of inter- and intradialytic sodium gain
• Restriction of sodium intake to <65 mmol (1.5 g of sodium or 4 g of sodium chloride) per day
• Decreasing dialysate sodium towards pre-dialysis sodium in selected individuals.
• Avoidance of sodium-containing or sodium-exchanging drugs.
• Avoidance of short (i.e. <4 h) dialysis duration.
Paradoxical Intradialytic Hypertension
Main Components of PathWay

- Chronic Fluid Overload
- ↑ Stroke Volume
- Peripheral Vascular Resistance
  - Catecholamines
  - Vasopressin
  - Renin Angiotensin System
  - Endothelin 1
- Sodium & Volume Component
- Patient Profile
  - Vascular Stiffness
  - Calcification
  - Sodium Excess
  - Transplant
- Hemodialysis-Related
  - Positive D-P Na Gradient
  - High Ca - Mg
  - Low K
- Vasoreactive Component
  - Removal of antihypertensive medication
  - Hemoconcentration
  - Erythropoietin
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Fluid Volume and Blood Pressure Assessment

1. Clinical Assessment
   - Dry Weight
   - Blood Pressure
   - Fluid Status Assessment
   - Probing Dry Weight

2. Online HD Machine
   - UF & Na Profile
   - Relative Blood Volume
   - Hematocrit Change
   - Refilling Rate Capacity

3. Instrumental Assessment
   - Bioimpedance, BIA, BIS
   - US – IVC Diameter
   - US – Lung COMETS
   - Na MRI

4. Biomarker Assessment
   - BNP, NTproBNP, ANP
   - Copeptin
   - Troponin I & T
   - Others

5. Analytics Support
   - Artificial Intelligence
   - Artificial Neuronal Network
   - Fluid & Na Modeling
   - Advanced Analytics
   - Predictive Medicine
Clinical Assessment and ‘Dry Weight’ Probing
‘Necessary but Not Sufficient’ to Manage Sodium & Fluid in HD

Pre-Dialysis
Fluid Overload

- 78.0kg

Post-Dialysis
Fluid Depletion

- Weight Loss
  - 3.0kg

- Ultrafiltration
  - 3.4L

- Ultrafiltration Rate (UFR)
  - 11ml/kg/hr

- 75.0kg
Invariantial Ways of Assessing ECF
IVC Diameter, RBV Change, MF-BIA and Lung US
Fluid Status of HD Patients in Europe
Assessment by BIS

Wabel P et al, ERA-EDTA 2012 Poster

NephroCare 22 European Centres
1500 Prevalent Hemodialysis patients

63% Fluid Overload
- Moderately 39%
- Severely 24%

BIS - Blood Impedance Spectroscopy
Dry Weight Reduction and Lag Time Effect on Blood Pressure Decrease

Chazot Ch et al, *Nephrol Dial Transplant* 1999; 14:1212

Prospective Monocentric Study
Care Improvement
61 Incident HD pts
(F21, 59.8 yo, DM 21%)
24 Mo Follow-Up
Dry Weight Reduction Permits Control of Hypertension
Reduction of Blood Pressure at 4 and 8 Weeks

Δ Dry Weight

\[
\begin{align*}
\text{Cont.} & : 0.0\text{kg} & 0.0\text{kg} \\
\text{UF} & : -0.9\text{kg} & -1.0\text{kg}
\end{align*}
\]

Systolic Blood Pressure (mm Hg)

- Control
  - -0.5 (-5.5 to 4.5)
  - -3.8 (0.7 to -8.4)
  - -7.4† (-2.1 to -12.7)
  - -10.7‡ (-7.4 to -13.9)
- Ultrafiltration
  - -2.8 (-0.5 to -6.1)

Diastolic Blood Pressure (mm Hg)

- Control
  - -0.5 (-4.4 to 3.4)
  - -3.0* (-0.5 to -5.5)
  - -0.9 (1.7 to -3.5)
- Ultrafiltration
  - -6.1‡ (-4.3 to -7.9)
  - -3.6 (0.4 to -7.7)
  - -3.8 (0.2 to -7.9)

DRIP Study - RCT
Dry weight Reduction in Hypertensive HD Patients
91 (UF) vs 43 (C)

Effect of Active Dry Weight Reduction Guided by MF-BIA on Blood Pressure Control?

CKD5D Patients (n = 55)

- Dehydrated (n=12)
  - TAFO ≤ 0.25L
  - 3 Months FU

- Normovolemic (n=26)
  - TAFO 0.25-1.25L
  - Active Dry Weight Reduction Guided BCM Weekly
    - Outcomes
      - FO pre/post
      - BP pre/post
      - Weight pre/post
      - BNP
      - AHT
  - 3 Months FU

- Overloaded (n=17)
  - TAFO > 1.25L
  - 3 Months FU

Time Change of Fluid Overload (TAFO) and Blood Pressure

Chronic Fluid Overload is Associated with Higher Mortality Risk As an Independent Factor

Chazot Ch et al, Nephrol Dial Transplant 2012; 27: 2404–2410

Retrospective Cohort Study
- Tassin (ref) 50 HD pts
- Giessen 123 pts non-hypertensive
  - 35 pts hypertensive

P<0.001
Effect of Active Dry Weight Reduction Guided by Lung US on Blood Pressure Control?

CKD5D Patients
Hypertensive clinically euvolemic
(n = 71)

Intervention Group (n= 35)
Active Dry Weight Reduction Guided Lung US
Baseline 48h-ABPM
8 Week FU 48h-ABPM

Control Group (n=36)
Standard of Care
48h-ABPM
48h-ABPM

Prospective RCT Study
Dry Weight reduction guided Lung US Effect on ABPM

Active Intervention Guided by Lung US
Significant Reduction of DW and ABPM Values

Loutradis C et al, Kidney Int. 2019; 95, 1505-1513
Cardiac Biomarkers in Uremia
A Puzzle, Making Choice For The Nephrologist Not Easy

Fluid depletion is associated with a reduction of BNP

Fluid depletion is associated with a reduction of BNP levels. Cardiac patients keep higher BNP levels.
Change in BNP Before vs. After HD
Stratified by LV Ejection Fraction

BNP concentrations remain higher in cardiac patients and severity of heart disease

46 Incident HD patients (F/M: 21/25; 68.6±14.5yo) surviving at least 6 months after HD treatment

Role of Fluid Overload and Cardiac History on Plasma BNP Levels In Incident HD Patients

Fluid Overload Correction Is Accompanied By Significant Reduction of BNP and SBP In Incident HD Patients

High plasma BNP concentrations reflect fluid overload
BNP changes may be used to guide fluid management

Kaplan-Meier Survival Curves According to BNP at Second Quarter of Treatment

High plasma BNP concentration reflects cardiac remodeling and is associated with poor outcome.

Paradoxical Intradialytic Hypertension
Chronic Pressure Load

Paradoxical Intradialytic Hypertension
Control Case Study

Cardiac Medication in Outcome Clinical trials in HD patients

**Beta-blockers**
- **Carvedilol** reduced mortality compared with placebo in HD patients with dilated cardiomyopathy.
- Thrice-weekly **atenolol** reduced cardiovascular events compared with thrice-weekly **lisinopril** in HD patients with hypertension and LVH in the HDPAL trial.

**ACEIs**
- **Fosinopril** did not reduce cardiovascular events and mortality compared with placebo in HD patients with LVH in the FOSIDIAL trial.

**ARBs**
- **Losartan/valsartan/candesartan reduced cardiovascular events and mortality** compared with treatment not including ACEIs/ARBs in HD patients.
- **Olmesartan did not reduce cardiovascular events** or mortality compared with treatment not including ACEIs/ARBs in HD patients with hypertension in the OCTOPUS trial.

**CCBs**
- **Amlodipine reduced cardiovascular events** compared with placebo in HD patients with hypertension.

**MRAs**
- **Spironolactone** may reduce cardiovascular events and mortality compared with no additional treatment or placebo in HD and peritoneal patients.

HD, haemodialysis; LVH, left ventricular hypertrophy; HDPAL, Hypertension in Haemodialysis Patients Treated with Atenolol or Lisinopril trial; ACEIs, angiotensin-converting enzyme inhibitors; FOSIDIAL, Fosinopril in Dialysis trial; ARBs, angiotensin-II receptor blockers; OCTOPUS, Olmesartan Clinical Trial in Okinawa Patients under Dialysis Study; CCBs, calcium channel blockers; MRAs, mineralocorticoid receptor antagonists.

# Mineralocorticoid Receptor Antagonists

## Summary of Main Interventional Studies in CKD5 HD Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient characteristics</th>
<th>N</th>
<th>Design</th>
<th>Follow-up</th>
<th>BP medication</th>
<th>BP assessment</th>
<th>Baseline BP (mmHg)</th>
<th>Final BP (mmHg)</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto et al. [183]</td>
<td>Oligoanuric HD patients</td>
<td>157 versus 152</td>
<td>Open-label RCT</td>
<td>36 months</td>
<td>Spironolactone versus nothing</td>
<td>Pre-dialysis BP</td>
<td>152.8/77.8 versus 148.8/76.2</td>
<td>152.7/77.9 versus N/A</td>
<td>Spironolactone reduced the risk of death or hospitalization for CV event (HR: 0.38; 95% CI: 0.17–0.83)</td>
</tr>
<tr>
<td>Lin et al. [184]</td>
<td>HD or PD patients without CHF³</td>
<td>125 versus 128</td>
<td>Open-label RCT</td>
<td>24 months</td>
<td>Spironolactone versus placebo</td>
<td>Pre-dialysis BP</td>
<td>144.7/76.9 versus 141.9/77.4</td>
<td>N/A</td>
<td>Spironolactone reduced the risk of CV death, sudden death or aborted cardiac arrest (HR: 0.42; 95% CI: 0.26–0.78)</td>
</tr>
</tbody>
</table>

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## In Brief:

- **No significant effect on hypertension**
- **No significant change on cardiac structure and function (Echocardiography, Cardiac MRI, Cardiac PET scan)**
- **No significant increase of adverse events** (caution, increase trend of hyperkalemia)
- **Tend to reduce cardiovascular events and mortality**

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MRAs, mineralocorticoid receptor antagonists; BP, blood pressure; CV, cardiovascular; CHF, congestive heart failure; CI, confidence intervals; HD, hemodialysis; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; PD, peritoneal dialysis; RCT, randomized clinical trial; N/A, not applicable.

Risk of Cardiovascular Mortality for Blood Pressure Lowering Treatment vs Control

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (2003)\textsuperscript{17}</td>
<td>2/30</td>
<td>2/30</td>
</tr>
<tr>
<td>Takahashi et al (2006)\textsuperscript{19}</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tepel et al (2008)\textsuperscript{21}</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Cice et al (2003)\textsuperscript{10}</td>
<td>17/58</td>
<td>38/56</td>
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<tr>
<td>Suzuki et al (2008)\textsuperscript{20}</td>
<td>12/183</td>
<td>20/183</td>
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<tr>
<td>Nakao et al (2007)\textsuperscript{22}</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Zannad et al (2006)\textsuperscript{11}</td>
<td>31/196</td>
<td>30/201</td>
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<tr>
<td>Cice et al (2006)\textsuperscript{18}</td>
<td>59/151</td>
<td>75/152</td>
</tr>
<tr>
<td>Overall</td>
<td>121/618</td>
<td>165/622</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $P=54.6\%$, $Q=8.8$, $p=0.07$
## Study Treatment Discontinuation Rates

<table>
<thead>
<tr>
<th>Active agent</th>
<th>Active run-in*</th>
<th>Excluded during run-in</th>
<th>Patients who discontinued therapy</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active treatment</td>
</tr>
<tr>
<td>Cice et al (2003)</td>
<td>β blocker</td>
<td>Yes</td>
<td>18/132 (14%)</td>
</tr>
<tr>
<td>Li et al (2003)</td>
<td>ACE inhibitor</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Cice et al (2006)</td>
<td>ARB</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Takahashi et al (2006)</td>
<td>ARB</td>
<td>NR</td>
<td>N/A</td>
</tr>
<tr>
<td>Zannad et al (2006)</td>
<td>ACE inhibitor</td>
<td>Yes</td>
<td>6/417 (1%)</td>
</tr>
<tr>
<td>Nakao et al (2007)</td>
<td>β blocker</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Suzuki et al (2008)</td>
<td>ARB</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Tepel et al (2008)</td>
<td>Calcium-channel blocker</td>
<td>No</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme. ARB = angiotensin-receptor blocker. N/A = not applicable. NR = not reported. Data are n/N (%). *In the two studies with a preliminary run-in phase, all patients received study drug to determine before randomisation which patients were unable to tolerate the drug. Only patients who were able to tolerate the drug were randomly assigned to receive either treatment or placebo. In Zannad et al, 11 of 417 recruited patients were excluded after the run-in period because of symptomatic hypertension. Finally, 397 patients were randomised.

Managing Hypertension in CKD5HD Patient
Outline of the Presentation

1. Unmet needs in CKD5 hemodialysis patients
   • Hypertension and chronic fluid overload
   • Cause of poor cardiac outcomes
2. Diagnosis hypertension
   • Epidemiologic versus cardiac risk
3. Epidemiology of hypertension in CKD5D patients
4. Factors contributing to hypertension in CKD5D patients
5. Managing hypertension in CKD5D patients
   • Volume control first
   • Medication control second
   • Combined approach third
6. Take home message
<table>
<thead>
<tr>
<th>Assessment of</th>
<th>Instrumental: BIS, IVC, Lung US, RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of Sodium &amp; Volume Status</td>
<td>Biomarkers: BNP, NT-proBNP, Copeptin</td>
</tr>
<tr>
<td>Assessment of</td>
<td></td>
</tr>
<tr>
<td>Patient Centered Health Condition &amp;</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Assessment of</td>
<td></td>
</tr>
<tr>
<td>Intra &amp; Interdialytic Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Dialysis Unit BP: pre, post</td>
<td></td>
</tr>
<tr>
<td>standardized</td>
<td></td>
</tr>
<tr>
<td>Home BP specified conditions</td>
<td></td>
</tr>
<tr>
<td>ABPM 24-44hr</td>
<td></td>
</tr>
<tr>
<td>Assessment of</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic &amp; Cardiac Function</td>
<td></td>
</tr>
<tr>
<td>Lung X-Ray</td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>Non-Invasive Whole-Body Bioimpedance</td>
<td></td>
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<tr>
<td>Cardiograph</td>
<td></td>
</tr>
<tr>
<td>Assessment of</td>
<td></td>
</tr>
<tr>
<td>Tissue Sodium Content (future)</td>
<td></td>
</tr>
<tr>
<td>²³Sodium Tissue MRI</td>
<td></td>
</tr>
</tbody>
</table>
Visualized Workflow Model for Incident CKD5HD Patient

Incident CKD5D Patient

Renal Replacement Initiation

→ Yes

Fluid Overload?

→ Yes

Cardiac Condition?

→ No

Stop Antihypertensive Medications

Correct FO Probe Dry Weight

→ Yes

Cardioprotective Medication (β-blocker, RAASblocker)

Reassess Fluid Status & Hemodynamic Tolerance?

→ Yes

Maintain Dry Weight & Fluid Status

→ No

Correct FO Probe Dry Weight
Visualized Workflow Model for Prevalent Hypertensive CKD5HD Patient

1. **Prevalent Hypertensive CKD5HD**
   - ABPM? Home BP?  
     - yes
     - no
   - Fluid Overload?  
     - yes
     - no
     - 2<sup>nd</sup> Hypertension Work-Up & Cardiac Checkup + Cardioprotective & Antihypertensive Medication (BB, RAASb, CCab, AB)
   - no
   - Stop Antihypertensive Medications + Revise HD Conditions
   - Treatment Time & Frequency Dialysate [Na] + Correct FO Preserve ID hemodynamic

2. **Blood Pressure Inter & Intradialytic?**  
   - yes
     - Maintain HD Conditions
   - no
**Visualized Workflow Model for Paradoxical Intradialytic Hypertension**

1. **Paradoxical Intradialytic Hypertension**
   - ABPM? Home BP?
   - Instrumental FO & Hemodynamic Assessment

2. **Fluid Overload?**
   - yes: Stop Antihypertensive Medications + Revise HD Conditions
   - no: Explore Hemodynamic & Mediators Vasoreaction
     - Cardiac Medication if Needed

   - Treatment Time & Frequency Dialysate [Na]
   - Intensify Volume Depletion
   - Correct FO Preserve ID hemodynamic