The In-Center Hemodialysis Prescription as it Relates to Blood Pressure and Volume

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DISCLOSURES

Research funding
• National Institutes of Health
• Patient Centered Outcomes Research Institute

Member, Data and Safety Monitoring Board
• National Institute of Diabetes and Digestive and Kidney Diseases
• Proteon Therapeutics

Consulting
• GlaxoSmithKline

Compensation
• National Kidney Foundation: Deputy Editor, American Journal of Kidney Diseases
HEMODIALYSIS PRESCRIPTION AND BP / VOLUME MANAGEMENT: STATE OF THE EVIDENCE

• Most of the data come from observational studies, small mechanistic studies, or small trials

• As a community, we are now in a position to more efficiently conduct large RCTs evaluating components of the hemodialysis prescription
OUTLINE

- Target weight
- Ultrafiltration rate
- Treatment time
- Dialysate composition
- Dialysate temperature
- Residual kidney function

I will *not* provide an exhaustive review of the literature or the issues
TARGET WEIGHT

Associations of Post-Hemodialysis Weights Above and Below Target Weight with All-Cause and Cardiovascular Mortality

Risk increases with proportion of sessions with post-dialysis weight >2 kg above or >2 kg below target weight

~11,000 patients at a large US dialysis provider organization

TARGET WEIGHT

Associations of Post-Hemodialysis Weights Above and Below Target Weight with All-Cause and Cardiovascular Mortality


~11,000 patients at a large US dialysis provider organization
Failed Target Weight Achievement Associates with Short-Term Hospital Encounters among Individuals Receiving Maintenance Hemodialysis

- ~114,000 patients from large US dialysis provider
- 180-day baseline; 30-day exposure; 30-day f/u

- Risk higher if achieved post-dialysis weight $>\text{targeted post-dialysis weight in } \geq 30\% \text{ vs } <30\% \text{ of sessions}$
- Risk difference increased as the difference in targeted and achieved weight increased.

Is the high post-dialysis weight responsible for the outcome

OR

Is failure to meet the target (regardless of what it is) a marker of poor outcomes ("dose-targeting bias")?
**TARGET WEIGHT**

Failed Target Weight Achievement Associates with Short-Term Hospital Encounters among Individuals Receiving Maintenance Hemodialysis

**Target Weight Adjustment Post-Hospital Encounter**

- ~114,000 patients from large US dialysis provider
- 180-day baseline; 30-day exposure; 30-day f/u

Lower risk if target weight was adjusted after the hospital encounter supports a causal relationship between achieved weight and ER visit or hospitalization

Assimon MM et al J Amer Soc Nephrol 29: 217802188; 2018
TARGET WEIGHT: REDUCING “DRY” WEIGHT

Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP): A Randomized Controlled Trial

- Intervention: dry weight probing without increase in session duration or frequency
- 100 intervention; 50 control
- Run-in phase, then 8-week trial
- Primary outcome: change in systolic inter-dialytic BP

Intervention arm: 1 kg reduction in post-dialysis weight

Agarwal R et al. Hypertension; 53:500-507; 2009
TARGET WEIGHT: REDUCING “DRY” WEIGHT

BP in Dialysis: Results of a Pilot Study

- 126 hemodialysis patients
- Multiple centers in US
- Randomized to bp target 110-140 or 155-165 systolic
- Initial step to reduce BP was reduction in EDW

“Because many participants were intolerant to or refused these [dry weight] challenges, changes in antihypertensive medications were mainly responsible for achieving separation in SBP across treatment arms.”

**ULTRAFILTRATION RATE**

Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality

Post-hoc analysis of the HEMO Study
(n=1846)

Higher Ultrafiltration Rate Is Associated with Longer Dialysis Recovery Time in Patients Undergoing Conventional Hemodialysis

Hussein W.F. a,b, Arramreddy R. a,b, Sun S.J. b, Reiterman M. b, Schiller B. a,b

Recovery Time, Quality of Life, and Mortality in Hemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

Hugh C. Raynor MD, FRCP a, b, c, Lindsay Zepel MS a, c, Douglas S. Fuller MS a, Hal Morgenstern PhD a, c, d, Angelo Karaboyas MS b, Bruce F. Culloton MD e, Donna L. Mapes PhD b, Antonio A. Lopes MD, MPH, PhD f, Brenda W. Gillespie PhD g, Takeshi Hasegawa MD h, Rajiv Saran MD i, Francesca Tentori MD a, k, Manfred Hackling MD k, Ronald L. Pisoni PhD b, Bruce M. Robinson MD a, j
Two ways to reduce UFR:
1) lower inter-dialytic fluid intake
2) increase treatment time

Restricting fluid intake and increasing session duration are both burdensome to patients and may negatively affect quality of life.

Patients may leave dialysis volume overloaded.

Unpredictability of required session duration is logistically challenging for dialysis units.
Treatment time and mortality

**DOPPS**

![Graph showing treatment time vs. mortality](image1)

- < 211: 1.34 (P = 0.0001)
- 211-240: 1.19 (P = 0.01)
- > 240: Ref

**ANZDATA Registry**

![Graph showing treatment time vs. mortality](image2)

- Hazard ratio vs. HD session length


<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Longer Treatment Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tentori et al NDT 2012</td>
<td>DOPPS</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Flythe et al Kidney Int 2012</td>
<td>DaVita</td>
<td>Lower mortality</td>
</tr>
<tr>
<td>Ramirez et al CJASN 2012</td>
<td>CMS ESRD CPM Project</td>
<td>Higher mortality (trend)</td>
</tr>
<tr>
<td>Brunelli et al Kidney Int 2010</td>
<td>Fresenius</td>
<td>Lower mortality or not different depending on analytic approach</td>
</tr>
<tr>
<td>Miller et al, AJKD 2010</td>
<td>DaVita</td>
<td>Lower mortality but no difference beyond 3.5 hours</td>
</tr>
<tr>
<td>Saran et al Kidney Int 2006</td>
<td>DOPPS</td>
<td>Lower mortality</td>
</tr>
</tbody>
</table>
SESSION DURATION

DOPPS: Geographic variation in hemodialysis session duration

SESSION DURATION

Time to Reduce Mortality in ESRD (TiME) Trial

- Pragmatic trial demonstration project
- Cluster randomized trial fully embedded in clinical care delivery
- 7035 patients; 266 US dialysis units

- Other countries have longer dialysis sessions
- Many US dialysis units have longer dialysis sessions
- Dialysis unit culture is important
- Patient preferences are important

ClinicalTrials.gov Identifier NCT02019225
**Dialysate Composition:** $[\text{Na}^+]$

- **High $[\text{Na}^+]$ Dialysate:** More inter-dialytic volume overload
- **Low $[\text{Na}^+]$ Dialysate:** More intra-dialytic hypotension

KDIGO
DIALYSATE COMPOSITION: [Na\(^+\)]

High versus Low Dialysate Sodium Concentration in Chronic Haemodialysis Patients: A Systematic Review of 23 Studies

- N = 76,635
- 7 clinical trials (5 crossover, 3 randomized)
- High heterogeneity – intervention, f/u, outcomes
- “No clear evidence for superiority of low or high sodium dialysate on hard or surrogate outcomes”

DIALYSATE COMPOSITION: [Na⁺]

RESOLVE Trial: Randomized Evaluation of Sodium Dialysate Levels on Vascular Events

- Cluster randomized pragmatic trial of dialysate [Na⁺] 137 vs 140 mEq/L
- Multinational: Australia, New Zealand, China, Canada, Germany, US
- Primary outcome: composite of MACE and all-cause mortality
- Target sample size: ~40,000 to detect 10% risk reduction

ClinicalTrials.gov Identifier NCT02823821
DIALYSATE COMPOSITION: \([\text{Na}^+]\)


Ekbal NJ et al. Hemodialysis Int 20:S2-6; 2016
Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis:
A Systematic Review and Meta-Analysis

- 26 RCTs with 484 patients
- 17 included in meta-analysis

Intra-Dialytic Hypotension

- Favors Cool
- Symptoms of Discomfort

DIALYSATE TEMPERATURE

MY TEMP: Major Cardiovascular and Other Patient-Important Outcomes with Personalized Dialysate Temperature

• Cluster randomized pragmatic trial of dialysate temperature 0.5°C lower than pre-dialysis body temperature vs standard care (36.5°C)
• Primary outcome: composite of all-cause mortality or MACE
• Target sample size: 7500 patients; 80 units
• Ontario, Canada

ClinicalTrials.gov Identifier NCT02628366
RESIDUAL KIDNEY FUNCTION


Relative Contribution of Residual Renal Function and Peritoneal Clearance to Adequacy of Dialysis: A Reanalysis of the CANUSA Study

JOANNE M. BARGMAN,* KEVIN E. THORPE,† and DAVID N. CHURCHILL,‡ for the CANUSA Peritoneal Dialysis Study Group

CANUSA: solute clearance is associated with survival. However, residual renal function contribution to solute clearance is more important determinant of survival than is peritoneal clearance contribution.
Residual Kidney Function Decline and Mortality in Incident Hemodialysis Patients

- 6538 incident patients at DaVita with measurement of residual renal function at dialysis initiation and 1 year later (out of 44,000 incident patients)

Potential benefits of RKF
- Clearance of middle molecules and protein-bound solutes
- Volume management
- Endocrine functions
- Inflammation reduction?

Are we doing enough to protect RKF?

CHALLENGES

• Do we have sufficient data currently to weigh the advantages and disadvantages of dialysis prescription components? Which issues should be prioritized for RCTs?

• How do we individualize dialysis prescriptions to improve outcomes and to incorporate patient preferences and goals?

• How do we design rigorous clinical trials that incorporate individualization of treatment approaches?