KDOQI Hemodialysis Adequacy Clinical Practice Guideline Update 2015: What You Need to Know

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Presentation for National Renal Administrators’ Association
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Acknowledgements

This slide deck was originally created by Dr. Thomas Depner, KDOQI Hemodialysis Adequacy Co-Chair, and modified by Dr. Rita Suri, Workgroup member.

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Workgroup Disclosure:
All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or actual conflicts of interest. This document is updated annually and information is adjusted accordingly.

Disclosure Statement
Dr. Suri reports no relevant financial relationships.
Outline

- Defining “adequacy”
- Evidence Grading Scale
- Guideline Categories
  1. Timing of Dialysis Initiation
  2. Frequent and Long Duration Hemodialysis
  4. Volume and Blood Pressure Control
  5. Hemodialysis Membranes and Convective Therapies
- Summary of Differences between 2015 Update and 2006
- Discussion
“Adequacy” of Dialysis

• Has traditionally reflected adequacy of small solute clearance
• Thus, these guidelines pertain to the dialysis procedure itself

HOWEVER:

Adequacy of dialysis ≠ adequacy of patient care

✓ Optimal patient care entails attention to many aspects other than small solute clearance

eg. nutrition, anemia, metabolic control, vascular access, diabetes, cardiovascular disease, etc.

✓ Quality of life, caregiver burden, and individual patient values and preferences also require consideration
Recommendation Strength

Level 1
“We recommend”
Most patients should receive the recommended course of action.

Level 2
“We suggest”
Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.
## Grade of the Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade A</strong></td>
<td><strong>High quality</strong> of evidence. We are confident that the true effect is close to that of the estimate of the effect.</td>
</tr>
<tr>
<td><strong>Grade B</strong></td>
<td><strong>Moderate quality</strong> of evidence. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td><strong>Grade C</strong></td>
<td><strong>Low quality</strong> of evidence. The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td><strong>Grade D</strong></td>
<td><strong>Very low quality</strong> of evidence. The estimate of effect is very uncertain and often will be far from the truth.</td>
</tr>
<tr>
<td><strong>Ungraded</strong></td>
<td>Typically included to provide guidance based on common sense, where adequate evidence is lacking.</td>
</tr>
</tbody>
</table>
Guideline 1: Timing of Hemodialysis Initiation

1.1 Patients who reach **CKD stage 4** (GFR < 30 mL/min/1.73 m²), including those who have imminent need for maintenance dialysis at the time of initial assessment, should receive **education about kidney failure and options** for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure. *(Ungraded)*

This is an ungraded statement as there is minimal to no evidence evaluating the value of patient education in this setting; however, the potential for education and knowledge to improve patient empowerment and autonomous decision-making was recognized by the workgroup.
Guideline 1. Timing of Hemodialysis Initiation

1.2 The decision to initiate maintenance dialysis in patients who choose to do so should be based primarily upon an assessment of signs and/or symptoms associated with uremia, evidence of protein-energy wasting, and the ability to safely manage metabolic abnormalities and/or volume overload with medical therapy rather than on a specific level of kidney function in the absence of such signs and symptoms. (Ungraded)

This statement was based primarily on the findings of the IDEAL trial. However, given the controversy in this field, and that the symptoms and signs of the uremic syndrome are ill-defined, this statement was left ungraded.
Observational studies show higher eGFR at dialysis initiation is associated with increased mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Study Site</th>
<th>Study Period</th>
<th>Measure of Kidney Function</th>
<th>HR (95% CI) for Association of Kidney Function at Time of Dialysis Initiation With Death Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fink64 (1999)</td>
<td>5,388</td>
<td>Veterans Affairs, Maryland, USA</td>
<td>04/1995-12/1996</td>
<td>Scr</td>
<td>For every 1-mg/dL higher Scr: 0.96 (0.93-0.99)</td>
</tr>
<tr>
<td>Trayno55 (2002)</td>
<td>235</td>
<td>Glasgow, UK</td>
<td>1987-2000</td>
<td>Cockcroft-Gault CLcr</td>
<td>For every 1-mL/min higher CLcr: 1.11 (1.01-1.21)</td>
</tr>
<tr>
<td>Bedhu66 (2003)</td>
<td>2,920</td>
<td>Dialysis Morbidity and Mortality Study, USA</td>
<td>1996-1997</td>
<td>eGFR by MDRD Study equation</td>
<td>For every 5-mL/min/1.73 m² higher eGFR: 1.14 (1.06-1.22)</td>
</tr>
<tr>
<td>Kazmi67 (2005)</td>
<td>302,287</td>
<td>USRDS</td>
<td>1996-1999</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 10 (reference, &lt;5) mL/min/1.73 m²: 1.42</td>
</tr>
<tr>
<td>Sawhney68 (2009)</td>
<td>7,299</td>
<td>Canada and Scotland</td>
<td>2000-2005</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 15 and 10-15 (reference, 5-10) mL/min/1.73 m²: 1.65 (1.39-1.95) and 1.37 (1.19-1.59), respectively</td>
</tr>
<tr>
<td>Stel69 (2009)</td>
<td>6,716</td>
<td>Europe</td>
<td>2003</td>
<td>eGFR by MDRD Study equation</td>
<td>For every 1-mL/min/1.73 m² higher eGFR: 1.02 (1.01-1.04)</td>
</tr>
<tr>
<td>Evans70 (2011)</td>
<td>901</td>
<td>Sweden</td>
<td>05/1996-05/1998</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 7.5 (reference: &lt;7.5) mL/min/1.73 m²: 0.84 (0.64-1.10)</td>
</tr>
<tr>
<td>Hwang71 (2010)</td>
<td>23,551</td>
<td>Taiwan</td>
<td>07/2001-12/2004</td>
<td>eGFR by MDRD Study equation</td>
<td>For quintile 5 eGFR (&gt;6.52 mL/min/1.73 m²) (reference, quintile 1, &lt;3.29 mL/min/1.73 m²): 2.44 (2.11-2.81)</td>
</tr>
<tr>
<td>Lassalle72 (2010)</td>
<td>11,685</td>
<td>France</td>
<td>2002-2006</td>
<td>eGFR by MDRD Study equation</td>
<td>For every 5-mL/min/1.73 m² higher eGFR: 1.09 (1.05-1.14)</td>
</tr>
<tr>
<td>Wright73 (2010)</td>
<td>895,293</td>
<td>USRDS</td>
<td>01/1995-09/1996</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 15 and 10-15 (reference, 5-10) mL/min/1.73 m²: 1.44 (1.43-1.45) and 1.15 (1.15-1.16), respectively</td>
</tr>
<tr>
<td>Grootendorst74 (2011)</td>
<td>569</td>
<td>Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)</td>
<td>1997-2005</td>
<td>eGFR by MDRD Study equation</td>
<td>For highest tertile of eGFR (reference: lowest tertile): 1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Rosansky75 (2011)</td>
<td>81,176</td>
<td>USRDS (nondiabetics, aged 45-64 y)</td>
<td>1995-2006</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 15.0 and 10.0-14.9 (reference, &lt; 5) mL/min/1.73 m²: 1.74 and 1.47, respectively</td>
</tr>
<tr>
<td>Crews76 (2014)</td>
<td>84,654; propensity-matched: 61,930</td>
<td>USRDS (aged ≥ 67 y, ≥2 y of prior Medicare coverage)</td>
<td>2006-2008</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR ≥ 10 (reference, &lt;10) mL/min/1.73 m²: 1.11 (1.08-1.14) for propensity-matched analyses</td>
</tr>
<tr>
<td>Crews77 (2014)</td>
<td>652 (187 initiating dialysis)</td>
<td>Cleveland Clinic</td>
<td>2005-2009</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR ≥10 (reference, &lt;10) mL/min/1.73 m²: OR, 0.85 (0.65-1.11) for inverse probability weighted analyses</td>
</tr>
<tr>
<td>Jain78 (2014)</td>
<td>8,047 initiating PD</td>
<td>Canadian Organ Replacement Register</td>
<td>2001-2009</td>
<td>eGFR by MDRD Study equation</td>
<td>For eGFR &gt; 10.5 and 7.5-10.5 (reference, &lt;7.5) mL/min/1.73 m²: adjusted HRs of 1.08 (0.96-1.23) and 0.96 (0.86-1.09), respectively</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; PD, peritoneal dialysis; Scr, serum creatinine; UK, United Kingdom; USA, United States; USRDS, US Renal Data System.
However, higher residual kidney clearance at dialysis initiation is NOT associated with increased mortality

### Table 3. Summary Data From Observational Studies That Assessed the Association Between Measured Kidney Function at the Time of Initiation of Dialysis and Risk for Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Study Site</th>
<th>Study Period</th>
<th>Measure of Kidney Function</th>
<th>HR (95% CI) for Association of Kidney Function at Time of Dialysis Initiation With Death Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonomini\textsuperscript{79} (1985)</td>
<td>340</td>
<td>Single Italian center</td>
<td>1991-1992</td>
<td>Renal Kt/V\textsubscript{urea}</td>
<td>12-y survival in early dialysis group: (mean CL\textsubscript{cr}, 12.9 mL/min), 77%; late dialysis group (mean CL\textsubscript{cr}, 2.1 mL/min): 51%; no adjustment made for differences in patient characteristics</td>
</tr>
<tr>
<td>Tattersal\textsuperscript{80} (1995)</td>
<td>63</td>
<td>Single UK center</td>
<td>1991-1992</td>
<td>Renal Kt/V\textsubscript{urea}</td>
<td>Mean renal Kt/V\textsubscript{urea} lower in 6 individuals who died; no adjustment made for differences in patient characteristics</td>
</tr>
<tr>
<td>Churchill\textsuperscript{81} (1997)</td>
<td>680</td>
<td>Canadian-USA Study on Adequacy of Peritoneal Dialysis (CANUSA)</td>
<td>9/1990-12/1992</td>
<td>Assumed 24-h urinary urea clearance and CL\textsubscript{cr}</td>
<td>For every 5-L/wk higher mGFR: 0.95 (0.91-0.99)</td>
</tr>
<tr>
<td>Beddu\textsuperscript{66} (2003)</td>
<td>1,072</td>
<td>Dialysis Morbidity and Mortality Study, USA</td>
<td>1996-1997</td>
<td>Assumed 24-h urinary CL\textsubscript{cr}</td>
<td>For every 5-mL/min higher CL\textsubscript{cr}: 0.98 (0.86-1.14)</td>
</tr>
<tr>
<td>Grootendorst\textsuperscript{74} (2011)</td>
<td>569</td>
<td>Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)</td>
<td>1997-2005</td>
<td>Assumed 24-h urinary CL\textsubscript{cr}</td>
<td>Highest tertile of mGFR (reference: lowest tertile of mGFR): 1.0 (0.7-1.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CL\textsubscript{cr}, creatinine clearance; HR, hazard ratio; mGFR, measured glomerular filtration rate; UK, United Kingdom; USA, United States.
IDEAL Randomized Controlled Trial
Cooper et al, NEJM, 363:609-619, 2010

- 32 centers in Australia/NZ
- **828 patients** with CrCl 10-15 ml/min/1.73 m²
- Randomized to start HD early (CrCl = 10-14) vs. late (CrCl = 5-7).
- High crossover rate:
  - 19% earlies started late; 76% of lates started early
  - as treated CrCl values were 12.0 vs. 9.8 (eGFR 9.0 vs. 7.8).
- There were **no observed differences in mortality** (primary outcome) or in **secondary outcomes** (cardiovascular events*, infectious events, complications of dialysis, cost, nutritional status, quality of life, cardiac structure or function).

*CV death, nonfatal MI, nonfatal stroke, Transient ischemic attack, new angina
IDEAL Study: Time to Start of Dialysis

Hazard ratio, 2.09 (95% CI, 1.81–2.41)
P<0.001

<table>
<thead>
<tr>
<th>Year</th>
<th>Early-start group</th>
<th>Late-start group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at Risk</td>
<td>No. at Risk</td>
</tr>
<tr>
<td></td>
<td>Early start</td>
<td>Late start</td>
</tr>
<tr>
<td>0</td>
<td>404</td>
<td>424</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>118</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
IDEAL Study: Time to Death

Hazard ratio, 1.04 (95% CI, 0.83–1.30)
P = 0.75

No. at Risk
Early start  404  358  305  249  177  99  59  32
Late start   424  385  333  254  187  115  60  32
Guideline 2: Frequent and Long Duration HD

**In-center Frequent Hemodialysis**

2.1 **We suggest** that patients with end-stage kidney disease be offered in-center short frequent hemodialysis as an alternative to conventional in-center thrice weekly hemodialysis after considering individual patient preferences, the potential quality of life and physiological benefits, and the risks of these therapies. (2C)

2.2 **We recommend** that patients considering in-center short frequent hemodialysis be informed about the risks of this therapy, including a possible increase in vascular access procedures (1B) and the potential for hypotension during dialysis. (1C)
Guideline 2: Frequent and Long Duration HD

**Home Long Hemodialysis**

2.3 **Consider** home long hemodialysis (6-8 hours, 3 to 6 nights per week) for patients with end-stage kidney disease who prefer this therapy for lifestyle considerations. *(Ungraded)*

2.4 **We recommend** that patients considering frequently administered home long hemodialysis be informed about the risks of this therapy, including possible increase in vascular access complications, potential for increased caregiver burden, and accelerated decline in residual kidney function. *(1C)*

2.5 **During pregnancy,** women with end-stage kidney disease should receive frequent long hemodialysis either in-center or at home, depending on convenience. *(Ungraded)*
Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis

Robert N. Foley, M.B., David T. Gilbertson, Ph.D., Thomas Murray, M.S., and Allan J. Collins, M.D.

A Annualized Mortality Rate

All causes

Cardiac causes

Infectious causes

Vascular causes

Day of Week

Rate per 100 Person-Yr.

0 5 10 15 20 25

HD1 HD1+1 HD2 HD2+1 HD3 HD3+1 HD3+2

Daily Variation in Death in Patients Treated by Long-term Dialysis: Comparison of In-Center Hemodialysis to Peritoneal and Home Hemodialysis

Rathika Krishnasamy, MD,1,2 Sunil V. Badve, MD,1,2 Carmel M. Hawley, M Med Sci,1,2 Stephen P. McDonald, PhD,1,3 Neil Boudville, M Med Sci,1,4 Fiona G. Brown, PhD,1,5 Kevan R. Polkinghorne, PhD,1,5 Kym M. Bannister, MD,1,3 Kathryn J. Wiggins, PhD,1,6 Philip Clayton, MM Clin Epi,1,7,8 and David W. Johnson, PhD1,2

Figure 2. Occurrence of cardiac deaths in 10,338 hemodialysis (HD; black bars) and 4,298 peritoneal dialysis (PD; white bars) patients in Australia and New Zealand in 1999-2008, according to the day of the week of death.
Physiological Rationale for Frequent and Long HD

- greater weekly small solute clearance as more time spent on the “steepest part” of removal curve
- decreased fluctuations in solute concentrations ...less “uremia”? 
- greater ease of ultrafiltration .....better volume/ BP control, ↓symptoms
- greater clearance of phosphate and beta-2M, whose removal is time dependent..... ....improved CV outcomes?

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Depner TA et al, as reproduced in:
Frequent Hemodialysis Network (FHN) randomized trials: Study design

- **DAILY TRIAL (N=245)**
  - in-center daily HD 1.5-2.75 hrs 6 d/wk OR In-center conventional HD

- **NOCTURNAL TRIAL (N=87)**
  - home nocturnal HD >6 hrs 6 days/wk OR home conventional HD

- Follow-up 1 year
- 2 co-primary outcomes: 1) LV mass or death 2) QOL or death
- Several secondary and safety outcomes, not powered for hard outcomes

Daily HD improved quality of life, left ventricular mass index, blood pressure, and pre-dialysis phosphorus.

FHN Trial Group. NEJM 363(24): 2287-300, 2010
Treatment Effect on LV Mass (g) by Level of Baseline LV Mass
Comparison of 6x/Week vs. 3x/Week

Chan CT et al. Circ Cardiovas Imaging 2012
Survival: FHN Daily Trial

Figure 2. (B) Displays the survival curves with follow-up censored at transplantation. (A) Displays the survival curves including follow-up after transplantation; patients randomized to the frequent and conventional hemodialysis groups. (A) Conventional Hemodialysis. Conventional hemodialysis may be smaller than the trial-averaged concentration of urea and longer versus shorter session lengths. (B) Frequent Hemodialysis. We also concluded that a clinically significant reduction in the mortality hazard is reasonably likely; posterior probabilities of a 12% hazard reduction ranged from 0.61 to 0.87 depending on the prior distributions that we considered. These analyses suggest that, although the actual benefit derived estimate, frequent in-center hemodialysis is likely to be harmful in contrast to results suggested by a large observational study on the basis of the International Quotidian Dialysis Registry.

Strengths of these analyses include the trial design—selective patients with ESRD, which reduces the likelihood of confounding and bias, especially bias relating to receiving dialysis in the home versus in center. With respect to determining the intervention significance, a 12-month frequent in-center hemodialysis was likely to differ from those who did not. Finally, these results should not be extrapolated to other methods of daily hemodialysis that do not offer greater intensity of hemodialysis therapy, wherein benefit was achieved in the FHN Daily Trial. The FHN Daily Trial was a multicenter, prospective, randomized, parallel group trial of frequent (six times per week) compared with conventional (three times per week) in-center hemodialysis.

We also concluded that a clinically significant reduction in the mortality hazard is reasonably likely; posterior probabilities of a 12% hazard reduction ranged from 0.61 to 0.87 depending on the prior distributions that we considered. These analyses suggest that, although the actual benefit derived estimate, frequent in-center hemodialysis is very unlikely to be harmful in contrast to results suggested by a large observational study on the basis of the International Quotidian Dialysis Registry.
FHN Nocturnal Trial RESULTS (n=87)

- Nocturnal trial largely negative, underpowered.
- No change in QOL.
- Some improvements in blood pressure, and pre-dialysis phosphorus.


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect measure</th>
<th>Estimated standardized effects, 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Physical health composite score</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Beck depression inventory</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Predialysis albumin</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Predialysis phosphorus</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>ESA dose</td>
<td>- Mean Δ log</td>
<td></td>
</tr>
<tr>
<td>Predialysis systolic BP</td>
<td>- Mean Δ</td>
<td></td>
</tr>
<tr>
<td>Trail making B</td>
<td>- Log RR</td>
<td></td>
</tr>
<tr>
<td>Non-access hospitalization/death</td>
<td>- Log HR</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>1 2</td>
<td>1.42 (0.69, 2.90)</td>
<td>0.34</td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>30 (16) 43 (19)</td>
<td>1.42 (0.69, 2.90)</td>
<td>0.34</td>
</tr>
<tr>
<td>Non-access hospitalizations</td>
<td>26 (15) 35 (17)</td>
<td>1.32 (0.60, 2.89)</td>
<td>0.48</td>
</tr>
<tr>
<td>Cardiovascular hospitalizations</td>
<td>4 (3) 6 (5)</td>
<td>1.60 (0.49, 5.22)</td>
<td>—</td>
</tr>
<tr>
<td>Infection hospitalizations</td>
<td>7 (5) 14 (8)</td>
<td>2.04 (0.80, 5.17)</td>
<td>—</td>
</tr>
<tr>
<td>Access hospitalizations</td>
<td>4 (3) 8 (5)</td>
<td>2.15 (0.67, 6.89)</td>
<td>0.20</td>
</tr>
<tr>
<td>All vascular access interventions</td>
<td>21 (15) 34 (23)</td>
<td>1.62 (0.91, 2.87)</td>
<td>0.10</td>
</tr>
<tr>
<td>Failures</td>
<td>13 (10) 17 (13)</td>
<td>1.27 (0.60, 2.71)</td>
<td>0.54</td>
</tr>
<tr>
<td>Other procedures</td>
<td>8 (6) 17 (12)</td>
<td>2.25 (0.87, 5.83)</td>
<td>0.095</td>
</tr>
<tr>
<td>Hypotensive episodes</td>
<td>136 (28) 71 (25)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0 8 (2)</td>
<td>—</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>16 (9) 62 (13)</td>
<td>—</td>
<td>0.47</td>
</tr>
</tbody>
</table>

The calculation of the standardized effect sizes is described in ref. 16.

BP, blood pressure; CI, confidence interval; ESA, erythropoiesis-stimulating agent; HR, hazard ratio; LV, left ventricular.
### Alberta Nocturnal Trial RESULTS (n=51)

#### Table 2. Outcomes for LV Mass, Blood Pressure, Anemia, and Mineral Metabolism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nocturnal Hemodialysis&lt;sup&gt;b&lt;/sup&gt; (n = 26)</th>
<th>Conventional Hemodialysis&lt;sup&gt;b&lt;/sup&gt; (n = 25)</th>
<th>Between-Group Comparison (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass, mean (SD), g</td>
<td>177.4 (51.1)</td>
<td>181.5 (92.3)</td>
<td>−4.1 (−49.5 to 41.3)</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exit 163.6 (45.2)</td>
<td>183.0 (84.2)</td>
<td>−19.4 (−60.5 to 21.7)</td>
</tr>
<tr>
<td>Change</td>
<td>−13.8 (23.0)</td>
<td>1.5 (24.0)</td>
<td>−15.3 (−29.6 to −1.0)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>LV mass, mean (SD), g/m²</td>
<td>92.4 (26.6)</td>
<td>101.8 (50.6)</td>
<td>−9.4 (−34.0 to 15.2)</td>
</tr>
<tr>
<td>Baseline</td>
<td>Exit 85.3 (23.2)</td>
<td>102.8 (46.1)</td>
<td>−17.5 (−39.8 to 4.6)</td>
</tr>
<tr>
<td>Change</td>
<td>−7.1 (12.4)</td>
<td>1.0 (14.1)</td>
<td>−8.1 (−16.2 to −0.1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Nocturnal HD improved LV mass, BP, and phosphate, but not quality of life or anemia.

---

Culleton et al, *JAMA* 298(11); 1291-1299, 2007
Survival: FHN Nocturnal Trial

Survival with Censoring of Kidney Transplants

Survival Probability

Years

0 1 2 3 4 5

Conventional Home Hemodialysis
Frequent Nocturnal Hemodialysis
HR 5.98, 95% CI (1.71-20.92), p = 0.002

Number at risk at beginning of each year and (number of deaths) during each interval

<table>
<thead>
<tr>
<th>Years</th>
<th>Conventional</th>
<th>Frequent Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42 (1)</td>
<td>45 (2)</td>
</tr>
<tr>
<td>1</td>
<td>39 (1)</td>
<td>38 (9)</td>
</tr>
<tr>
<td>2</td>
<td>36 (0)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>3</td>
<td>29 (1)</td>
<td>13 (0)</td>
</tr>
<tr>
<td>4</td>
<td>11 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Other cardiac deaths include one death from CHF with volume overload, one sudden death due to an arrhythmia, and one sudden death thought to be secondary to a cardiac arrest. Infection deaths include one death from endocarditis and one death from a perirenal abscess. Other deaths include one death for dementia and failure to thrive and 1 death due to subdural hematoma.

Abbreviations: CHF, congestive heart failure; GI, gastrointestinal.
Vascular access complications were increased with frequent HD in the FHN trials

- Primary composite outcome: time to 1st
  - Access repair = any procedure carried out on the access
  - Access loss = anytime a NEW access was required (this included catheter rewires but did NOT include elective catheter removals)
  - Access-related hospitalisation

Suri RS et al, JASN, Mar 2013
Nocturnal HD resulted in accelerated loss of residual kidney function
### Table 2: Cousineau Perceived Burden Scores Over Time

<table>
<thead>
<tr>
<th></th>
<th>3 times per week</th>
<th>6 times per week</th>
<th>Between group difference*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAILY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 4</td>
<td>−1.1 ± 2.8</td>
<td>−2.7 ± 2.5</td>
<td>−1.6 (−8.4, 5.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Month 12</td>
<td>−2.6 ± 3.1</td>
<td>−4.7 ± 2.7</td>
<td>−2.1 (−9.4, 5.3)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>NOCTURNAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 4</td>
<td>−0.3 ± 2.6</td>
<td>+5.9 ± 2.8</td>
<td>+6.2 (−0.8, 13.3)</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td>−2.8 ± 2.8</td>
<td>+9.6 ± 3.0</td>
<td>9.8 (2.4, 17.3)</td>
<td>0.0093</td>
</tr>
<tr>
<td>Month 12</td>
<td>−5.7 ± 2.7</td>
<td>+0.5 ± 2.7</td>
<td>+6.1 (−0.8, 13.1)</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>−5.4 ± 3.1</td>
<td>+4.0 ± 3.4</td>
<td>9.4 (0.55, 18.3)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

- There was **NO** increased perceived caregiver burden with daily HD.
- There was a **increased** perceived caregiver burden with nocturnal HD at home.

## Long frequent versus standard dialysis during pregnancy: Canadian Study

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
<th>Dialysis Hrs/wk</th>
<th>Pregnancy Duration</th>
<th>Birth rate</th>
<th>Birth wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>22</td>
<td>43 ± 6</td>
<td>36 wks</td>
<td>86.4%</td>
<td>2118 ± 857</td>
</tr>
<tr>
<td>USRDS</td>
<td>70</td>
<td>17 ± 5</td>
<td>27 wks</td>
<td>61.4%</td>
<td>1748 ± 949</td>
</tr>
</tbody>
</table>

Guideline 3: Measurement of Dialysis: Urea Kinetics

3.1 We recommend a *target single pool Kt/V (spKt/V)* of 1.4 per hemodialysis session for patients treated thrice weekly, with a minimum delivered spKt/V of 1.2. *(1B)*

3.2 In patients with significant *residual native kidney function* (Kr), the dose of hemodialysis may be reduced provided Kr is measured periodically. *(Ungraded)*

3.3 For hemodialysis schedules other than thrice weekly, a target standard Kt/V of 2.3 volumes per week with a minimum delivered dose of 2.1 using a method of calculation that includes the contributions of ultrafiltration and residual kidney function. *(Ungraded)*
- **National Cooperative Dialysis Study** (NCDS, NEJM 1981) randomized 151 patients to high vs. low urea concentration and short vs. long time

- **Re-analysis of the NCDS** that Kt/V 0.8 better than Kt/V 0.4

---

**Table 2. NCDS Data (12)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Target TAC urea* (mg/dL)</th>
<th>Achieved TAC urea† (mg/dL) (±SEM)</th>
<th>~URR ‡</th>
<th>~Kt/V ‡</th>
<th>Midweek predialysis BUN (mg/dL) (±SEM)</th>
<th>Medical withdrawal rate at 1 year (%)</th>
<th>Non-hospitalized at 1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4:29 ± 0:03</td>
<td>50</td>
<td>51.3 ± 1.1</td>
<td>0.57</td>
<td>0.85</td>
<td>71.2 ± 1.4</td>
<td>18</td>
<td>86</td>
</tr>
<tr>
<td>II</td>
<td>4:30 ± 0:03</td>
<td>100</td>
<td>87.7 ± 1.4</td>
<td>0.35</td>
<td>0.47</td>
<td>104.9 ± 1.7</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>III</td>
<td>3:19 ± 0:03</td>
<td>50</td>
<td>54.1 ± 1.1</td>
<td>0.55</td>
<td>0.80</td>
<td>73.1 ± 1.4</td>
<td>6</td>
<td>69</td>
</tr>
<tr>
<td>IV</td>
<td>3:14 ± 0:03</td>
<td>100</td>
<td>89.6 ± 1.2</td>
<td>0.30</td>
<td>0.45</td>
<td>109.1 ± 1.5</td>
<td>62</td>
<td>31</td>
</tr>
</tbody>
</table>

---

For medical withdrawal rates: p < 0.0001 for effect of TAC urea; p > 0.05 for effect of time. For hospitalization: p < 0.0001 for effect of TAC urea; p = 0.06 for effect of time

*To convert BUN to mmol/L, divide by 2.8

† Kt/V approximations assume an nPNA of 1.0 g/kg/day (which was the mean nPNA achieved in NCDS). For nPNA range of 0.6–1.2 the estimated Kt/V range is as follows: for groups I and III, Kt/V range is 0.4–1.05; for groups II and IV, Kt/V range is 0.2–0.6 (64)

‡ URR approximations assume ultrafiltration and urea generation rate of 0 (69)

---

How much dialysis is enough? - HEMO study

- After the NCDS, numerous observational studies suggested that higher urea clearances are associated with high mortality on thrice weekly HD

- HEMO Study\(^1\) randomized patients to eKt/V 1.0 vs. 1.4: NO CHANGE IN MORTALITY.

- eKt/V of 1.0 is approximately equal to spKt/V of 1.2

- Target spKt/V of 1.4 ensures that <10% of treatments are spent <1.2

• Treatment of the patient should not stop after achieving an "adequate" Kt/V_{urea}. Nor is target small solute clearance the only factor which should be considered during dialysis.

• Frequency and treatment time should be individualized considering small solute clearance, residual renal function, quality of life, predicted life-span, and patient values.

• Patients with significant residual function may not require 3 full treatments per week, and thus the dose of dialysis may be reduced. Conversely, other patients may require more frequent or longer treatments.

• Recommendations on how to measure pre- and post-dialysis urea have not changed:

  - predialysis: draw before injecting heparin, saline, or other potential diluents
  - post-dialysis: draw blood from the dialyzer inflow port after slowing blood flow to 100ml/min for 15 secs OR after stopping dialysate flow for 3 mins
Guideline 4. Volume and BP Control: Treatment Time and Ultrafiltration Rate

4.1 **We recommend** that patients with low residual kidney function (< 2 ml/min) undergoing thrice weekly hemodialysis be prescribed a **bare minimum of three hours per session.** *(1D)*

4.1.1 **Consider longer hemodialysis treatment times** or additional hemodialysis sessions for patients with large interdialytic weight gains, high ultrafiltration rates, poorly controlled blood pressure, difficulty achieving dry weight, or poor metabolic control (such as hyperphosphatemia, metabolic acidosis, and/or hyperkalemia). *(Ungraded)*
Guideline 4. Volume and BP Control: Treatment Time and Ultrafiltration Rate

4.2 We recommend both reducing dietary sodium intake as well as adequate sodium/water removal with hemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy. (1B)

4.2.1 Prescribe an ultrafiltration rate for each hemodialysis session that allows for an optimal balance among achieving euvolemia, adequate blood pressure control and solute clearance, while minimizing hemodynamic instability and intradialytic symptoms. (Ungraded)
Guideline 4. Volume & BP Control

• Strong recommendation to minimize dietary sodium (and water) intake is reaffirmed.

• Not enough evidence to raise minimum of 3 hours of hemodialysis delivered 3 days per week.
  - 3 hours 3 days per week is a bare minimum if no residual function.
  - Exceptions......
    - Patients suffering from poor QOL due to longer treatments
    - Ongoing TiME trial may shed more light on this.

• There is no evidence of harm from extending time.

• Studies advocating limits to ultrafiltration rate are based on observational data only.

• Not enough evidence to make recommendations with regard to dialysate sodium concentration.
Guideline 5. New Hemodialysis Membranes

5.1 We recommend the use of biocompatible high or low flux hemodialysis membranes for intermittent hemodialysis. (1B)
Guideline 5. High Flux Membranes

Three large clinical trials:


One meta-analysis:

Guideline 5. High Flux Membranes

- Three large randomized trials failed to show a survival benefit with high-flux membranes.
- One secondary outcome analysis (HEMO) and a meta-analysis showed reduced cardiovascular mortality with high vs. low-flux.
- Some showed reduced all-cause mortality in certain subgroups:
  - Low serum albumin (<4 g/dL) [MPO]
  - High vintage (> 3.7 years on dialysis) [HEMO]
  - Diabetes mellitus [MPO, EGE]
  - AV fistulas [EGE]
- None showed harm.
- Because cost of high-flux membranes without strong evidence of benefit, decision to use high vs. low-flux membranes is left up to the treating center.
Convective Therapies – not recommended at this time

Hemodiafiltration versus Low-Flux Hemodialysis

Grooteman, et al., CONTRAST Study, JASN 2012

Survival

Fatal & non-fatal CV events

Survival (%)

Time (years)

Patients at risk

356 337 307 269 230 201 169 140 102 83 65 52 32

Low flux HD

Online HDF

Cardiovascular event-free survival (%)

Time (years)

Patients at risk

358 346 324 287 237 203 160 131 103 77 57 44 18

Low flux HD

Online HDF
2006 and 2015: What’s different?

- GRADE: level of recommend (1 & 2) and grade (A-D) of the evidence
- Individualized prescriptions: include patient expectations and preferences
- More prescription flexibility: initiation, frequency, duration, Qf rate
- Less emphasis on absolute minimum or maximum cut-offs
- Recommendations regarding high frequency hemodialysis:
  - No compelling evidence that frequent dialysis is best for everyone
  - Consider for patients with special needs:
    - Left ventricular hypertrophy and/or congestive heart failure
    - Uncontrolled hypertension, fluid overload
    - Metabolic derangements (hyperphosphatemia, hyperkalemia)
    - Sleep apnea
    - Pregnancy (strong recommendation)
  - Acknowledges the risks of frequent hemodialysis
- Consider stdKt/V to measure frequent HD; adjust for Kru, Qf, BSA
- More emphasis on volume and BP control
KDOQI Leadership

Michael Rocco, M.D., KDOQI Chair
Holly Kramer, M.D., Vice Chair, Research and Commentaries
Michael Choi, M.D., Vice Chair, Education and Policy