NxStage System One®
FIRST and ONLY
CLEARANCE FOR HOME
nocturnal
HEMODIALYSIS THERAPY

HOME HEMODIALYSIS
CLINICAL EVIDENCE
PART 1: CARDIAC INJURY AND DIALYSIS

INVENTING a movement.

INSPIRING everyone.

APM1532, Rev.A
Important information

Despite the health benefits that more frequent home hemodialysis may provide to those with chronic kidney disease, this form of therapy is not for everyone. Home hemodialysis with the NxStage System One requires a patient and partner who are committed to being trained on and following the guidelines for proper system operation.

The reported benefits of home hemodialysis may not be experienced by all patients.

The NxStage System One is a prescription device and, like all medical devices, involves some risks. The risks associated with hemodialysis treatments in any environment include, but are not limited to, high blood pressure, fluid overload, low blood pressure, heart-related issues, and vascular access complications. The medical devices used in hemodialysis therapies may add additional risks including air entering the bloodstream, and blood loss due to clotting or accidental disconnection of the blood tubing set.Patients should consult with their doctor to understand the risks and responsibilities of home and/or more frequent hemodialysis using the NxStage System One.

Certain risks are unique to the home. Treatments at home are done without the presence of medical personnel and on-site technical support. Patients and their partners must be trained on what to do and how to get medical or technical help if needed.

Certain risks associated with hemodialysis treatment are increased when performing nocturnal therapy due to the length of treatment time and because therapy is performed while the patient and care partner are sleeping. These risks include, but are not limited to, blood access disconnects and blood loss during sleep, blood clotting due to slower blood flow or increased treatment time or both, and delayed response to alarms when waking from sleep. Patients should consult with their physician to understand the risks and responsibilities associated with home nocturnal hemodialysis using the NxStage System One.
Agenda

- The Association Between Cardiac Injury and Dialysis
- Current Dialysis Situation by Modality in the US
- Dialysis Induced Stress on the Heart by Modality
  - Blood Pressure Control
  - Left Ventricular Hypertrophy
  - Myocardial Stunning
- Frequency and Duration Matter
The Association Between Cardiac Injury and Dialysis
Cardiovascular Disease is More Prevalent in Chronic Kidney Disease Patients

USRDS 2013 ADR: Figure 4.1 (Volume 1). December 31, 2011 point prevalent Medicare enrollees with CVD, age 66 & older, with fee-for-service coverage for the entire calendar year.
Cardiovascular-Related Deaths Are Common

CAUSES OF DEATH IN PREVALENT DIALYSIS PATIENTS

- CHF 5%
- Arrhythmia/cardiac arrest 27%
- Other cardiac 2%
- Other vascular 4%
- Infection 10%
- Malignancy 4%
- Withdrawal 11%

Nearly 40% of dialysis patient deaths are cardiovascular-related.
Cardiovascular Mortality Significantly Higher in Dialysis Patients vs. General Population

Current Dialysis Situation by Modality in the United States

- **88%** | In-center dialysis treatment
- **10%** | Peritoneal dialysis
- **2%** | Home hemodialysis

Data source: 2013 Census Data by MAC and State, 2013 ESRD Network Annual Report
Informing Patients’ Decisions

Fine, et.al survey:
Patients want to be informed about modality options\(^1\)

CMS Conditions for coverage
- Providers need to ensure that comprehensive education is provided and that patients’ preferences are incorporated into their care plan

Most patients want to know...
- Side effects: 96%
- Quality of life implications: 99%
- Bodily impact: 97%
- Survival data: 97%

The Heart of the Matter
Dialysis Induced Stress on the Heart Varies by Modality

Effective fluid management is associated with better cardiovascular outcomes. Effectiveness varies by modality.
Cardiovascular Improvement is a Hallmark Benefit of More Frequent Therapy

<table>
<thead>
<tr>
<th></th>
<th>HNHD</th>
<th>HHD</th>
<th>PD</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive / Blood</td>
<td>5% ▼</td>
<td>7% ▼</td>
<td>3% ▲</td>
<td>≤1% ▼</td>
</tr>
<tr>
<td>Pressure Control</td>
<td>Systolic BP(^1)</td>
<td>Systolic BP(^2)</td>
<td>Systolic BP(^3)</td>
<td>Systolic BP(^1,2)</td>
</tr>
<tr>
<td>Occurrence of</td>
<td>50% Patients(^5)</td>
<td>75% Patients(^5)</td>
<td>-</td>
<td>100% Patients(^5)</td>
</tr>
<tr>
<td>Myocardial Stunning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional Wall</td>
<td>38% ▼</td>
<td>31% ▼</td>
<td>-</td>
<td>Index RWMAs</td>
</tr>
<tr>
<td>Motion Abnormalities</td>
<td>RWMAs(^5)</td>
<td>RWMAs(^5)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Left Ventricular Mass</td>
<td>8% ▼</td>
<td>11% ▼</td>
<td>14% ▲</td>
<td>2% ▼</td>
</tr>
<tr>
<td>Index</td>
<td>LV Mass(^3)</td>
<td>LV Mass(^2)</td>
<td>LV Mass(^3)</td>
<td>LV Mass(^2)</td>
</tr>
</tbody>
</table>

HNHD=Home Nocturnal Hemodialysis (5+x/week), HHD=More Frequent Hemodialysis (5+x/week), PD=Peritoneal Dialysis, CHD=Conventional In-Center Hemodialysis (3x/week)

\(^{1}\)Rocco, et al., The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. International Society of Nephrology, 2011


\(^{4}\)Culleton BF, et al., Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life. JAMA. September 2007; Vol 298, No. 11, 1291 – 1299.

\(^{5}\)Jefferyes et.al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Nephrol 2011 June, 6(6); 1326-1332.
# More Frequent Hemodialysis Associated with Better Blood Pressure Control

**As Compared to Conventional Hemodialysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. with Data</th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change from Baseline to 12 Months</th>
<th>Adjusted Mean (±SE) Change from Baseline</th>
<th>Difference in Change (Frequent-Conventional) (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoiesis-stimulating agents — EPO equivalent units</td>
<td>90</td>
<td>57,070±65,456</td>
<td>53,093±63,552</td>
<td>-3,976±69,525</td>
<td>-5%±10%</td>
<td>-10.1 (-14.3 to -6.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Conventional hemodialysis</td>
<td>103</td>
<td>56,176±102,288</td>
<td>41,877±44,636</td>
<td>-14,299±76,191</td>
<td>-18%±8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly average predialysis systolic blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional hemodialysis</td>
<td>93</td>
<td>146±18</td>
<td>147±18</td>
<td>0.9±16.2</td>
<td>0.9±1.6</td>
<td>-10.1 (-14.3 to -6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequent hemodialysis</td>
<td>104</td>
<td>147±19</td>
<td>137±19</td>
<td>-9.7±18.2</td>
<td>-9.2±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive agents consumed — no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional hemodialysis</td>
<td>92</td>
<td>2.80±1.69</td>
<td>2.58±1.68</td>
<td>-0.23±1.35</td>
<td>—</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequent hemodialysis</td>
<td>93</td>
<td>2.69±1.80</td>
<td>1.82±1.73</td>
<td>-0.87±1.85</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

**Conventional Hemodialysis Reported insigniﬁcant blood pressure control**

**More Frequent Hemodialysis associated with a 7% decrease in systolic blood pressure**

---

Home Nocturnal Hemodialysis Associated with Better Blood Pressure Control

5-6 Nights/week, ≥6 hours/treatment as compared to conventional hemodialysis

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>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>129 (23)</td>
<td>135 (19)</td>
<td>−6 (−17 to 6)</td>
</tr>
<tr>
<td>Exit</td>
<td>122 (23)</td>
<td>139 (20)</td>
<td>−17 (−28 to −4)</td>
</tr>
<tr>
<td>Change</td>
<td>−7 (29)</td>
<td>4 (17)</td>
<td>−11 (−24 to 2)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75 (14)</td>
<td>77 (16)</td>
<td>−2 (−10 to 7)</td>
</tr>
<tr>
<td>Exit</td>
<td>68 (16)</td>
<td>75 (12)</td>
<td>−7 (−15 to 1)</td>
</tr>
<tr>
<td>Change</td>
<td>−7 (16)</td>
<td>−2 (12)</td>
<td>−5 (−13 to 2)</td>
</tr>
</tbody>
</table>

More Frequent Home Nocturnal Hemodialysis Associated with a 5% Decrease in Mean Systolic Blood Pressure

Conventional Hemodialysis showed little systolic blood pressure change from baseline to exit.

Long-term Evolution of Blood Pressure in Dialysis Patients

30-Month Follow-Up

- Foley et al., performed baseline and yearly blood pressure measurements in a prospective inception cohort of 433 dialysis patients
- Reported results showed
  - No change in blood pressure with conventional thrice-weekly HD therapy

Left Ventricular Hypertrophy
Clinical Consequences of Increased Left Ventricular Mass

The impaired ventricular function present in Left Ventricular Hypertrophy can actually simulate a vicious cycle:

- May cause LVH progression
- Complicated by ESRD uremic risk factors.
More Frequent Hemodialysis During the Day or Overnight is Associated With Significantly Better Left Ventricular Hypertrophy Control\(^1,2\)

- 70-90% of patients exhibit Left Ventricular Hypertrophy (LVH) of varying degrees of severity prior to the initiation of renal replacement therapy\(^3,4\)
- Many patients continue to exhibit LVH despite initiating dialysis\(^5\)
- Persistence of vascular volume increase due to inadequate ultrafiltration has been reported as a major factor in the failure of LVH to regress\(^5\)
- LVH represents a major predictor of the development of cardiovascular complications


FHN Daily Trial: Significant Reduction in Left Ventricular Mass

The FHN Trial Group. In-Center Hemodialysis Six Times per Week versus Three Times per Week. The New England Journal of Medicine. 010:363;2287-2300.

Mean Change:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect Measure</th>
<th>Estimated Standardized Effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass</td>
<td>Mean decrease</td>
<td></td>
</tr>
<tr>
<td>Physical-health composite score</td>
<td>Mean increase</td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>Mean decrease</td>
<td></td>
</tr>
<tr>
<td>Predialysis albumin</td>
<td>Mean increase</td>
<td></td>
</tr>
<tr>
<td>Predialysis phosphorus</td>
<td>Mean decrease</td>
<td></td>
</tr>
<tr>
<td>ESA dose</td>
<td>Mean decrease in log</td>
<td></td>
</tr>
<tr>
<td>Predialysis systolic blood pressure</td>
<td>Mean decrease</td>
<td></td>
</tr>
<tr>
<td>Trail Making Test Part B</td>
<td>Negative log relative risk</td>
<td></td>
</tr>
<tr>
<td>Death or hospitalization unrelated to vascular access</td>
<td>Negative log hazard ratio</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Ventricular Mass (g)</th>
<th>Baseline</th>
<th>Month 12</th>
<th>Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>141 ± 49</td>
<td>138 ± 52</td>
<td>-2.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequent</td>
<td>142 ± 59</td>
<td>125 ± 46</td>
<td>-16.4</td>
<td></td>
</tr>
</tbody>
</table>

11% DECREASE IN LV MASS During study period
Canadian Home Nocturnal Hemodialysis Trial
Left Ventricular Mass Regression

5-6 NIGHTS/WEEK, ≥6 HOURS/TREATMENT
AS COMPARED TO CONVENTIONAL HEMODIALYSIS

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nocturnal Hemodialysis(^b) (n = 26)</th>
<th>Conventional Hemodialysis(^b) (n = 25)</th>
<th>Between-Group Comparison (95% CI)(^c)</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exit</td>
<td>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)(^d)</td>
</tr>
<tr>
<td>LV mass, mean (SD), g/m(^2)</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exit</td>
<td>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)(^d)</td>
</tr>
</tbody>
</table>

MORE FREQUENT HOME NOCTURNAL HD ASSOCIATED WITH AN 8% DECREASE IN LV MASS
Similar LV mass regression observed in HHD patients with benefits attributable to better fluid management

CONVENTIONAL HD SHOWED INSIGNIFICANT LEFT VENTRICULAR MASS REGRESSION
Although the short daily FHN trial showed a 2% improvement in LV mass, Culleton’s nocturnal trial reported no significant improvement

Long-term Evolution of Left Ventricular Mass in Dialysis Patients

30-Month Follow-Up

- Foley et al conducted echocardiograms taken at baseline, 2, 18, 30 and 43-months of 433 dialysis patients.
- Reported results showed
  - Small decrease in Left Ventricular Hypertrophy associated with conventional thrice-weekly HD therapy.

Figure 1: Foley, et al., Long-term evolution of cardio myopathy in dialysis patients.
Stunning Consequences of Thrice-Weekly IHD
Frequent Hemodialysis Schedules are Associated with Reduced Levels of Dialysis-Induced Cardiac Injury (Myocardial stunning)

Study Design
- Cross-sectional, observation study

Patient Population
- 18+ years of age, on current therapy for 3 months
- Patients with severe LV or heart transplant were excluded

Location:
- Satellite Dialysis and WellBound, Mountain View, CA

Enrollment Size
- 46 well-matched subjects
- 12 Conventional in-center hemodialysis (not studied on the day after 2 day intradialytic interval)
- 12 Center Short-daily (5+/week)
- 12 Home more frequent (5+/week)
- 10 Home more frequent Nocturnal (5+/week)
Intradialytic Hypotension Increases with Conventional In-Center Hemodialysis

Methods

- Pre-dialysis BP measurements after 5 minutes of rest
- Subsequent BP measurement taken 15 minutes before the end of treatment (“peak stress”)

Results

- Strong correlation between ultrafiltration volume and intradialytic hypotension

CHD3=Conventional In-Center HD (3x/week), CSD=Center Short Daily (5+x/week), HSD=Home Short Daily (5+x/week), HN=Home Nocturnal (5+x/week)

Jefferies et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Nephrol 2011 June, 6(6); 1326-1332.
Myocardial Stunning is Cardiac Injury Associated with Regional Wall Motion Abnormalities

- Rapid removal of fluid can induce RWMAs
- Repeated occurrences of myocardial stunning results in permanent injury resulting in heart failure

CHD3=Conventional In-Center HD (3x/week), CSD=Center Short Daily (5+x/week), HSD=Home Short Daily (5+x/week), HN=Home Nocturnal (5+x/week)

Jefferies et.al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Nephrol 2011 June, 6(6); 1326-1332.
Fluid Dynamics in the Body

Compartments
- Intracellular: 2/3
- Extracellular: 1/3
  - Plasma: 20%
  - Interstitial: 80%

Hemodialysis only directly cleans the blood
- Blood is only about 15% of total body mass
- The majority of the excess fluid must shift from the other compartments into the blood to be removed
Ultrafiltration Rate Implications for Patient Care

- 2/3 of patients suffer from recurrent HD-induced ischemic injury\(^1\)
- The way that the heart moves changes as parts of the heart die

---

\(^1\)Jefferies et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Nephrol 2011 June, 6(6); 1326-1332.
Stunning Consequences of Thrice-Weekly In-Center Hemodialysis

“Although patients may look comfortable during hemodialysis, in reality this innocuous-appearing procedure has much more stunning effect than meets the eye.”

Dr. Joel Glickman

Facts

- Not reported in PD patients
- Much less prevalent in more frequent HHD patients than IHD patients and correlated with ultrafiltration rates

Conclusion

- High ultrafiltration rates were associated with increased all-cause and cardiovascular mortality
  - Rates greater than 10 - 13 mL/kg/hr were associated with congestive heart failure
Myocardial Stunning May Be Due to the Treatment Itself

- Intravascular volume contraction may begin to occur during HD if fluid is removed at a rate >5–6 mL/kg/hour.
- Reduced organ perfusion is risked if fluid is removed during HD at a rate >10 mL/kg/hour.
- Reduced organ perfusion will likely result if fluid is removed during HD at a rate >13 mL/kg/hour.

<table>
<thead>
<tr>
<th>Factor associated with presence of myocardial stunning</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF volume during HD of 1L</td>
<td>5.1</td>
</tr>
<tr>
<td>UF volume during HD of 1.5L</td>
<td>11.6</td>
</tr>
<tr>
<td>UF volume during HD of 2L</td>
<td>26.2</td>
</tr>
<tr>
<td>Maximum SBP reduction during HD of 10 mmHg</td>
<td>1.8</td>
</tr>
<tr>
<td>Maximum SBP reduction during HD of 20 mmHg</td>
<td>3.3</td>
</tr>
<tr>
<td>Maximum SBP reduction during HD of 30 mmHg</td>
<td>6.0</td>
</tr>
</tbody>
</table>

HD-induced RWMA Patient Survival After 12 Months

- LVEF at rest had significantly deteriorated in patients with RWMAs but remained unchanged in those patients without
  - (62.1, 11.4% versus 54.7, 10.1%, $P = 0.0008$)
- The presence of HD-induced RWMAs was associated with increased relative mortality at 12 months ($P = 0.019$)
- Patient Deaths
  - With HD-induced RWMAs: 13
  - Without HD-induced RWMAs: 1

Death resulted overwhelmingly from cardiovascular causes.
Frequency and Duration Matter
A Question of Balance

- Shorter post-dialysis recovery time
- Reduced mortality
- Reduced cardiovascular hospitalization
- Improved blood pressure control
- Improved quality-of-life
- Reduced depression
- Improved sleep
- Reduced restless leg
- Improved sex life
- Ability to go back to work
- Reduced cachexia (withdrawal from dialysis)

Vascular Access Complications

- Technique survival
  - But better than PD

Infection risk
  - Similar to, if not better than, PD with substantial opportunities for technique improvement
Frequency and Duration Matter

Duration matters, even with more frequent therapy

**Shorter**  
**Longer**

**Lower Risk of Death**
Performing more frequent nocturnal hemodialysis has shown similar 5-year survivability as deceased donor transplantation.¹

**Better Cardiovascular Outcomes**
Patients performing more frequent hemodialysis with lower UF volumes resulted in a mean reduction of Regional Wall Motion Abnormalities (RWMAs), which are associated with elevated mortality risk, per patient as compared to conventional, thrice-weekly therapy with higher UF volumes.²

**Improved Phosphorus Control and Middle Molecule Clearance**
Compared to conventional thrice weekly in-center hemodialysis, more frequent hemodialysis is associated with improved control of hyperphosphatemia.³ Nocturnal therapy is associated with greater clinical benefits with significantly higher total cleared volume both of Phosphorus and β2-microglobulin.⁴

**More Energy and Vitality**
More frequent dialysis, during the day or overnight, provides significant and wide-reaching therapeutic benefits. Quicker time to recovery.⁵ Less dietary restriction.⁶⁻⁷ Better blood pressure control with fewer medications.⁸⁻⁹
Frequency and Duration Matter

References


2Jefferies et.al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Nephrol 2011 June, 6(6); 1326-1332.


What Nephrologists Would Choose for Themselves Should be Considered

- A significant majority of nephrologists agree…
  - Home dialysis therapies are an effective alternative to in-center treatments

- Broader access to home therapies is essential
  - 26% of ESRD providers offer home hemodialysis
  - 49% are certified to offer PD

Dialysis Facility Compare Website provided by the Centers for Medicare & Medicaid Services. Updated July 14, 2014.