IMPROVING lives.

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





INVENTING a movement.

INSPIRING everyone.



HOME HEMODIALYSIS CLINICAL EVIDENCE

PART 1: CARDIAC INJURY AND DIALYSIS

MSTAGE[®]

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



USRDS 2013 Annual Data Report, Figure 4.1 (continued; Volume 2,Incident & prevalent dialysis patients, 2009–2011.

Cardiovascular Mortality Significantly Higher in Dialysis Patients vs. General Population



Current Dialysis Situation by Modality in the United States



PARTICIPATION 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 options¹

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...





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

		HNHD	HHD	PD	CHD
Hypertensive / Blood	•	5% ▼	7% ▼	3%▲	≤1%▼
Pressure Control		Systolic BP¹	Systolic BP ²	Systolic BP ³	Systolic BP ^{1,2}
Occurrence of	•	50%	75%	-	100%
Myocardial Stunning		Patients⁵	Patients⁵	Not reported	Patients⁵
Regional Wall	۷	38% ▼	31%▼	-	Index
Motion Abnormalities		RWMAs⁵	RWMAs⁵	Not reported	RWMAs
Left Ventricular Mass	•	8%▼	11%▼	14%▲	2%▼
Index		LV Mass ³	LV Mass ²	LV Mass ³	LV Mass ²

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

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

²FHN Trial Group. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363(24):2287-2300.

³Foley, et al., Long-term evolution of cardio myopathy in dialysis patients. Kidney International, Vol. 54 (1998), pp. 1720–1725.

⁴Culleton 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. ⁵Jefferies et.al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (Myocardial stunning). Clin J Am Soc Neprhol 2011 June, 6(6); 1326-1332.



Blood Pressure Control



More Frequent Hemodialysis Associated with Better Blood Pressure Control

AS COMPARED TO CONVENTIONAL HEMODIALYSIS

Qutcome	No. with Data	Baseline	12 Months	Change from Baseline to 12 Months	Adjusted Mean (±SE) Change from Baseliner	Difference in Change (Frequent- Conventional) (95% CD	P Value
Erythropoiesis-stimulating agents — EPO equivalent units $^{\dagger \dagger}$		Dustille					1 Vulue
Conventional hemodialysis	90	57,070±65,456	53,093±63,552	-3,976±69,525	-5%±10%		0.24
Frequent hemodialysis	103	56,176±102,288	41,877±44,636	-14,299±76,191	-18%±8%		
Weekly average predialysis systolic blood pressure — mm Hg							
Conventional hemodialysis	93	146±18	147±18	0.9±16.2	0.9±1.6	-10.1 (-14.3 to -6.0)	< 0.001
Frequent hemodialysis	104	147±19	137±19	-9.7±18.2	-9.2±1.5		
Antihypertensive agents consumed — no.							
Conventional hemodialysis	92	2.80±1.69	2.58±1.68	-0.23±1.35	—		<0.001##
Frequent hemodialysis	3	2.69±1.80	1.82±1.73	-0.87±1.85			
More Frequent Hemodialysis Associated with a 7% decrease in systolic BLOOD PRESSURE				ional Hemod ant blood f	DIALYSIS REP PRESSURE CO	PORTED	

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 ^e		
Characteristic	Nocturnal Hemodialysis ^b (n = 26)	Conventional Hemodialysis ^b (n = 25)	Between-Group Comparison (95% Cl) ^c
Blood pressure, mean (SD), mm Hg			
Systolic Baseline	129 (23)	135 (19)	-6 (-17 to 6)
Exit	122 (23)	139 (20)	–17 (–28 to –4)
Change	-7 (29)	4 (17)	–11 (–24 to 2)
Diastolic Baseline	75 (14)	77 (16)	-2 (-10 to 7)
Exit	68 (16)	75 (12)	-7 (-15 to 1)
Change	-7 (16)	-2 (12)	–5 (–13 to 2)

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

Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. 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.

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 thriceweekly 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 dialysis⁵
- Persistence of vascular volume increase due to inadequate ultrafiltration has been reported as a major factor in the failure of LVH to regress⁵
- LVH represents a major predictor of the development of cardiovascular complications

¹Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. 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. ²Ayus JC, Mizani MR, Achinger SG, et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. J Am Soc Nephrol. 2005;16(9):2778-2388.

³Zoccali C, et al., Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. J Am Soc Nephrol. 2001;12:2768-2774

⁴McMahon LP, Roger SD, Levin A. Development, prevention, and potential reversal of left ventricular hypertrophy in chronic kidney disease. J Am Soc Nephrol. 2004;15:1640-1647. ⁵Richard J. Glassock, Roberto Pecoits-Filho, Silvio Barbareto, Increased Left Ventricular Mass in Chronic Kidney Disease and End-Stage Renal Disease: What Are the Implications? Dialysis & Transplantation. January 2010: 1-4

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.

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.

	Characteristic	Nocturnal Hemodialysis ^b (n = 26)	Conventional Hemodialysis ^b (n = 25)	Between-Group Comparison (95% Cl) ^c
LV	mass, mean (SD), g Baseline	177.4 (51.1)	181.5 (92.3)	-4.1 (-49.5 to 41.3)
	Exit	163.6 (45.2)	183.0 (84.2)	-19. 4 (-60.5 to 21.7)
	Change	-13.8 (23.0)	1.5 (24.0)	–15.3 (–29.6 to –1.0) ^d
LV	mass, mean (SD), g/m ² Baseline	92.4 (26.6)	101.8 (50.6)	-9.4 (-34.0 to 15.2)
	Exit	85.3 (23.2)	102.8 (46.1)	-17. 5 (-39.8 to 4.6)
	Change	-7.1 (12.4)	1.0 (14.1)	–8.1 (–16.2 to –0.1) ^d

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

Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. Effect of frequent nocturnal hemodialysis vs conventional A hemodialysis on left ventricular mass and quality of life. JAMA. September 2007; Vol 298, No. 11, 1291 – 1299.

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 thriceweekly HD therapy



Figure 1: Foley, et al., Long-term evolution of cardio myopathy in dialysis patients. Kidney International, Vol 54 (1998):1720-1725



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



Change in systolic BP (predialysis to peak stress).

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 dialysisinduced cardiac injury (Myocardial stunning). Clin J Am Soc Neprhol 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 dialysisinduced cardiac injury (Myocardial stunning). Clin J Am Soc Neprhol 2011 June, 6(6); 1326-1332.

26

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

TOTAL BODY MASS:

Medical Education Institute, Inc. in cooperation with the National Association of Nephrology Technicians/Technologists (NANT) with review and approval by Jim Curtis, CHT, CCHT, nationally recognized dialysis technician trainer and consultant.



Ultrafiltration Rate Implications for Patient Care

- 2/3 of patients suffer from recurrent HDinduced ischemic injury¹
- The way that the heart moves changes as parts of the heart die

Image source: Flythe JE, Brunelli SM: The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. Semin Dial 24(3):259-265, 2011



¹Jefferies et.al. Frequent hemodialysis schedules are associated with reduced levels of dialysisinduced cardiac injury (Myocardial stunning). Clin J Am Soc Neprhol 2011 June, 6(6); 1326-1332.

Stunning Consequences of Thrice-Weekly In-Center Hemodialysis

"Although patients may look comfortable during hemodialysis, in reality this innocuousappearing 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.

Factor associated with presence of myocardial stunning	Odds Ratio
UF volume during HD of 1L	5.1
UF volume during HD of 1.5L	11.6
UF volume during HD of 2L	26.2
Maximum SBP reduction during HD of 10 mmHg	1.8
Maximum SBP reduction during HD of 20 mmHg	3.3
Maximum SBP reduction during HD of 30 mmHg	6.0

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

Home/More Frequent

Hemodialysis

Frequency and Duration Matter

Duration matters, even with more frequent therapy

SHORTER

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 ß2-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

LONGER

Frequency and Duration Matter References

¹Pauly RP, Gill JS, Rose CL, Asad RA, Chery A, Pierratos A, Chan CT. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. Nephrol Dial Transplant. 2009;24:2915-2919.

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

³FHN Trial Group. Effects of Frequent Hemodialysis on Measures of CKD Mineral and Bone Disorder. J Am Soc Nephrol. 23:727–738, 2012.

⁴Eloot S, Van Biesen W, Dhondt A, Van de Wynkele H, Glorieux G, Verdonck P, Vanholder R. Impact of hemodialysis duration on the removal of uremic retention solutes. Kidney International. 2008, 73, 765-770 (Nocturnal)

⁵Heidenheim PA, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. Am J Kidney Dis. 2003;42(S1)(S1):S36-S41.

⁶Charra B, Charzot C. The neglect of sodium restriction in dialysis patients: a short review. Hemodial Int 2003;7(4):342-347.

⁷Pierratos A. Daily nocturnal home hemodialysis. Kidney Int 2004;65(5)1975-1986.

⁸Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. 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. (Nocturnal)

⁹Chan C, et al. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialsys. Kidney International, 2002;61:2235-2239. (Nocturnal)

What Nephrologists Would Choose for Themselves Should be Considered



90% would choose home dialysis

Mendelssohn	4.5 Sc	ALE		4.5
American Journal of	Nephr 4.3 - 1	ologist ra Nost Und	ted HHD ER-UTILIZE	4.3
Kidney Disease ²		2	3	4

- A significant majority of nephrologists agree...
 - Home dialysis therapies are an effective alterative to in-center treatments
- Broader access to home therapies is essential
 - 26% of ESRD providers offer home hemodialysis
 - 49% are certified to offer PD³

¹Schiller B, Neitzer A, Doss S. Perceptions about renal replacement therapy among nephrology professionals. Nephrol News Issues. 2010; 24(10):36-44. ²Mendelssohn DC, et al. What do American Nephrologists think about dialysis modality selection? Am J Kidney Dis. 2001;37(1):22-29. ³Dialysis Facility Compare Website provided by the Centers for Medicare & Medicaid Services. Updated July 14, 2014.





350 Merrimack Street • Lawrence, MA 01843 • www.nxstage.com

© 2016 NxStage Medical, Inc. NxStage is a registered trademark of NxStage Medical, Inc. PureFlow and System One are trademarks of NxStage Medical, Inc. CAUTION: Federal law restricts this device to sale by or on the order of a physician. APM1532 Rev. A