Journal Club du 25 novembre 2010

The NEW ENGLAND JOURNAL of MEDICINE

In-Center Hemodialysis Six Times per Week versus Three Times per Week

The FHN Trial Group

N Engl J Med 2010

Frequent Hemodialysis Network

1. Determinants of cardiac autonomic dysfunction in ESRD.
Chan CT, Levin NW, Chertow GM, Larive B, Schulman G, Kotanko P; Frequent Hemodialysis Network Daily Trial Group.
Clin J Am Soc Nephrol. 2010 Oct;5(10):1821-7. Epub 2010 Jul 8.
PMID: 20616163 [PubMed - in process]
Related citations Remove from clipboard

2. Recruitment and training for home hemodialysis: experience and lessons from the nocturnal dialysis trial.
Pipkin M, Eggers PW, Larive B, Rocco MV, Stokes JB, Suri RS, Lockridge RS Jr; Frequent Hemodialysis Network Trial Group.
Clin J Am Soc Nephrol. 2010 Sep;5(9):1614-20. Epub 2010 Jun 24.
PMID: 20576829 [PubMed - in process]
Related citations Remove from clipboard

3. Prevalence and correlates of cognitive impairment in hemodialysis patients: the frequent hemodialysis network trials.
Tamura MK, Larive B, Unruh ML, Stokes JB, Nissenson A, Mehta RL, Chertow GM; Frequent Hemodialysis Network Trial Group.
Clin J Am Soc Nephrol. 2010 Aug;5(8):1429-38. Epub 2010 Jun 24.
PMID: 20576825 [PubMed - in process]
Related citations Remove from clipboard

4. Effects of reduced intradialytic urea generation rate and residual renal clearance on modeled urea distribution volume and Kt/V in conventional, daily, and nocturnal dialysis.
Daugirdas JT, Depner TA, Greene T, Levin NW, Chertow GM, Rocco MV, Stokes JB; Frequent Hemodialysis Network (FHN) Trial Group.
Semin Dial. 2010 Jan-Feb;23(1):19-24.
PMID: 20331814 [PubMed - indexed for MEDLINE]
Related citations Remove from clipboard

5. Standard Kt/Vurea: a method of calculation that includes effects of fluid removal and residual kidney clearance.
Daugirdas JT, Depner TA, Greene T, Levin NW, Chertow GM, Rocco MV; Frequent Hemodialysis Network Trial Group.
Kidney Int. 2010 Apr;77(7):637-44. Epub 2010 Jan 27.
PMID: 20107428 [PubMed - indexed for MEDLINE]
Related citations Remove from clipboard

6. Solute clearances and fluid removal in the frequent hemodialysis network trials.
Greene T, Daugirdas JT, Depner TA, Gotch F, Kuhlman M; Frequent Hemodialysis Network Study Group; National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health.
Am J Kidney Dis. 2009 May;53(5):835-44. Epub 2009 Apr 1.
PMID: 19339093 [PubMed - indexed for MEDLINE]
Related citations Remove from clipboard

7. High-frequency hemodialysis: rationale for randomized clinical trials.
Kliger AS; Frequent Hemodialysis Network Study Group.
Clin J Am Soc Nephrol. 2007 Mar;2(2):390-2. Epub 2006 Dec 20. Review. No abstract available.
PMID: 17699439 [PubMed - indexed for MEDLINE] Free Article
Related citations Remove from clipboard

8. Frequent Hemodialysis Network (FHN) randomized trials: study design.
Suri RS, Garg AX, Chertow GM, Levin NW, Rocco MV, Greene T, Beck GJ, Gassman JJ, Eggers PW, Star RA, Ornt DB, Kliger AS; Frequent Hemodialysis Network Trial Group.
Kidney Int. 2007 Feb;71(4):349-59. Epub 2006 Dec 13.
PMID: 17164834 [PubMed - indexed for MEDLINE]
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Introduction

- fréquence? dose?
- physiological experiments, assessments of patient acceptance, feasability, logistics, and costs

EBPG guidelines on dialysis strategies *Nephrol Dial Transplant 2007*

The minimum frequency and dosage of dialysis is **three times per week**, **4 hours per treatment** for most patients. More frequent or longer dialysis is associated with **improved BP**, reduced dosage of erythropoiesis-stimulating agent, **better phosphorus control**, improved sleep, but increased costs if performed in-center.

Perl et al. *Am J Kidney Dis 2009*

1. Conventional hemodialysis (HD): Intermittent HD performed in-center for 4 hours three times a week
2. Intensive HD can be because of increased frequency or time
    a. **Quotidian HD**: Five to seven sessions per week («daily dialysis»)
        i. Nocturnal HD: Long nightly dialysis during sleep; often performed at home
        ii. **Short daily HD (SDHD)**: Shortened duration but more frequent
    b. Long intermittent HD: increased duration
        i. Nocturnal intermittent HD
        ii. Hemeral: (From the Greek *hemera* for days as opposed to night) long intermittent HD

Frequent Dialysis

Nocturnal versus conventional haemodialysis: Some current issues. *Nephrol Dial Transplant* 2009

More intensive hemodialysis. *Clin J Am Soc Nephrol* 2009

Ten years experience of in-center thrice weekly long overnight hemodialysis. *Clin J Am Soc Nephrol* 2009

Effects of nocturnal hemodialysis on melatonin rhythm and sleep-wake behavior *Am J Kidney Dis* 2009

Nocturnal haemodialysis increases pharyngeal size in patients with sleep apnoea and end-stage renal disease. *Nephrol Dial Transplant* 2008

Nocturnal haemodialysis is associated with improved vascular smooth muscle cell biology. *Nephrol Dial Transplant* 2009

Nocturnal hemodialysis does not improve overall measures of quality of life compared to conventional hemodialysis. *Kidney Int* 2009

Clinical effectiveness and quality of life of conventional haemodialysis versus short daily haemodialysis: A systematic review. *Nephrol Dial Transplant* 2008

Short daily haemodialysis: Survival in 415 patients treated for 1006 patient-years. *Nephrol Dial Transplant* 2008

Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transplant* 2009

Solute clearances and fluid removal in the frequent hemodialysis network trials. *Am J Kidney Dis* 2009

Utility and limitations of a multicenter nocturnal home hemodialysis cohort. *Clin J Am Soc Nephrol* 2008

INCLUSION CRITERIA

- Patients with end-stage renal disease requiring chronic renal replacement therapy
- Age > 13 years
- Achieved mean eKt/V > 1.0 for last two baseline hemodialysis sessions
- Weight > 30 kg

EXCLUSION CRITERIA

- Unable or unwilling to follow the study protocol for any reason (including mental incompetence)
- Unable or unwilling to provide informed consent or sign the Institutional Review Board-approved consent form
- Requires HD >3 times per week due to medical comorbidity (such as, but not limited to: systemic oxalosis or
- requiring total parenteral nutrition). Occasional ultrafiltration on a fourth day per week is not an exclusion criterion.
- Current pregnancy, or actively planning to become pregnant in the next 12 months
- History of poor adherence thrice weekly HD
- Inability to come for in-center HD 6 days per week, including inability to arrange adequate transportation
- Expected geographic unavailability at a participating HD unit for >2 consecutive weeks or >4 weeks total
- during the next 14 months (excluding unavailability due to hospitalizations)
- Currently in an acute or chronic care hospital
- Contraindication to heparin, including allergy or heparin induced thrombocytopenia
- Expectation that native kidneys will recover
- Residual renal clearance >3ml/min per 35 L
- Currently on daily or nocturnal HD or less than 3 months since the subject discontinued daily or nocturnal HD
- Less than 3 months since patient returned to HD after acute rejection resulting in allograft failure
- Current use of investigational drugs or participation in another clinical trial that contradicts or interferes with the
- therapies or measured outcomes in this trial
- Scheduled for living donor kidney transplant, change to peritoneal dialysis, or plans to relocate to a non-study
- center within the next 14 months
- Life expectancy less than 6 months
- Medical history that might limit the patient's ability to take the trial treatments and complete the 12 month
- duration of the study, including: currently receiving chemo or radiotherapy for a malignant neoplastic disease other than localized non-melanoma skin cancer, active systemic infection (including tuberculosis, disseminated fungal infection, active AIDS but not HIV), and cirrhosis with encephalopathy
- Medical conditions that would prevent the subject from performing the cardiac MRI procedure (e.g., inability to remain still for the procedure, a metallic object in the body, including cardiac pacemaker, inner ear (cochlear) implant, brain aneurysm clips, mechanical heart valves, recently placed artificial joints, and older vascular stents)
- Inability to communicate verbally in English or Spanish
- Vascular access being used for HD is a non-tunneled catheter

METHODS

Study protocole

multicenter, prospective, randomized parallel-group trial

January 2006 and March 2009, 11 university-based HD facilities in North America

frequent vs conventionnal

Intervention

Thrice weekly: 120 patients
Kt/V > 1.1 and session length 2.5 to 4 hours

Six weekly: 125 patients
Kt/V > 0.9 and session length 1.5 to 2.75 hours

Outcome

No adequate statistical power to assess individual end points of death, cause specific death, hospitalization, or other events

two composite coprimary outcomes
death or 12-month change in LVM
death or 12-month change in RAND 36-items

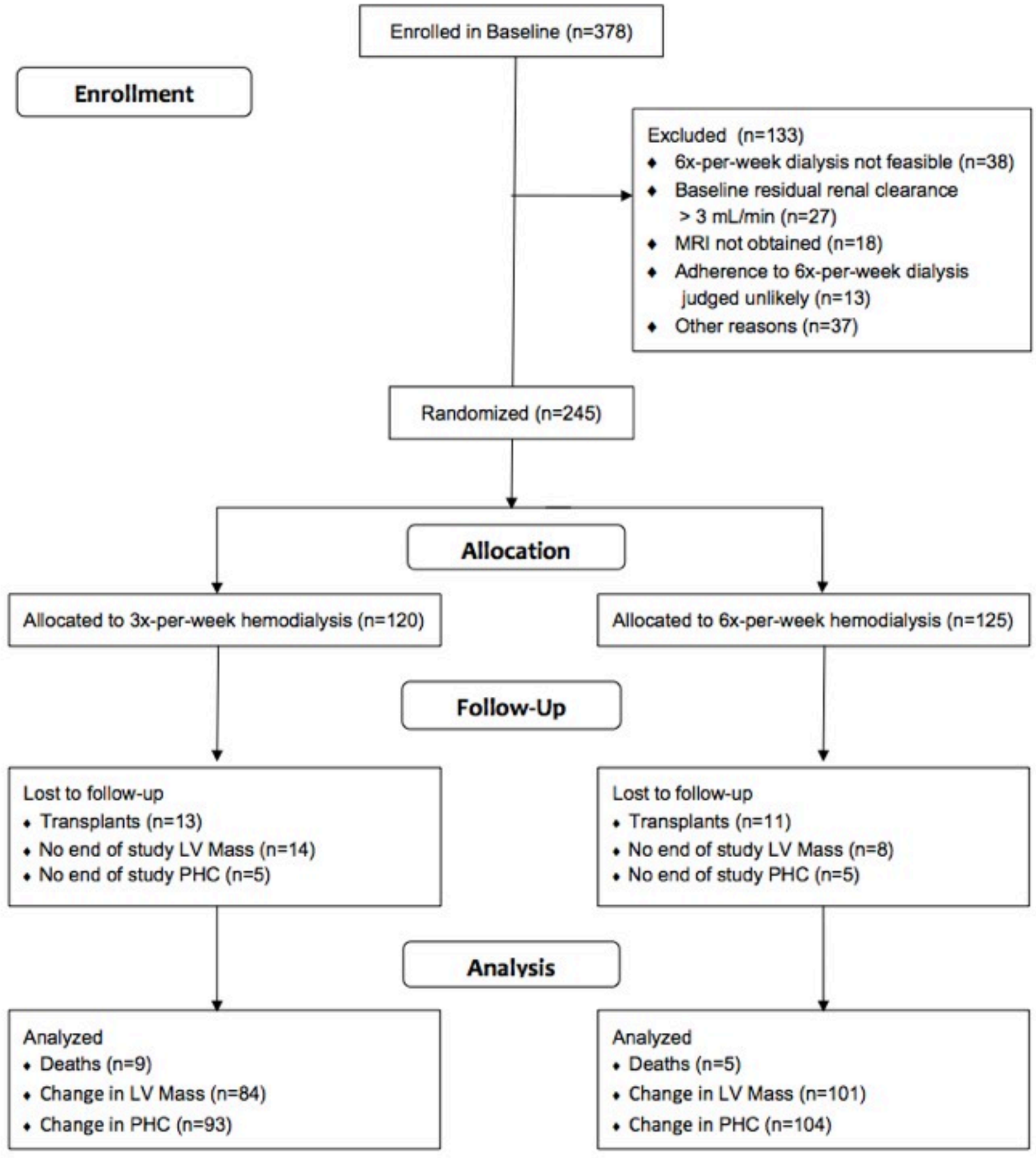

Enrolled in Baseline (n=378)
Enrollment
Excluded (n=133)
6x-per-week dialysis not feasible (n=38)
Baseline residual renal clearance > 3 mL/min (n=27)
MRI not obtained (n=18)
Adherence to 6x-per-week dialysis judged unlikely (n=13)
Other reasons (n=37)
Randomized (n=245)
Allocation
Allocated to 3x-per-week hemodialysis (n=120)
Allocated to 6x-per-week hemodialysis (n=125)
Follow-Up
Lost to follow-up
Transplants (n=13)
No end of study LV Mass (n=14)
No end of study PHC (n=5)
Lost to follow-up
Transplants (n=11)
No end of study LV Mass (n=8)
No end of study PHC (n=5)
Analysis
Analyzed
Deaths (n=9)
Change in LV Mass (n=84)
Change in PHC (n=93)
Analyzed
Deaths (n=5)
Change in LV Mass (n=101)
Change in PHC (n=104)

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	P Value
Age (yr)	52.0±14.1	48.9±13.6	0.07
Female sex (%)	39.2	37.6	0.80
Race or ethnic group (%)†			0.32
Black	44.2	39.2	
White	38.3	34.4	
Native American, Aboriginal Canadian, Alaskan Native, or First Nation	3.3	3.2	
Asian	4.2	8.8	
Native Hawaiian or other Pacific Islander	2.5	0.8	
Other or mixed	7.5	13.6	
Body-mass index‡	27.5±7.1	27.3±6.5	0.82
Weight after dialysis (kg)	78.7±20.5	77.6±20.6	0.68
Anthropometric volume (liters)§	39.5±8.3	39.3±8.1	0.90
Cause of end-stage renal disease (%)			0.89
Diabetic nephropathy	32.5	36.0	
Glomerulonephritis	19.2	19.2	
Hypertensive nephrosclerosis	20.0	21.6	
Polycystic kidney disease	5.0	3.2	
Other	23.3	20.0	

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	P Value
Duration of end-stage renal disease (%)			0.38
<2 yr	16.7	16.0	
2–5 yr	42.5	35.2	
>5 yr	40.8	48.8	
Coexisting medical conditions (%)			
Hypertension	87.3	91.5	0.12
Myocardial infarction	13.3	8.8	0.26
Heart failure	20.0	20.0	1.00
Atrial fibrillation	7.5	4.0	0.24
Peripheral arterial disease	8.3	12.0	0.34
Abdominal aortic aneurysm repair or bypass grafting	1.7	2.4	0.68
Stroke	7.5	7.2	0.93
Dementia	0.8	0.0	0.31
Tumor without metastases	6.7	1.6	0.04
Diabetes and complications of diabetes	41.7	40.0	0.79
Hemiplegia	0.8	1.6	0.59
Chronic pulmonary disease	4.2	4.8	0.81
Moderate or severe liver disease	0.8	0.8	0.98

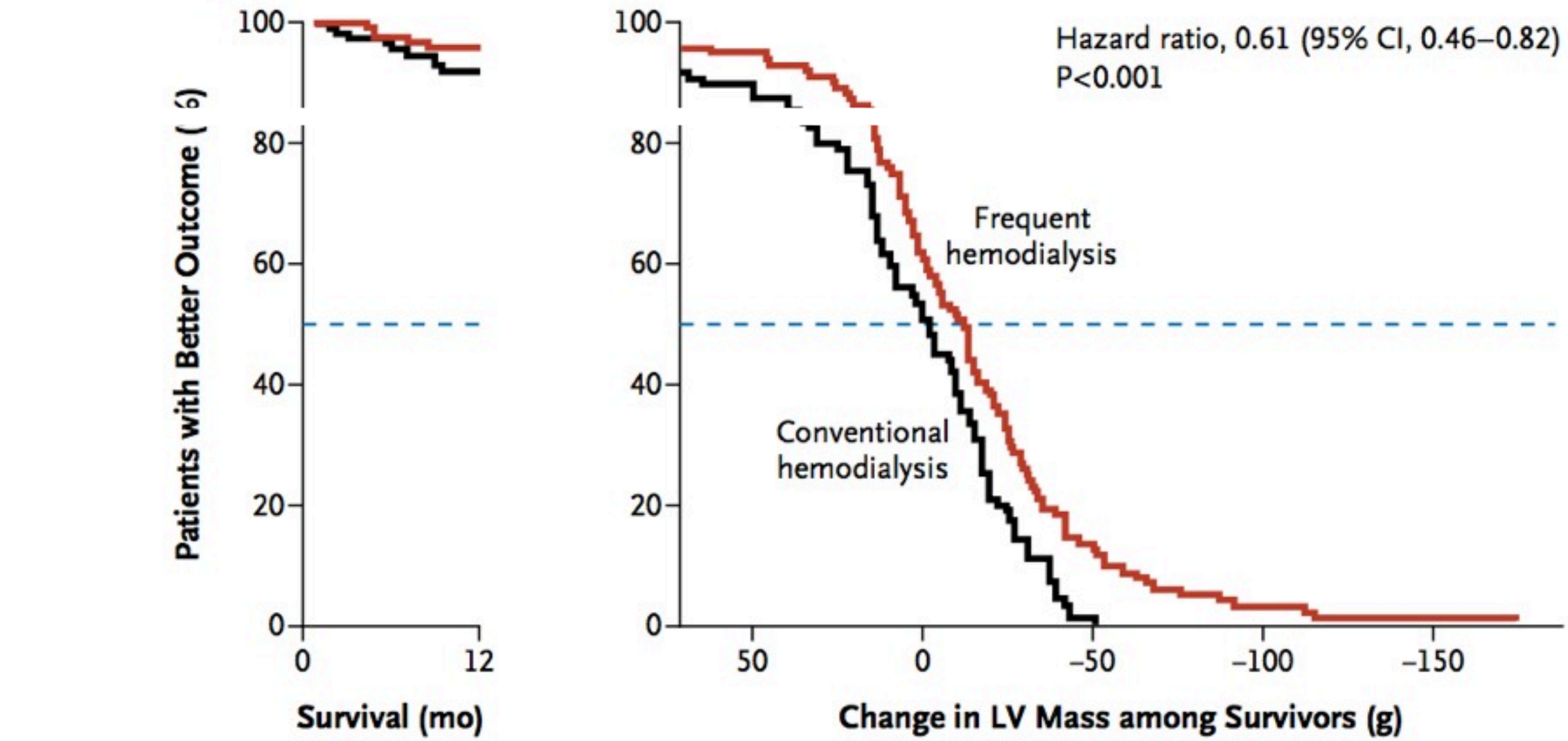
Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	P Value
Residual kidney function (%)			0.17
Anuria	60.0	72.0	
>0 to 1 ml/min	15.8	14.4	
>1 to 3 ml/min	24.2	13.6	
Diastolic blood pressure before dialysis (mm Hg)	78.4±11.7	81.0±11.2	0.08
Serum creatinine (mg/dl)¶	10.3±2.5	10.8±3.0	0.21
Kt/V_{urea}‖			
Weekly standard	2.54±0.39	2.50±0.31	0.45
Equilibrated	1.43±0.28	1.43±0.25	0.94
Dialysis access (%)**			0.86
Fistula	62.5	65.6	
Synthetic graft	18.3	16.0	
Catheter	19.2	18.4	

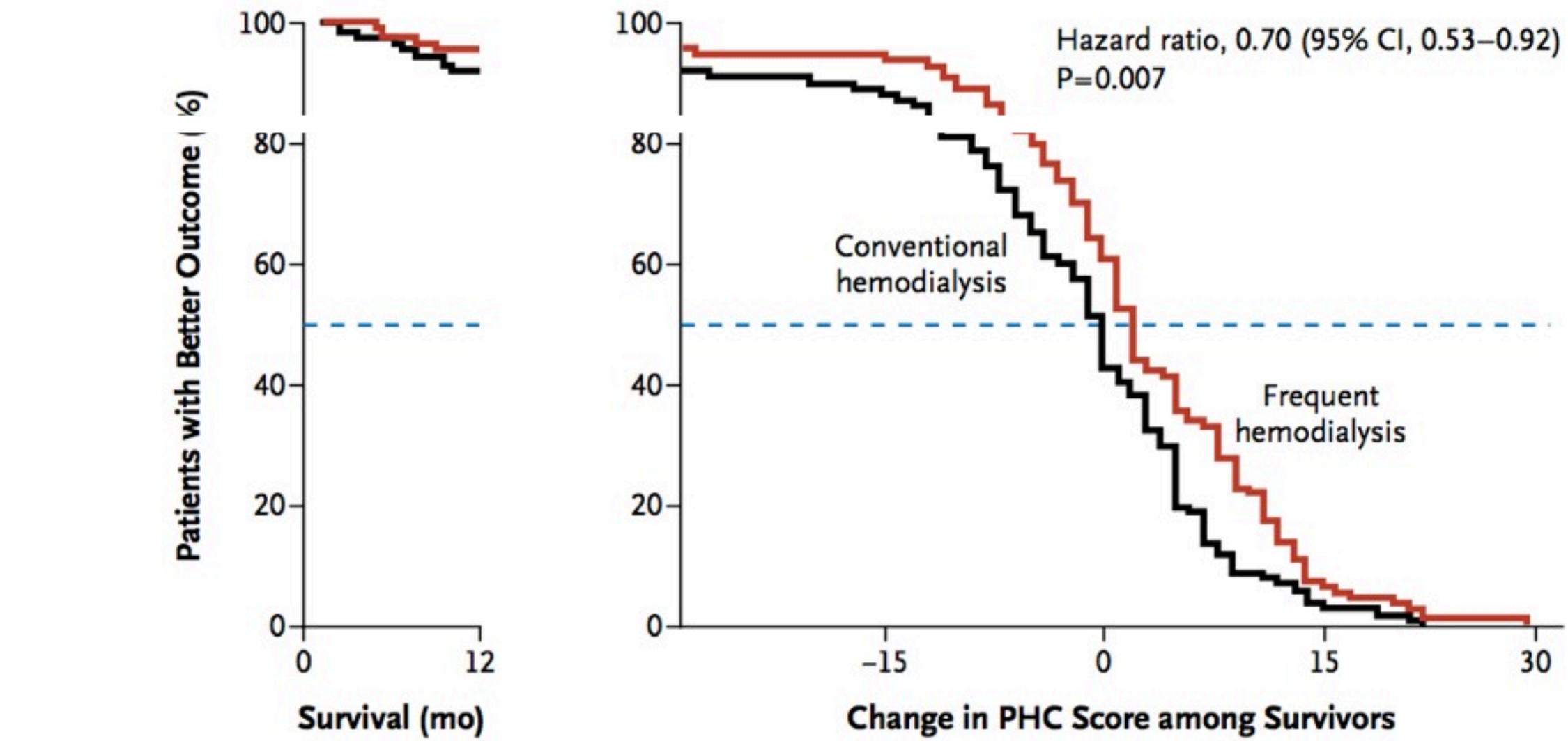
* Plus–minus values are means ±SD.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Anthropometric volume was calculated with the use of the Watson equation.
¶ To convert the values for creatinine to micromoles per liter, multiply by 88.4.
‖ The weekly standard Kt/V_{urea} is defined as the ratio of the generation rate of urea to the average urea concentration before dialysis and is commonly used to compare small-molecule clearance among different methods and schedules of dialysis.[22] The equilibrated Kt/V (the ratio of the equilibrated urea clearance during each dialysis session [Kt] to the pa-

Table 2. Features of Intervention.*

Variable	Conventional Hemodialysis (N=120)	Frequent Hemodialysis (N=125)	Ratio of Means (Frequent vs. Conventional)	P Value
Hemodialysis treatments per week (no.)	2.88±0.39	5.17±1.11	1.80	<0.001
Expected treatments attended (% of patients)†				
>80%	94.9	77.7	—	<0.001
65–80%	3.4	8.0	—	
<65%	1.7	14.4	—	
Time per dialysis session (min)	213±28	154±25	0.72	<0.001
Total dialysis time per week (hr)	10.4±1.6	12.7±2.2	1.23	<0.001
Blood flow rate (ml/min)	402±41	396±42	0.99	0.26
Dialysate flow rate (ml/min)	710±106	747±68	1.05	0.001
Dialyzer urea clearance (ml/min)	269±22	271±21	1.01	0.47
Ultrafiltration				
Per session (liters)	3.06±0.99	2.12±0.74	0.69	<0.001
Per session (% of weight after dialysis)	3.99±1.26	2.83±1.00	0.71	<0.001
Per week (liters)	8.99±3.03	10.58±3.83	1.18	<0.001
Kt/V_{urea}‡				
Total weekly standard	2.57±0.26	3.60±0.57	1.40	<0.001
Dialysis weekly standard	2.49±0.27	3.54±0.56	1.42	<0.001
Equilibrated per session	1.41±0.21	1.06±0.21	0.75	<0.001



Favorable change in coprimary outcomes



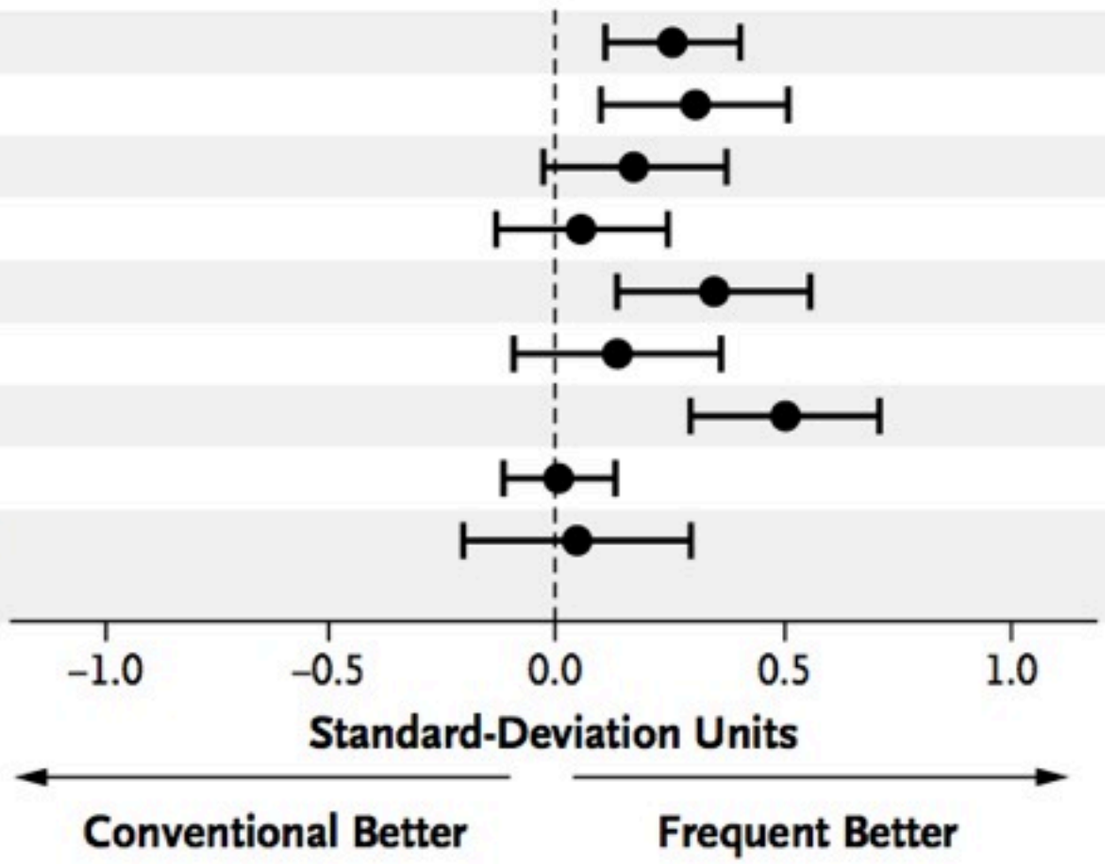
Favorable change in coprimary outcomes

Table 3. Secondary Outcomes.*

Outcome	No. with Data†	Baseline	12 Months	Change from Baseline to 12 Months	Adjusted Mean (±SE) Change from Baseline‡	Difference in Change (Frequent–Conventional) (95% CI)	P Value
Left ventricular mass — g§							
Conventional hemodialysis	84	141±49	138±52	−2.4±25.9	−2.6±3.2	−13.8 (−21.8 to −5.8)	<0.001
Frequent hemodialysis	101	142±59	125±46	−16.3±35.3	−16.4±2.9		
Physical-health composite score¶							
Conventional hemodialysis	93	38.5±9.3	38.5±9.6	0.1±8.7	0.2±0.8	3.2 (1.0 to 5.4)	0.004
Frequent hemodialysis	104	38.4±11.0	41.7±10.7	3.3±8.9	3.4±0.8		
Beck Depression Inventory‖							
Conventional hemodialysis	88	12.4±9.0	12.2±9.9	−0.2±7.7	−0.4±0.7	−1.6 (−3.4 to 0.3)	0.10
Frequent hemodialysis	101	12.6±8.7	10.4±8.5	−2.2±6.5	−2.0±0.7		
Predialysis albumin — g/dl							
Conventional hemodialysis	94	3.98±0.44	3.96±0.40	−0.02±0.36	−0.02±0.03	0.02 (−0.06 to 0.10)	0.56
Frequent hemodialysis	103	3.99±0.37	4.00±0.36	−0.01±0.31	0.01±0.03		
Predialysis phosphorus — mg/dl**							
Conventional hemodialysis	94	5.68±1.55	5.65±1.75	−0.03±1.54	−0.08±0.14	−0.56 (−0.91 to −0.22)	0.002
Frequent hemodialysis	102	5.88±1.65	5.24±1.20	−0.63±1.60	−0.64±0.14		
Erythropoiesis-stimulating agents — EPO equivalent units††							
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	103	2.69±1.80	1.82±1.73	−0.87±1.85	—		

C Main Secondary Outcomes

Outcome	Effect Measure
LV mass	Mean decrease
Physical-health composite score	Mean increase
Beck Depression Inventory score	Mean decrease
Predialysis albumin	Mean increase
Predialysis phosphorus	Mean decrease
ESA dose	Mean decrease in log
Predialysis systolic blood pressure	Mean decrease
Trail Making Test Part B	Negative log relative risk
Death or hospitalization unrelated to vascular access	Negative log hazard ratio



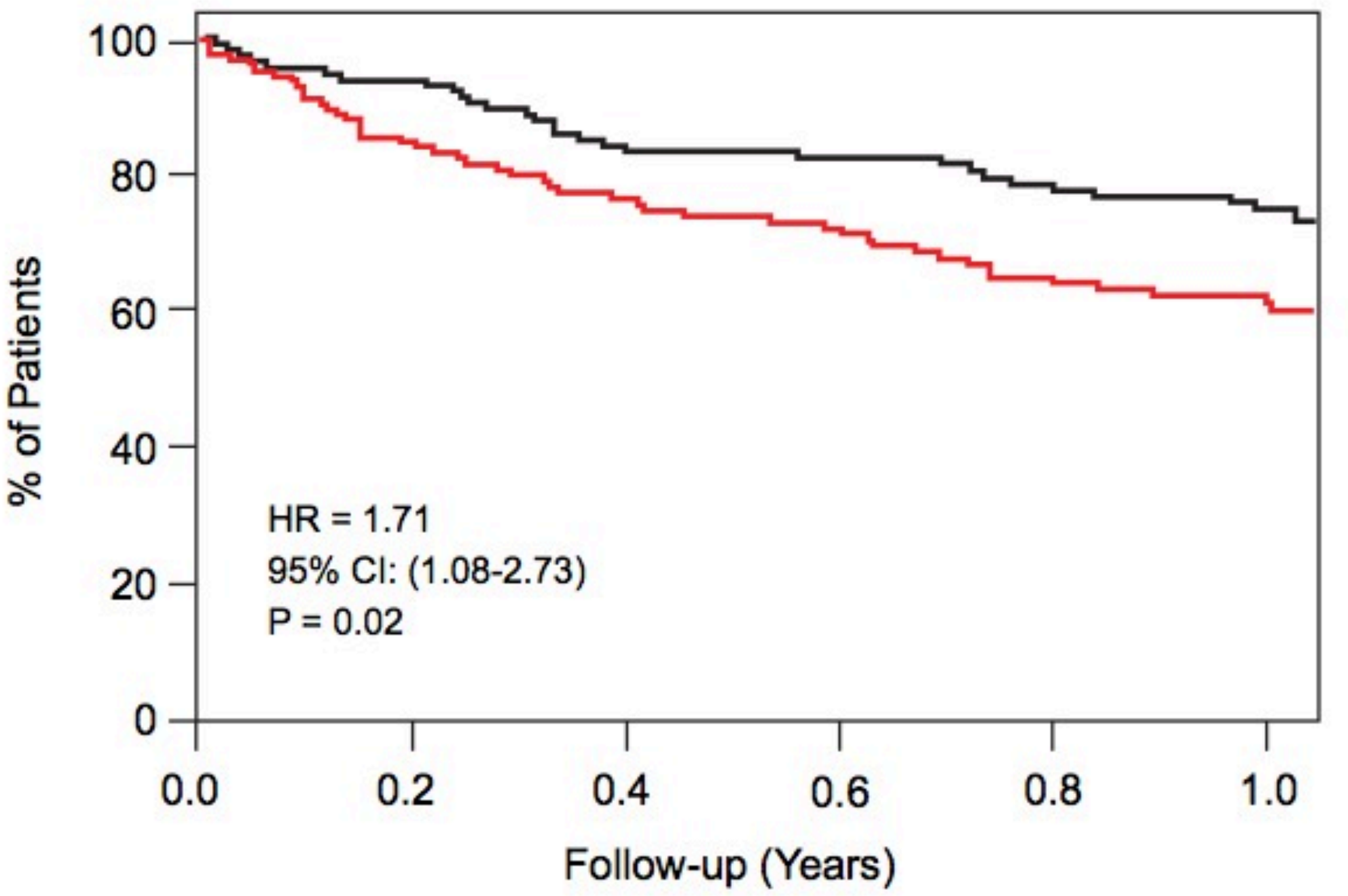
Significant effect: LV mass, RAND-36, phosphorus, predialysis systolic blood pressure

Table 4. Adverse Events during the 12-Month Follow-up Period of the Study.*

Outcome	Conventional Hemodialysis (N=120)		Frequent Hemodialysis (N=125)		Hazard Ratio (95% CI)	P Value
	no. of events	*no. of patients with event*	*no. of events*	*no. of patients with event*		
Death	9		5		—	—
All hospitalizations	114	47	109	58	0.88 (0.60–1.28)	0.50
Unrelated to vascular access	90	44	79	47	0.80 (0.53–1.21)	0.30
Related to vascular access	24	14	30	20	0.99 (0.54–1.82)	0.97
Cardiovascular-related	15	12	17	15	0.83 (0.44–1.59)	—
Infection related	27	20	27	23	0.83 (0.49–1.40)	—
All interventions related to vascular access	65	29	95	47	1.35 (0.84–2.18)	0.22
Correction of access failure	23	15	19	15	0.71 (0.35–1.44)	0.35
Other procedures	42	21	76	38	1.71 (0.98–2.97)	0.06
Episodes of hypertension†	470	87	724	99	—	—
Hypokalemia						
Potassium <3.0 mmol/liter	0	0	0	0	—	—
Potassium <3.5 mmol/liter	6	5	13	8	—	0.57‡
Hypophosphatemia§	9	7	15	9	—	0.80‡

* The hazard ratios and P values for rates of events (including multiple events per patient) between the frequent-hemodialysis group and the conventional-hemodialysis group were calculated with the use of the Andersen–Gill model, except where otherwise noted.
† The percentage of dialysis treatments with recorded hypotensive episodes, defined as the need for a lower ultrafiltration rate, reduced blood flow, or saline administration to ameliorate hypotension, was 10.9% in the frequent-hemodialysis group and 13.6% in the conventional-hemodialysis group (P=0.04 with the use of generalized estimating equations).
‡ The P values for the comparison of the number of patients with at least one event of hypokalemia or hypophosphatemia were calculated with the use of Fisher's exact test.
§ Hypophosphatemia was defined as a phosphorus concentration of less than 2.17 mg per deciliter (0.7 mmol per liter).

Time to First Vascular Access Intervention



Comparaison avec HEMO (2002, 1846 patients, spKt/V 1.3 vs 1.7)

Limitation car pas d'effet sur mortalité Postule que diminution masse VG = diminution mortalité Button-hole?