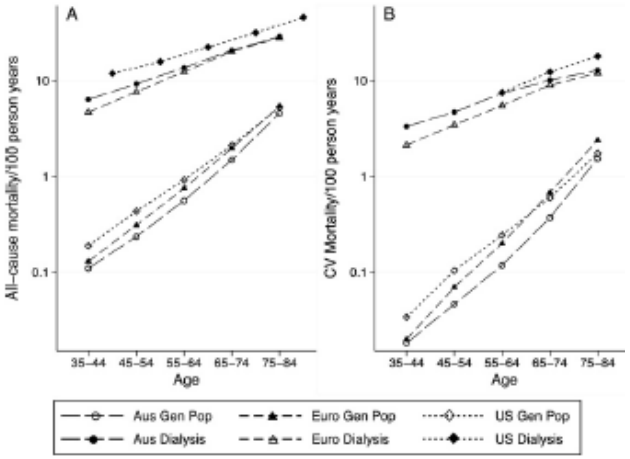


Hemodialysis: frequency, duration, and location

KDIGO Controversies Conference

Paris, October 2011

Jonathan Craig

With thanks to Kevan Polkinghorne, Peter Kerr, Carmel Hawley, Vlado Perkovic, Giovanni Strippoli and Meg Jardine

Disclosure of interest

- I am a skeptic of claims of benefit
- I know little about hemodialysis
- I am a paediatrician
- My father was on hemodialysis

Standard EBM/Guidelines framework: PICO

- Population
  - Stage IV cannot/do not want a kidney transplant
  - HD the preferred option
- Outcome
  - What problem are we trying to fix?
  - Why are we here in Paris?
- Intervention/Comparator
  - >3 versus 3 per week
  - >3-4 hours versus 3-4 hours per week
  - Home versus satellite/in centre

What problems are we trying to fix

OUTCOMES

Outcomes: survival in children

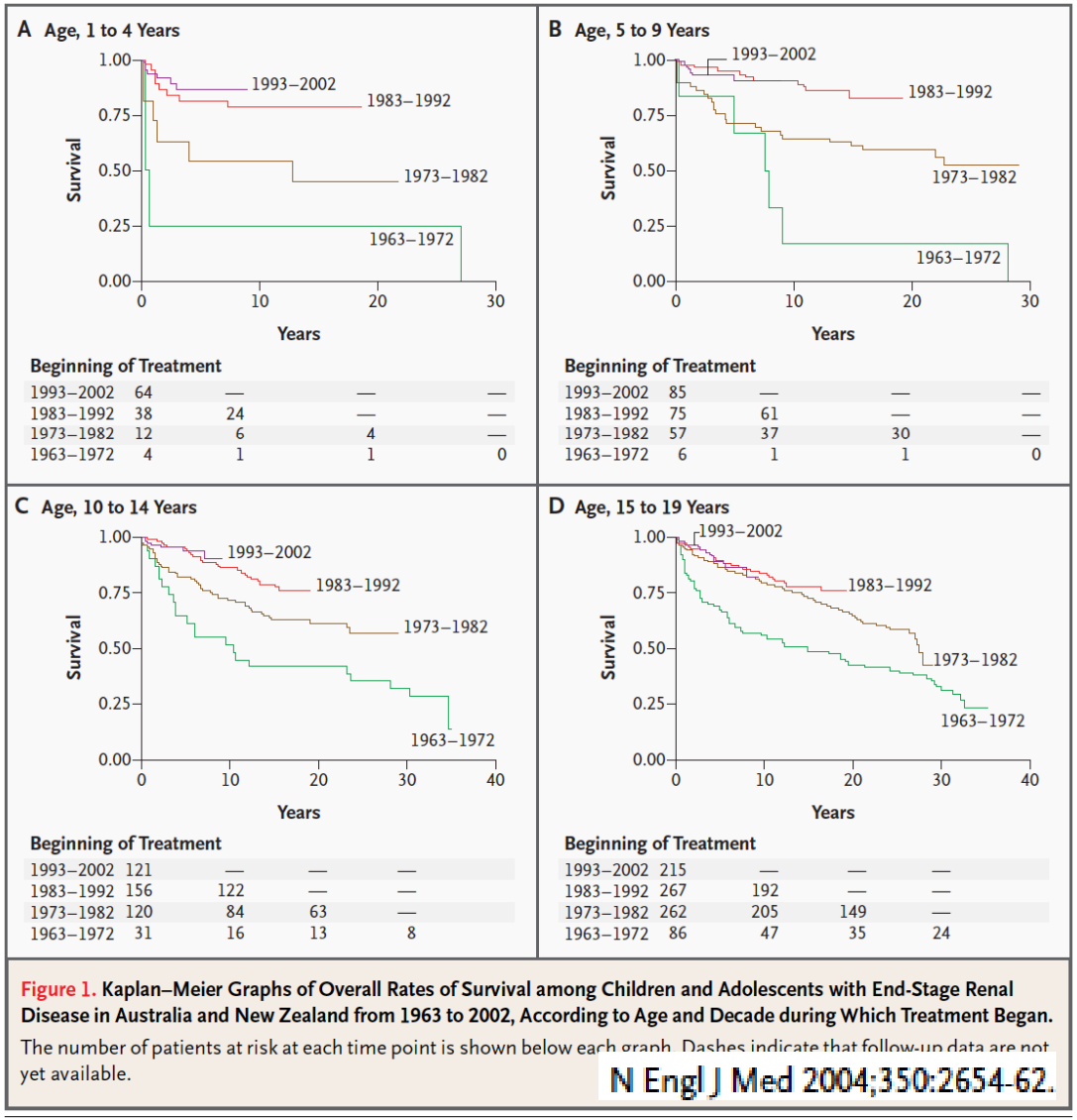


Figure 1. Kaplan–Meier Graphs of Overall Rates of Survival among Children and Adolescents with End-Stage Renal Disease in Australia and New Zealand from 1963 to 2002, According to Age and Decade during Which Treatment Began.

The number of patients at risk at each time point is shown below each graph. Dashes indicate that follow-up data are not yet available.

N Engl J Med 2004;350:2654-62.

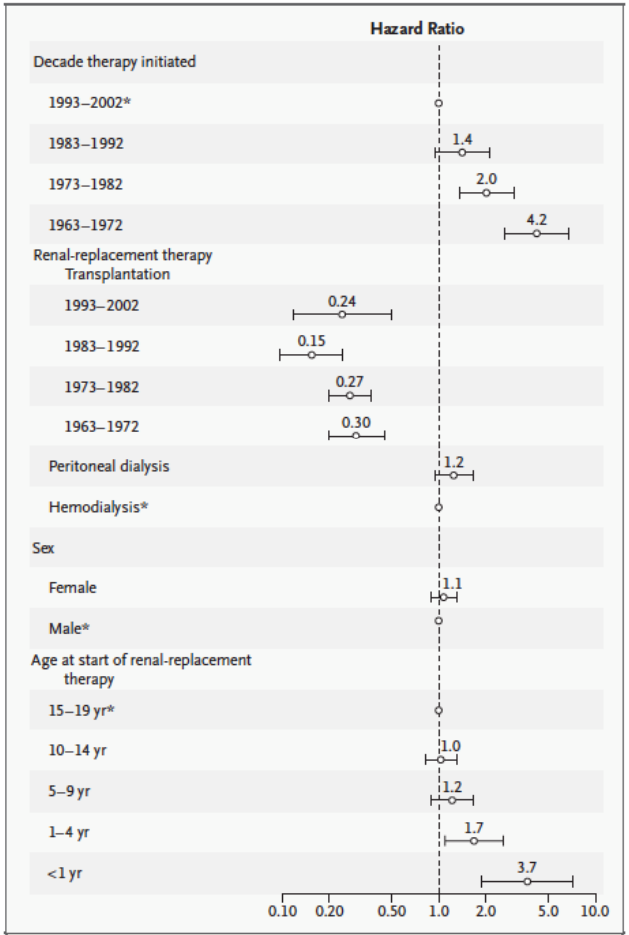


Figure 2. Hazard Ratios for Death among Children and Adolescents with End-Stage Renal Disease in Australia and New Zealand, According to Selected Predictive Variables.

Hazard ratios were derived in a multivariate Cox proportional-hazards model. The asterisks indicate the reference categories. Horizontal bars indicate 95 percent confidence intervals.

Outcomes:
survival in children

- No improvement since the 1980s
- 25% of children are dead within 20 years
  - Similar to non-cure rates for childhood leukaemia (that are improving)
- HD confers 80% excess hazard for early death compared with kidney transplantation

Quality of life

A study of the quality of life and cost-utility of renal transplantation

ANDREAS LAUPACIS, PAUL KEOWN, NANCY PUS, HANS KRUEGER, BERYL FERGUSON, CINDY WONG, and NORMAN MUIRHEAD

Kidney International, Vol. 50 (1996), pp. 235–242

TTO		
Good dialysis	167	0.54
Bad dialysis	167	0.34
Good transplant	167	0.77
Bad transplant	167	0.47
Patients themselves	167	0.57

Utility 0-1, 0 equivocal about life or death, 1 perfect health

Quality of life

KDQ		
Physical	167	4.38
Fatigue	168	4.27
Depression	168	4.80
Relationships	168	5.00
Frustration	168	4.63
SIP		
Sleep & rest	167	24.4
Emot. behavior	167	12.8
Body care and movement	167	4.6
Home management	167	15.7
Mobility	167	5.4
Social interaction	167	14.4
Ambulation	167	11.6
Alertness behavior	167	16.6
Communication	167	3.7
Work	167	40.4
Recreation & pastimes	167	31.9
Eating	167	9.0
Total physical	167	6.4
Total psychosocial	167	12.4
Overall SIP	167	13.1

Kidney Disease Questionnaire
Renal-specific multidimensional
0-7, high is good

Sickness Impact Profile
Generic measure
0-100, low is good

SPECIAL ARTICLE

Patients' Experiences and Perspectives of Living With CKD

Allison Tong, PhD,[1,2] Peter Sainsbury, PhD,[2,3] Steven Chadban, PhD,[4] Rowan G. Walker, PhD,[5] David C. Harris, PhD,[6] Stacy M. Carter, PhD,[2] Bronwyn Hall, MAAPD,[2] Carmel Hawley, MBBS,[7] and Jonathan C. Craig, PhD[1,2]

Patients frequently described dialysis as an unrelenting routine that dominated their lives physically, emotionally, and mentally. It diminished their self-esteem and constrained their daily activities. Patients on dialysis therapy lost their independence and had to rearrange many aspects of their life.

Dialysis patients felt immobilized by the constant, intense, and overwhelming fatigue and exhaustion. They felt drained and physically and mentally incapacitated.

Dialysis patients desired involvement in decision making and wanted to be recognized as having expertise in their treatment. They believed medical care was too focused on clinical targets and that more psychological and emotional support was needed.

their lives. Some patients despised the dialysis machine and the unyielding pressure it imposed on them. A few hid the dialysis machine in a closed room, refusing to integrate it into their family living environment.

Dialysis patients struggled to keep their jobs and some forced themselves to keep working despite feeling fatigued and sick.

Am J Kidney Dis 53:689-700. © *2009 by the National Kidney Foundation, Inc.*

Life on hemodialysis

Some dialysis patients lost self-esteem and confidence. They perceived their friends were uncomfortable around them because of the dialysis. Although some family and friends were sympathetic, patients still experienced a profound sense of isolation and loneliness because others could not fully relate and understand what they were going through. A few felt ostracized by their work place, alienated by social groups, and abandoned by family and friends. A few patients became antisocial and withdrawn.

A few dialysis patients had to relocate from rural or remote areas for better access to health care services. Some struggled to maintain

Dialysis was an overwhelming stress for the patients' family caregivers. Many noted that dialysis constrained the lives of their caregivers, and it exacted a physical and emotional toll. Patients believed they had to console their family members and believed CKD was more difficult on their caregivers than on themselves. One patient's husband was unable to cope and left the family.

Life on hemodialysis

"If you made that machine the center of your life, and you made love to the machine 3 times a week, and it was the center of your life, everything else went blurgh. You have to make it part of your life, so you live life as much as your energy levels and limitations allow, that's part of your life, you don't allow it to become your center." (Woman, 60s, CKD stage 2T)

"Treat it like the friend you don't like, you could certainly attempt to try and appreciate it for what it really is, rather than this inconvenient mess that gives you pain or whatever." (Man, 30s, CKD stage 5D)

Outcomes on hemodialysis

Unique in healthcare

- Poor, largely unchanged, survival
  - 15% mortality per annum
- 0.6 utility
  - Disutility of CKD
  - Disutility of the treatment

- Chronic health state and treatment
- Patient preferences particularly important
- … but it is also life saving

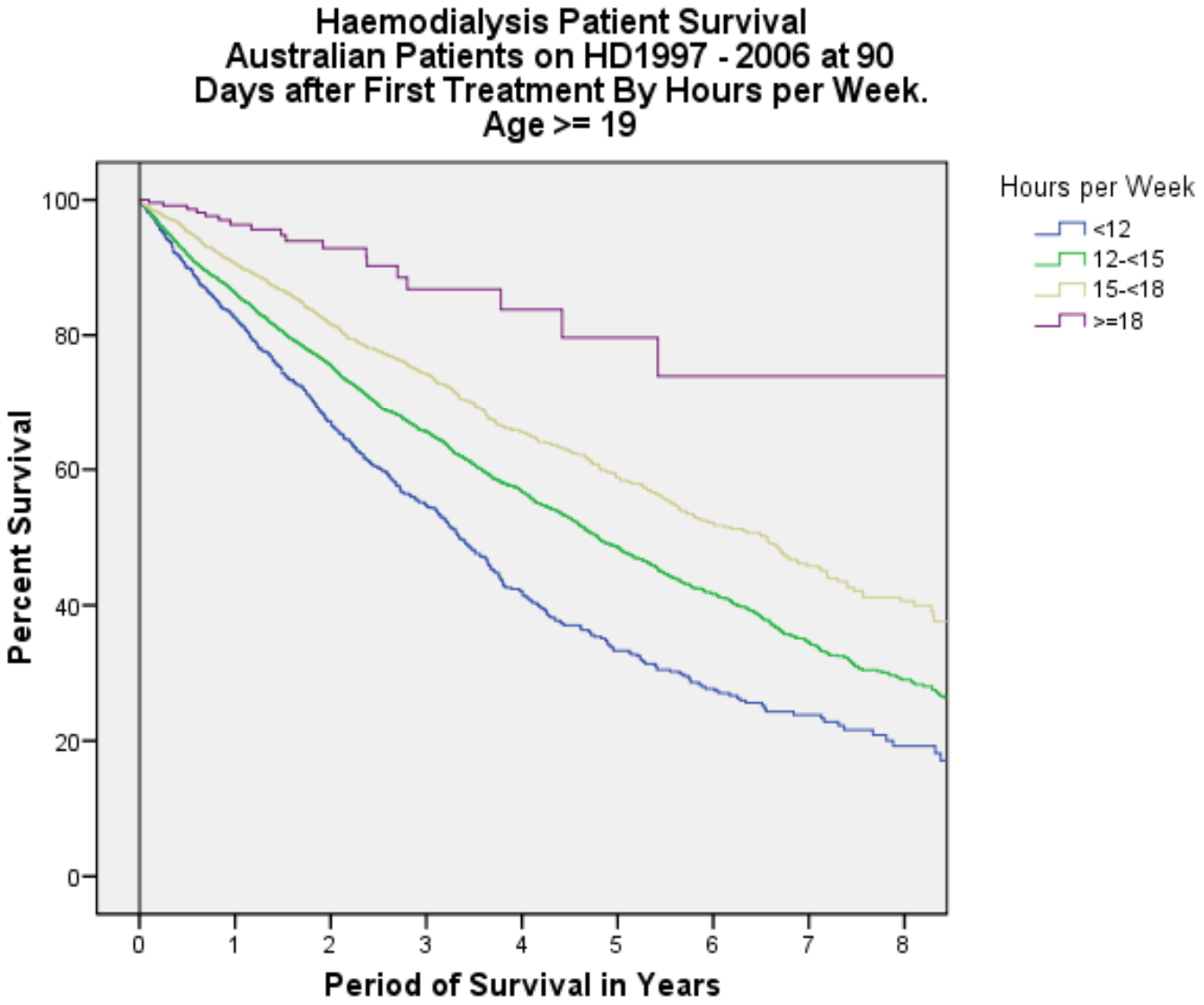
Beware residual confounding

Beware surrogates

Frequency, dose, location

INTERVENTIONS

Observational studies: ANZDATA




THE
PERFECT STORM

Observational (Exploratory) studies in CKD

- The 'Perfect Storm' for bias
  - POWER: Low type II error (random error)
    - Large routinely collected registries (DOPPS, ERA, ANZDATA, USRDS…)
    - Frequent end points
    - Exposure (type of HD) and outcome (death) measured in all
  - PLACE: High type I error (systematic error)
    - Selection bias – good prognosis patients receive more intensive dialysis
    - Confounders not measured, misclassified or incompletely adjusted for
    - Multiplicity of analysis (within and across registries)

HRT – Nurses health study: 2001

Annals of Internal Medicine | ARTICLE

A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease

Francine Grodstein, ScD; JoAnn E. Manson, MD; Graham A. Colditz, MD; Walter C. Willett, MD; Frank E. Speizer, MD; and Meir J. Stampfer, MD

Table 2. **Risk for Major Coronary Heart Disease among Current Postmenopausal Hormone Users and Nonusers, Nurses' Health Study, 1976–1996**

Hormone Use	Person-Years of Follow-up	Cases, *n*	Age-Adjusted Relative Risk (95% CI)	Multivariate-Adjusted Relative Risk (95% CI)*
Never	358 125	662	1.0 (referent)	1.0 (referent)
Past	185 497	337	0.88 (0.77–1.00)	0.82 (0.72–0.94)
Current	265 203	259	0.54 (0.46–0.62)	0.61 (0.52–0.71)
<1 y†	20 091	9	0.30 (0.16–0.58)	0.40 (0.21–0.77)
1–1.9 y†	19 155	9	0.32 (0.16–0.61)	0.41 (0.21–0.80)
2–4.9 y†	78 928	60	0.47 (0.36–0.61)	0.53 (0.41–0.70)
5–9.9 y†	77 435	74	0.51 (0.40–0.65)	0.58 (0.45–0.74)
≥10 y†	69 594	107	0.69 (0.56–0.85)	0.74 (0.59–0.91)

The authors' conclusion

mones and those who do not (6). All of our analyses were carefully adjusted for potential confounders, including the two variables that seem to be most important: cigarette smoking and body mass index. In numerous analyses in which we have isolated samples of even more homogeneous participants (for example, only those who report regular physician visits or only those with no cardiovascular risk factors) (6), our results have been consistently almost identical to those in the entire cohort, which strongly suggests that confounding by lifestyle or health practice probably does not explain our observations.

The authors' conclusion

Ongoing randomized clinical trials such as the Women's Health Initiative will provide additional data in the coming years, but women today must make informed decisions about their hormone use. Furthermore, clinical trials usually cannot provide information on diverse hormone doses or regimens. The Nurses' Health Study investigation of primary prevention indicates that hormone therapy may be associated with coronary benefits and that low doses of estrogen as well as estrogen combined with progestin may be equally effective in providing these benefits. However, the risk for

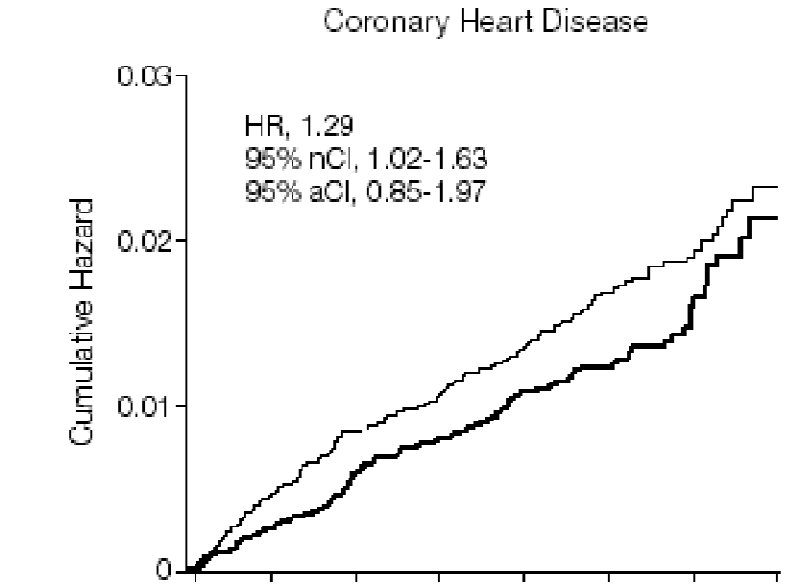
HRT – WHI trial : 2002

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.



Health Technology Assessment 2003; Vol. 7: No. 27

Evaluating non-randomised intervention studies

JJ Deeks
J Dinnes
R D'Amico
AJ Sowden
C Sakarovitch
F Song
M Petticrew
DG Altman

Health Technology Assessment
NHS R&D HTA Programme

Conclusions: Results of non-randomised studies sometimes, but not always, differ from results of randomised studies of the same intervention. Non-randomised studies may still give seriously misleading results when treated and control groups appear similar in key prognostic factors. Standard methods of case-mix adjustment do not guarantee removal of bias. Residual confounding may be high even when good prognostic data are available, and in some situations adjusted results may appear more biased than unadjusted results.

Frequency/duration/location RCTs

Exposure	Trial	N	Intervention	Comparator	Primary outcome
frequency + duration + location	Culleton, 2007	52(51)	Nocturnal home 6x/week for 6 hours (30-48 hours)	3x week 'conventional' (10.5-13.5 hours)	6 month change in LVM
mostly frequency	FHN, 2010	245 (185)	6x week (1.5-2.75 hours)Kt/V 0.9 (2.6 Kt/V and 10 hours)	3x week (2.5-4 hours) Kt/V 1.1(3.6 Kt/V and 13 hours)	12 month change in death/LVM and death/SF36
frequency + duration + location	FHN Nocturnal, 2011	87(76) *	Nocturnal home 6x/week for 6 hours (mean 30.8 hours)	3x week in-centre for 4 hours (mean 12.6 hours)	12 month change in death/LVM and death/SF36
+ HEMO					

ACTIVE DIALYSIS
A CLINICAL TRIAL OF INTENSIVE DIALYSIS

Effect of Frequent Nocturnal Hemodialysis vs Conventional Hemodialysis on Left Ventricular Mass and Quality of Life

A Randomized Controlled Trial

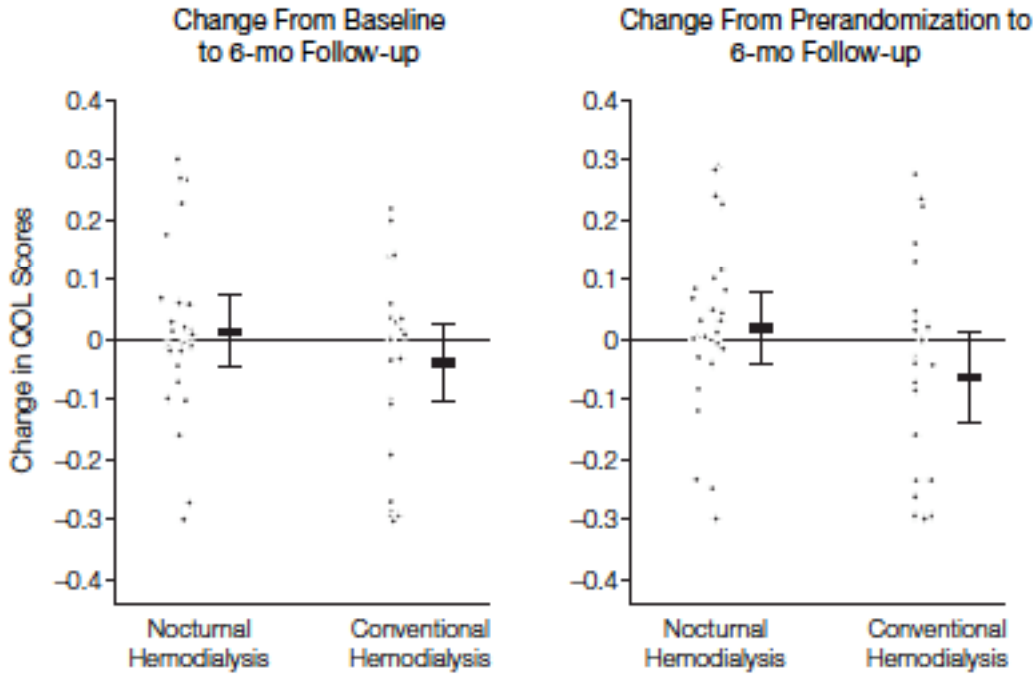
JAMA. 2007;298(11):1291-1299

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

Characteristic	Nocturnal Hemodialysis[b] (n = 26)	Conventional Hemodialysis[b] (n = 25)	Between-Group Comparison (95% CI)[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]
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)

HrQol outcomes

Figure 2. Change in Quality-of-Life Scores (EuroQol-5D Index) by Intent-to-Treat Analysis



The horizontal bars indicate mean change and error bars indicate 95% confidence intervals (CIs). Quality-of-life (QoL) scores at baseline were –0.003 (–0.10 to 0.096) for nocturnal hemodialysis patients and –0.05 (–0.12 to 0.02) for conventional hemodialysis patients. Values at prerandomization were 0.683 (95% CI, 0.579-0.786) for nocturnal hemodialysis patients and 0.705 (95% CI, 0.611-0.800) for conventional hemodialysis patients.

The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial

Michael V. Rocco[1], Robert S. Lockridge Jr[2], Gerald J. Beck[3], Paul W. Eggers[4], Jennifer J. Gassman[3], Tom Greene[5], Brett Larive[3], Christopher T. Chan[6], Glenn M. Chertow[7,8], Michael Copland[9], Christopher D. Hoy[10], Robert M. Lindsay[11], Nathan W. Levin[12], Daniel B. Ornt[13], Andreas Pierratos[14], Mary F. Pipkin[2], Sanjay Rajagopalan[15], John B. Stokes[16], Mark L. Unruh[17], Robert A. Star[4] and Alan S. Kliger[18], and the Frequent Hemodialysis Network (FHN) Trial Group[19]

Outcome	Treatment	*N*[a]	Baseline	Follow-up	Change from baseline to follow-up	Adjusted mean change from baseline ± s.e.	Treatment comparison of change: nocturnal vs conventional (95% CI)	*P*-value
Left ventricular mass (g)[b,c]	Conventional	39	132 ± 41	133 ± 42	0.6 ± 24.9	1.7 ± 4.5	−10.9 (−23.7, 1.8)	0.09
	Nocturnal	37	141 ± 48	132 ± 55	−8.2 ± 31.7	−9.2 ± 4.6		
Physical health composite[b]	Conventional	38	38.4 ± 8.5	40.6 ± 9.2	2.1 ± 9.6	2.1 ± 1.5	0.6 (−3.4, 4.7)	0.75
	Nocturnal	39	37.0 ± 9.3	40.3 ± 12.3	3.3 ± 9.0	2.7 ± 1.4		
Beck depression inventory[b]	Conventional	38	11.7 ± 9.3	11.1 ± 10.2	−0.6 ± 9.6	−0.4 ± 1.3	−1.5 (−4.9, 1.9)	0.39
	Nocturnal	39	11.8 ± 7.9	9.7 ± 8.6	−2.1 ± 5.2	−1.9 ± 1.2		
Predialysis albumin (g/dl)[b,d]	Conventional	39	3.93 ± 0.53	4.12 ± 0.38	0.19 ± 0.46	0.19 ± 0.06	−0.02 (−0.18, 0.15)	0.85
	Nocturnal	37	3.88 ± 0.49	4.08 ± 0.53	0.20 ± 0.41	0.18 ± 0.06		
Predialysis phosphorus (mg/dl)[b,e]	Conventional	39	5.65 ± 1.84	5.91 ± 2.00	0.25 ± 2.01	0.3 ± 0.3	−1.4 (−2.1, −0.7)	<0.001
	Nocturnal	37	5.75 ± 1.63	4.72 ± 1.31	−1.03 ± 1.71	−1.1 ± 0.3		
Erythropoiesis-stimulating agents (EPO equivalent units)[b,f]	Conventional	39	42,600 ± 53,761	42,735 ± 53,261	135 ± 75,813	−2 ± 17%	1.35 (0.87, 2.09)	0.18
	Nocturnal	37	43,939 ± 68,173	56,678 ± 58,436	12,739 ± 63,244	33 ± 24%		
Weekly average predialysis systolic BP (mm Hg)	Conventional	39	153 ± 22	151 ± 19	−1.9 ± 16.0	−0.1 ± 2.6	−9.7 (−16.9, −2.5)	0.009
	Nocturnal	38	145 ± 14	137 ± 21	−7.9 ± 18.4	−9.8 ± 2.7		
Number of prescribed antihypertensive agents	Conventional	39	1.74 ± 1.27	2.00 ± 1.43	0.26 ± 1.43	—	—	<0.001
	Nocturnal	37	2.38 ± 1.66	1.41 ± 1.92	−0.97 ± 2.09	—		
			N patients (%)	*N* patients (%)	—	—	Risk ratio, nocturnal vs conventional (95% CI)	*P*-value

PHC 0-50, high is good

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

The FHN Trial Group*

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±50	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	—		

This article (10.1056/NEJMoa1001593) was published on November 20, 2010, at NEJM.org.

PHC 0-50, high is good

Risk of bias

- Low but
  - self-reported unblinded HrQoL measures
  - imprecise
  - missing outcomes data
  - surrogate only

No validated surrogates in CKD

JAMA 1999;282:771-778

Table 2. Selected Examples of Applied Validity Criteria for the Critical Evaluation of Studies Using Surrogate End Points

Types of Intervention	Criterion: Is There a Strong, Independent, Consistent Association Between the Surrogate End Point and the Clinical End Point?	Criterion: Is There Evidence From Randomized Trials in Other Drug Classes That Improvement in the Surrogate End Point Has Consistently Led to Improvement in the Target Outcome?	Criterion: Is There Evidence From Randomized Trials in the Same Drug Class That Improvement in the Surrogate End Point Has Consistently Led to Improvement in the Target Outcome?	Surrogate End Point	End Point
Calcimimetics	**+/-**	**-**	**?**	**Ca/P/PTH**	**CV/fractures**
Statins	**+**	**-**	**-**	**Chol/LDL**	**CV death**
EPO	**+**	**-**	**-**	**LVM**	**CV death**
Hemo dose	**+**	**?**	**?**	**LVM**	**CV death**

Conclusions

- We have a major problem
  - High mortality, low utility health state
  - Low utility intervention
  - Non dialysis co-interventions spectacularly unsuccessful
  - Reliance on observational and/or surrogate endpoints

Conclusions

- We have a major opportunity
  - Duration (Fxt) trials appear promising
    - 10mmHg reduction in SBP/15g reduction in LVM/very small ?imperceptible benefit in HrQol
  - Location per se unlikely to be important for survival gains
  - Flexibility to incorporate patient preference is critical (probably more important than frequency or time)
  - International large scale RCT with clinical, HrQol, and economic endpoints are required