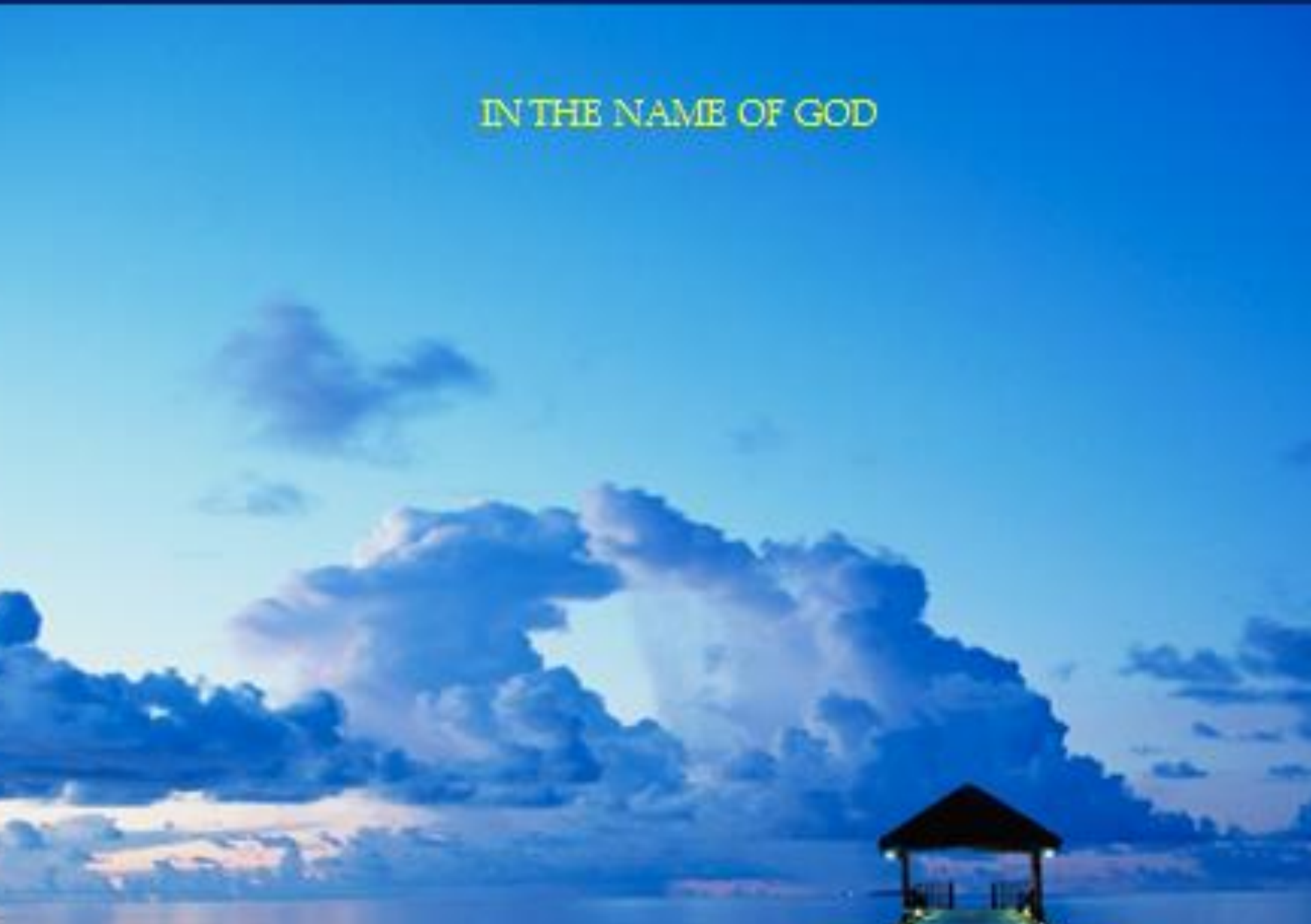
IN THE NAME OF GOD



Incremental hemodialysis

- Dr.F.hagvhverdi MD

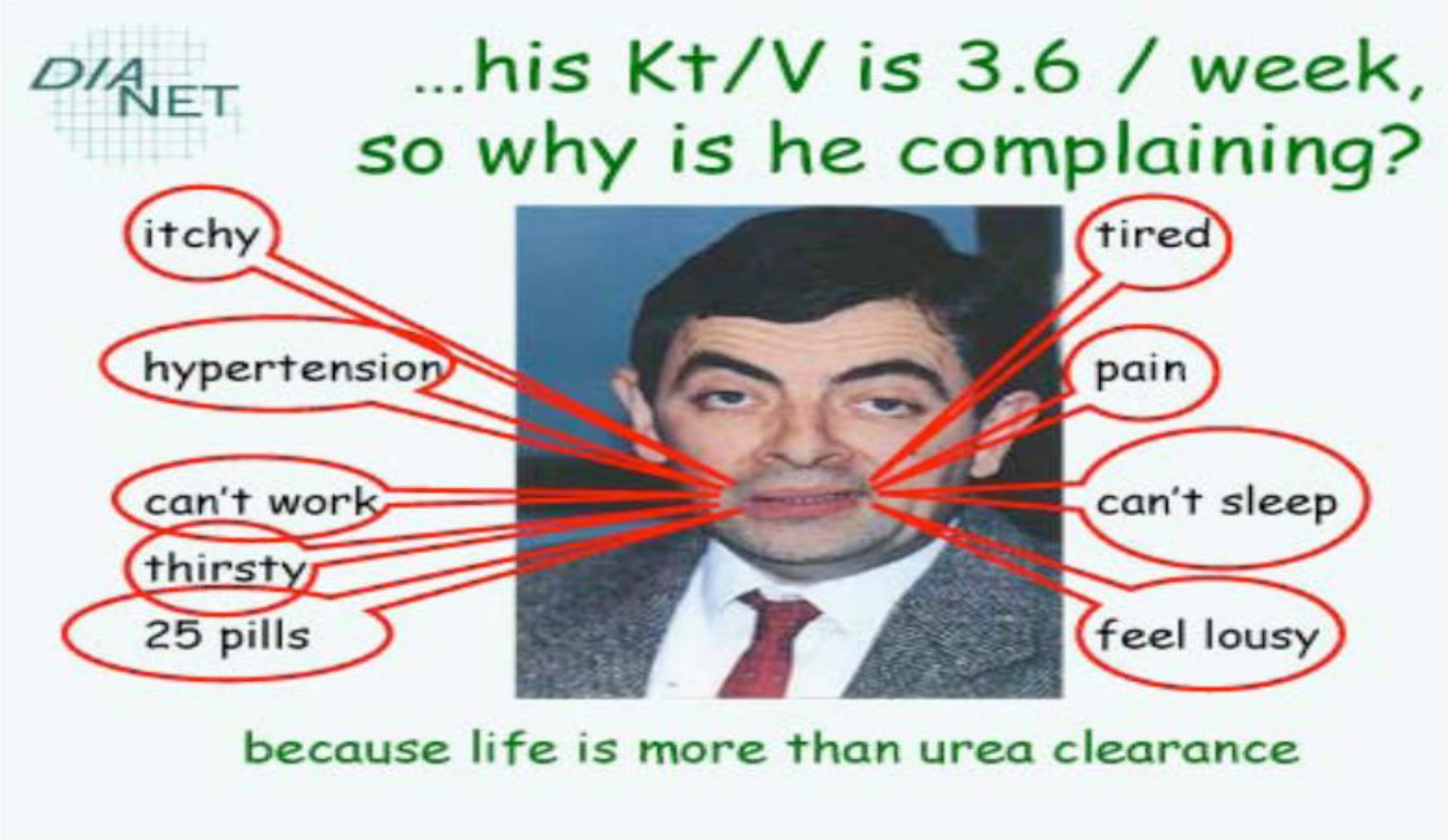
Outline

- Case and Question?
- Adequacy of dialysis vs optimal dialysis?
- Incremental HD: Twice weekly HD vs Thrice weekly HD?

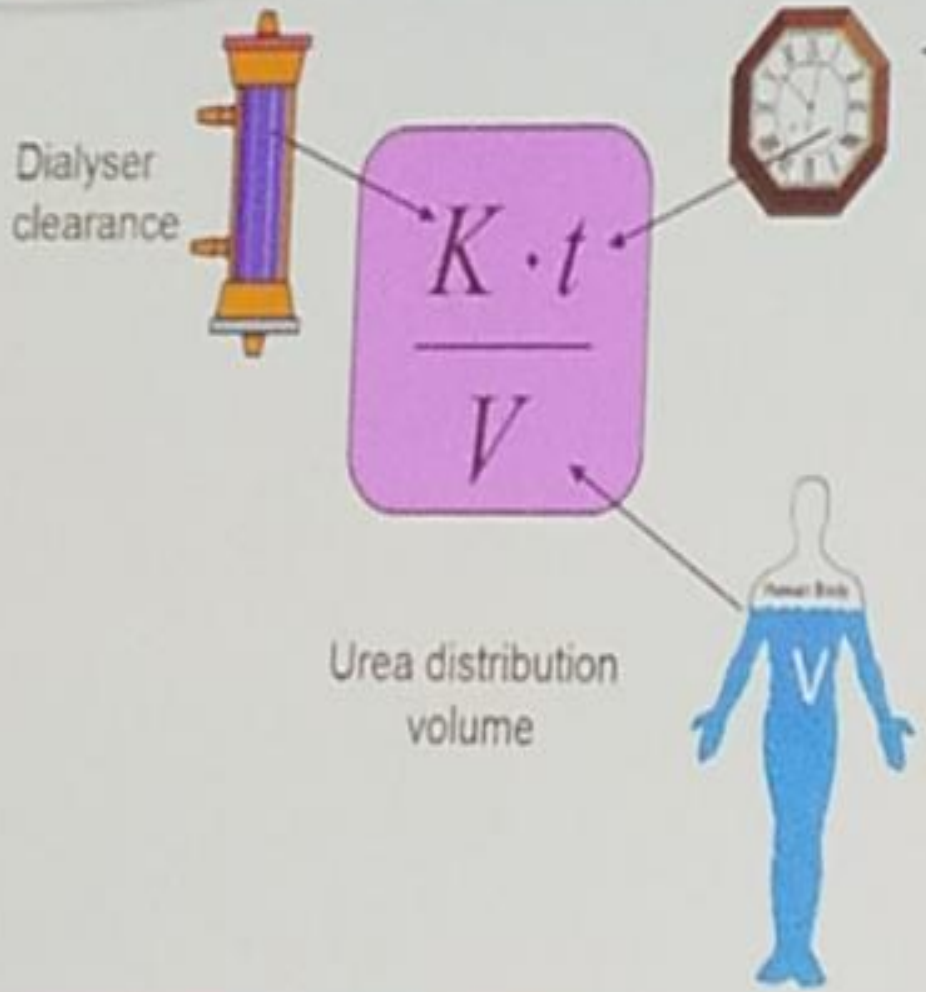
Case:

- A 35 years_ old man presented to nephrology clinic. He was known case of CKD from 10 years ago. He complains nuasa and vomiting and loss of appetite since one month ago..BP=160/100, NO edema, His last lab Cr =10 , Hb=10 K=5 , ph = 5, His urine out is 1 lit per day and eGFR= 8 cc/ min. Weight =60 kg. He has a matured AVF .Nephrologist decides to start hemodialysis because of uremic symptoms. Can we initiate HD twice weekly?

Adequate dialysis vs Optimal dialysis



Dialysis dose concepts

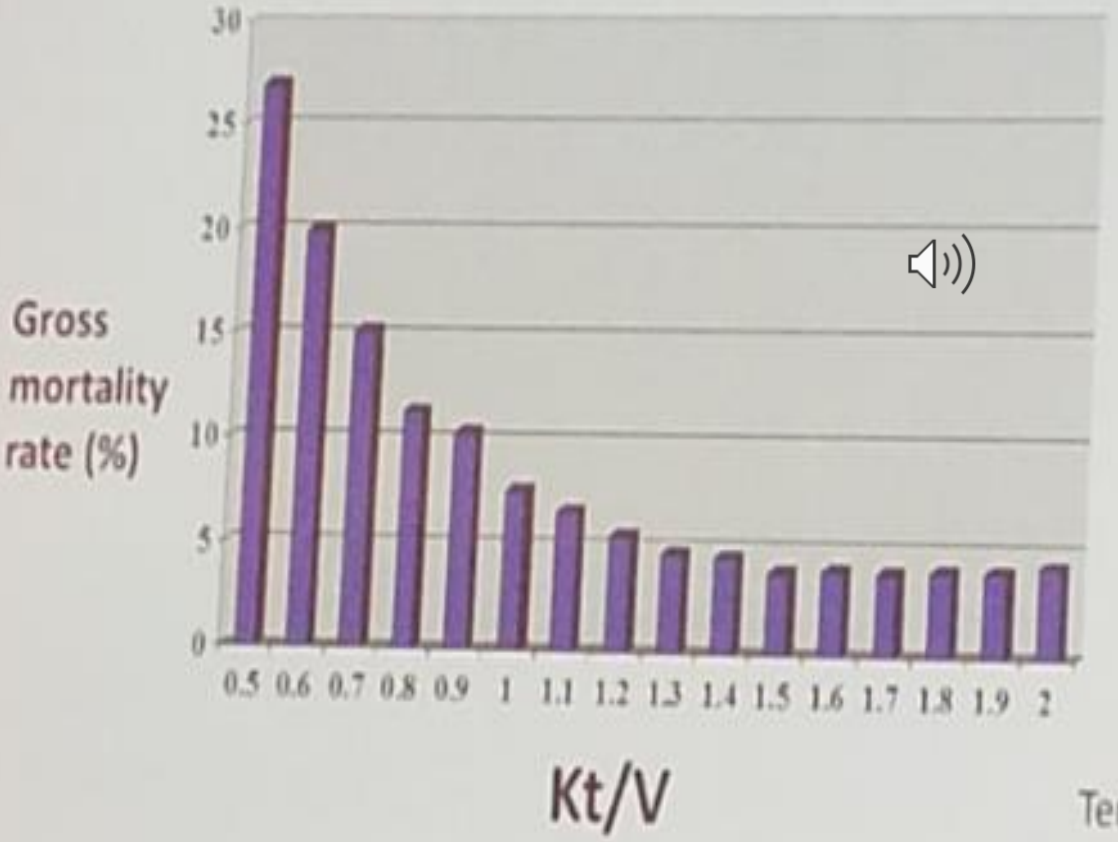


- We favor a more comprehensive “umbrella” concept for what is currently referred to as adequacy
  - Should include multiple components including small solute clearance (Kt/V), residual kidney function, volume status, biochemical measures, nutritional status, symptoms, patient experience

Clinical Performance Measures in Hemodialysis 2015

- **1.sp Kt/V >1.4**
- 2.Alb>3.5 g/dl
- 3. Hb> 10 and <12 g/dl
- 4. Ph> 2.5 and <5.5 mg /dl
- 5. Ferritin> 200 and<800 ng/ml
- 6. Ca*Ph < 55
- 7.iPTH > 150 and <600 pg/ml
- 8.Predialysis MAP< 105 mmhg
- 9.Interdialytic weight gain<4% dry weight
- 10.Weekly treatment> 720 min
- 11. Prevalence of AVF> 90%

Threshold effect of Kt/V on mortality in thrice weekly HD



Japanese Registry

N = 43341

Teraoka et al AJKD 25:151, 1995

Dialysis Adequacy:

- Urea is small molecule (60 D)
- Urea is easily cleared by dialysis
- We know the Kinetic of urea
  URR (urea reduction ratio)
- KT/V

Limitation of spKt/V:

- **1**.Kinetics of other toxins are not similar to urea clearance (middle and large molecules)

Uremic toxin and mortality evidences:

- Unfortunately RCTs does not strongly support
- uremic toxins hypothesis:
- A-Urea is less toxic than other molecules
- B-Low urea means malnutrition or adequate dialysis

C-Better dialysis/better removal did not improve outcome in patients.

D-Urea is not a surrogate marker for uremic toxicity and optimal dialysis.

E-Kt/V is a marker of adequate dialysis no optimal dialysis.

F- Middle molecules clearance is more important.

Spectrum of toxic molecules contributing to uraemia

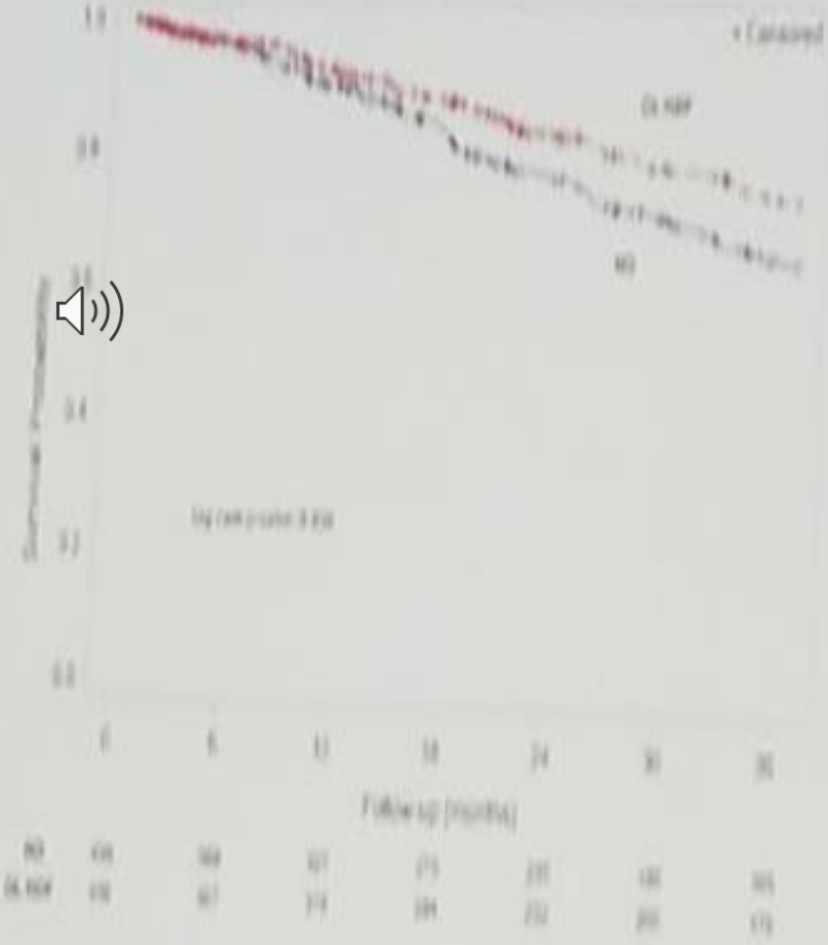
Small water soluble molecules (<0.5kDa)	Middle molecules (>0.5kDa)	Protein bound molecules
Sodium	Advanced glycation end products	Indoxyl sulphate
Phosphorus	Beta-2 microglobulin	P-cresyl sulphate
Potassium	endothelin	homocysteine
Urea	leptin	Hippuric acid
Creatinine	Cystatin C	polyamines
Uric acid	Kappa IgG light chain	
Asymmetric dimethylarginine	Lambda IgG light chain	

ESHOL Study: Kaplan–Meier curves for 36-month survival

906 HD patients

HD (90+% High-flux v high-efficiency (>20L session) on-line HDF

?Residual Kidney Function



HDF conveyed:

30% lower risk of all-cause mortality (P=0.01)

Maduell F et al. JASN 2013;24:487-497

Incremental Hemodialysis

Incremental Hemodialysis

Tailoring hemodialysis parameters to the patient's renal function

lower hemodialysis dose until patient has renal function

+

all possible measures to preserve residual renal function

For patient starting hemodialysis with *"sufficient"* kidney function.

Less intensive hemodialysis

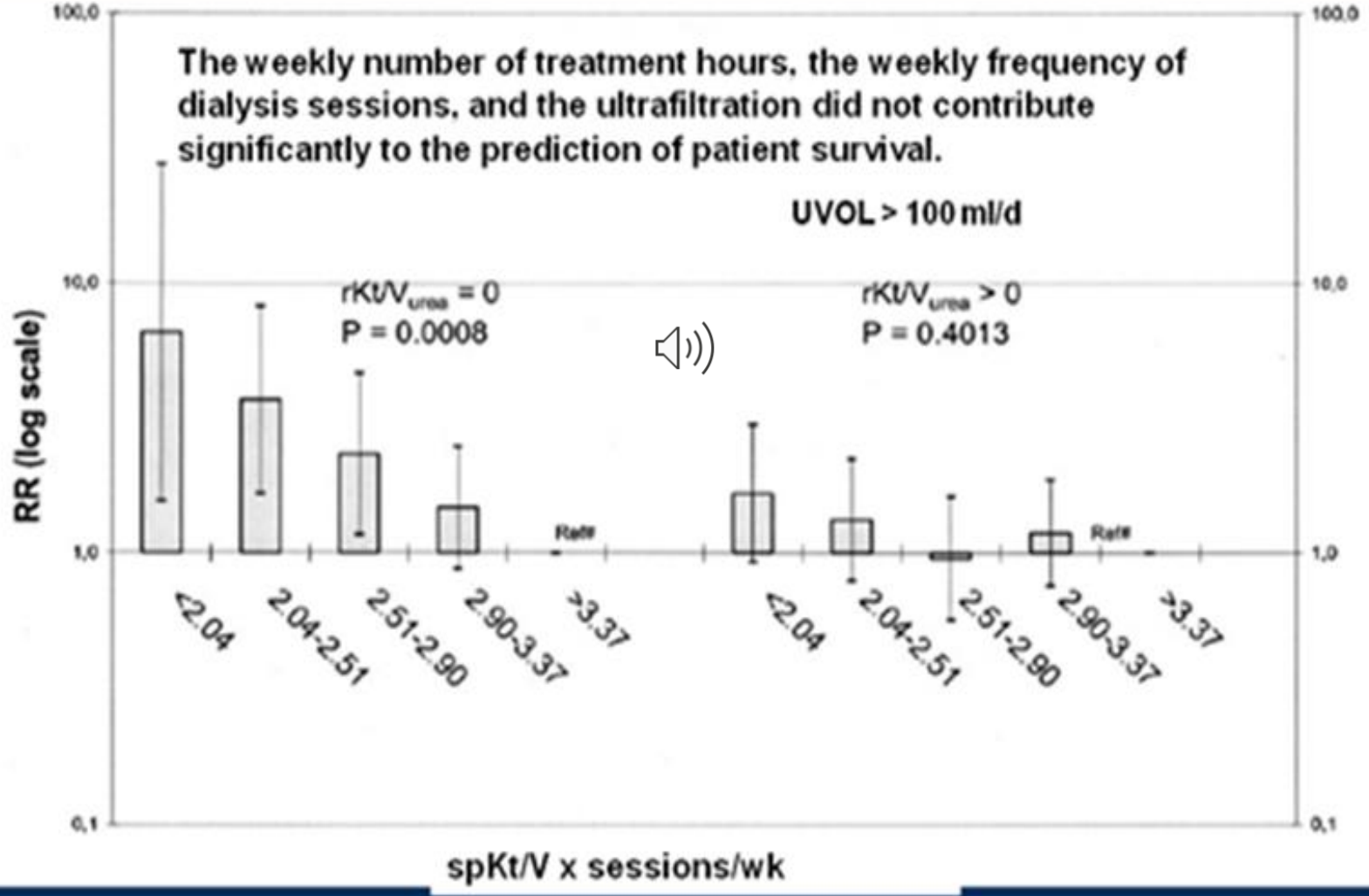
?

Preserved residual renal function

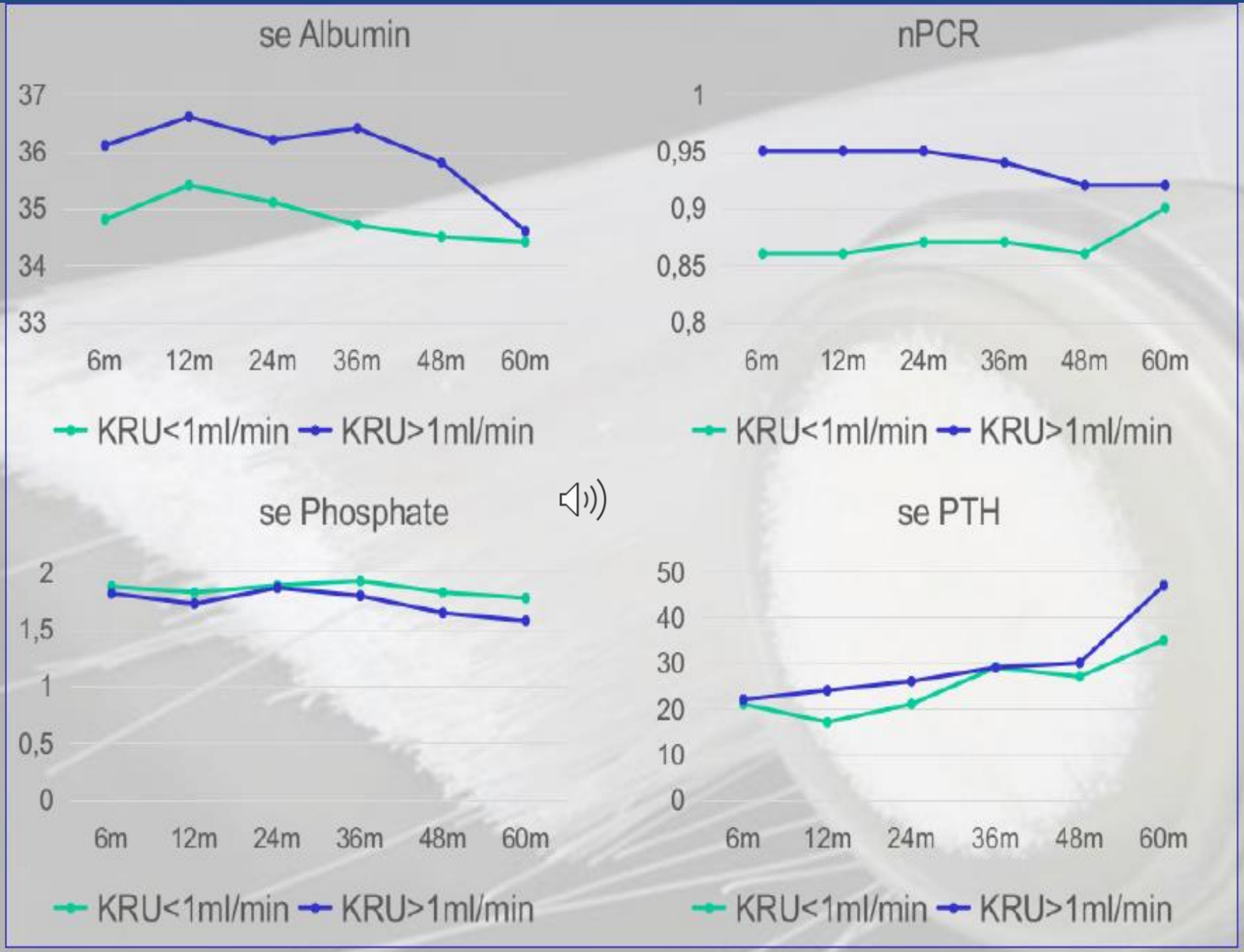
?

Improved survival

Dose of dialysis may not mater when you have some urine output (NECOSAD-2)



Termorshuizen et al. J Am Soc Nephrol 15: 1061–1070, 2004



KRU: renal urea clearance

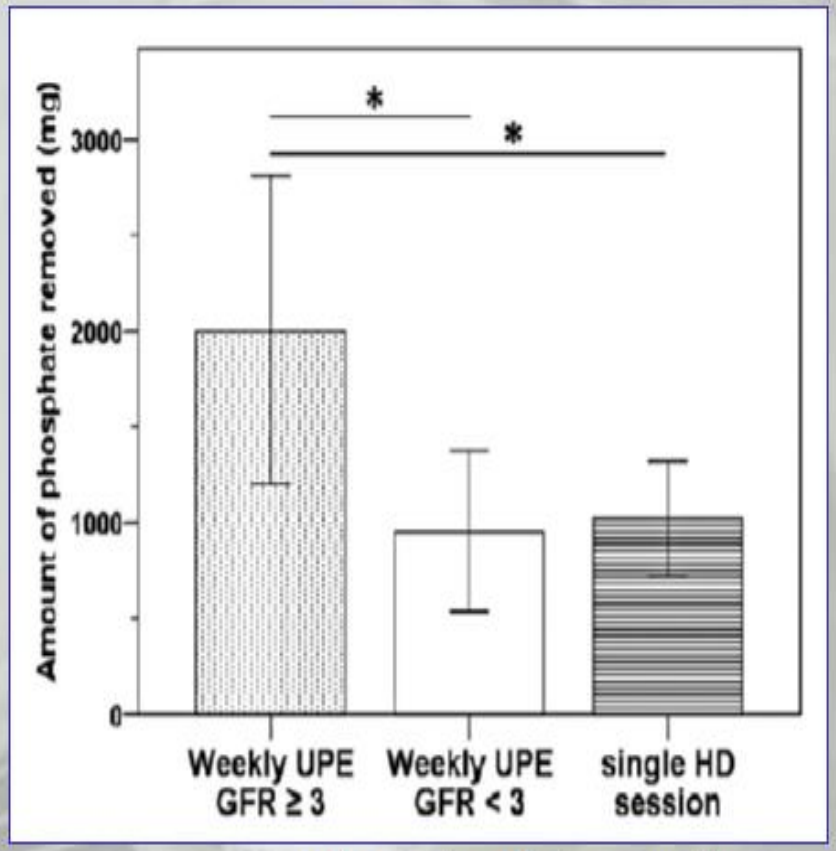
Vilar et al, Nephrol Dial Transplant (2009) 24: 2

Residual kidney function and urinary phosphate excretion

79 prevalent HD patients, with urine output > 100ml/min

35 patients with GFR>3ml/min vs 44 patients with GFR<3ml/min

Parameter	All Patients ($n = 79$)	Group A (GFR ≥ 3, $n = 35$)	Group B (GFR < 3, $n = 44$)	*P*-value
sPi (mg//dL)	5.8 ± 1.1	5.5 ± 1.1	6.1 ± 1.1	0.02
(mmol/L)	1.9 ± 0.4	1.8 ± 0.4	2.0 ± 0.4	
iPTH (ng/L)	250 ± 182	306 ± 232	206 ± 113	0.02
FGF-23 (ng/L)†	2008 ± 1933	1296 ± 2142	2423 ± 1760	0.23
uPi (mg/dL)	17.2 ± 6.1	18.8 ± 6.0	15.9 ± 6.0	0.03
(mmol/L)	5.6 ± 2.0	6.1 ± 1.9	5.1 ± 1.9	
TRP (%)	35.0 ± 13.9	39.2 ± 13.3	31.7 ± 13.6	0.02
TmP/GFR (mg/dL)	2.0 ± 0.8	2.2 ± 0.9	1.9 ± 0.8	0.12
(mmol/L)	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	
UPE (mg/day)	203 ± 113	283 ± 115	139 ± 57	0.001
(mmol/day)	6.6 ± 3.6	9.1 ± 3.7	4.5 ± 1.8	



urinary phosphate excretion

Iwasawa et al, Nephrology 18 (2013) 285–291

How residual renal function affects survival?

- RRF is just associated with being a healthier patient
- better clearence of middle molecular weight and protein bound uremic toxins
- better maintenance of euvolemia
  - less hypervolemia → better BP control and decreased LVH
  - less ultrafiltration → fewer hypotensive episodes
- better nutritional status
- intrinsic anti-inflammatory effect
- lower potassium, phosphate levels (FGF-23 ?)
- less calcification
- ... ?

Ajanovic et al, BANTAO Journal 2015; 13(2): 73-78;
Fernández-Lucas et al, Nefrologia 2012;32(6):767-76
Weerd et al, PLoS ONE 2012; 7(7): 1-18;
Penne et al, Clin J Am Soc Nephrol. 2011 Feb; 6(2): 281–289.
Merkus et al, Am J Kidney Dis. 1997 Apr;29(4):584-92.
Shin et al, PLoS ONE 2017;12(9): e0185296

GFR estimation in HD patients:
(Kr urine= UUN / SUN* urine flow rate cc/min)

Estimating renal function in Hemodialysis
beta-2 microglobulin

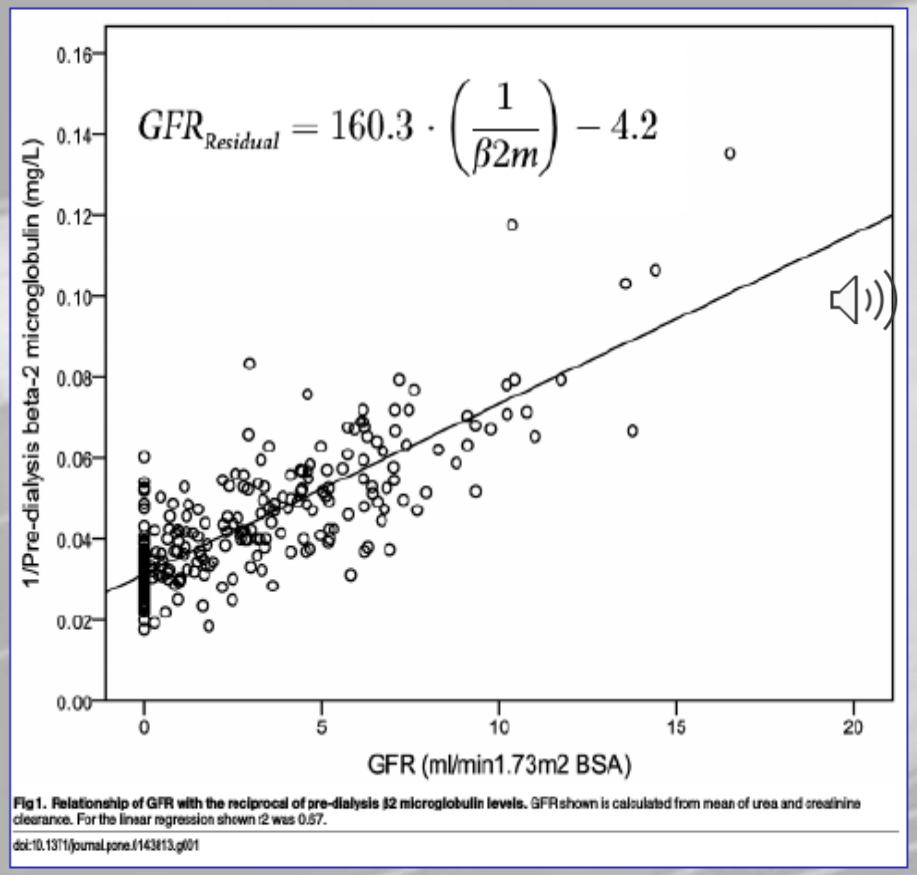


Fig 1. Relationship of GFR with the reciprocal of pre-dialysis β2 microglobulin levels. GFR shown is calculated from mean of urea and creatinine clearance. For the linear regression shown r2 was 0.57.

doi:10.1371/journal.pone.0143813.g001

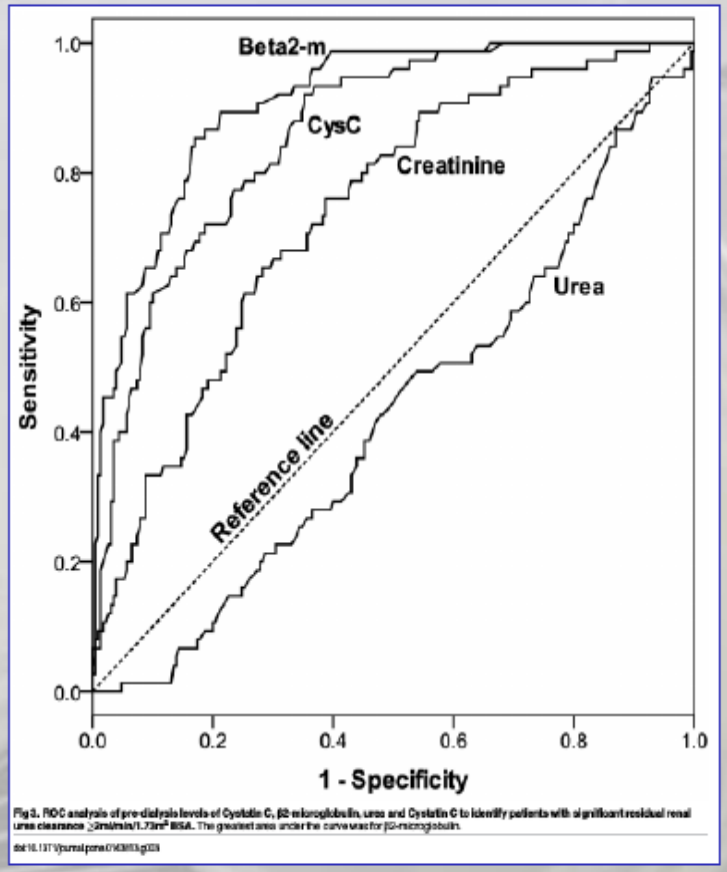


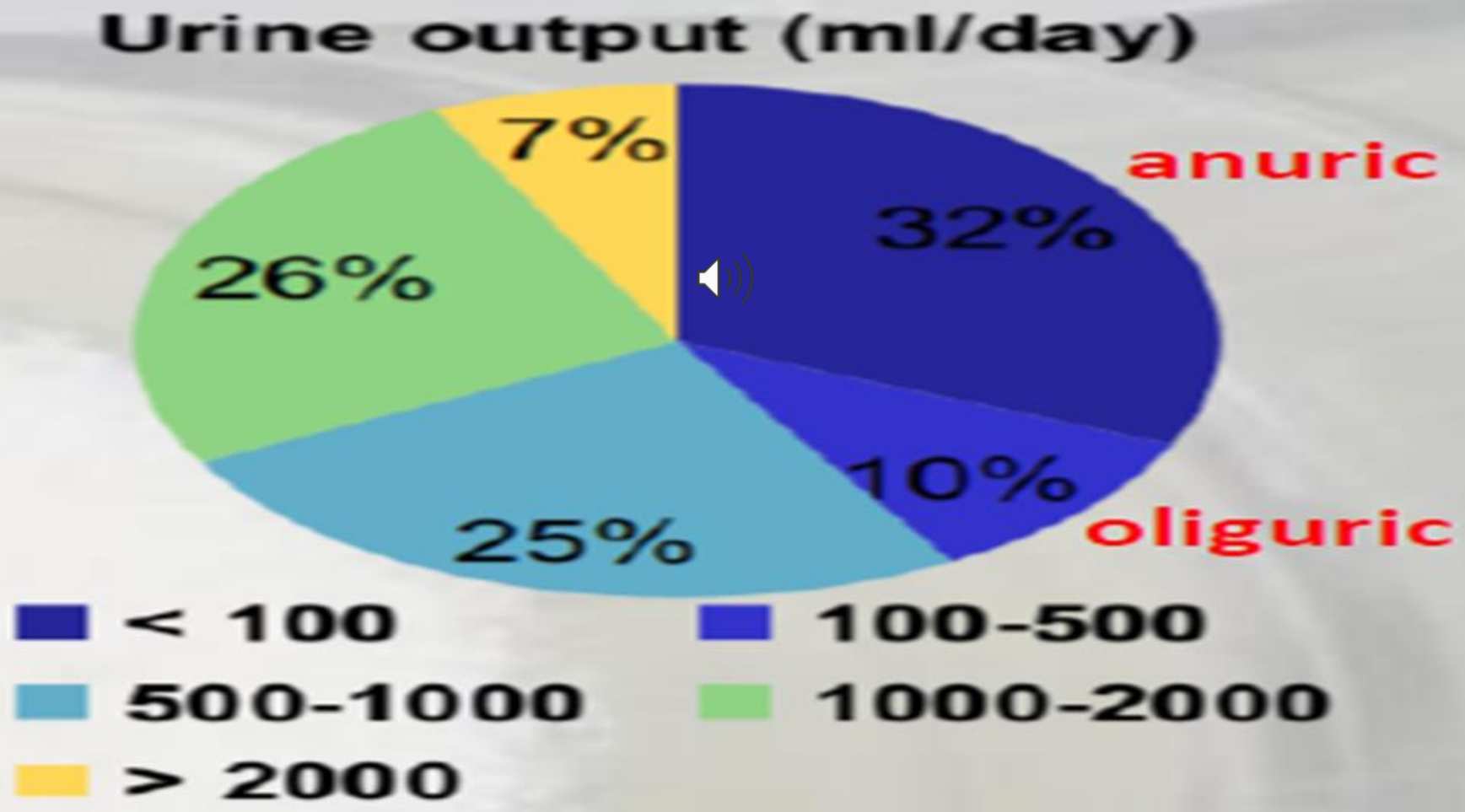
Fig 3. ROC analysis of pre-dialysis levels of Cystatin C, β2-microglobulin, urea and Cystatin C to identify patients with significant residual renal urea clearance ≥2ml/min/1.73m² BSA. The greatest area under the curve was for β2-microglobulin.

doi:10.1371/journal.pone.0143813.g003

Predicting eGFR > 2ml/min : beta2-MG < 19.2mg/l (90% specificity, 65% sensitivity)

Vilar et al, PLoS ONE 2015, 10(12): e0143813.

Residual Renal Urine



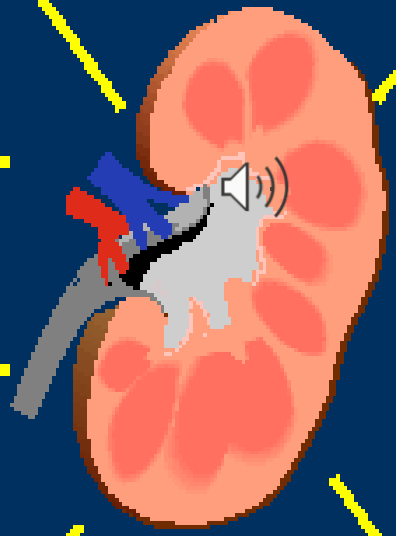
Benefits of Residual Renal Function

Provides endocrine functions

- Erythropoietin production
- Ca^{++}, phosphorus and vitamin D homeostasis

Contributes to total solute clearance *(1 ml/min CrCl = 10 liter CrCl/week)*

Reduces Mortality



Improves β_2-microglobulin and middle molecule clearance

Improves QOL

Facilitates volume control

Increases nutritional status

Allows for more liberal diet and fluid intake

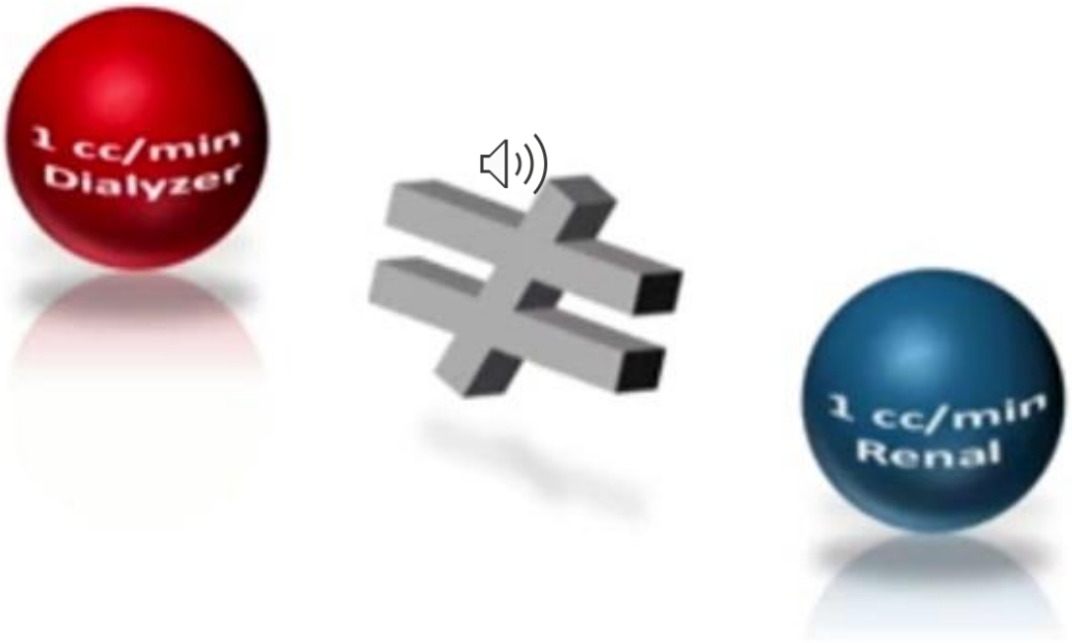
RRF and outcome

- Each 1 ml of r GFR equals
  C Cr of 10 liters/week/1.73 m^2
  Urea Kt/V of 0.25/week

- The contribution of RRF to the clearance of middle and larger molecules is proportionately larger

- RRF in HD is understudied

Native renal function “worth” more than dialyzer clearance



Contributing factors for preservation of RRF

Control of hypertension
Prevention of dialysis hypotension
Choice of antihypertensive medication
Optimal dry weight
Optimal ultrafiltration speed
Avoidance of nephrotoxic agents
Prevention of hypercalcemia
High-flux biocompatible membrane dialyzer
Ultrapure dialysate (UPD)
Hemodiafiltration (HDF)
HMG-CoA reductase inhibitors?

Nephrol Dial Transplant. 2019 Jun 1;34(6):1017-1025. doi: 10.1093/ndt/gfy321.

Initiating haemodialysis twice-weekly as part of an incremental programme may protect residual kidney function.

Kaja Kamal RM[1,2], Farrington K[1,2], Busby AD[2], Wellsted D[2], Chandna H[1], Mawer LJ[1], Sridharan S[1,2], Vilar E[1,2].

Abstract

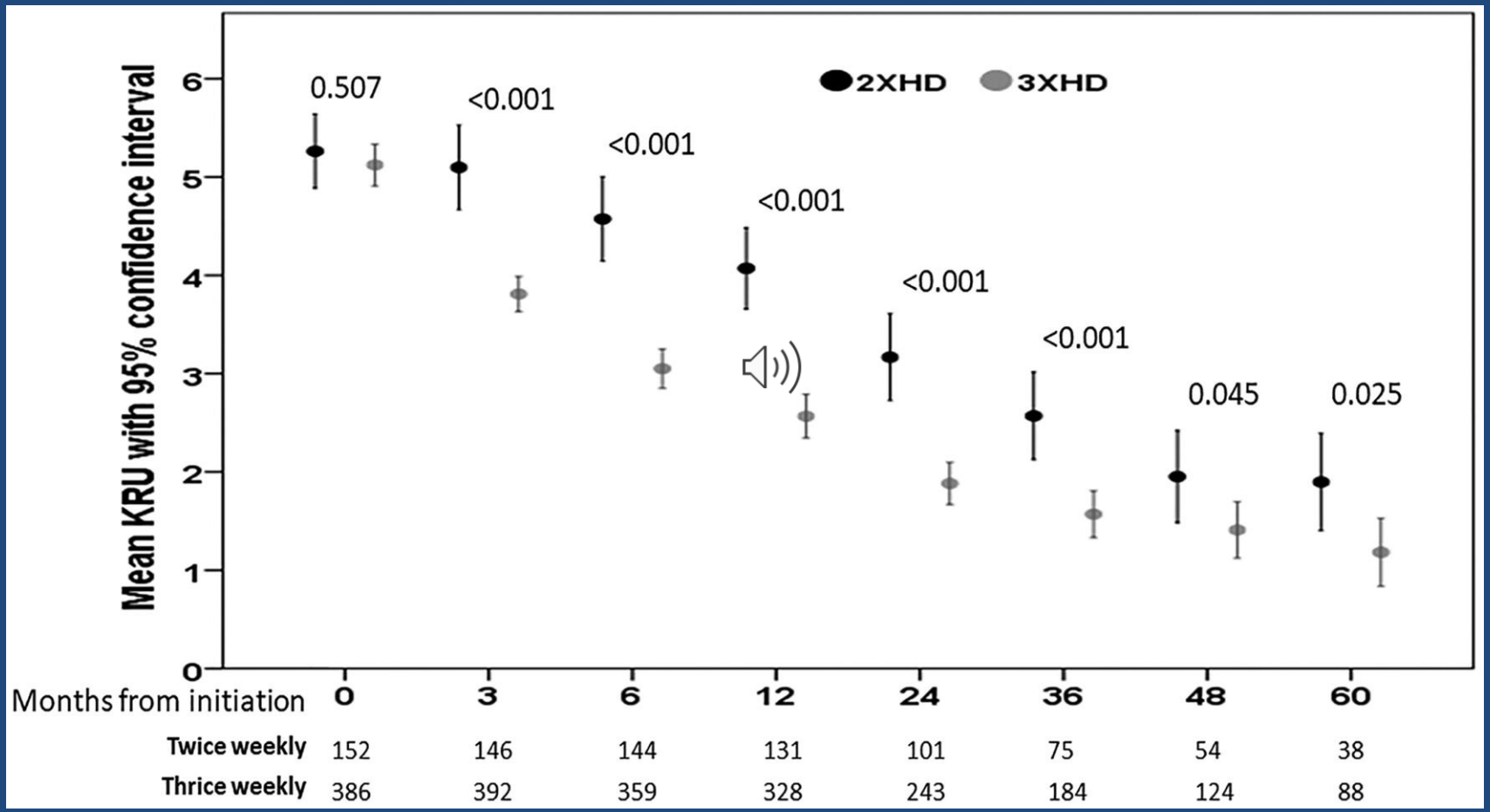
BACKGROUND: Initiating twice-weekly haemodialysis (2×HD) in patients who retain significant residual kidney function (RKF) may have benefits. We aimed to determine differences between patients initiated on twice- and thrice-weekly regimes, with respect to loss of kidney function, survival and other safety parameters.

METHODS: We conducted a single-centre retrospective study of patients initiating dialysis with a residual urea clearance (KRU) of ≥3 mL/min, over a 20-year period. Patients who had 2×HD for ≥3 months during the 12 months following initiation of 2×HD were identified for comparison with those dialysed thrice-weekly (3×HD).

RESULTS: The 2×HD group consisted of 154 patients, and the 3×HD group 411 patients. The 2×HD patients were younger (59 ± 15 versus 62 ± 15 years: P = 0.014) and weighed less (70 ± 16 versus 80 ± 18 kg: P < 0.001). More were females (34% versus 27%: P = 0.004). Fewer had diabetes (25% versus 34%: P = 0.04) and peripheral vascular disease (PVD) (13% versus 23%: P = 0.008). Baseline KRU was similar in both groups (5.3 ± 2.4 for 2 × HD versus 5.1 ± 2.8 mL/min for 3 × HD: P = 0.507). In a mixed effects model correcting for between-group differences in comorbidities and demographics, 3×HD was associated with increased rate of loss of KRU and separation of KRU. In separate mixed effects models, group (2×HD versus 3×HD) was not associated with differences in serum potassium or phosphate, and the groups did not differ with respect to total standard Kt/V. Survival, adjusted for age, gender, weight, baseline KRU and comorbidity (prevalence of diabetes, cardiac disease, PVD and malignancy) was greater in the 2×HD group (hazard ratio 0.755: P = 0.044). In sub-analyses, the survival benefit was confined to women, and those of less than median bodyweight.

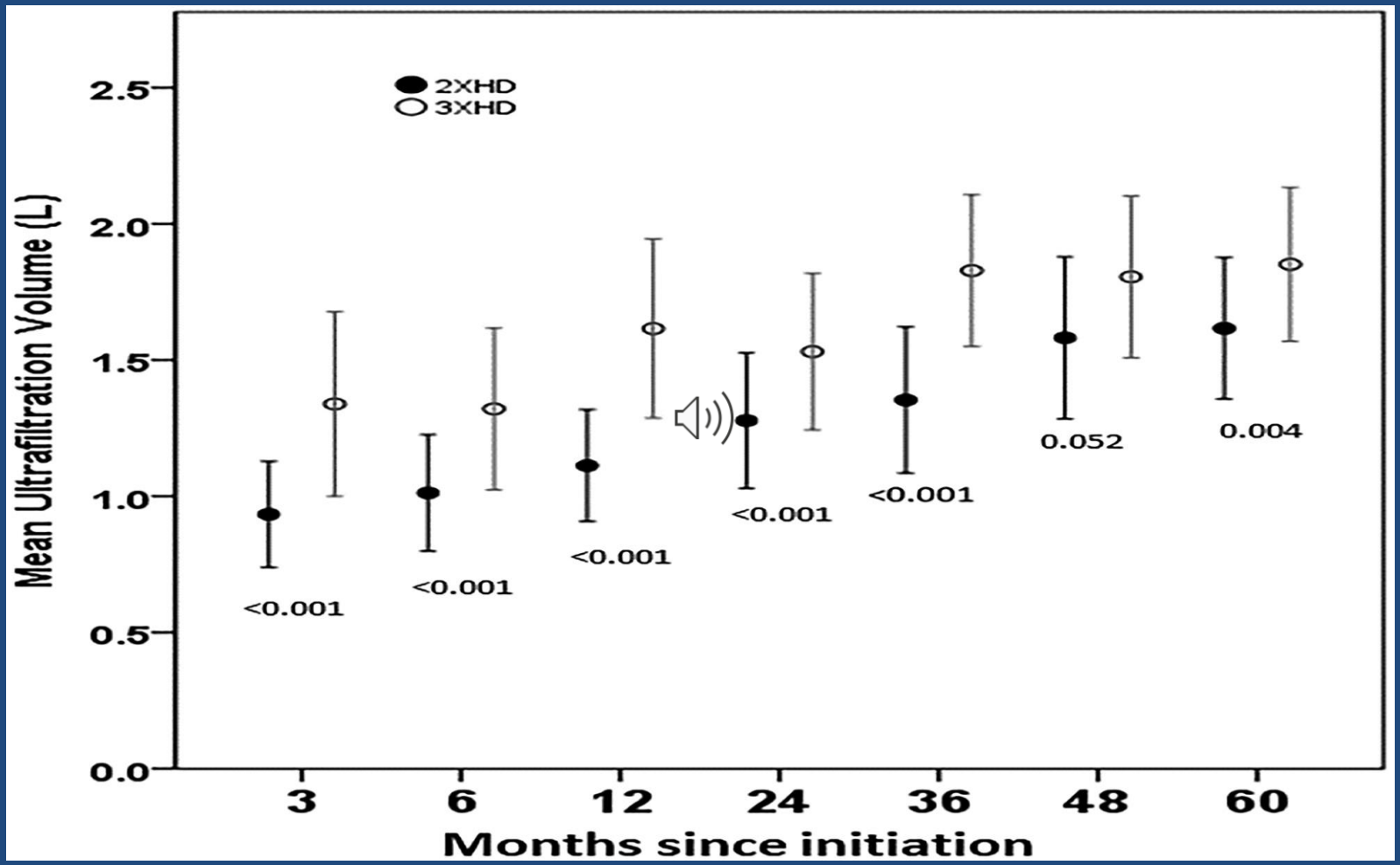
CONCLUSION: 2×HD initiation as part of an incremental programme with regular monthly monitoring of KRU was safe and associated with a reduced rate of loss of RKF early after dialysis initiation and improved survival. Randomized controlled trials of this approach are indicated.

FIGURE 1 Decline of KRU over 5 years in patients with KRU of ≥3 mL/min, initiated on 2×HD and 3×HD.



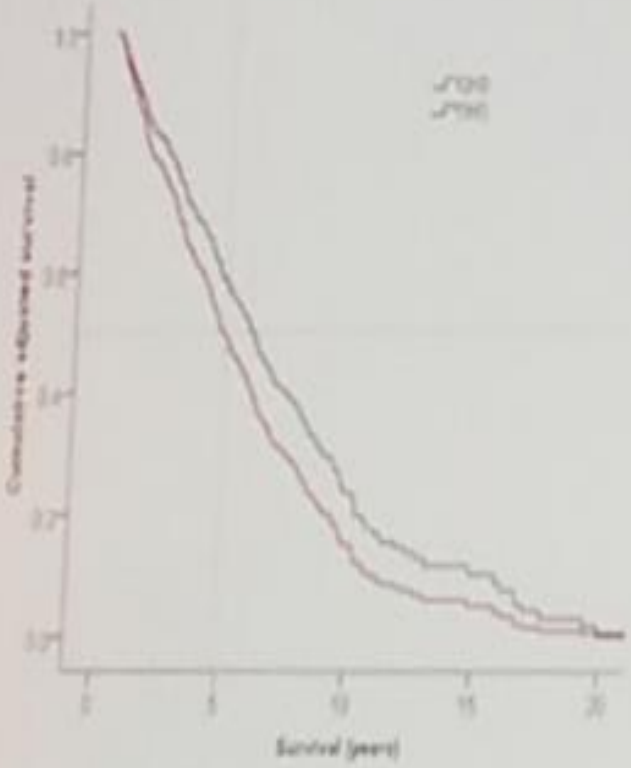
Nephrol Dial Transplant, Volume 34, Issue 6, June 2019, Pages 1017–1025, https://doi.org/10.1093/ndt/gfy321

FIGURE 6 Ultrafiltration volume over 5 years following initiation of dialysis in 2×HD and 3×HD groups.



Nephrol Dial Transplant, Volume 34, Issue 6, June 2019, Pages 1017–1025, https://doi.org/10.1093/ndt/gfy321

Twice v thrice weekly HD initiation



Kaja Kamal, Farrington, Vilar et al, NDT 2018 Oct 23

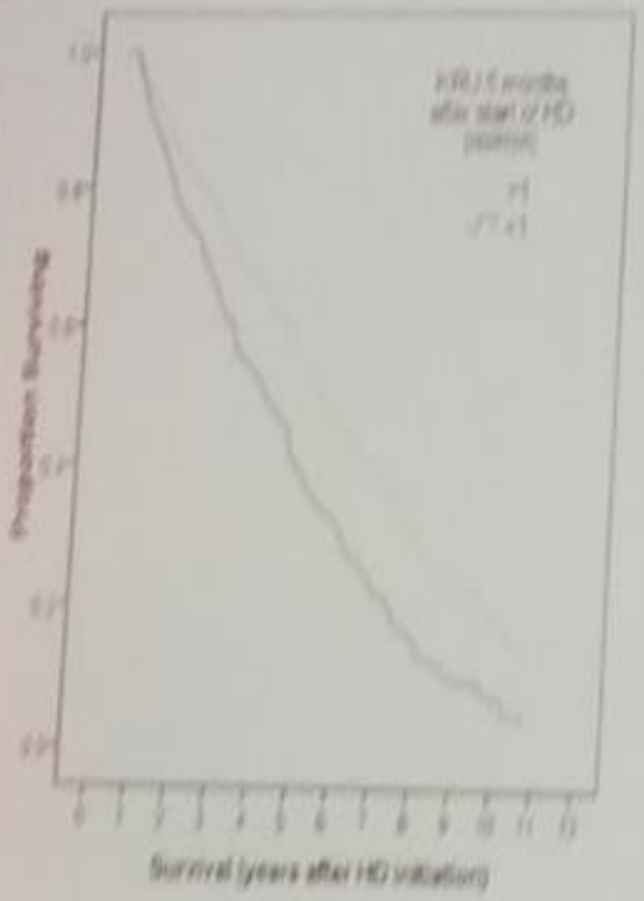
2x weekly HD initiation compared to 3x weekly HD

24% reduced risk death (p=0.04)

Correcting for:

- Age
- Gender
- Diabetes
- Ischaemic heart disease
- Malignancy
- Peripheral vascular disease
- Albumin
- Maximum urea clearance in year 1 of HD

Residual renal function considerations



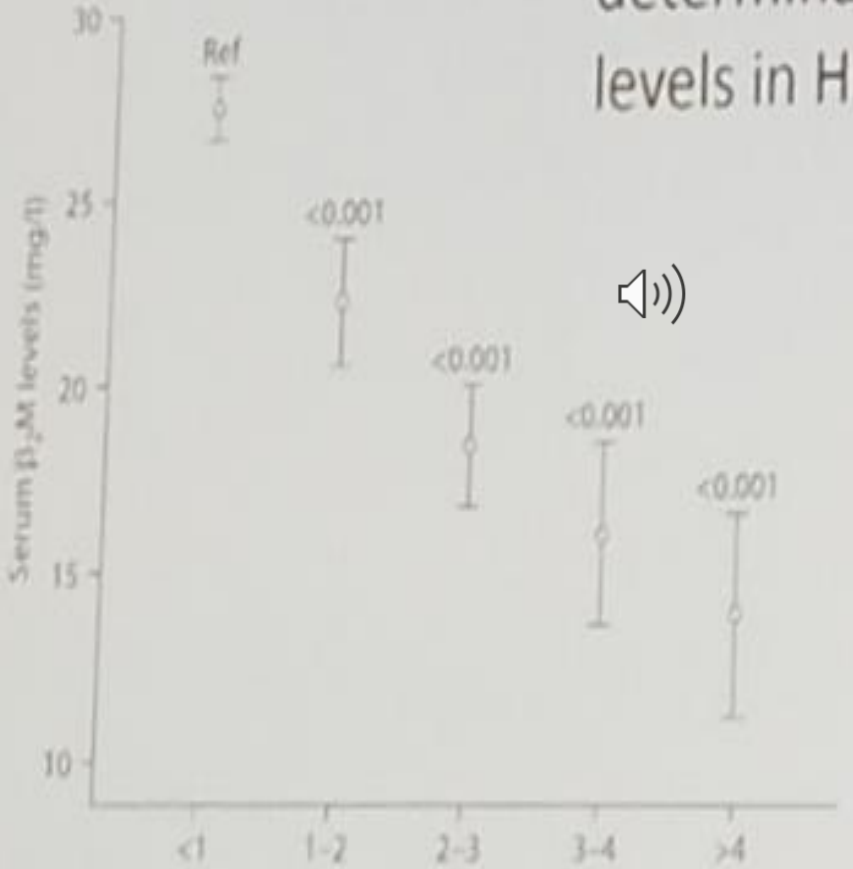
Urea clearance ≥1ml/min
31% lower risk death (p=0.01)

Correcting for:

- Diabetes
- Age
- Albumin
- HDF use
- Malignancy
- Ischaemic heart disease
- Peripheral vascular disease

Vilar et al, Residual kidney function improves outcomes... NDT 2009

Residual renal function: the major determinant of β2 microglobulin levels in HD patients



Fry, Farrington et al. Blood Purif 2007;25:295–302

Outcomes with Incremental Hemodialysis

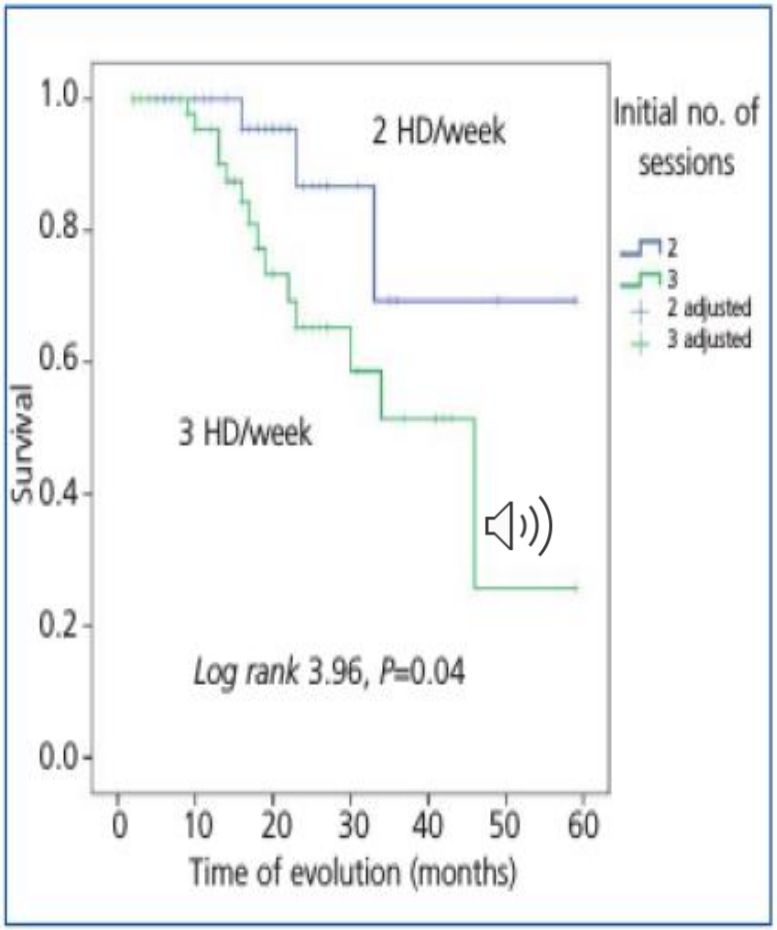


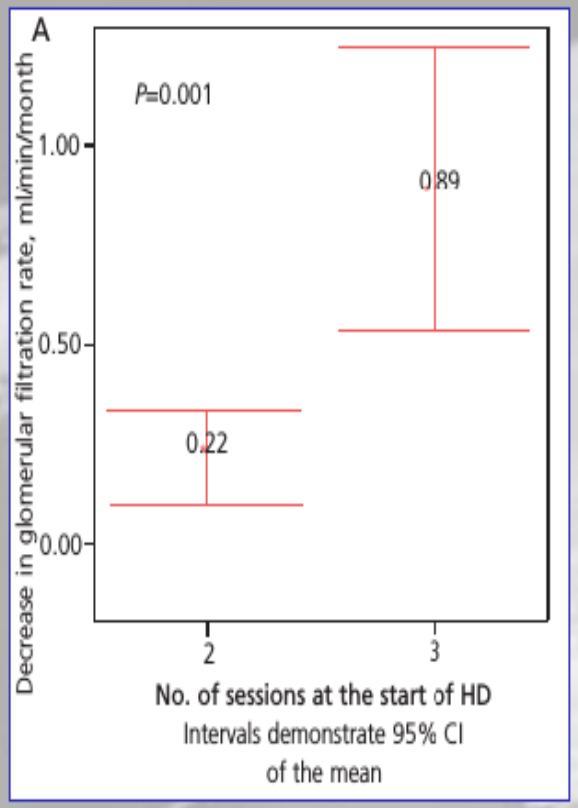
Figure 1. Actuarial survival in both patient groups.
2 HD/week: two haemodialysis sessions per week; 3 HD/week: three haemodialysis sessions per week.

greater survival

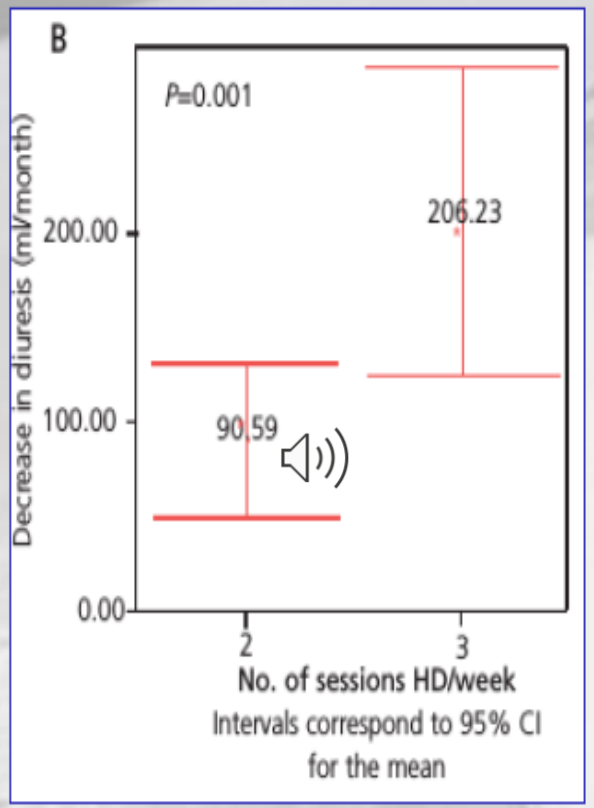
Fernández-Lucas et al, Nefrologia 2012;32(6):767-76

Outcomes with Incremental Hemodialysis

changes after 5 years



preservation of GFR



preservation of urine output

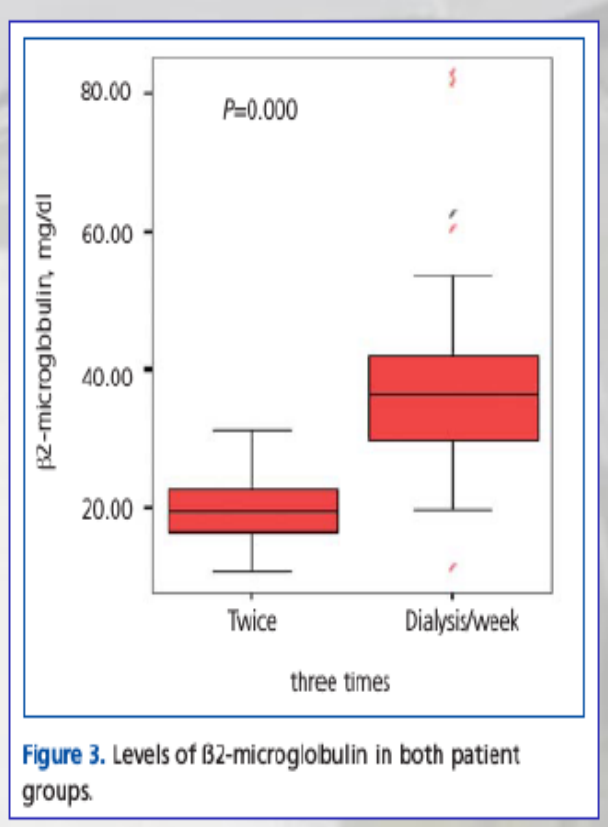
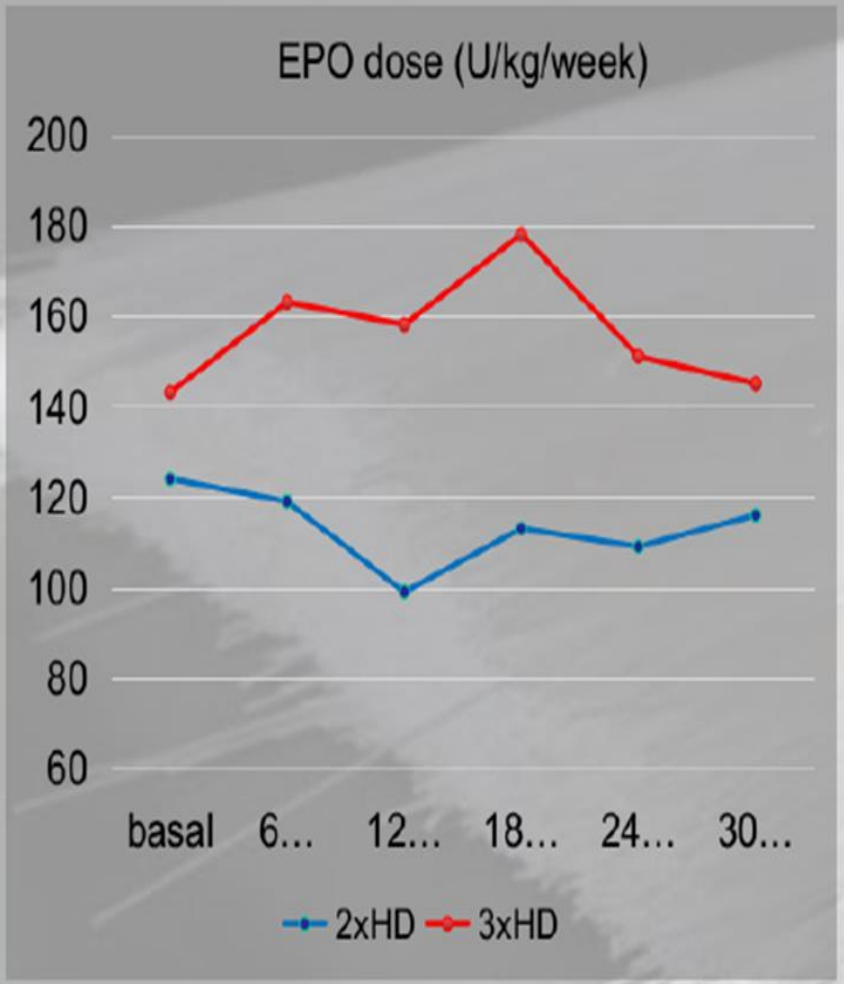


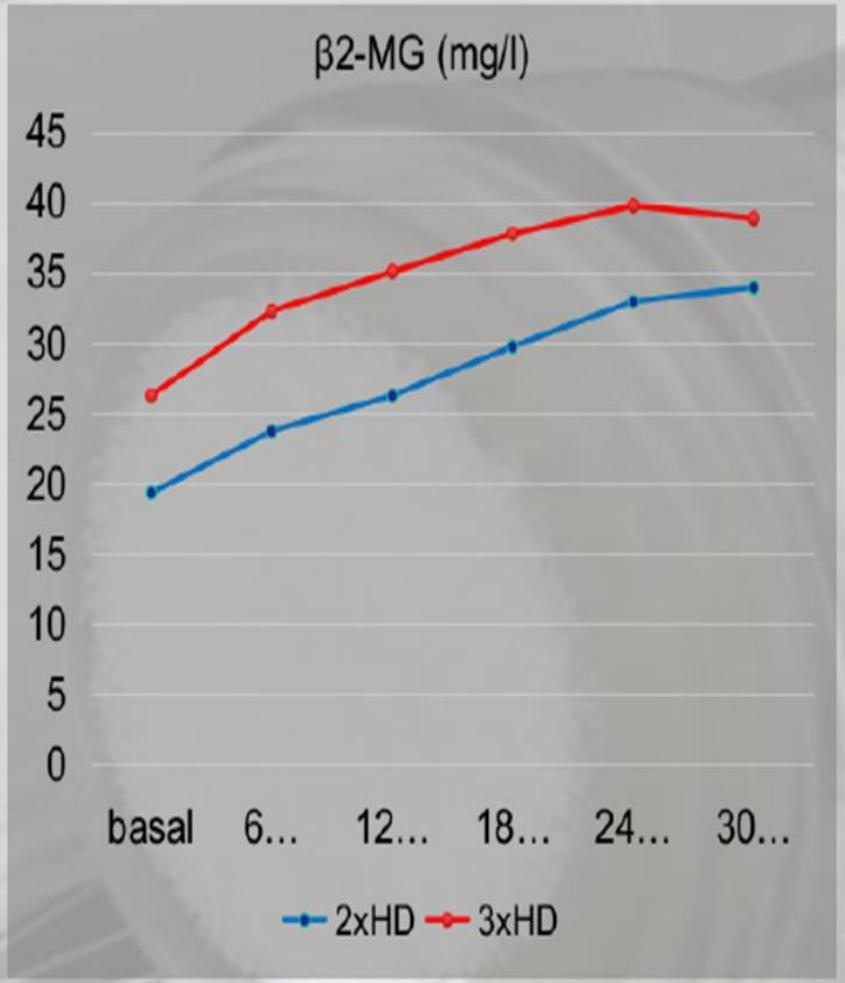
Figure 3. Levels of ß2-microglobulin in both patient groups.

greater clearence of β2-MG

Fernández-Lucas et al, Nefrologia 2012;32(6):767-76

Outcomes with Incremental Hemodialysis





Fernández-Lucas et al, Adv in Nephrol, 2014, ID 236245

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Incremental and Once- to Twice-Weekly Hemodialysis: From Experience to Evidence

Yoshitsugu Obi[1] and Kamyar Kalantar-Zadeh[1,2,3]

[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, California, USA; [2]Nephrology Section, Tibor Rubin Veterans Affairs Medical Center, Long Beach, California, USA; and [3]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA

Kidney Int Rep (2017) **2**, 781–784; http://dx.doi.org/10.1016/j.ekir.2017.07.006

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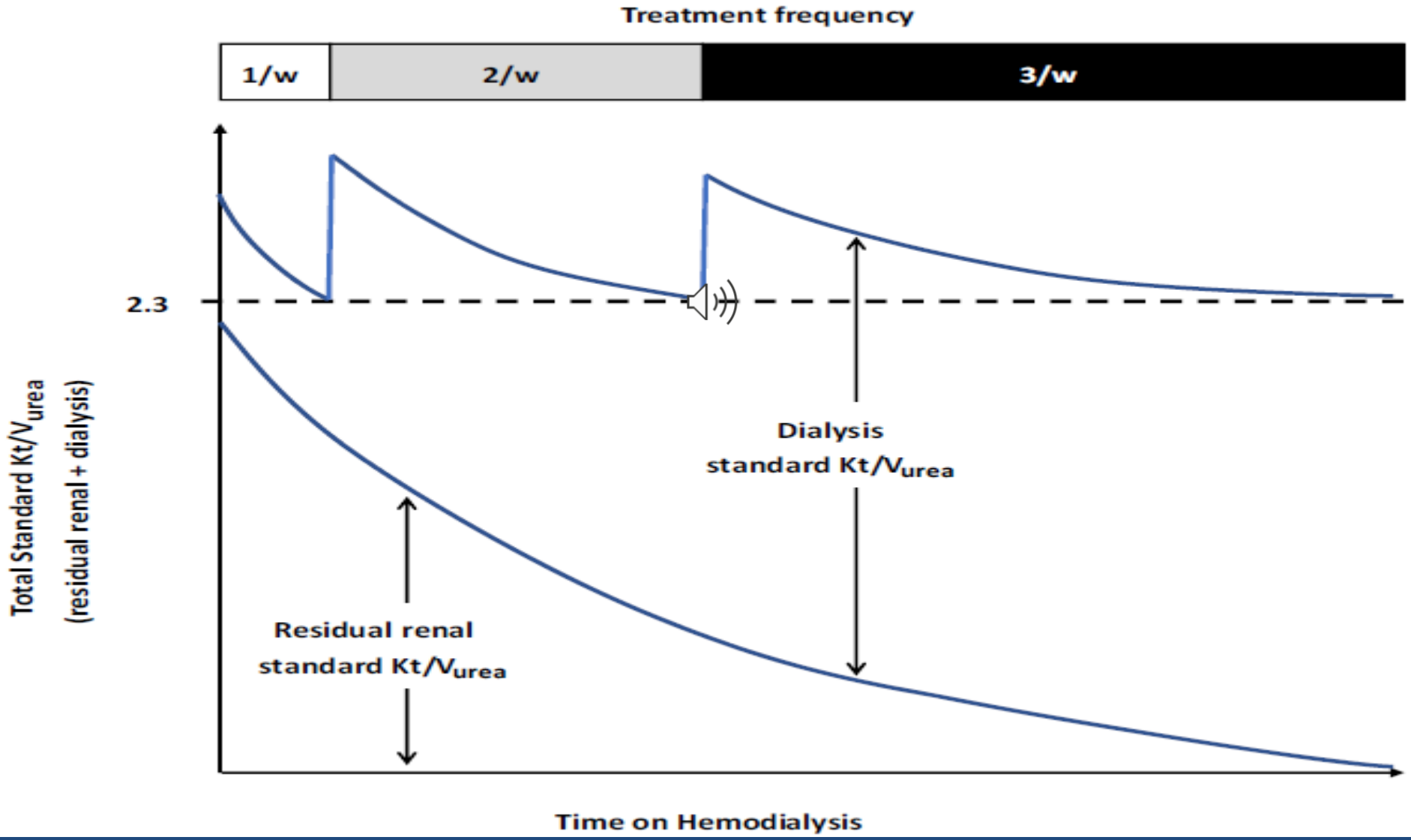
Incremental and Once- to Twice-Weekly Hemodialysis: From Experience to Evidence

Yoshitsugu Obi[1] and Kamyar Kalantar-Zadeh[1,2,3]

- Incremental HD transitioning to a thrice weekly over time as needed include better quality of life, preservation of Kru, and longer time of AVF patency.

Incremental HD



Outcomes with Incremental / less frequent HD

Observational cohorts, most retrospective, very heterogenous, different criteria and indications for less frequent HD.

authors (year of publication)	cohort (n)	survival: 2x (*1x) vs 3x weekly HD
Hanson (1999)	incident (4888), prevalent (10179)	better survival
Vilar (2009)	incident (650)	better survival
Stankuviene (2010)	incident (2428)	* higher mortality
Lin (2012)	incident (639), prevalent (673)	*similar survival*
Elamin (2012)	prevalent (2012)	higher 1 year mortality
Fernandez-Lucas (2012)	incident (95)	better survival
Fernandez-Lucas (2014)	incident (134)	*similar survival*
Obi (2016)	incident (23645)	better survival
Obi (2016)	incident (6538)	better survival
Mathew (2016)	incident (50756)	*similar survival*
Hwang (2016)	prevalent (685)	higher mortality
Park (2017)	incident (927)	*similar survival*
Yan (2018)	prevalent (1265)	*similar survival*

based on: Basile et al, J Nephrol. 2017;30(4):521.

Table 2. Summary of randomized pilot trials in the study of less frequent hemodialysis

Principal investigator(s), study, N = planned participant enrollment (per arm)	Intervention arm	Comparator arm	Key enrollment criteria	Primary Outcome
Diera *et al.*[105] Incremental Hemodialysis in Incident Patients (IHDIP) N = 75	Once-weekly HD. The number of HD sessions per week is increased to 2 and later to 3 per criteria for progression.	Thrice-weekly HD	• Age ≥18 yr • CKD stage 5 • KrU ≥ 4 ml/min per 1.73 m^2	Patient survival
Fernándex and Teruel[106] Incremental Hemodialysis as a Starting Way of Renal Replacement Therapy N = 42	Twice-weekly HD	Thrice-weekly HD	• Kru ≥ to 2.5 ml/min • Urine output: nonanuric	Change in R
Vilar[107] Incremental HD N = 25	Twice-weekly HD. The dialysis dose is adjusted according to measurement of RKF.	Thrice-weekly HD	• Age ≥18 yr • HD vintage ≤3 mo • Kru ≥3 ml/min per 1.73m^2	Feasibility
Murea[108] The TWOPLUS-HD Pilot Trial N = 101	Twice-weekly HD for 6 wk plus adjuvant pharmacologic therapy (diuretics, potassium binder, sodium bicarbonate) followed by thrice-weekly HD.	Thrice-weekly HD	• Age ≥18 yr • ESKD due to CKD progression • HD vintage ≤7 d • Urine output ≥500 ml/d	Feasibility
White[109] Dialysis-Less Frequently In The Elderly (D-LITE) N = 20	Twice-weekly HD	Thrice-weekly HD	• Age ≥70 yr • Incident ESKD and survived on HD ≥7 wk	Feasibility
Sirich[110] Efficacy of Twice Weekly Hemodialysis in Patients With Residual Kidney Function N = 25	Twice-weekly HD for 4 wk, cross-over design	Thrice-weekly HD for 4 wk; cross-over design	• Kru ≥ 2.5 ml/min	Kidney disease–rela QoL

CKD, chronic kidney disease; ESKD, end-stage kidney disease; HD, hemodialysis; Kru, residual renal urea clearance measured by timed urine collection; QoL, quality of life; RKF, residual kidney function.

Important questions about incremental HD

- Who is eligible?
- What is sufficient kidney function?
- How can we reliably measure kidney function on hemodialysis?
- What are the benefits?
- What are the risks?
- For how long can we maintain residual renal function?

Who is eligible for twice weekly hemodialysis?

- Expert opinion suggested:
- **URINE OUT > 600 cc / d and Kru> 3 cc/ min and 5 or more of 9 criteria:**
- 1. IDWG<2.5 kg 2.stable cardiovascular 3. Infrequent hospitalization 4.Satisfactory health quality of life 5.small to normal body size 6.Good nutritional status 7.absence of hyperkalemia 8. absence of hyperphosphatemia 9. absence of profound anemia

How many patients do you have ? ...

... who could be eligible for incremental hemodialysis ?

Potential benefits of Incremental Hemodialysis

- Better preservation of residual kidney function
- Better survival (?)
- Better quality of life
- Better preservations of functional status (elderly patients)
- Fewer access complications
- Lower costs (?)

Potential risks of Incremental Hemodialysis?

- Under-dialysis
  - unrecognized loss of kidney function - frequent reassessment needed !
  - inappropriate assessment of kidney function
  - patient refuses increasing dialysis frequency
- Subclinical chronic fluid overload
  - how can we diagnose without drying out the patient?
- Low adherence to volume control and diet
- Malnutrition ?
- Increased risk of hypertension, heart failure, metabolic complications

Potential problems with Incremental Hemodialysis?

- Only observational studies
  - The amount of residual kidney function was not used to determine the prescribed dose
- Need for frequent reassessment.
  - is the patient still doing well on 2x HD? When to switch to 3x HD?
  - "uremic symptoms"
- The cut-off for "significant RRF" needs to be defined.
- Measurement of residual renal function is problematic
  - urine output itself is not very reliable
  - urea based models are not sufficient
    - influenced by dialysis, chalenging calculation or requires urine collection
  - other tools in development: β2-microglobulin, β-trace protein, cystatin C, ... ?

Summary - recommendations

- Start patients on dialysis only when necessary (early start has no benefit!)

- If patient has residual kidney function (eGFR>3-5ml/min ?)
  - start on Peritoneal Dialysis
  - or on Incremental Hemodialysis (2x weekly)
- Use diuretics and avoid ultrafiltration whenever possible

- Other measures to preserve kidney function
  - prescribe ACEi, ARB, avoid nephrotoxins

- <u>Reassess patient and dialysis requirement</u>
  Increase dialysis dose when
  kidney function deteriorates