



## Could incremental haemodialysis be a new standard of care?

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# Ancient Greek colonies and their dialect groupings in Southern Italy (Magna Graecia)




# Taranto

- **Founded by Spartans in the 8th century BC**

They called the city Taras (Τάρᾱς) after the mythical hero Taras

- **Taranto was among the most important poleis in Magna Graecia, becoming a cultural, economic and military power**
- **By 500 BC, the city was among the largest in the world, with a population estimated up to 300,000 people**

## **Is incremental hemodialysis ready to return on the scene? From empiricism to kinetic modelling**

**Carlo Basile<sup>1</sup>  · Francesco Gaetano Casino<sup>1,2</sup> · Kamyar Kalantar-Zadeh<sup>3,4,5</sup>**

- **Most people who make the transition to maintenance dialysis therapy are treated with a fixed dose of thrice-weekly haemodialysis (3HD/wk) regimen without considering their residual kidney function (RKF).**
- **Although the regulatory agencies might consider the 3HD/wk regimen as “standard of care” and “adequate requirement”, it is by no means perfect.**
- **The 3HD/wk regimen has been assumed, until recently, almost as a dogma in the dialysis community. Incredibly, it has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatments would be inadequate or harmful.**

# Early mortality is elevated in the first 6-12 months after initiating dialysis

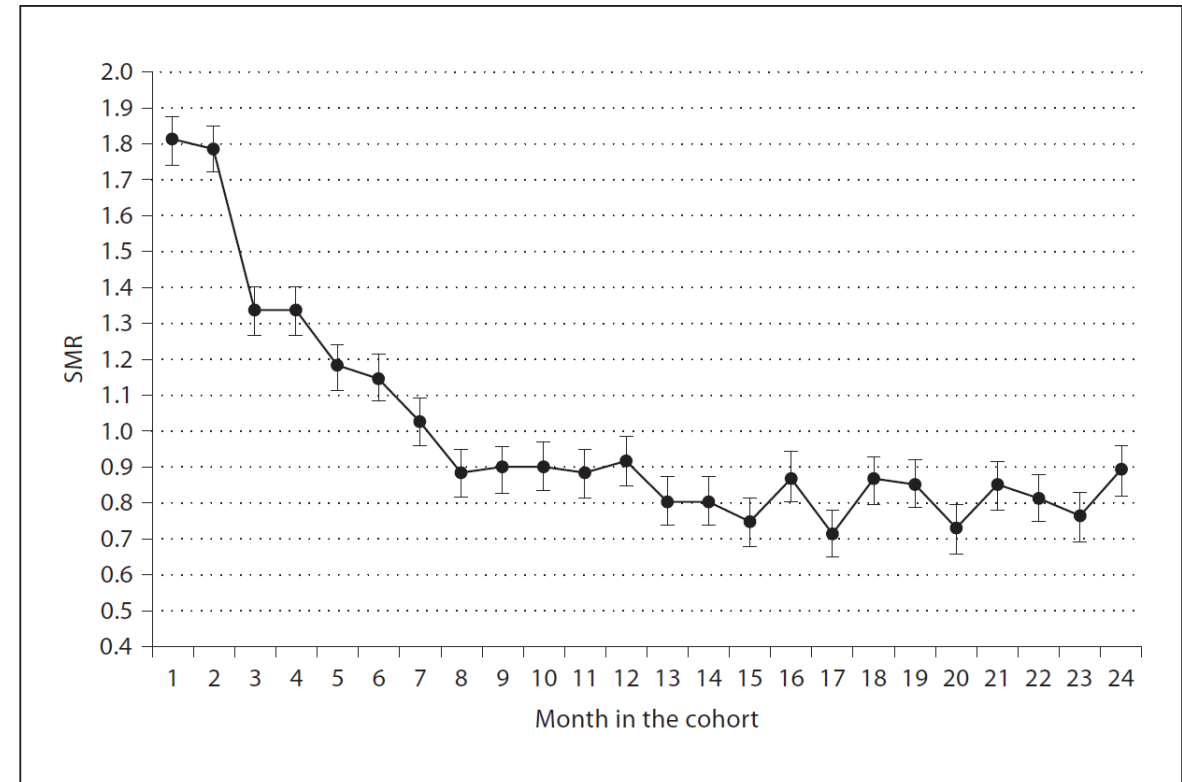
- Standardised mortality, n=18707 incident patients
- Reference group for comparison: 57456 HD patients (Da Vita cohort, US)

## Possible causes:

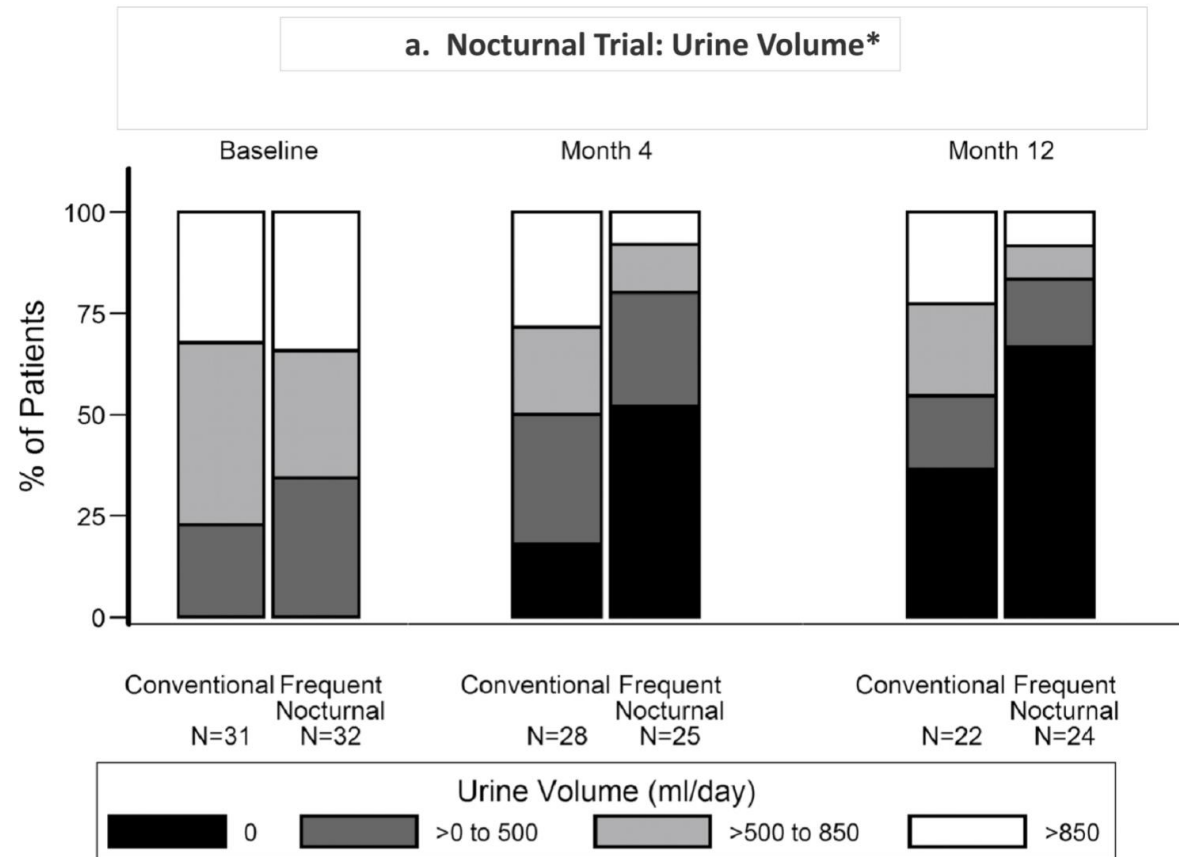
Patient selection ?

Dialysis “shock” ?

Excessive ultrafiltration  
/cardiovascular events ?



# Frequent HD regimes may result in loss of residual kidney function (RKF)

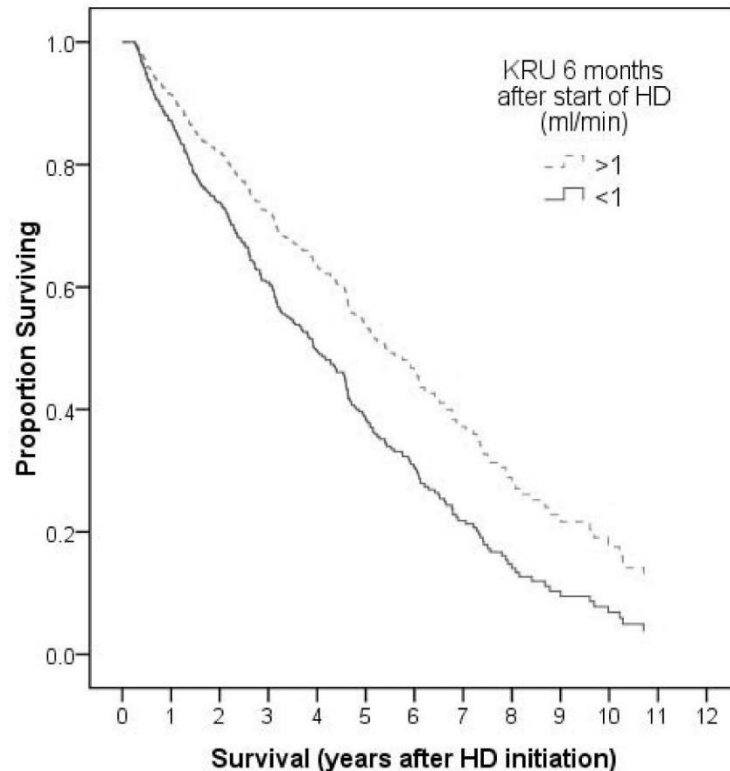


\*In subjects with nonzero urine volume at baseline.

## Loss of RKF in nocturnal HD:

Data from the Frequent Haemodialysis Network: In the **frequent** dialysis group, urine volume had declined to zero in 52% and 67% of patients at months 4 and 12, respectively, compared with 18% and 36% in controls

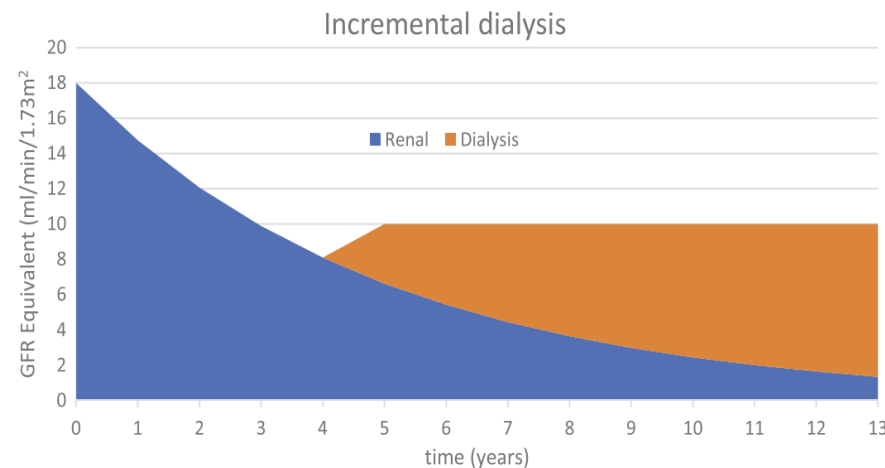
# Residual kidney function: a key predictor of outcomes in HD



	Sig (p)	Hazard ratio
<b>6 month KRU<math>\geq</math>1ml/min</b>	0.01	0.693
<b>Diabetic status</b>	0.306	1.210
<b>Age</b>	<0.001	1.029
<b>Albumin</b>	0.002	0.959
<b>HDF use</b>	<0.001	0.523
<b>Malignancy</b>	0.001	1.814
<b>Ischaemic heart disease</b>	0.620	0.931
<b>Peripheral vascular disease</b>	0.543	1.107

# What is incremental dialysis ?

- Aims to provide the required amount of dialysis at the right time, based on RKF
- Based on step-wise or incremental increase in dialysis as RKF falls
- Based on the premise that a gradual increase in dialysis dose may preserve RKF
- Aims to reduce the “shock” of starting dialysis and reduce exposure to the harmful effects of dialysis



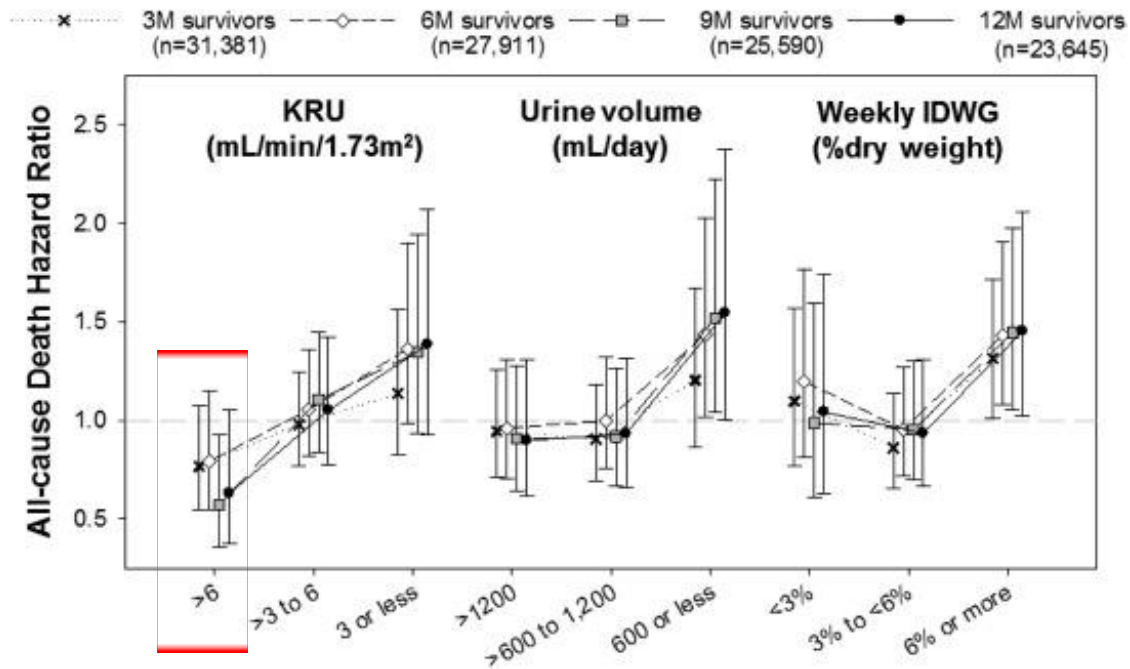


# Possible benefits of incremental HD

- Less exposure to harmful effects of haemodialysis
- Less usage of vascular access, less complications
- Gentle start of dialysis in the early period in which mortality is high
- Dialysis-free time
- Reducing dialysis frequency can allow to dialyse others more frequently
- Quality of life
- Less burden of treatment
- Less exposure to aggressive attempts at ultrafiltration
- Lower therapy cost

# Who is safe for incremental HD?

- Literature supports twice-weekly dialysis likely to be safe if kidney urea clearance (KRU) above 3mL/min/1.73m<sup>2</sup> BSA



N=23645

DaVita US cohort

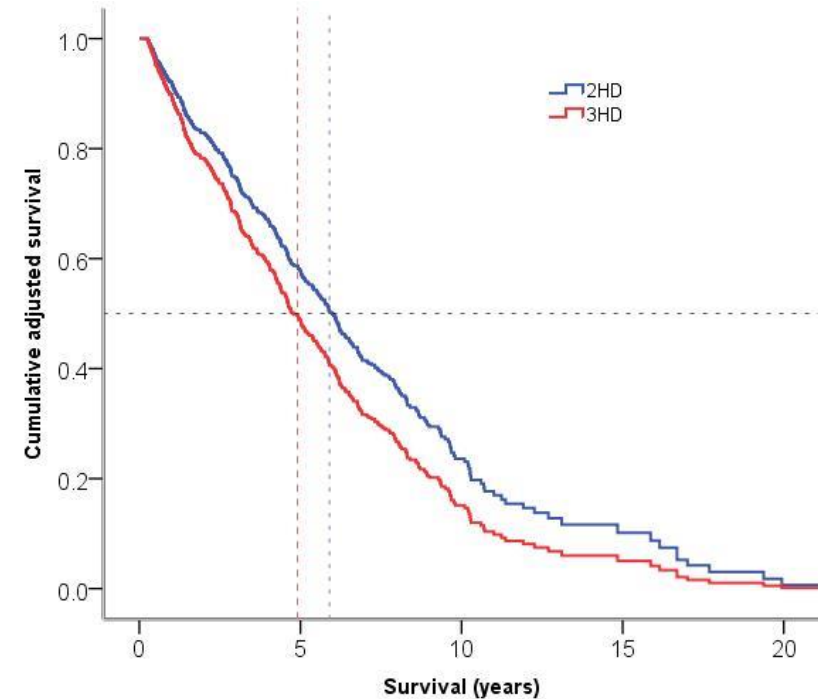
Initiated HD 2007-2010

Incremental HD showed similar mortality if KRU >3mL/min/1.73m<sup>2</sup>

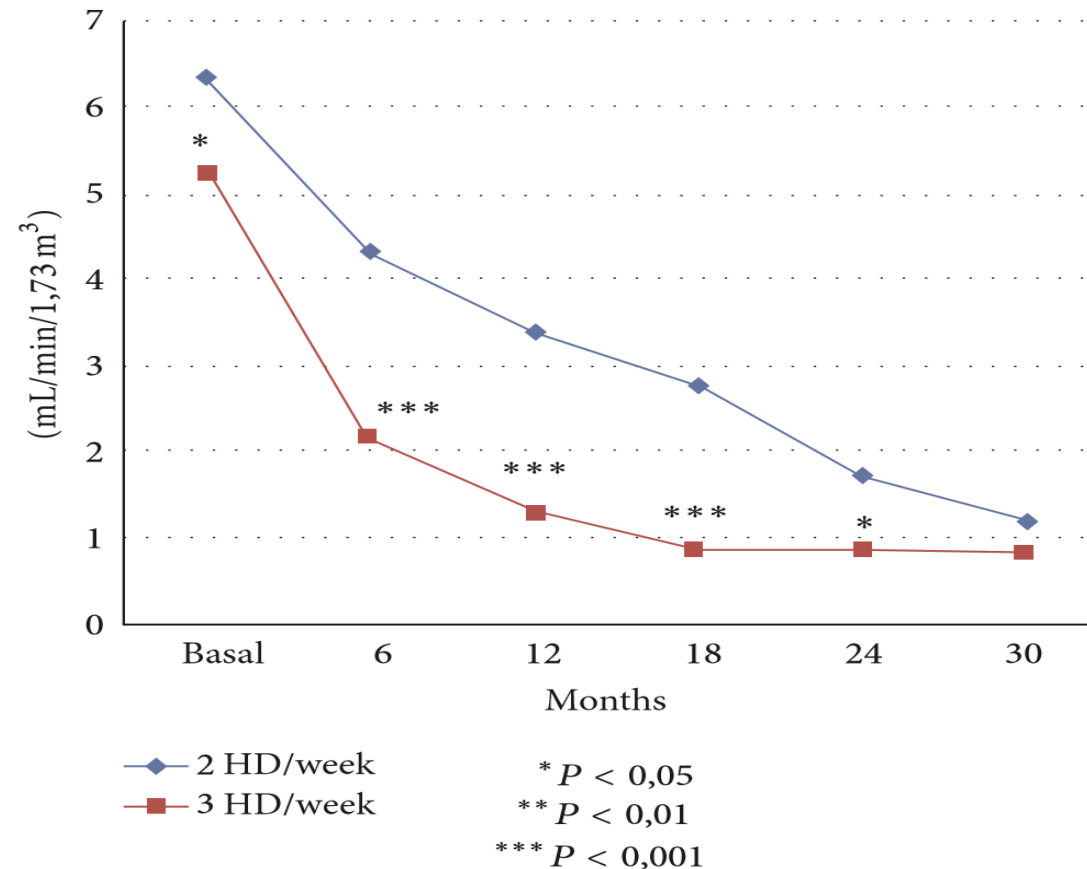
Higher mortality below this

# Safety of incremental HD for patients with KRU $>3\text{ml}/\text{min}/1.73\text{m}^2$ BSA

- Retrospective, single centre UK study
  - n=154 2x weekly patients
  - n=411 3x weekly patients
  - >5 year follow up
  - Baseline KRU  $\geq 3\text{ml}/\text{min}$
- 
- Multivariate analysis: hazard ratio for death 0.76 in incremental HD compared to 3x weekly



# Slower loss of kidney function in twice-weekly HD: data from Spain



# Loss of RKF in an observational cohort in Taiwan: twice-weekly vs. thrice-weekly HD

		2x weekly	3x weekly	p
Urine Volume	Start	1072 ± 700	1048 ± 703	0.901
	End	1551±1094	660± 1106	0.005
	Changes per month	160 ± 442	-20 ± 102	0.022

Mean follow up 18 months  
N=23 2x weekly v 51 3x weekly

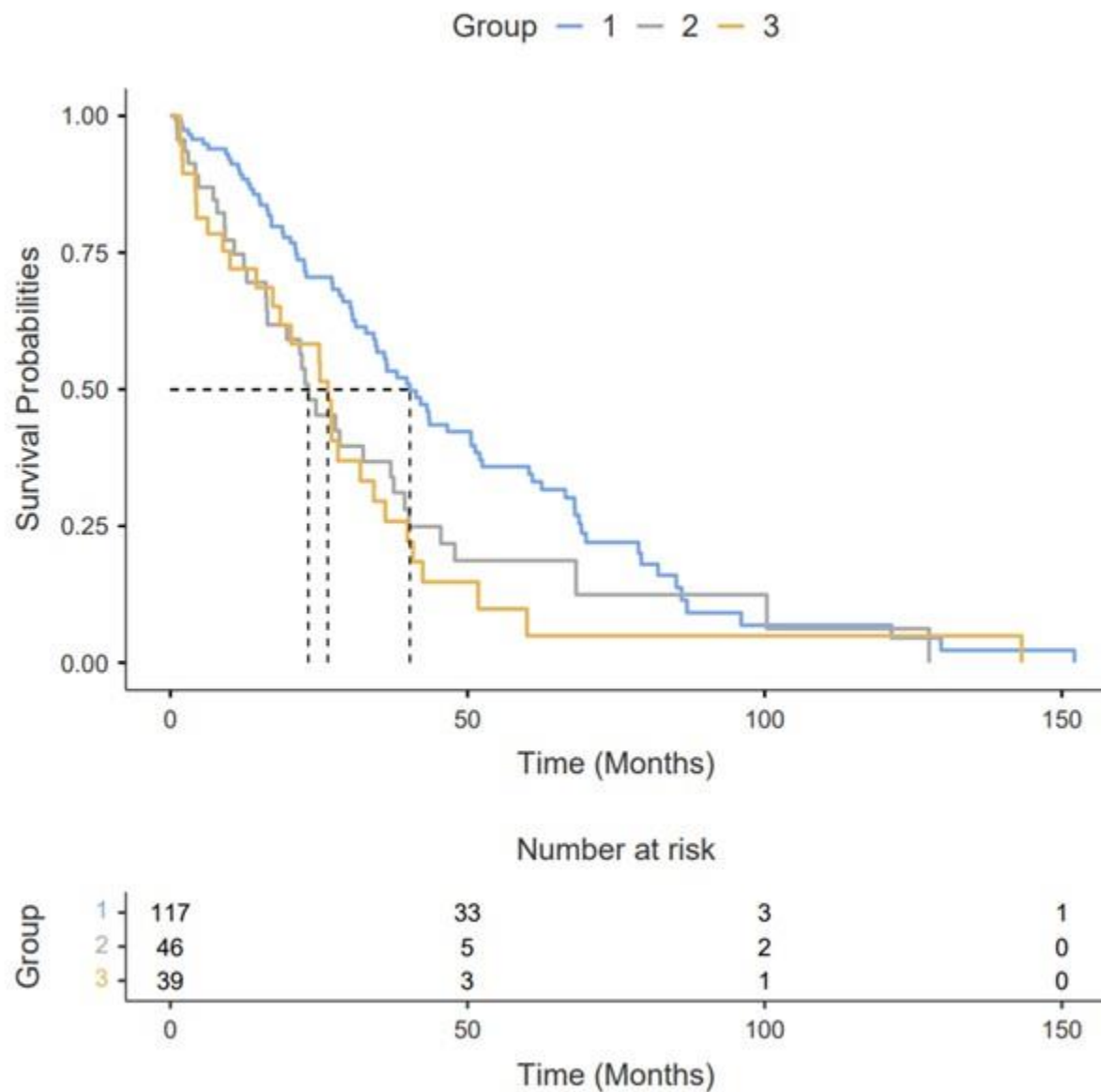
# Main demographic, clinical and laboratory data of the 202 patients enrolled into the study

Age (years)	66 ± 15
Gender (male/female)	120/82
Body weight (kg)	63.2 ± 13.3
Blood urea nitrogen (mg/dl)	99 ± 33
Serum creatinine (mg/dl)	8.0 ± 3.1
Kru (ml/min/1.73 m <sup>2</sup> )	4.5 ± 1.6
CrCl (ml/min/1.73 m <sup>2</sup> )	8.0 ± 2.9
Urine Output (ml/day)	1800 ± 700
<b>Group 1 (G1): start on 1HD/wk</b>	<b>117 (57.9%)</b>
<b>Group 2 (G2): start on 2HD/wk</b>	<b>46 (22.8%)</b>
<b>Group 3 (G3): start on 3HD/wk</b>	<b>39 (19.3%)</b>
Charlson comorbidity index	6.9 ± 2.6

## Duration of dialysis treatments in the three groups of patients

	G1 (N=117)	G2 (N=46)	G3 (N=39)
Months on 1HD/wk	11.9 ± 14.8	0	0
Months on 2HD/wk	13.0 ± 20.3	16.7 ± 23.2	0
Months on 3HD/wk	37.4 ± 46.5	34.7 ± 38.6	56.3 ± 55.3
Months of follow-up	62.6 ± 48.8	51.4 ± 40.8	56.3 ± 55.3

# Time to event (UO $\leq$ 200 ml/day)



## Median Estimates

	Median	Lower	Upper
1	40.3	34.5	52.0
2	23.2	16.3	39.4
3	26.5	18.5	36.2

## Analysis of the differences

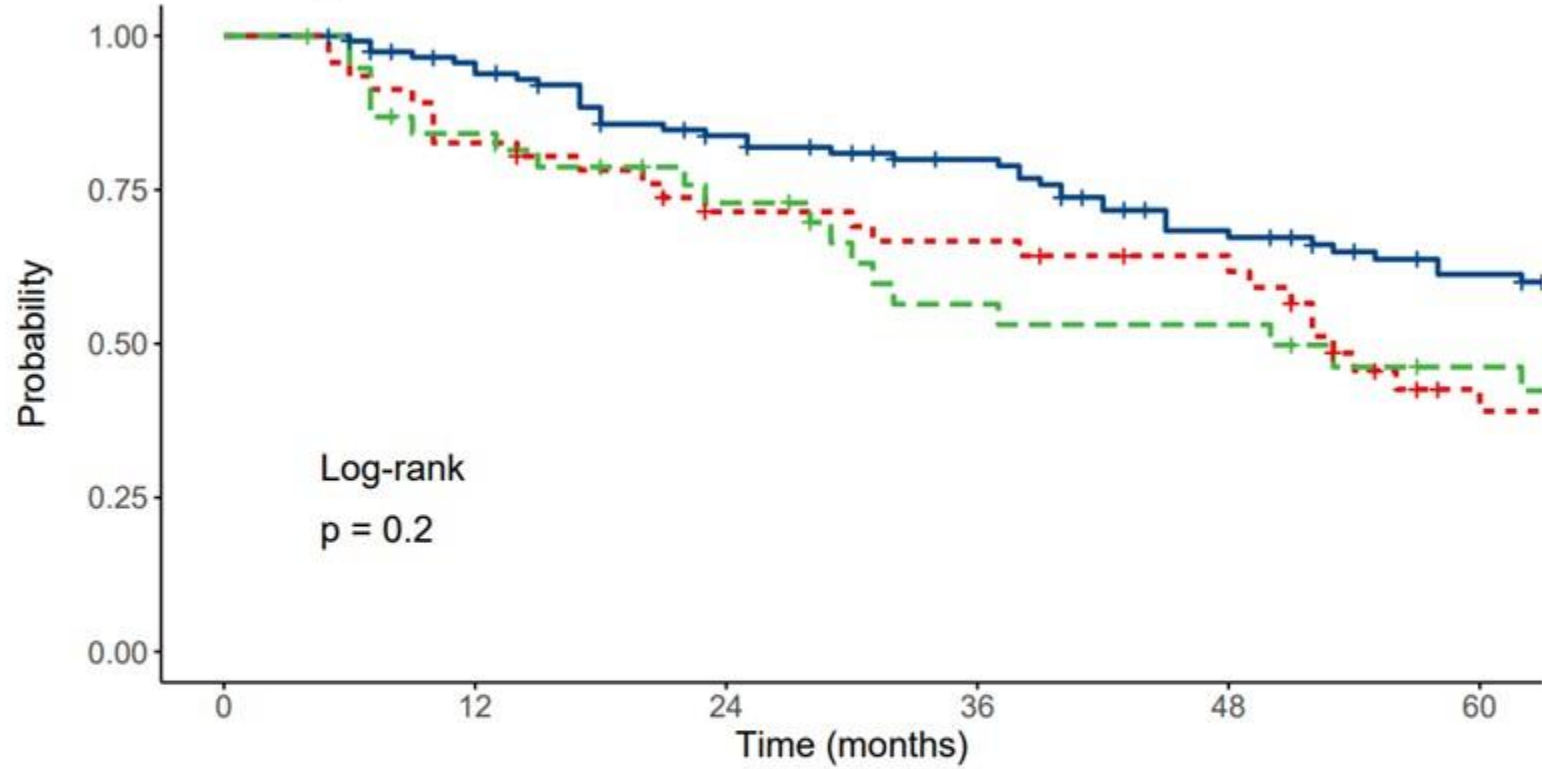
Test	$\chi^2$	df	p
Log-rank	11.8	2	0.003

## Pairwise Comparisons

	Test	v	SE	z	p
1 2	Log-rank	10.42	4.28	2.435	0.015
1 3	Log-rank	11.85	3.73	3.174	0.002
2 3	Log-rank	1.71	3.87	0.443	0.658



Survival curves for Group  
Based on Kaplan-Meier estimates



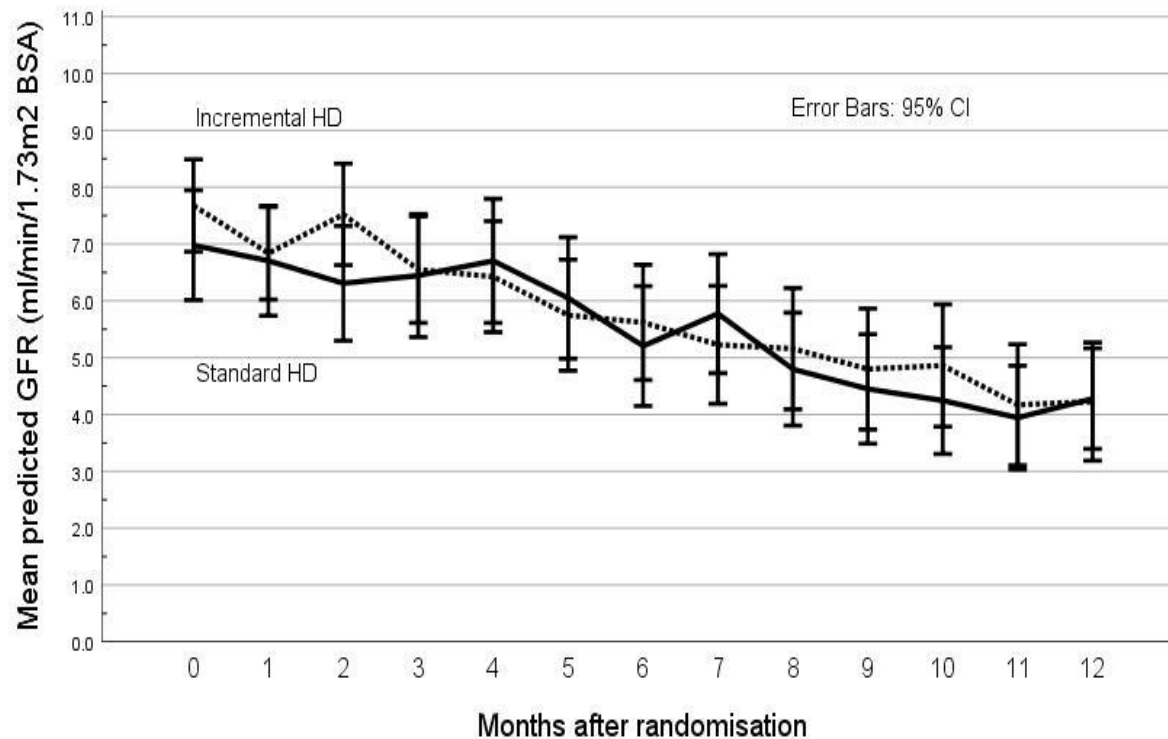
1, 3, 5 year Survival - Group

Levels	time	Number at Risk	Number of Events	Survival	95% Confidence Interval	
					Lower	Upper
Group=1	12	107	7	93.8 %	89.5 %	98.4 %
Group=1	36	78	15	79.9 %	72.7 %	87.8 %
Group=1	60	50	17	61.3 %	52.3 %	71.8 %
Group=2	12	38	8	82.6 %	72.4 %	94.3 %
Group=2	36	28	7	66.7 %	54.2 %	82.0 %
Group=2	60	12	10	39.0 %	26.1 %	58.3 %
Group=3	12	31	6	84.1 %	73.2 %	96.6 %
Group=3	36	17	9	56.4 %	41.8 %	76.1 %
Group=3	60	12	3	46.2 %	31.8 %	67.3 %

Number at risk

Group=1	117	107	88	78	62	50
Group=2	46	38	30	28	25	12
Group=3	39	31	25	17	16	12

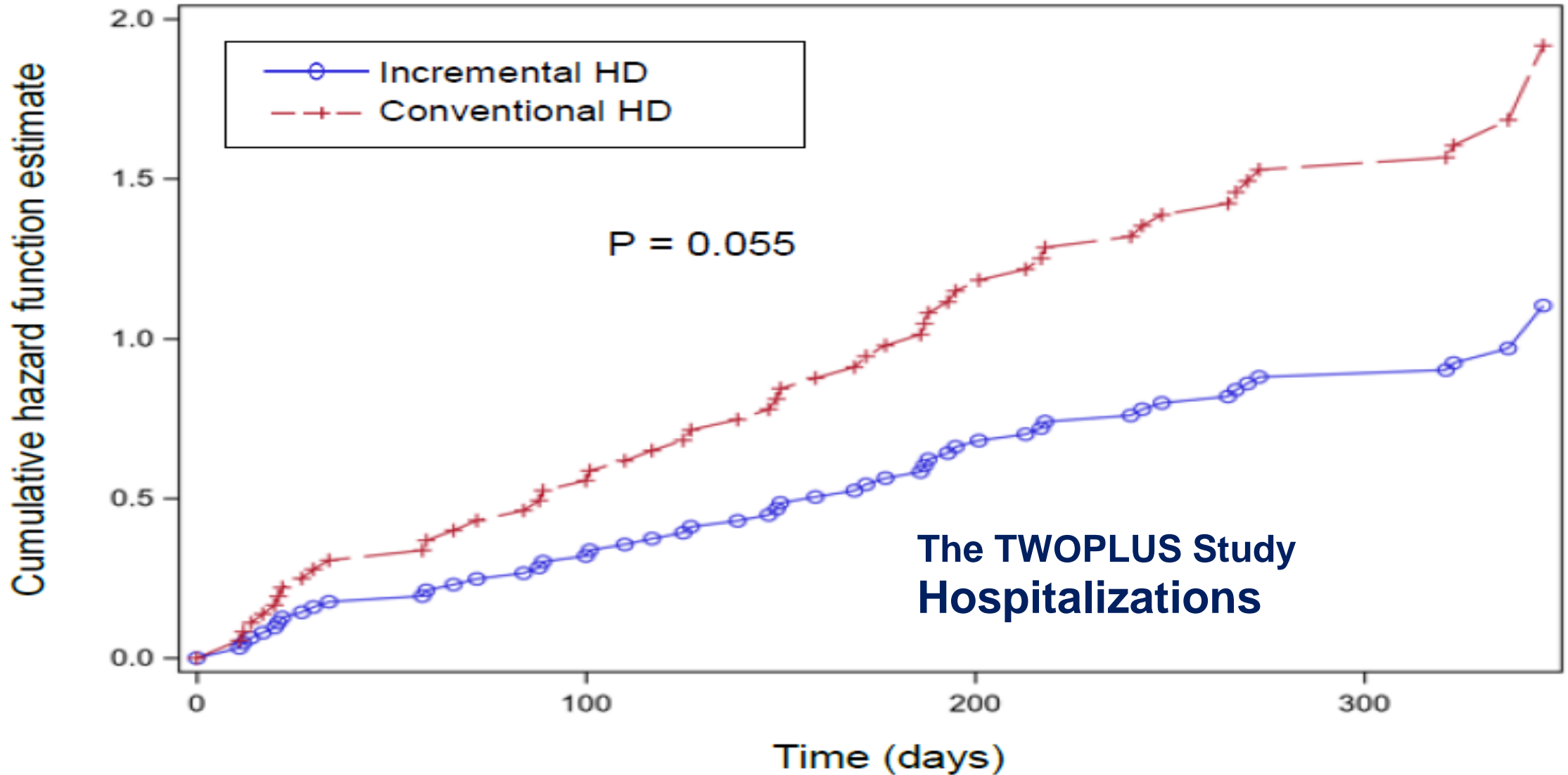
# Multicenter feasibility RCT to assess the impact of incremental versus conventional initiation of hemodialysis on RKF



- Trend towards slower decline in RKF (not significant though)

# Twice-weekly hemodialysis with adjuvant pharmacotherapy and transition to thrice-weekly hemodialysis: a pilot study

Murea et al, Am J Kidney Dis 2022;80:227–40



Nephrol Dial Transplant (2023) 38: 855–857

<https://doi.org/10.1093/ndt/gfac281>

Advance Access publication date 7 October 2022



# Towards a tailored prescription of dialysis adequacy: the key role of incremental haemodialysis

Carlo Basile<sup>1</sup>, Francesco Gaetano Casino<sup>2</sup> and Sandip Mitra<sup>3</sup>; on behalf of the EuDial Working Group of the European Renal Association



**“The quest for a reliable dialysis adequacy index/criteria has been a constant feature through the decades in dialysis. While agreeing that evaluating dialysis adequacy should not rely on a single index, we would like to point out the need to keep urea kinetic model (UKM) as the gold standard, as it is the only established tool for assessing and prescribing dialysis.”**

**Its reference solute is urea**

National Kidney Foundation. KDOQI clinical practice guidelines for hemodialysis adequacy: 2015 update. Am J Kidney Dis 2015; 66: 884-930

European Best Practice Guidelines. II.3 Haemodialysis dose and residual renal function (Kr). Nephrol Dial Transplant 2002; 17 (Suppl 7): 24

# Common methods of performing calculations for incremental HD (1)

- **Standard Kt/V**

$$\text{Std Kt/VTOTAL} = \text{StdKt/V RENAL} + \text{StdKt/V DIALYSIS}$$

Gotch / Daugirdas

# Common methods of performing calculations for incremental HD (2)

Nephrol Dial Transplant (1996) 11: 1574–1581

*Original Article*

**The equivalent renal urea clearance: a new parameter to assess dialysis dose**

F. G. Casino and T. Lopez

**Nephrology  
Dialysis  
Transplantation**

## Casino-Lopez Equivalent Continuous Clearance

Convert intermittent dialysis clearance (Kt/V) to an equivalent dialytic urea clearance (EKRd) and add to native kidney urea clearance (Kru)

$$\text{total EKR} = \text{EKRd} + \text{Kru}$$

European Best Practice Guidelines. II.3 Haemodialysis dose and residual renal function (Kr). Nephrol Dial Transplant 2002; 17 (Suppl 7): 24








### Guideline II.3

A. In the case of significant residual renal function (Kr), the amount of therapy to be delivered with HD may be estimated with the aid of the equivalent renal urea clearance (EKR).

(Evidence level: B)



# Prescribing the dialysis dose and treatment frequency in home haemodialysis

Francesco Gaetano Casino <sup>1</sup>, Maria Fernanda Slon Roblero<sup>2</sup>, Silvia González-Sanchidrian <sup>3</sup>, Sandra Gallego Dominguez<sup>3</sup>, Ignacio Lorenzo Ferris<sup>2</sup>, Valerie A. Luyckx <sup>4,5,6</sup>, Vassilios Liakopoulos <sup>7</sup>, Sandip Mitra <sup>8</sup>, Javier Deira Lorenzo <sup>3</sup> and Carlo Basile <sup>9</sup>; on behalf of the EuDial Working Group of the European Renal Association (ERA)

# The prescription graph shows that treatment frequency depends essentially on KRUn

Simplified prescription rule

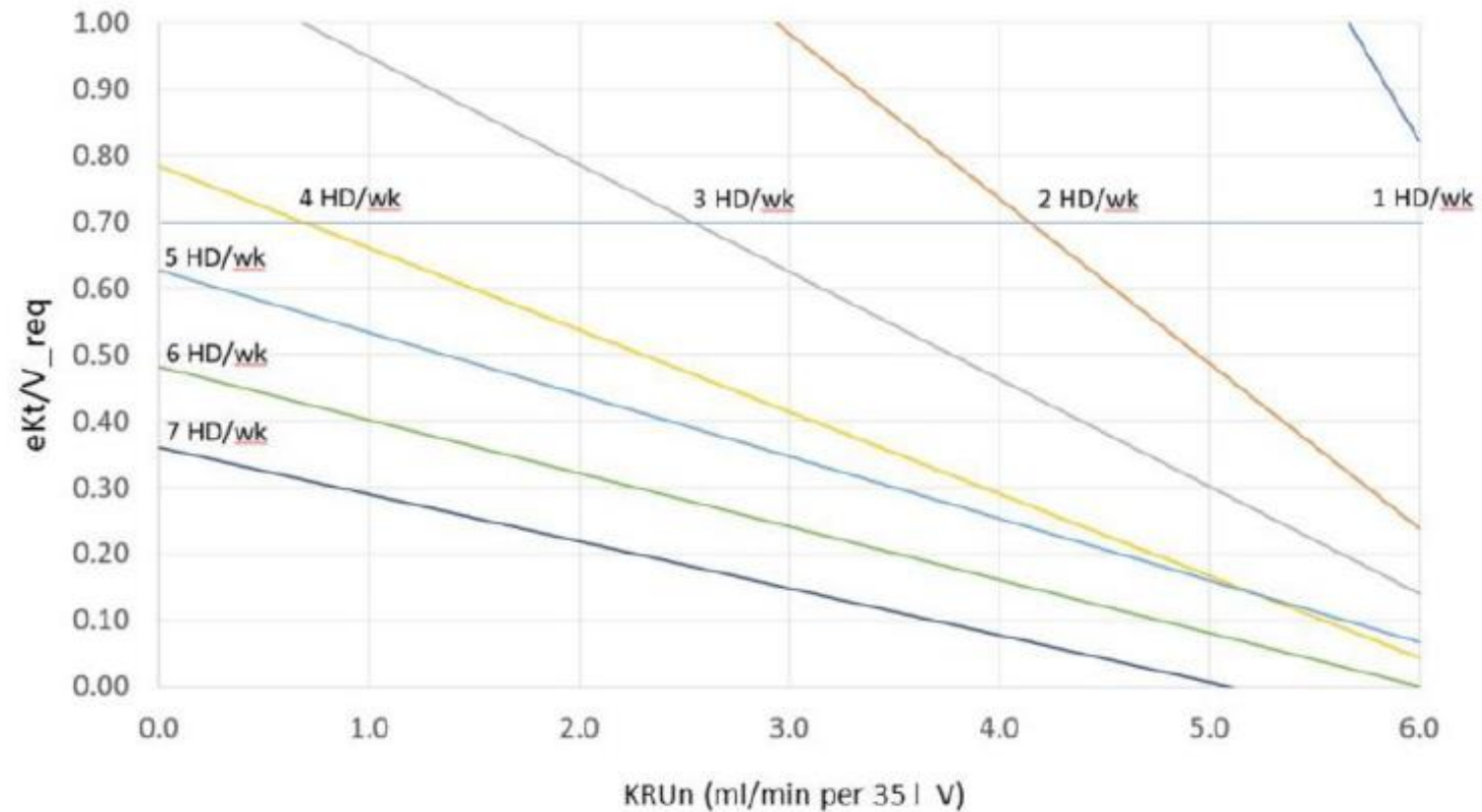
KRUn >6 -> 1 HD/wk

KRUn ≥4 -> 2 HD/wk

KRUn ≥2 -> 3 HD/wk

KRUn ≥1 -> 4 HD/wk

KRUn <1 -> 5+ HD/wk



**To our knowledge, these are the ongoing RCTs on incremental dialysis**

**The recently started RCT in Australia-NZ-Canada not listed**

**Upcoming Veterans INCHVETS not listed**

Investigator(s), study, N=planned enrollment/arm	Intervention arm	Control arm	Key enrollment criteria	Primary Outcome	Country, start date	Trial Registry
Deira et al. Incremental HD in Incident Patients (IHDIP), N=75	1x/wk HD, then to be increased to 2 and 3 x/wk per criteria	3x/wk HD	<ul style="list-style-type: none"> <li>• CKD stage 5</li> <li>• KrU <math>\geq</math> 4 ml/min</li> </ul>	Patient survival	Spain/Italy, 8/2017	NCT03239808
Fernández & Teruel Incremental HD, N=42	2x/wk HD	3x/wk HD	<ul style="list-style-type: none"> <li>• Kru <math>\geq</math> to 2.5 ml/min</li> <li>• UOP: non-anuric</li> </ul>	Change in RKF	Spain, 10/2017	NCT03302546
Casino et al Incremental HD, N=190	1x/wk HD, then to be increased to 2 and 3 x/wk per criteria	3x/wk HD	<ul style="list-style-type: none"> <li>• CKD stage 5</li> <li>• KrU <math>\geq</math> 4 ml/min</li> </ul>	Time to anuria	EuDial WG 07/2022	NCT04360694
White, Less Frequently In The Elderly (D-LITE), N=20	Twice-weekly HD	3x/wk HD	<ul style="list-style-type: none"> <li>• Age <math>\geq</math>70 yr</li> <li>• Incident HD <math>\geq</math>7 wk</li> </ul>	Feasibility	Canada, 12/2018	NCT03787719
Sirich, Efficacy of Twice Weekly HD in Patients With RKF, N = 25	Twice-weekly HD for 4 wk, cross-over design	3x/wk HD for 4 weeks	<ul style="list-style-type: none"> <li>• Kru <math>\geq</math> 2.5 ml/min (cross-over design after 4 weeks)</li> </ul>	KD-QoL	California, USA, 3/2019	NCT03874117



DEPARTMENT OF NEPHROLOGY  
POLICLINICO OF BARI



DIVISION OF NEPHROLOGY  
MIULLI HOSPITAL



# REAL LIFE

Randomiz**E**d clinic**A**L trial**L** on the eff**i**cacy and sa**F**ety of incremental ha**E**modialysis

[www.IncrementalDialysis.eu](http://www.IncrementalDialysis.eu)

If you need more information about the RCT REAL LIFE (above all how to participate into the study), you can contact:

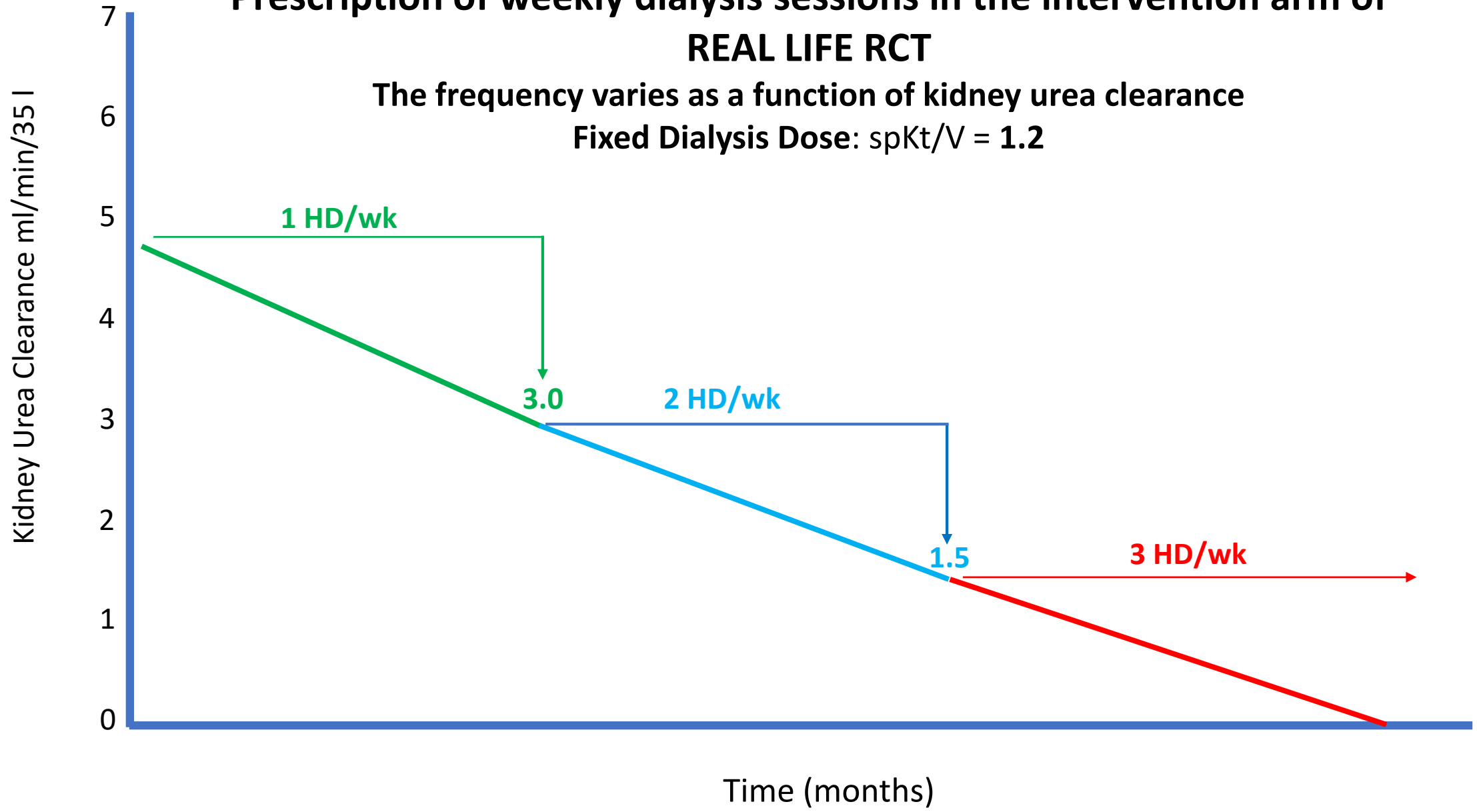
- [Francesco Casino](#)
- [Carlo Basile](#)
- [Valentina Cocchi](#)

Study Protocol  
Informed Consent



# Prescription of weekly dialysis sessions in the intervention arm of REAL LIFE RCT

The frequency varies as a function of kidney urea clearance  
Fixed Dialysis Dose:  $spKt/V = 1.2$



# Educational aspects of incremental HD

- Requires patients to have education in importance of the individualised therapy and an acceptance that dialysis intensity may have to be increased in future
- Patient education in accurate measurement of RKF
- Investment of time needed in pre-dialysis education stage
- Requires staff education: clear and consistent messaging
- Requires investment of staff time in measurement of RKF and dialysis dose

# Summary (1)

- Growing interest in incremental haemodialysis which was previously a minority sport
- SARS-CoV-2 pandemic has drawn attention to benefits of less frequent dialysis regimes
- In HD, there are complexities with combining dialysis dose with RKF but tools have been developed to facilitate this

# Summary (2)

- Retrospective data suggest RKF may be lost less quickly if dialysis is initiated less frequently than 3 times a week
- Prospective data from RCTs do not indicate any signal of harm and may indicate incremental HD has a protective effect for RKF
- Definitive data from RCTs are required to define the benefits of incremental HD
- Patient and staff education are a key aspect of a successful incremental dialysis programme





Marcus Valerius Martialis  
(40? AD - 104? AD)  
Roman poet

***The real voyage of discovery  
consists not in seeking new  
lands, but in having new eyes***