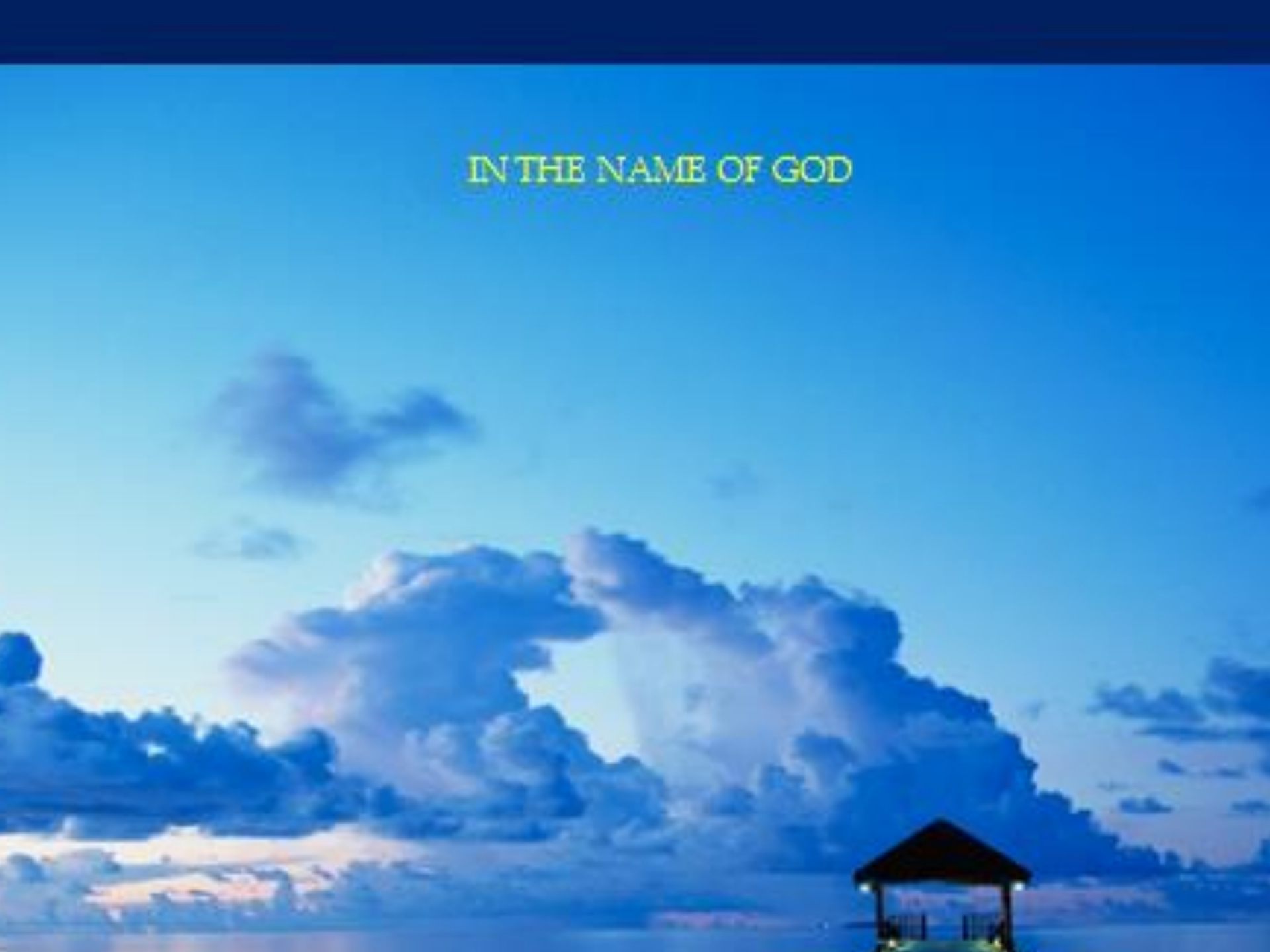

IN THE NAME OF GOD

What's new about chronic hemodialysis adequacy ?

Dr.F.Haghverdi MD

Outline

- History of HD adequacy?
- Kt / V limitation?
- Kt /BSA? , Kt /TEE?
- Incremental hemodialysis ?
- Survival benefit with HDF? (CONVINCE study),Are we convinced?

History of HD

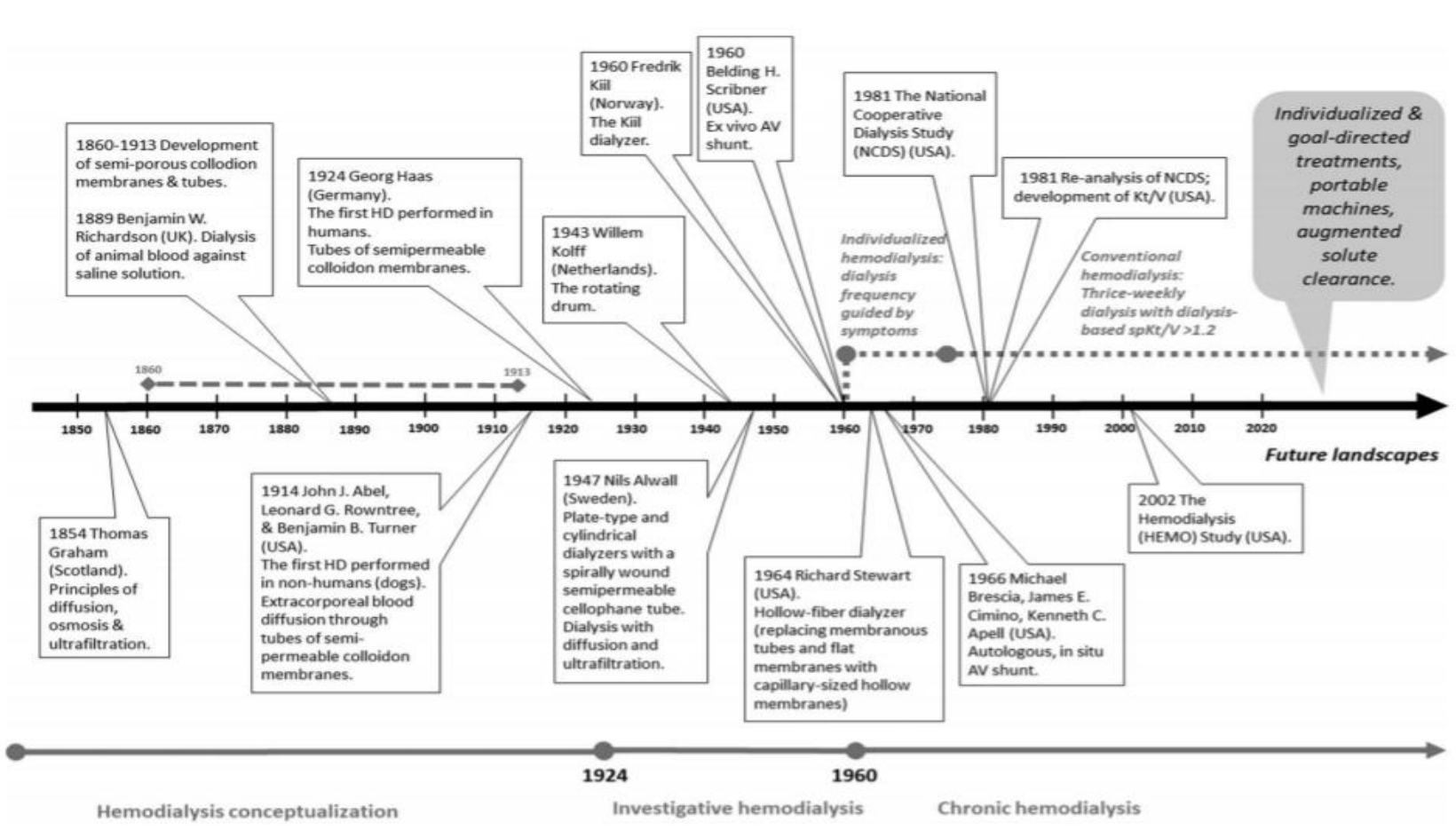
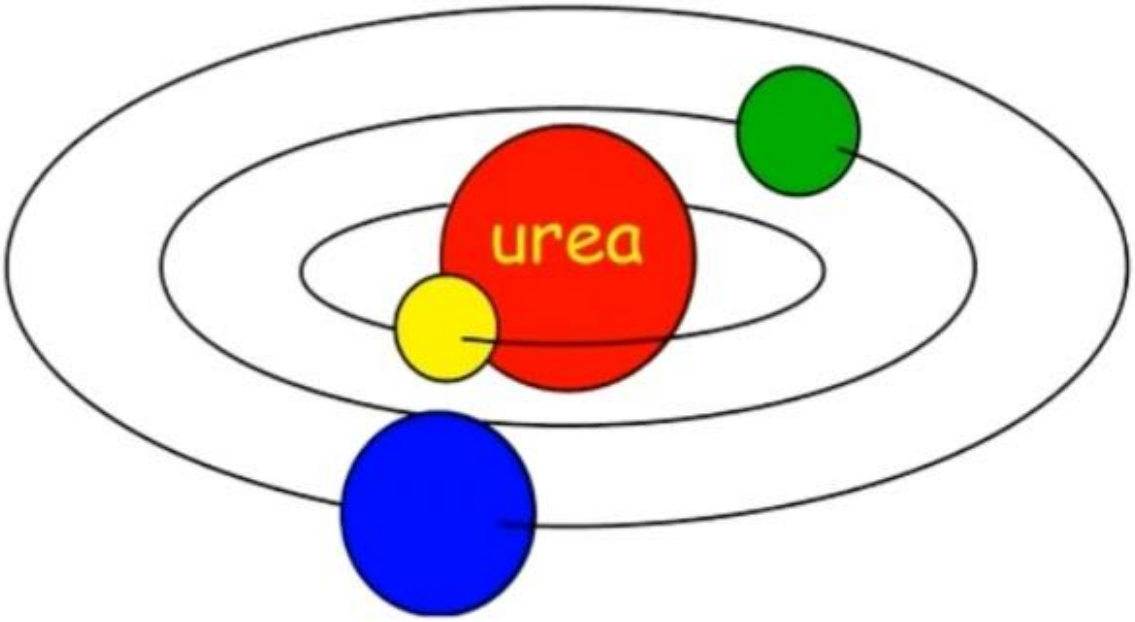


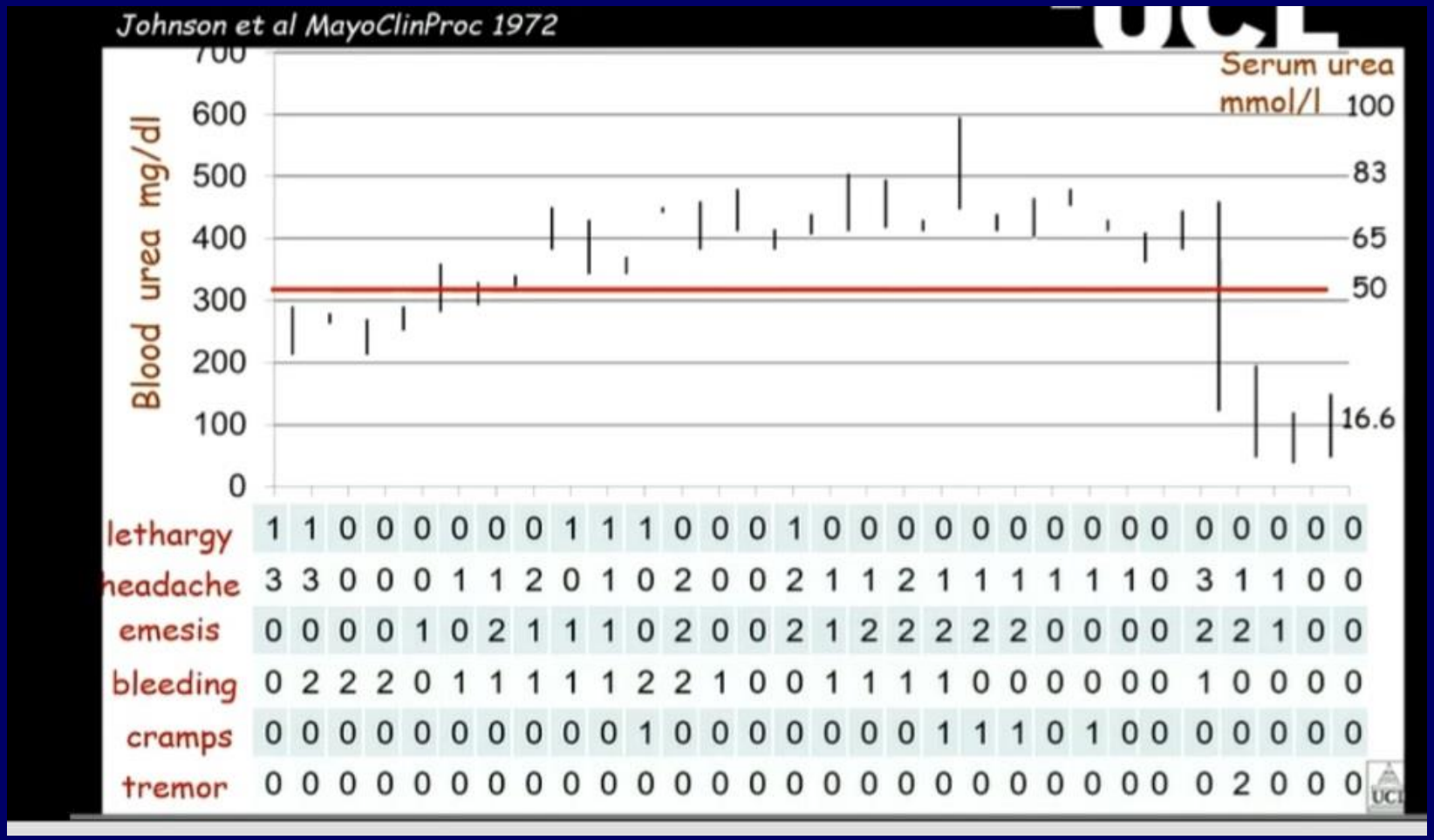
Figure 1. A timeline of the evolution of HD. From conceptualization to contemporary practice, HD transformed from individualized treatments offered to a small patient population to uniform prescription offered to a large patient population. We envision a future that borrows elements from the past (*i.e.*, individualized treatments) and capitalizes on scientific and technological progress. HD, hemodialysis; NCDS, National Cooperative Dialysis Study.

Urea

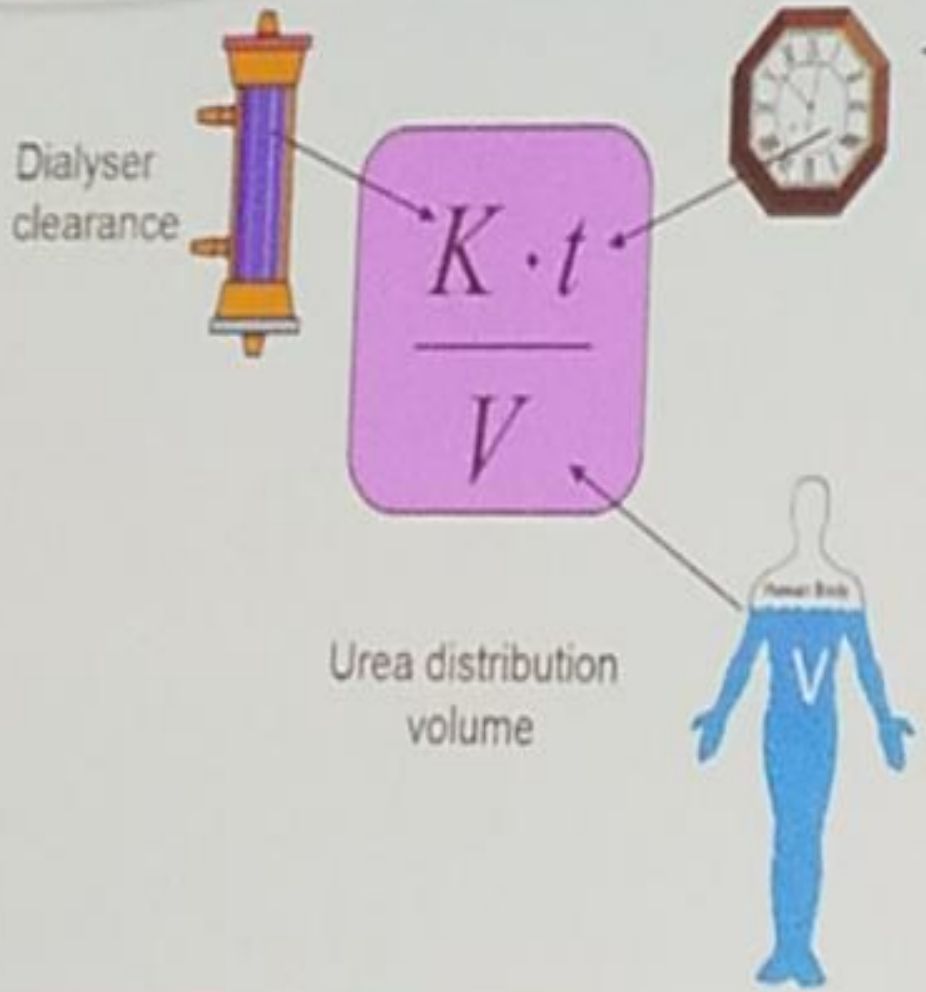


original Kt/Vurea target > 1.0

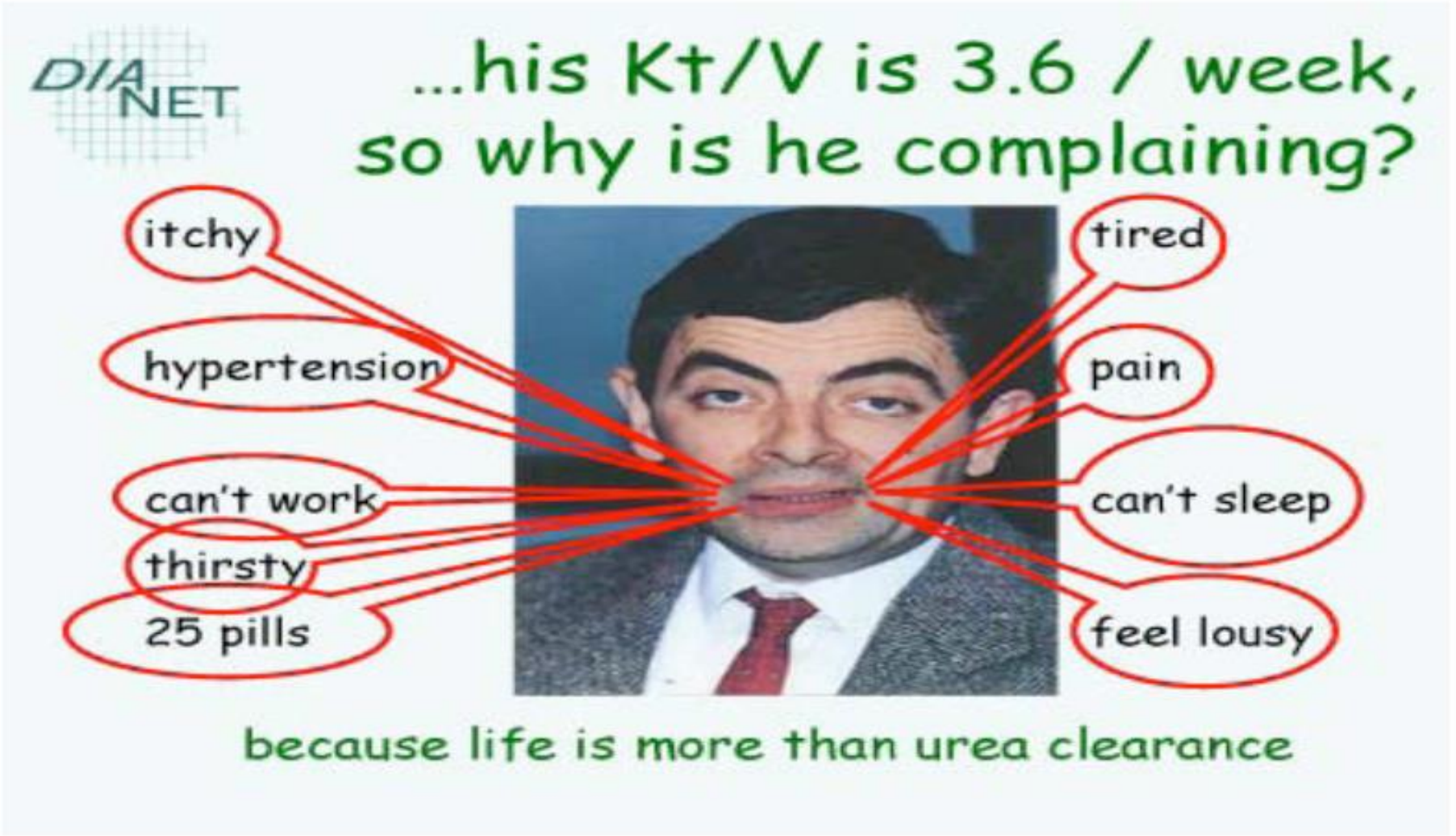
How toxic is urea?



Dialysis dose concepts



Adequate dialysis vs Optimal dialysis

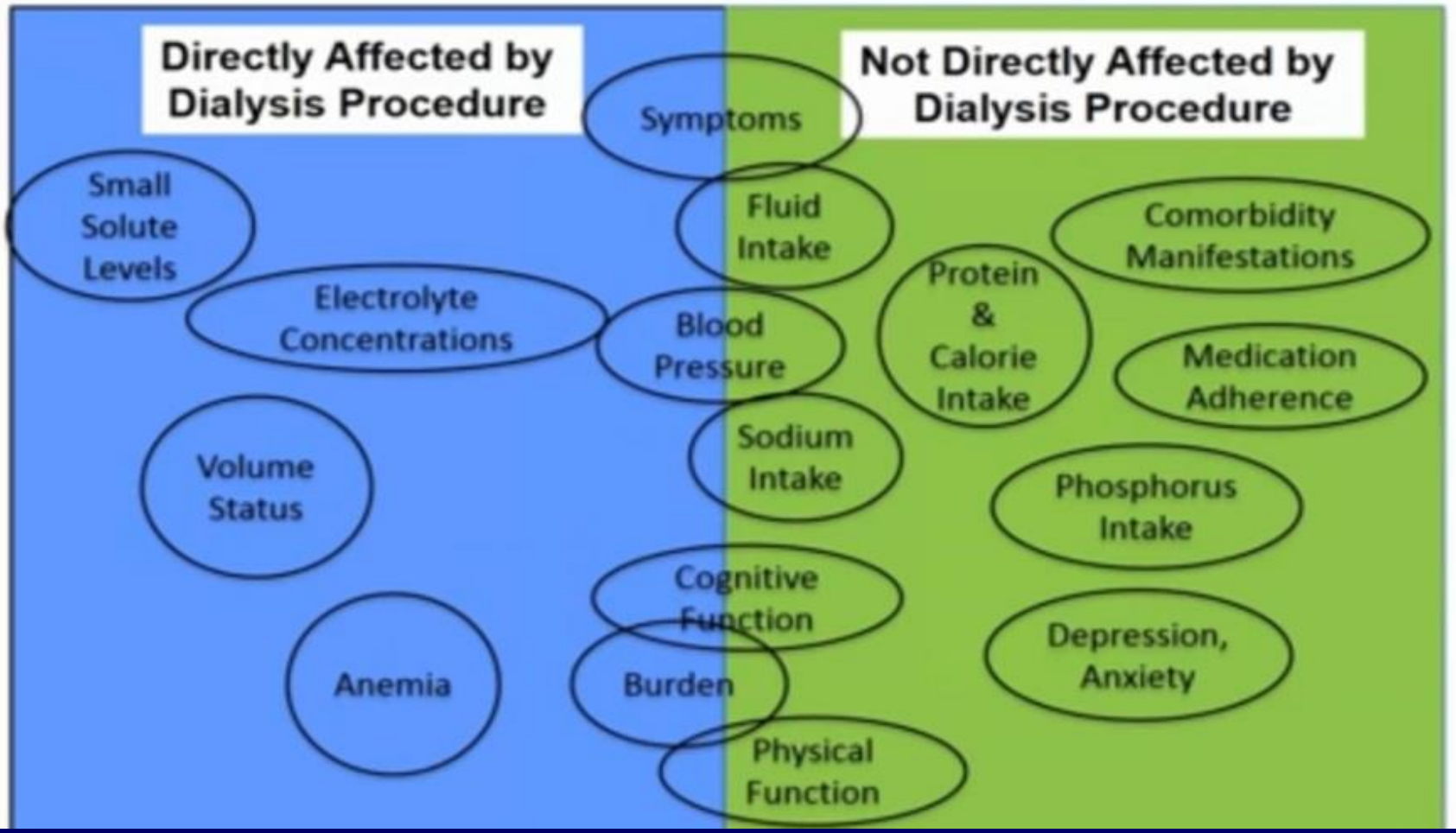


Proposal: Terminology Change

- Change from "adequate" dialysis to:
  - Optimal dialysis
  - High-quality dialysis
  - Goal-directed dialysis
  - Individualized dialysis
  - Patient-centered dialysis

Using shared decision making between patient and care team to establish realistic care goals that will allow the patient to meet his/her own life goals and allow the clinician to provide individualized, high quality clinical care

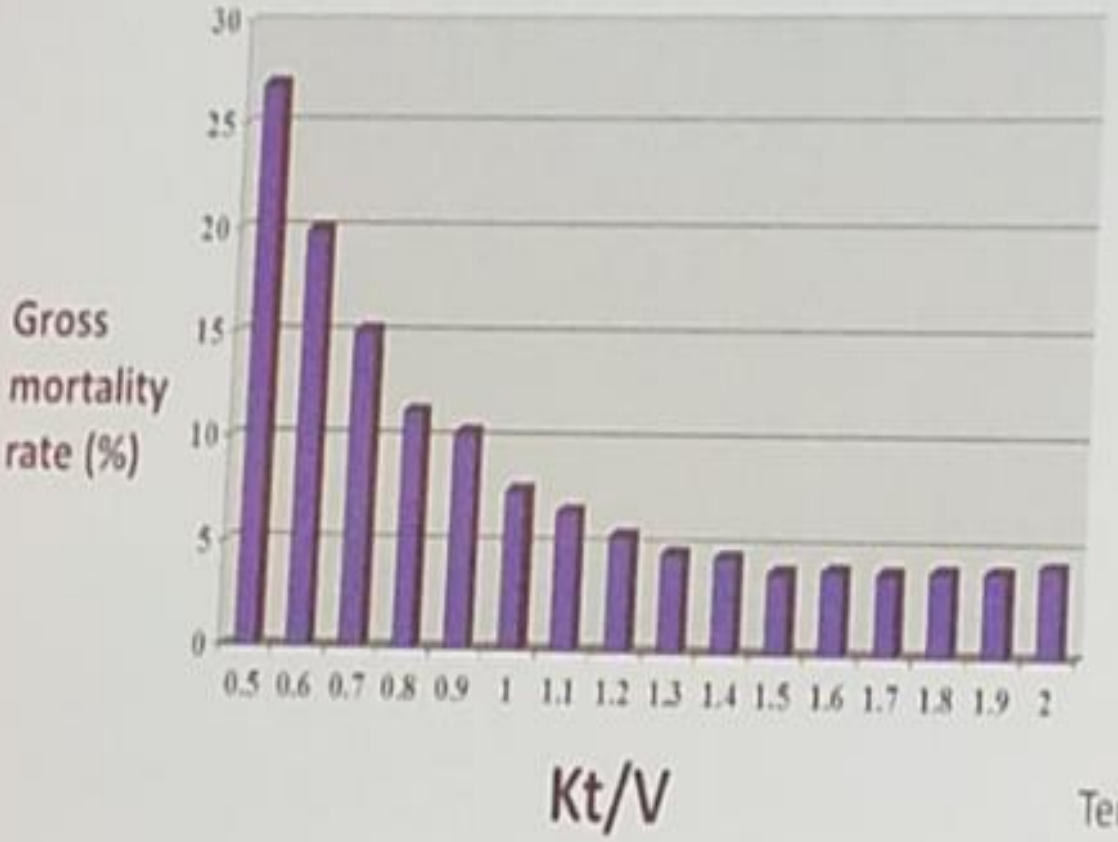
Components of Goal-Directed Dialysis



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

Uremic toxin clearance based on the dialyzer characteristics

Table 2. Uremic toxin clearance based on the dialyzer characteristics

Uremic toxin source	Molecular characteristics	Prototype uremic toxin	Low-flux HD	High-flux HD	High-flux HDF	Medium cutoff HD	High cutoff HD
Exogenous	Gut-derived, protein-bound <80%	homocysteine, indoxyl sulfate, paracresyl sulfate, carboxymethyl lysine, and kynurenines	✓	✓	✓	✓	✓
	Gut-derived, protein-bound ≥80%	Hcy, IS, pCS, CML, kynurenines		✓	✓	✓	✓
Endogenous Water-soluble	Small molecules <0.5 kDa	ADMA, SDMA, uric acid, carbamylated compounds, urea, TMAO	✓	✓	✓	✓	✓
	Small-middle molecules 0.5–15 kDa	β2-microglobulin, IL-8		✓	✓	✓	✓
	Medium-middle molecules >15–25 kDa	TNF, IL-18, IL-10, IL-6, kappa-FLC, myoglobin, sTNFR2, FGF-2, prolactin, complement factor D			✓	✓	✓
	Large-middle molecules >25–58 kDa	Pentatraxin-3, sTNFR1, AGEs, FGF-23, lambda-FLC, CX3CL1, CXCL12, IL-2, YKL-400				✓	✓
	Large molecules >58–170 kDa	Albumin					✓

ADMA, asymmetric dimethylarginine; AGEs, advanced glycosylation end products; CML, carboxymethyl lysine; CXCL12, C-X-C motif chemokine 12; CX3CL1, chemokine (C-X3-C motif) ligand 1; DMA, dimethylamine; FGF, fibroblast growth factor; FLC, free light chain; HCO, high cutoff; Hcy, homocysteine; HD, hemodialysis; HDF, hemodiafiltration; HDx, expanded hemodialysis; IGF-1, insulin-like growth factor-1; IL, interleukin; IS, indoxyl sulfate; MCO, medium cutoff; MMA, monomethylamine; PAG, phenylacetylglutamine; pCS, paracresyl sulfate; SMDA, symmetric dimethylarginine; sTNFR, soluble tumor necrosis factor receptor; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; YKL-40, chitinase-3-like protein 1.

HEMO study: largest RCT in HD:

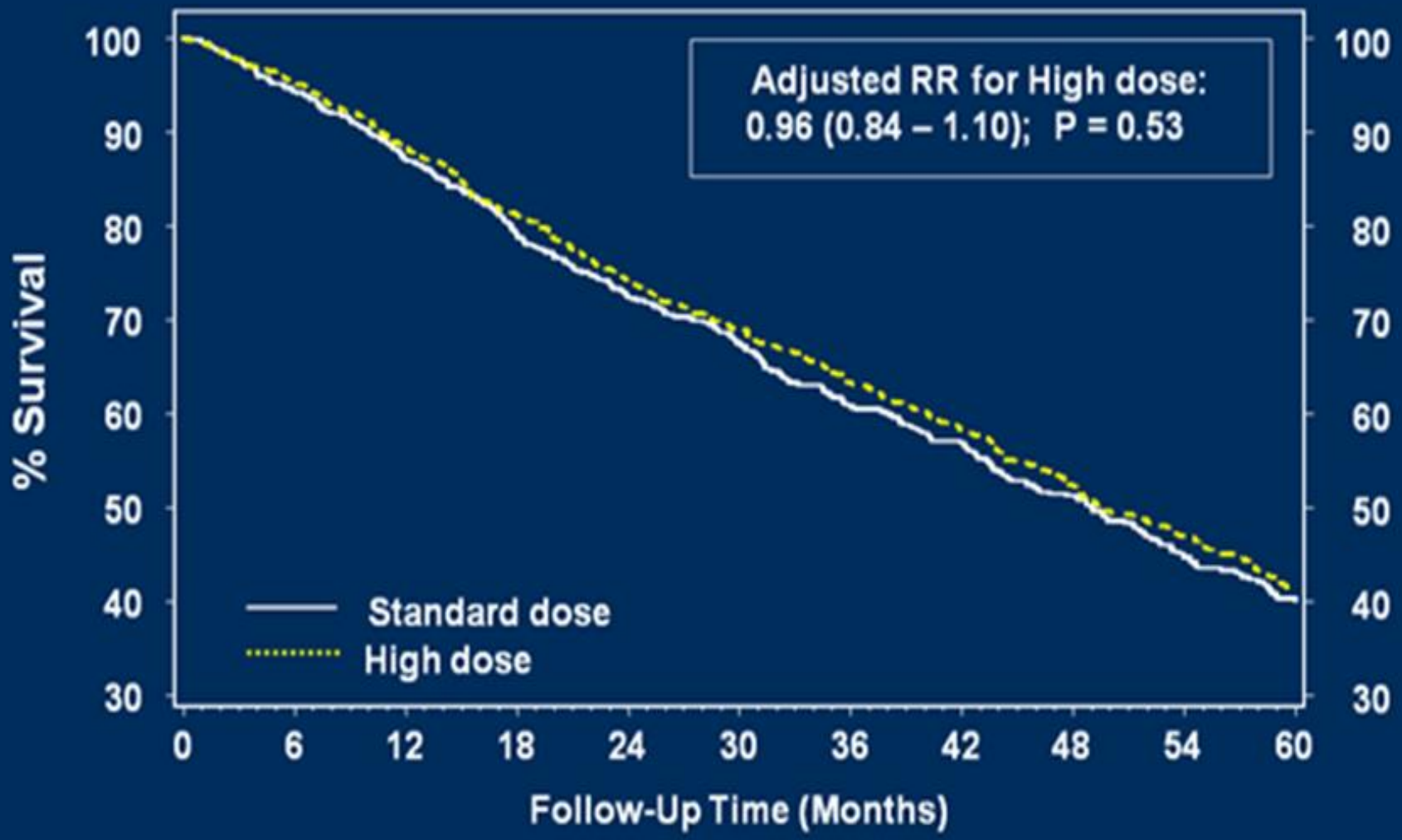
Higher dialysis dose

- spKt/V=1.71±0.11
- eKt/V=1.53±0.09
- High flux
  (B2 M clearance> 20 cc/min
  or
  Low flux(B2 M clearance<10 cc/min)

Standard dialysis dose

- spKt/V=1.32±0.09
  eKt/V=1.16±0.08
- High flux
  (B2 M clearance> 20 cc/min
  or
  Low flux(B2 M clearance<10 cc/min

Survival by Dose Group in HEMO Trial*



* 871 deaths during mean follow-up of 2.84 years

HEMO study: Conclusion

- *Among patients undergoing maintenance hemodialysis who were receiving thrice-weekly treatment lasting 2.5-4.5 hours each, neither a higher dose nor the use of high-flux membranes significantly improved survival or reduced morbidity*
- *This support the current guidelines of single-pool kt/v of 1.2-1.4 , and make no recommendation for or against routine use of high-flux membranes*

1. *Nephrol. Dial. Transplant. (2012) doi: 10.1093/ndt/gfr786* First published online: January 23, 2012

Kt/V urea does not tell it all

Carlo Basile and Carlo Lomonte
+ Author Affiliations

Correspondence and offprint requests to: Carlo Basile; E-mail: basile.miulli@libero.it

Received November 20, 2011.

The clinical illogicality of *Kt/V* urea

Currently, >93% of the US patients reach the recommended target *Kt/V* urea [21]; however, the survival of dialysis patients remain unsatisfactory: the mortality of patients on maintenance haemodialysis (HD) is four times higher than that of the general population aged >65 years [21]. This suggests that there may be factors that influence survival and that dialysis, as quantified by *Kt/V* urea, does not correct. On the other hand, it is important to underline that many observational studies have suggested that longer treatment times and/or more frequent dialyses may lead to better outcomes and improved laboratory results [22–28].

Limitations of spKt/V:

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

Limitations of spKt/V:

- **2.Effect of gender**: spKt/V overestimates delivered dialysis among women. We need SAN Kt/V.
  (surface_Area _ Normalized, Daugirdash 2009)

The ratio V/BSA in women 12%-15% is lower than men, so women need about 15% more dialysis than men.

We suggest the minimum spKt/V in women should be about 25%-30% higher than men,

Limitations of spKt/V:

- **3. Smaller patients**: Whit four reasons smaller patients should get more dialysis when dose is measured as spKt/V:
- a.Small patients(small V) would get a larger amount of dialysis if dose were scaled to BSA
- b.The KDOQI dose targets are in the form of spKt/V and not eKt/V; postdialysis urea rebound tends to be larger in smaller patients.

Limitations of spKt/V:

- c .it is easy to deliver a high Kt/V to small patients in a short session (2.5 hours) ,but may not be sufficient to allow for removal of middle molecules nor for adequate removal of excess fluid and this may result of chronically overhydrated patient.
- d. short session length treatment may give adequate Kt/V but need high UF and associated whit poor outcome.

Urea Rebound

- Organs with low blood flow (skin, bone, muscles) may serve as reservoir for urea 70% of TBW is contained in organs that receive only 20% of CO

So: during HD, there is loss of urea from well perfused areas, this result in ↑ in BUN over 60 minutes post dialysis.

Post Dialysis BUN Sampling

Avoid 2 rebound:

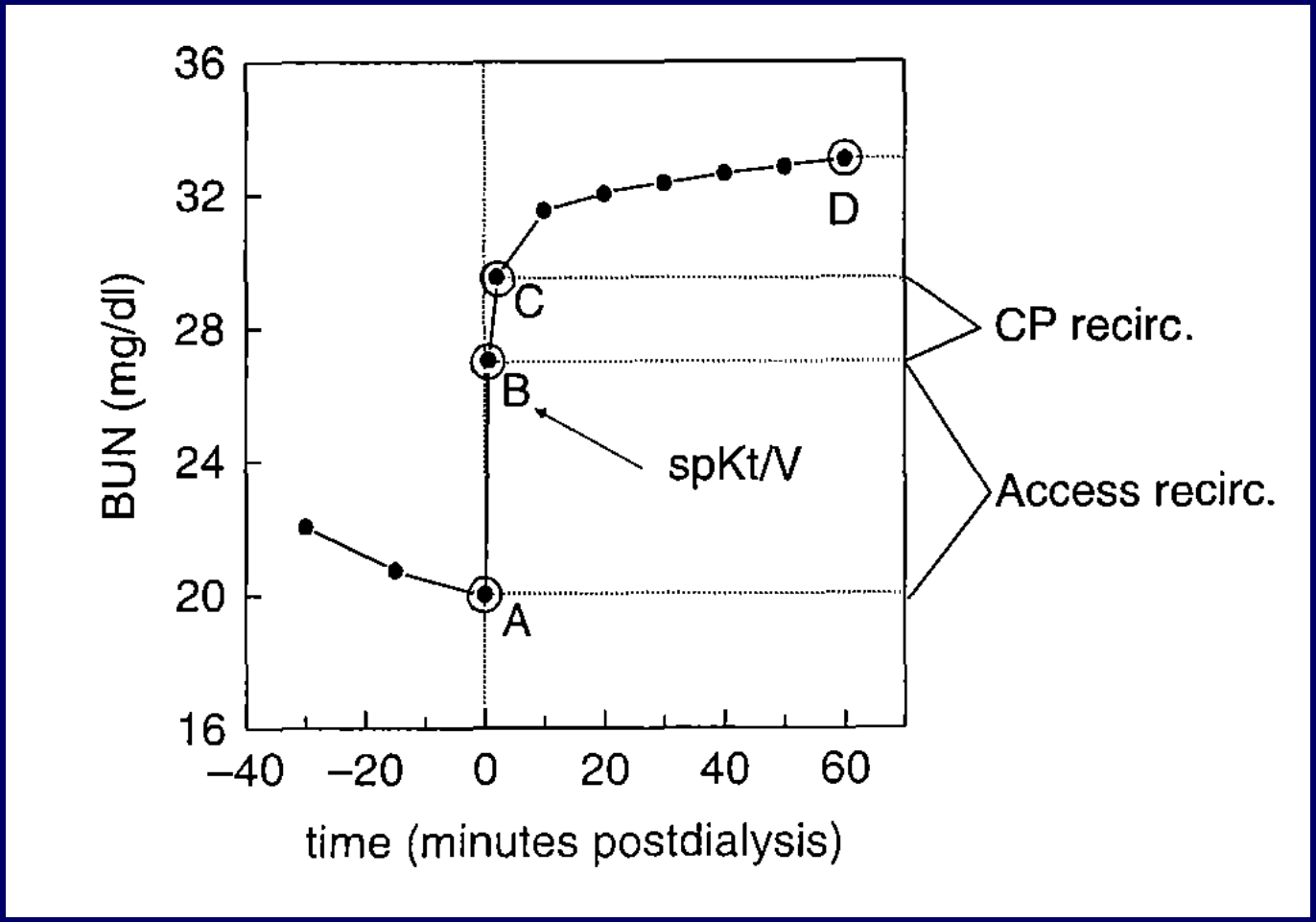
Early (<3min post dialysis)

- Access recirculation,begin immediately post hemodialysis and rebound in 20 seconds
- Cardiopulmonary recirculation, begin 20 seconds post hemodialysis and is completed in 2-3 minutes after slowing or stopping the blood pump.

Late (>3 min)

- Completed within 30-60 minutes due to flow-volume disequilibrium.

Urea Rebound



rebound (>50% is AR,15%CP,31% D)

Limitations of spKt/V:

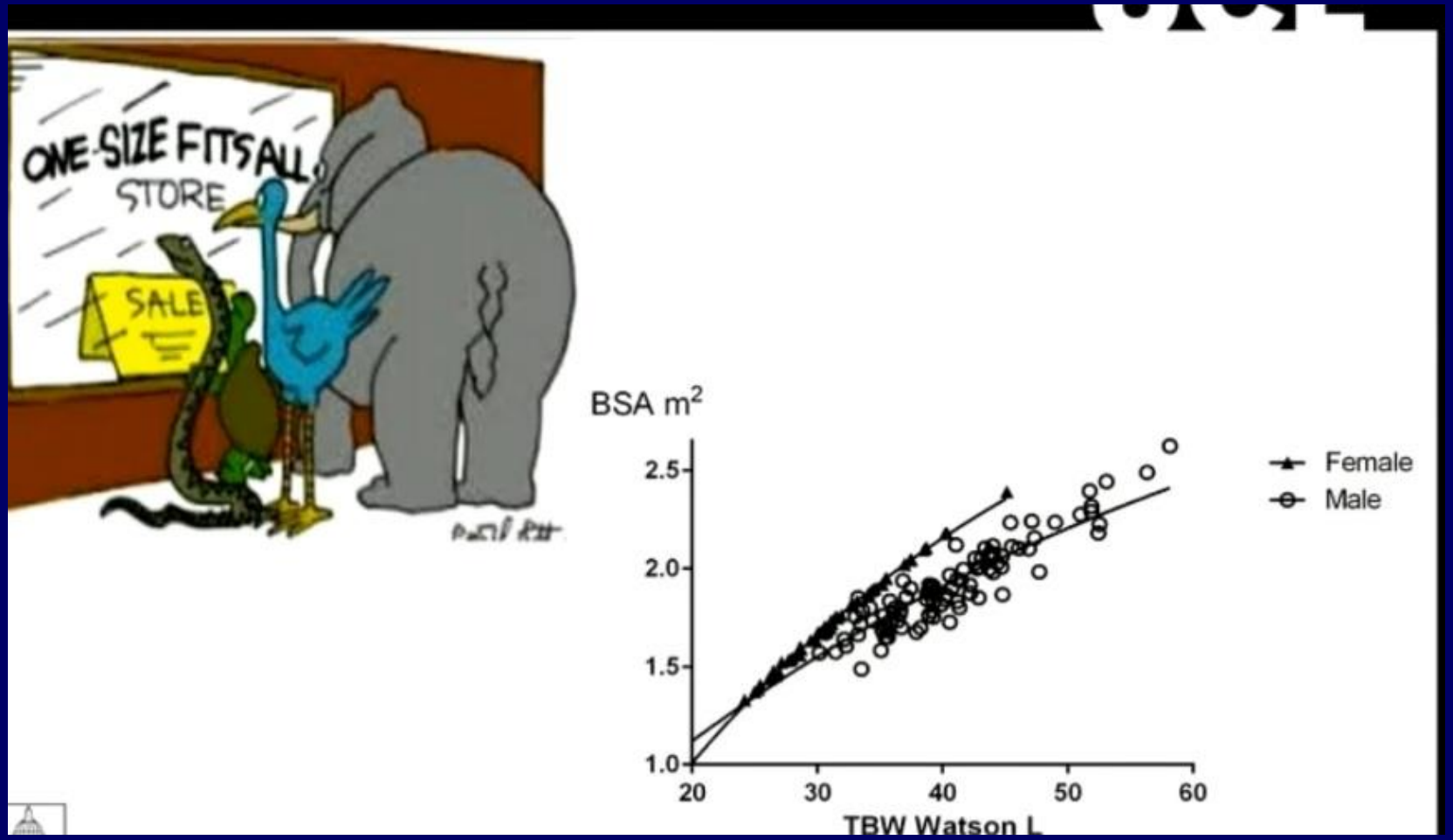
- **4**.spKt/V ignores the mass transfer between body compartments and across the plasma membrane (intracellular & extracellular transport), which has been shown to be important for the clearance of molecules such as phosphate.

Limitations of spKt/V:

- **5**. spKt/V measures urea clearance in a single session

- **6**.Errors in timing of postdialysis BUN may affect spKt/V
- 7. we can adjust Kt/V with Kt/BSA, Kt/TEE…
- (Total Energy Expenditure)

Kt/V and BSA


ONE SIZE FITS ALL
STORE
SALE
BSA m2
2.5
2.0
1.5
1.0
20
30
40
50
60
TBW Watson L
Female
Male

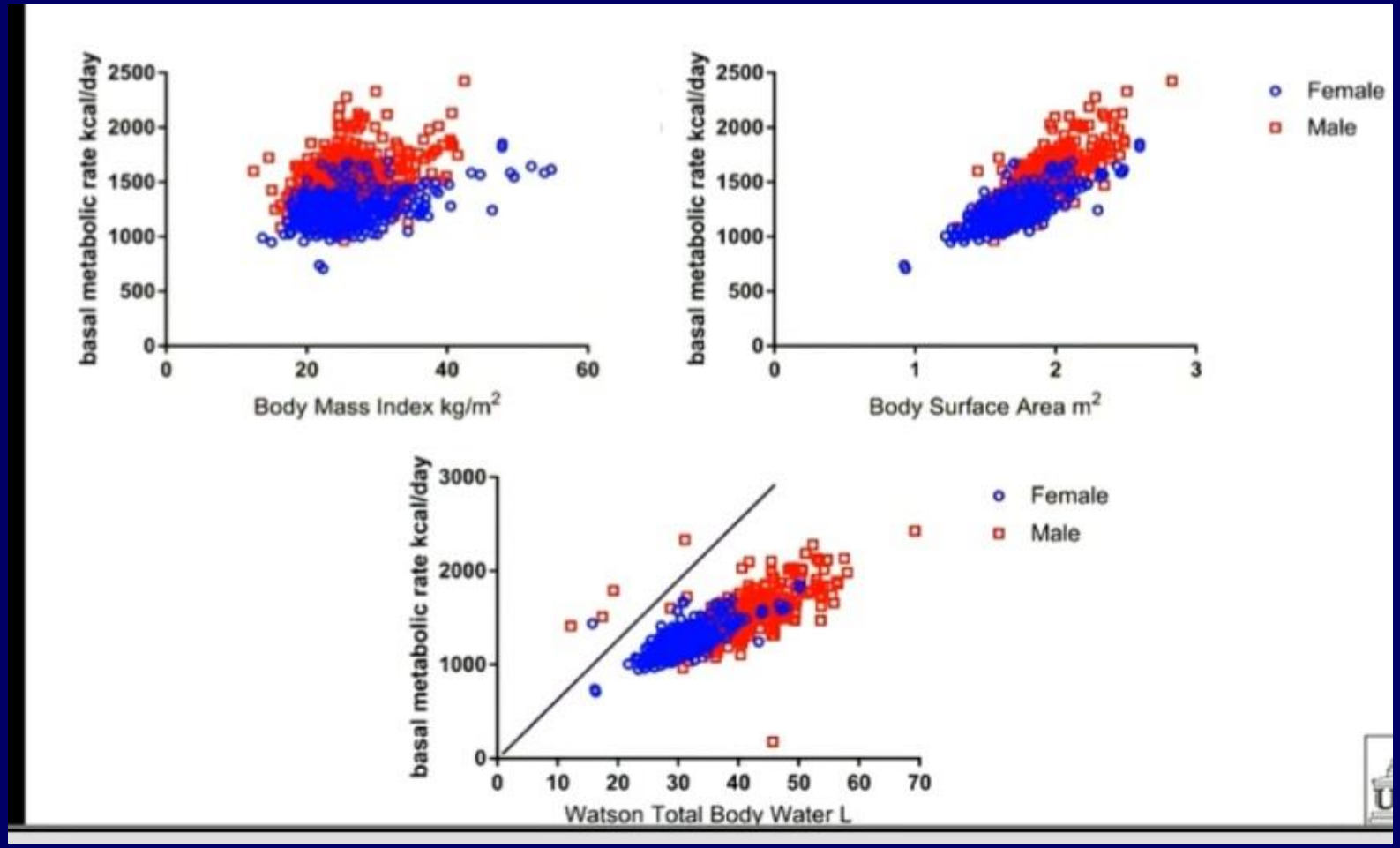
Energy expenditure

Resting EE, Active EE, Total EE

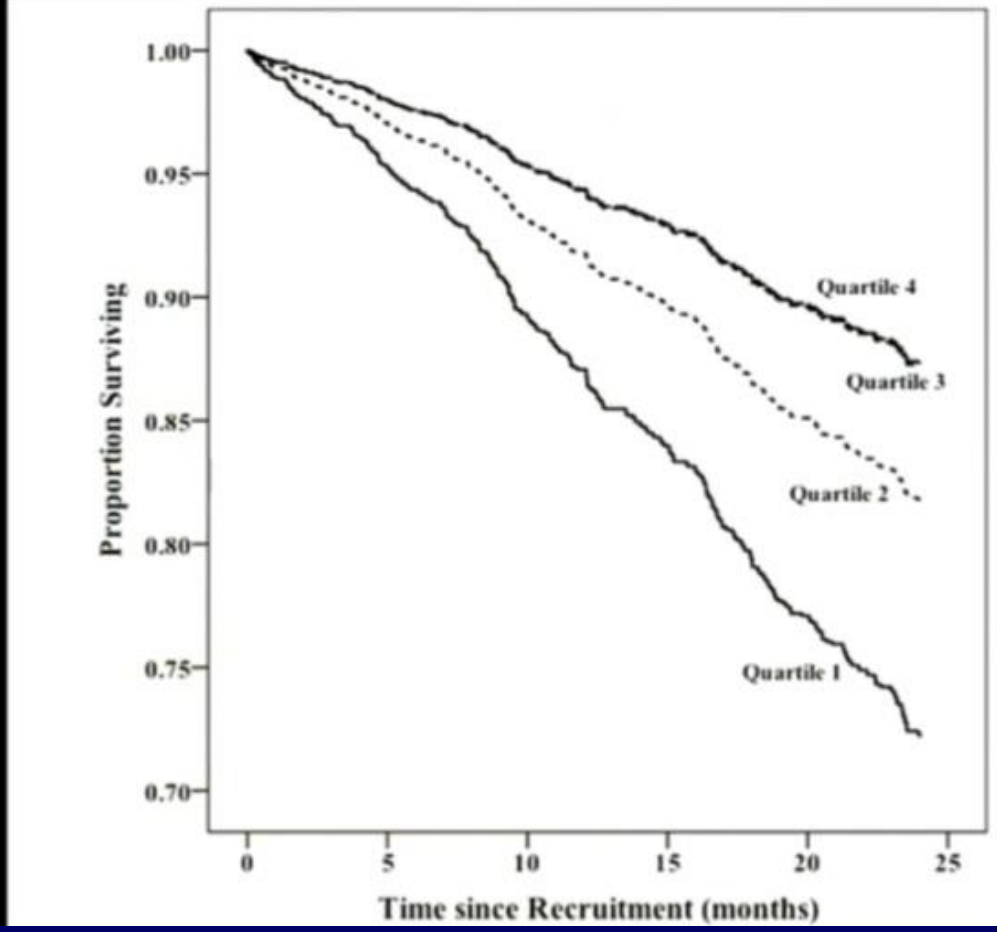
UCL

Cell metabolism generates waste products

Kt/V and Basal metabolic rate and BSA

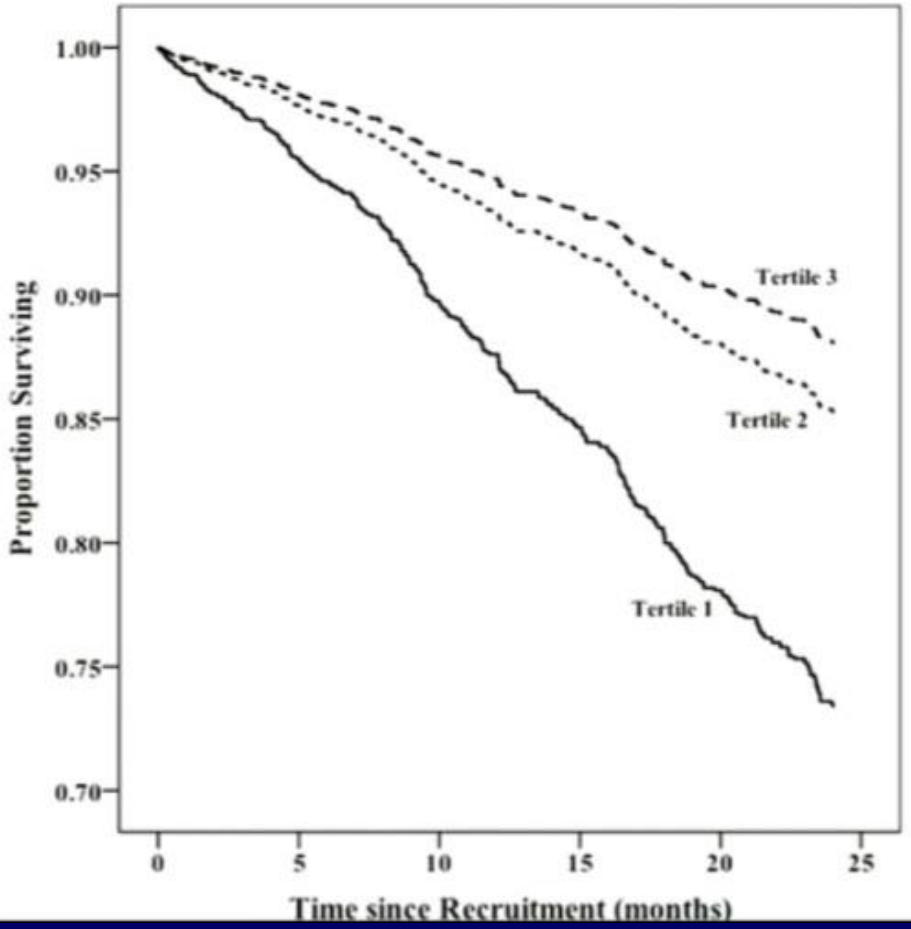


Adult patient specific dosing based on BSA



Kt/BSA quartiles adjusted for age, sex, ethnicity, comorbidity, dialysis vintage, BMI and physical activity level

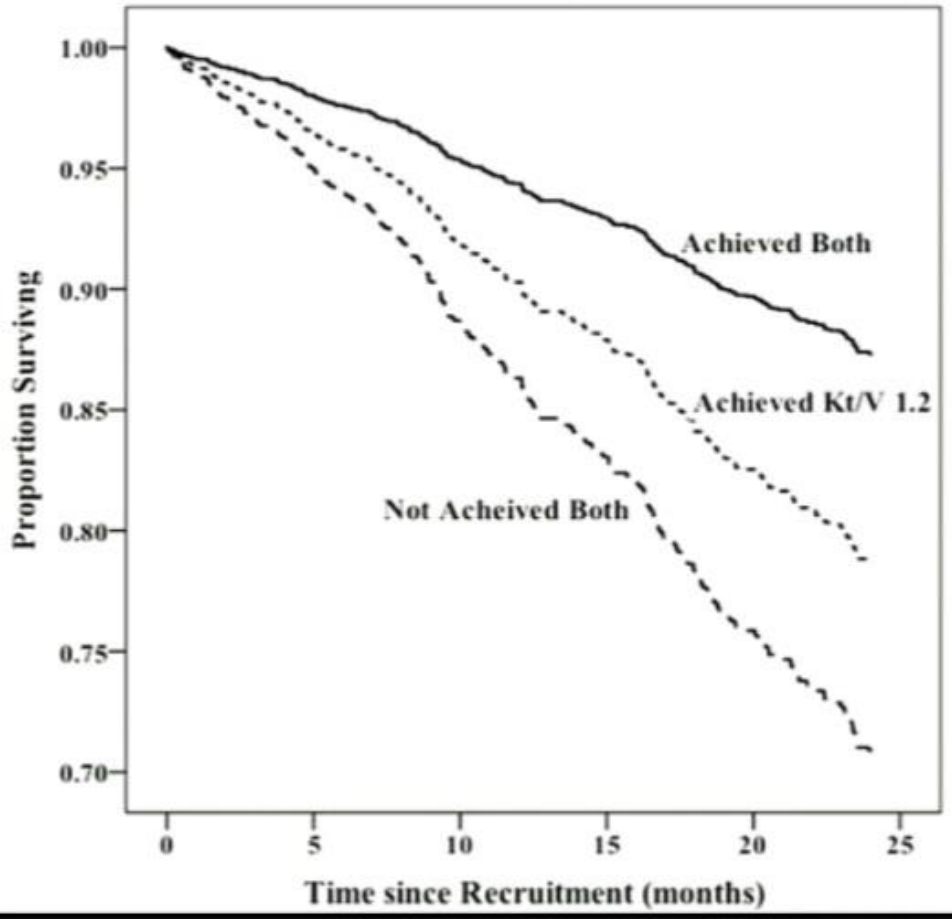
Adult patient specific dosing based on TEE



Kt/TEE tertiles
adjusted for age, sex,
ethnicity, comorbidity,
dialysis vintage, BMI
and physical activity level

UCL

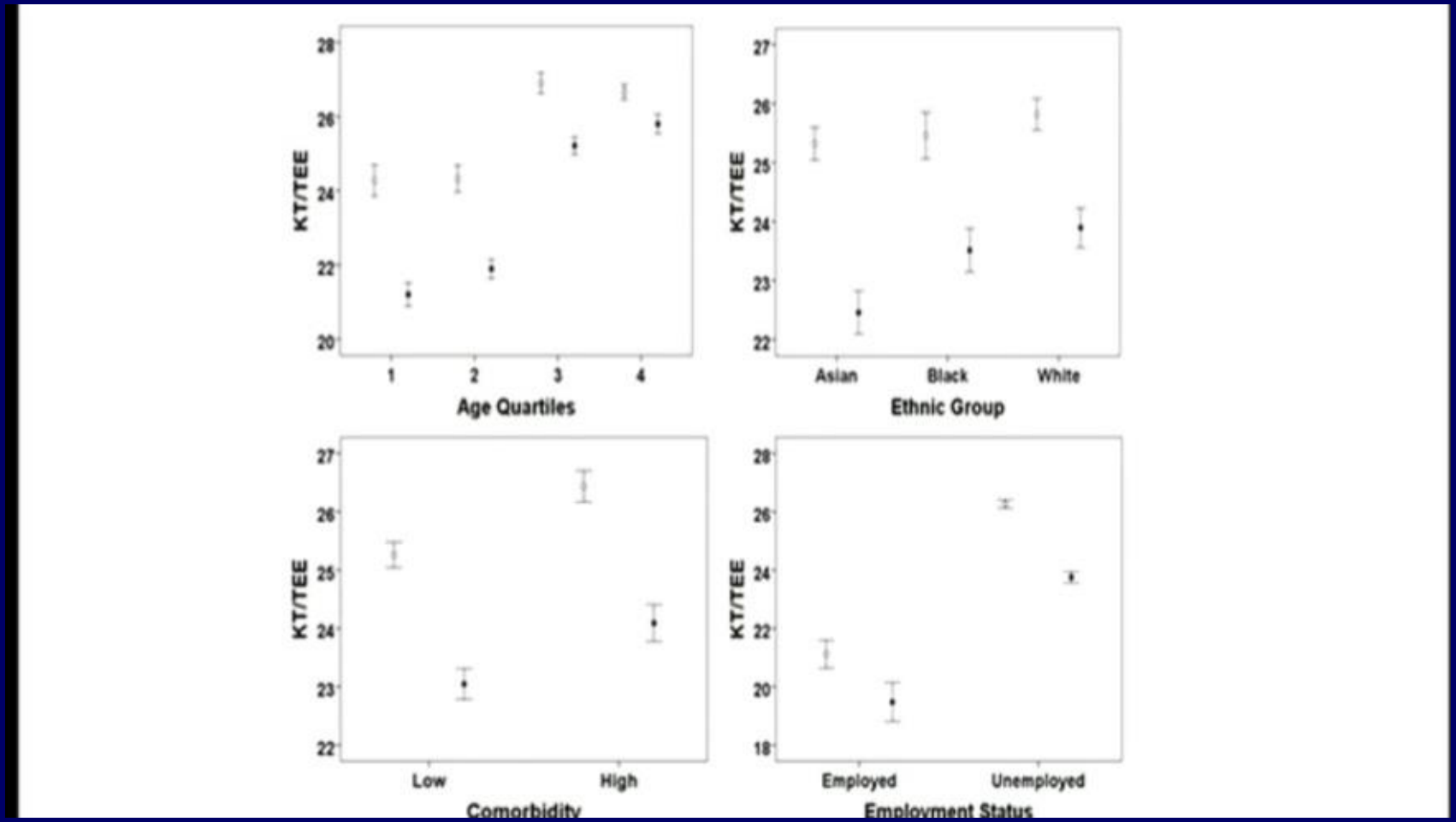
Adult patient specific dosing based on TEE



Kt/TEE tertiles adjusted survival according to achievement of recommended spKt/V adequacy targets based on gender, body size and physical activity and by conventional criteria (spKt/V >1.2)

UCL

Same Kt/V and TEE



Some adult patients need greater clearance

1. Younger
2. Women
3. Smaller
4. Less comorbidity
5. Physically active

8.On line Kt/V is more reliable than formulated Kt/V ? (online conductivity monitoring using Na flux as a surrogate of urea)

Indian J Nephrol. 2012 Sep-Oct; 22(5): 333–339.
doi: 10.4103/0971-4065.103906
PMCID: PMC3544053

The Kt/V by ionic dialysance: Interpretation limits

A. Alayoud, D. Montassir, A. Hamzi, Y. Zajjari, A. Bahadi, D. El Kabbaj, O. Maoujoud, T. Aatif, K. Hassani, M. Benyahia, and Z. Oualim

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Abstract

The availability of hemodialysis machines equipped with online clearance monitoring (OCM) allows frequent assessment of dialysis efficiency and adequacy without the need for blood samples. Accurate estimation of the urea distribution volume (V) is required for Kt/V calculated from OCM to be consistent with conventional blood sample-based methods. A total of 35 patients were studied. Ionic dialysance was measured by conductivity monitoring. The second-generation Daugirdas formula was used to calculate the Kt/V single-pool (Kt/VD). Values of V to allow comparison between OCM and blood-based Kt/V were determined using Watson formula (VWa), bioimpedance spectroscopy (Vimp), and blood-based kinetic data (Vukm). Comparison of Kt/Vw ocm calculated by the ionic dialysance and Vw (Kt/Vw ocm) with Kt/VD shows that using VW leads to significant systematic underestimation of dialysis dose by 24%. Better agreement between Kt/V ocm and Kt/VD was observed when using Vimp and Vukm. Bio-impedancemetry and the indirect method using the second-generation Daugirdas equation are two methods of clinical interest for estimating V to ensure greater agreement between OCM and blood-based Kt/V.

Keywords: Bioimpedance, ionic dialysance, Kt/V, urea distribution volume, urea kinetic, modeling, Watson formula

- 9. Usually we don’t Calculate Kr urine , so we can’t use incremental hemodialysis.

Benefits of Residual Renal Function

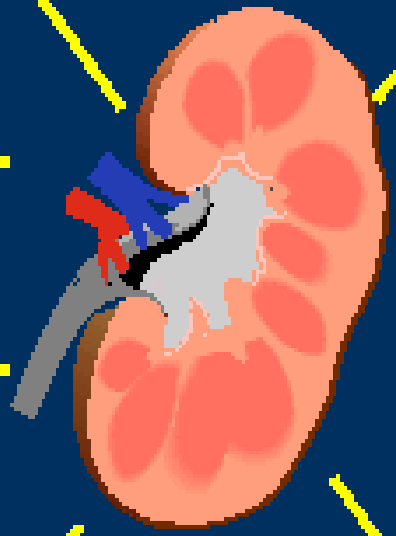
Provides endocrine functions

- 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

Residual Kidney Function and Cause-Specific Mortality Among Incident Hemodialysis Patients

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods & cohort

- Longitudinal cohort study
- Adults initiating on 3x weekly in-center HD
  N = 39,623
- Collected data on CL_{urea} & urine volume
- 2007-2011

Results

Higher trend towards higher mortality risk in lower RKF irrespective of cause of death (i.e., SCD, non-SCD CVD, and non-CVD) $P_{trend} < 0.05$

Increased cause-specific mortality risk with $CL_{urea} < 3.0$ml/min/1.73m^2

Risk attenuated by adjustment of ultrafiltration rate

Adjustment for highest potassium did not affect mortality risk

Among those with data on change in RKF

There was a graded association between 6-month decline in CL_{urea} and SCD, non-SCD CVD and non-CVD risk

Clear graded association between faster 6-month decline in UOP & higher death risk was observed for SCD and non-CVD

CL_{urea}, renal urea clearance; RKF, residual kidney function; SCD, sudden cardiac death; CVD cardiovascular death; UOP, urine output

KI REPORTS
Kidney International Reports

Okazaki M et al. 2023

Visual abstract by:
Sophia Ambruso, DO
@Sophia_kidney

Conclusion: Lower RKF and loss of RKF were associated with higher cause-specific mortality among patients initiating thrice-weekly in-center hemodialysis.

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

Estimating renal function in Hemodialysis
beta-2 microglobulin

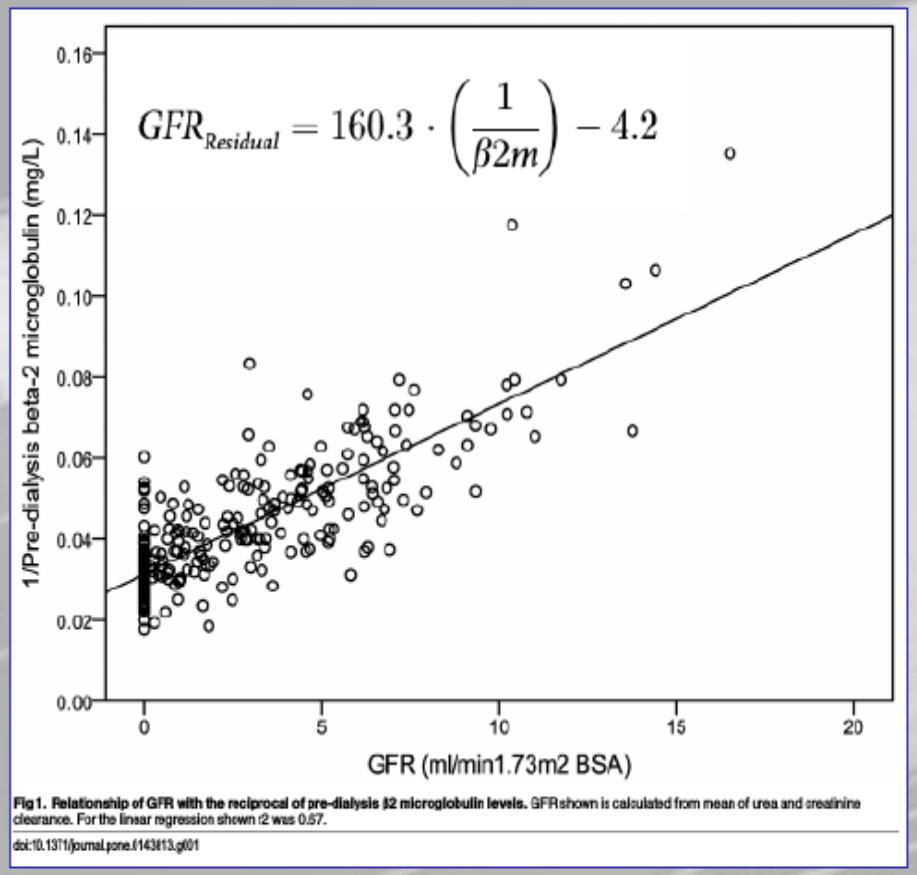


Fig 1. Relationship of GFR with the reciprocal of pre-dialysis β2 microglobulin levels. GFR shown is calculated from mean of urea and creatinine clearance. For the linear regression shown r2 was 0.57.

doi:10.1371/journal.pone.0143813.g001

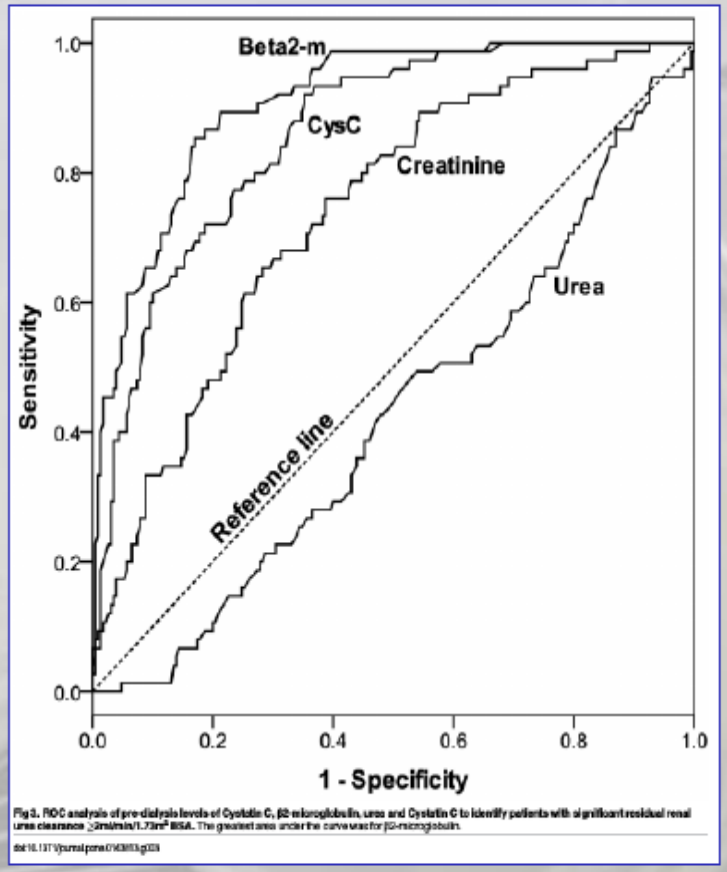


Fig 3. ROC analysis of pre-dialysis levels of Cystatin C, β2-microglobulin, urea and Cystatin C to identify patients with significant residual renal urea clearance ≥2ml/min/1.73m² BSA. The greatest area under the curve was for β2-microglobulin.

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.

KI REPORTS
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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

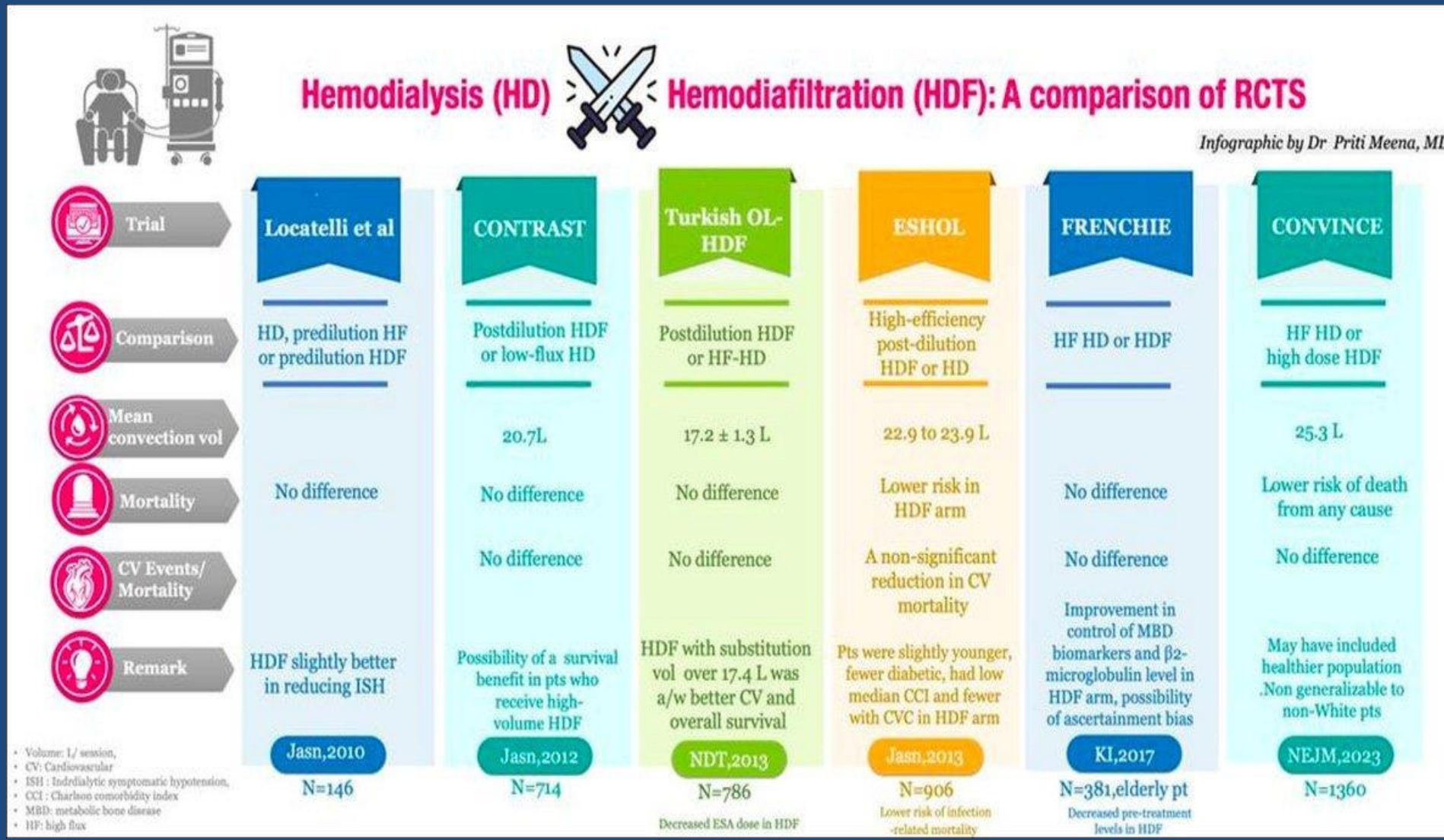
Yoshitsugu Obi[1] and Kamyar Kalantar-Zadeh[1,2,3]

- 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.

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

Survival benefit of HDF? Are we convinced?

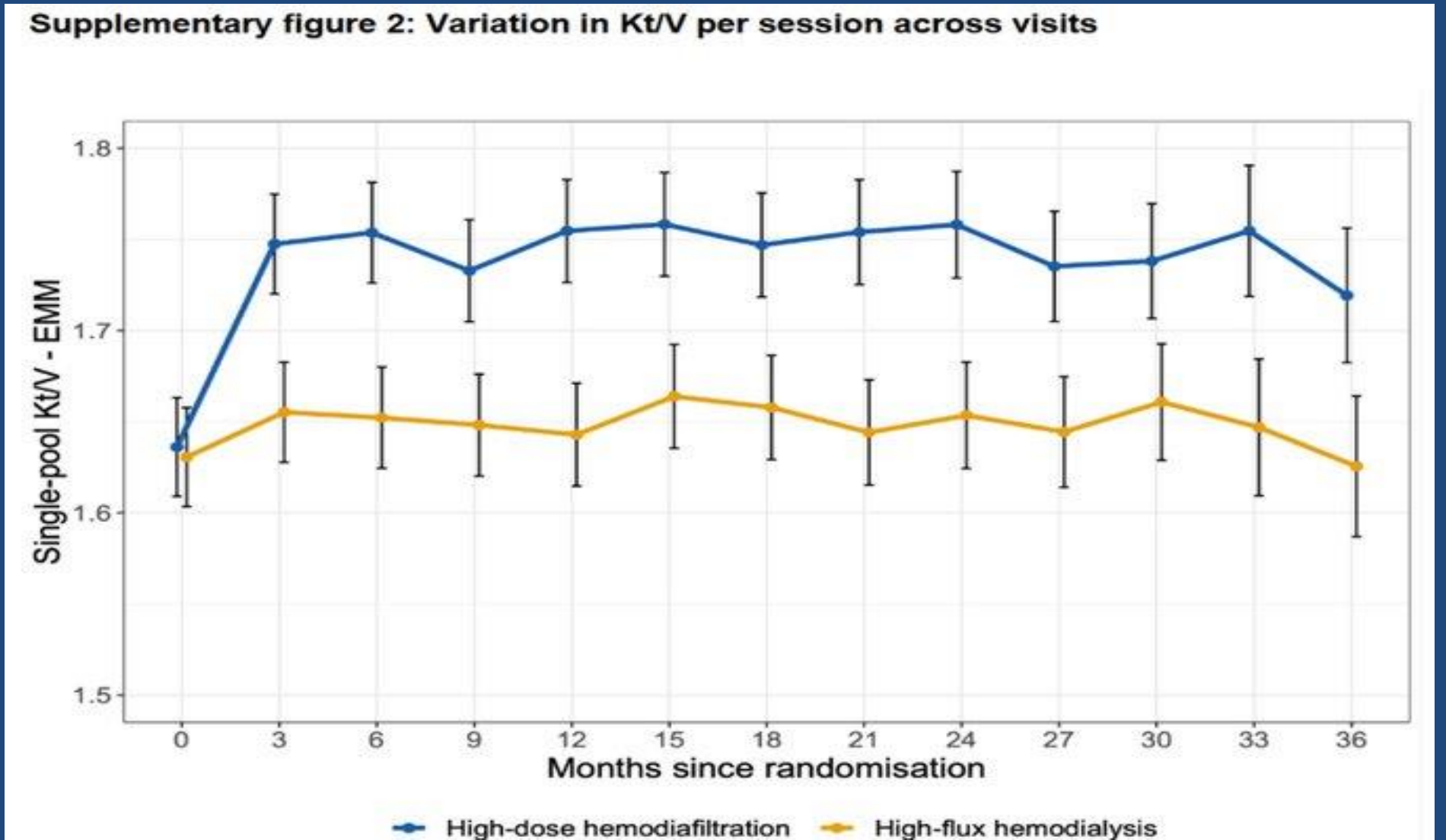


CONVINCE study:

Table S2: Mean characteristics of dialysis parameters and laboratory variables during follow-up

Characteristic	High-dose HDF N = 683	High-flux HD N = 677	Mean difference
Number of dialysis sessions / week	3 (2.99-3.01)	3 (2.99-3.01)	-0.01 (0.02-0)
Duration of dialysis session – min	244 (243-246)	245 (244-246)	-1 (-2-0)
Blood flow rate – ml/min*	374 (367-382)	369 (362-376)	5 (3-8)
Single-pool Kt/V_{urea}	1.74 (1.71-1.77)	1.65 (1.62-1.68)	0.09 (0.07-0.11)
Hemoglobin (g/dL)	11.2 (11.1-11.3)	11.3 (11.2-11.4)	-0.1 (-0.2-0)
Phosphate (mg/dL)	4.8 (4.7-4.9)	4.9 (4.8-5.0)	-0.1 (-0.2-0)
Creatinine (mg/dL)	8.4 (8.3-8.5)	8.5 (8.4-8.6)	-0.1 (-0.2-0.1)
C-reactive protein (mg/L)	1.1 (1.0-1.3)	1.2 (1.1-1.3)	-0.1 (-0.2-0.1)
HDF specific characteristics			
Convection volume – (L/session)	25.2 (24.8-25.7)	NA	-

Sp Kt/V in HDF vs HD (CONVINCE study)



Theoretical mechanisms suggested for survival benefit in HDF group:

- 1. HDF increases the removal of middle _ large molecules.(B2 – microglobulin,protein bound toxins such as indoxyl sulfate and p- cresyl sulfate)
- 2. IDH occurrence is reduced in HDF patients. high volumes replacement fluid can lower temperature.
- 3. UF rate ? (no information is provided in CONVINCE trial regarding UF rate)
- 4. Dialysis solution used in HDF is more pure than HD.
- 5. HDF resulted in better maintenance of residual Kidney function than HD.

Conclusion:

- **1-spKt/V is only a marker of a adequacy of urea removal not optimal dialysis.**

- 2-spKt/V does not tell anything about clearance of middle and large molecules during hemodialysis.

3-spKt/V has many limitation specially in smaller patients and women and malnourished patients.

4-.We should consider eKt/V in smaller patients .

Conclusion:

- **5. Ignoring residual renal function might be harmful.**
- **6- Incremental HD may be benefit some patients, twice weekly in patients with Kr >3 cc/min and Urine out > 500 cc/day (nearly 1/3 of HD patients).**

(Kr urine= UUN / SUN* urine flow rate cc/min)

7.Younger adult, women, smaller,less comorbidity, physically active patients need more dialysis .

8. According to CONVINCE study HDF is superior to conventional HD but it is still too early to reach a conclusion on HDF.

Conclusion:

One size does not fit all

tailored to residual renal function
and energy expenditure