



# The Intact Nephron Hypothesis in Reverse: An Argument In Favor of Incremental Initiation Of Dialysis (With Residual Kidney Function)

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Conflict of interest disclosures: None

# Theme Outline

- Brief definition and history of incremental dialysis
- Value of residual kidney function (RKF) to patients on dialysis
- Incremental dialysis may preserve RKF
- How incremental dialysis may represent the intact nephron hypothesis in reverse
- Examples of incremental dialysis

# Incremental Dialysis

Golper TA JASN 9:S107, 1998

- Working definition
  - adding dialysis in specific doses over time to achieve a total delivered dose of residual kidney plus artificial kidney function
- Conditions of utilization
  - ideally, when significant RKF can contribute to total therapy
  - possibly, when psychological, social, and/or economic conditions dictate

# History of the Practice Of Incremental Initiation in US

- Tzamaloukas, Adv in PD 15:175, 1999
  - 1/3 of nephrologists practiced incremental initiation at times
  - 3/4 used nutritional indices and/or RKF to initiate
  - Reasons to not do incremental dialysis:
    - **anticipated patient noncompliance (36%)**
    - **desire to achieve highest possible clearance (34%)**
    - **disagree with DOQI Guidelines (21%)**
- Hanson et al Am J Neph 19:625, 1999
  - 4 to 6% of all patients, predominantly older Caucasian women with RKF

# Practice Of Incremental Initiation in Asia

- Mostly for cost containment and only if physicians allowed it
  - Lin et al Nephrology (Carlton)14:59, 2009
  - Zhang et al Am J Nephrol 40:140,2014
  - Lin et al Blood Purif 33:66, 2012
  - Bieber et al NDT 29:1770, 2014
  - Hwang et al Medicine 95 (7):1, 2016
- Typical practice in India

# Experience With Incremental

- US
  - Burkart and Satko PDI 20:418, 2000
  - Hanson et al Am J Neph 19:625, 1999
- Japan
  - Kawanishi et al Adv PD 15:127, 1999
  - Kanno et al Adv PD 19:143, 2003
  - Jap Soc Dial Ther 1997
- Italy
  - Bonomini et al KI 28;S57, 1985
  - Locatelli et al AJKD 24:192, 1994
  - Neri et al Adv PD 19:93, 2003
  - De Vecchi et al PDI 20:412, 2000
- England
  - Williams PF AJKD 34:594, 1999
  - Vilar et al NDT24:2502, 2009
- Spain
  - Fernandez-Lucas et al Nefrologia 32:767, 2012

**No major unpredicted problems**

# Advantages of Incremental Dialysis versus Full Dose Dialysis

- Improved quality of life for the patient
  - Only true if patient stays healthy
- May reduce number of needed stations
- Less expensive per patient and for society
  - But less profitable for US dialysis companies
- May increase longevity of HD access
  - FHN trial, DOPPS
- May prolong residual kidney function

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# RKF Is Important in HD

## Early Observations

- Suda et al NDT 15:396, 2000
  - Single center study of 41 pts on HD at least 2 yrs
  - Nutritional status was significantly better if urine output was > 200 mL/d
- Shemin et al AJKD 38:85, 2001
  - Single center, 114 HD pts followed for 2 yrs
  - Presence of RKF ( $\geq 100$  mL/d) lowered risk of death by 56%
    - adjusted for duration of HD, age, smoking, DM, CV disease, albumin and dialysis clearance

# RKF Is Important in HD

## More Contemporary Observations

- Vilar et al NDT 24:2502, 2009
  - 650 incident patients, single center in UK
  - Corrected for albumin, age co-morbidities
  - Lower mortality with RKF
- Shafi et al CHOICE Study AJKD 56:348, 2010
  - UO > 250 mL/d at 1 yr = lower all-cause mortality
- Obi et al JASN 27:3758, 2016
  - > 6000 incident HD patients (DaVita cohort)
  - Correcting for co-morbidities and many confounders
  - Those with more rapid decline in RKF had higher all-cause mortality

# Why is Residual Kidney Function Associated with Better Outcome?

- Maybe it is just an overall marker of better health
  - Confounding by indication?
  - Usually “adjusted for”
- Better excretion of middle molecules e.g. toxins, “anorexigens”
  - Anderstam et al (Bergstrom) JASN 7:2453, 1996
- Better nutritional status
- Better fluid volume control?
- Better BP control?
- Preserved endocrine function?

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- **Incremental dialysis may preserve RKF**
- How incremental dialysis may represent the intact nephron hypothesis in reverse
- Examples of incremental dialysis

# Preserved RKF With Incremental Dialysis over Full Dose

- Lin et al Nephrology (Carlton) 14:59, 2009 (China)
  - Prevalent thrice weekly pts converted to twice weekly based on RKF had slower decline than those remaining on thrice weekly
- Fernandez-Lucas et al Nefrologia 32:767, 2012 (Spain)
  - 41 of 95 started twice/week
  - 2 sessions/week lasted 11 months
  - Survival and RKF better in twice/week pts
- Zhang et al Am J Nephrol 40:140,2014 (China)\*\*\*\*\*
  - 30/85 pts able to perform twice/week HD preserved RKF 1.6 times longer than thrice weekly dialyzers
- Obi et al Am J Kid Dis 68:256, 2016 (US)
  - 351 case matched patients

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# The Intact Nephron Hypothesis (1)

Bricker et al Am J Med 28:77, 1960

- Based on earlier work of:
  - Hayman et al JCI18:195, 1939
  - Platt R Br Med J 1:1313 and 1:1372,1952
- States simply that
  - As kidney disease progresses, not all nephrons are equally damaged
  - The remaining nephrons increase their excretory capacity to compensate for the lost nephrons
  - The surviving nephrons of the diseased kidney largely retain their essential functional integrity

# The Intact Nephron Hypothesis (2)

- Surviving nephrons become “super” nephrons
- Process to achieve this is slow and adaptive
  - Differs by disease states
  - Different by processes
    - Single nephron GFR
    - Decreased tubular reabsorption
    - Increased tubular secretion
  - Different by retained substances
  - Degrees of regulation from none to complete
    - Control systems
- The adaptations are designed to “deactivate” the stimulus

# Studies on the Characteristics of the Control

## System Governing Sodium Excretion in Uremic Man

*The Journal of Clinical Investigation* Volume 47 1968 521

EDUARDO SLATOPOLSKY, IVAN O. ELKAN, CAROL WEERTS, and NEAL S. BRICKER

*From the Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri*

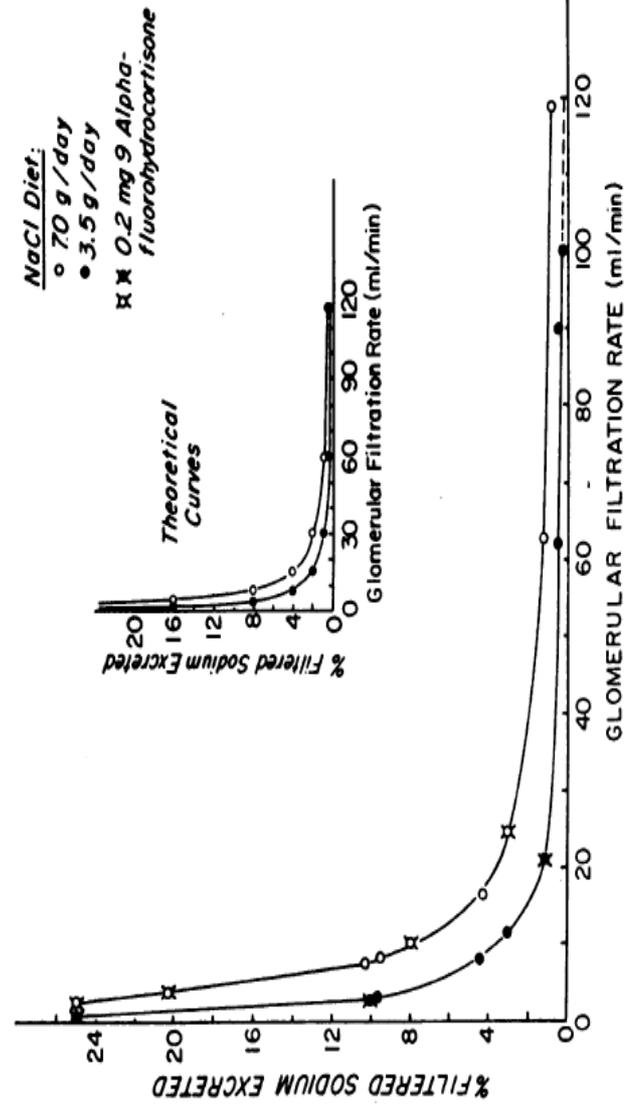


FIGURE 2 The relationship between steady-state GFR and the fraction of filtered sodium excreted on 3.5 and 7.0 g salt diets.

# Maintenance Of Na Balance

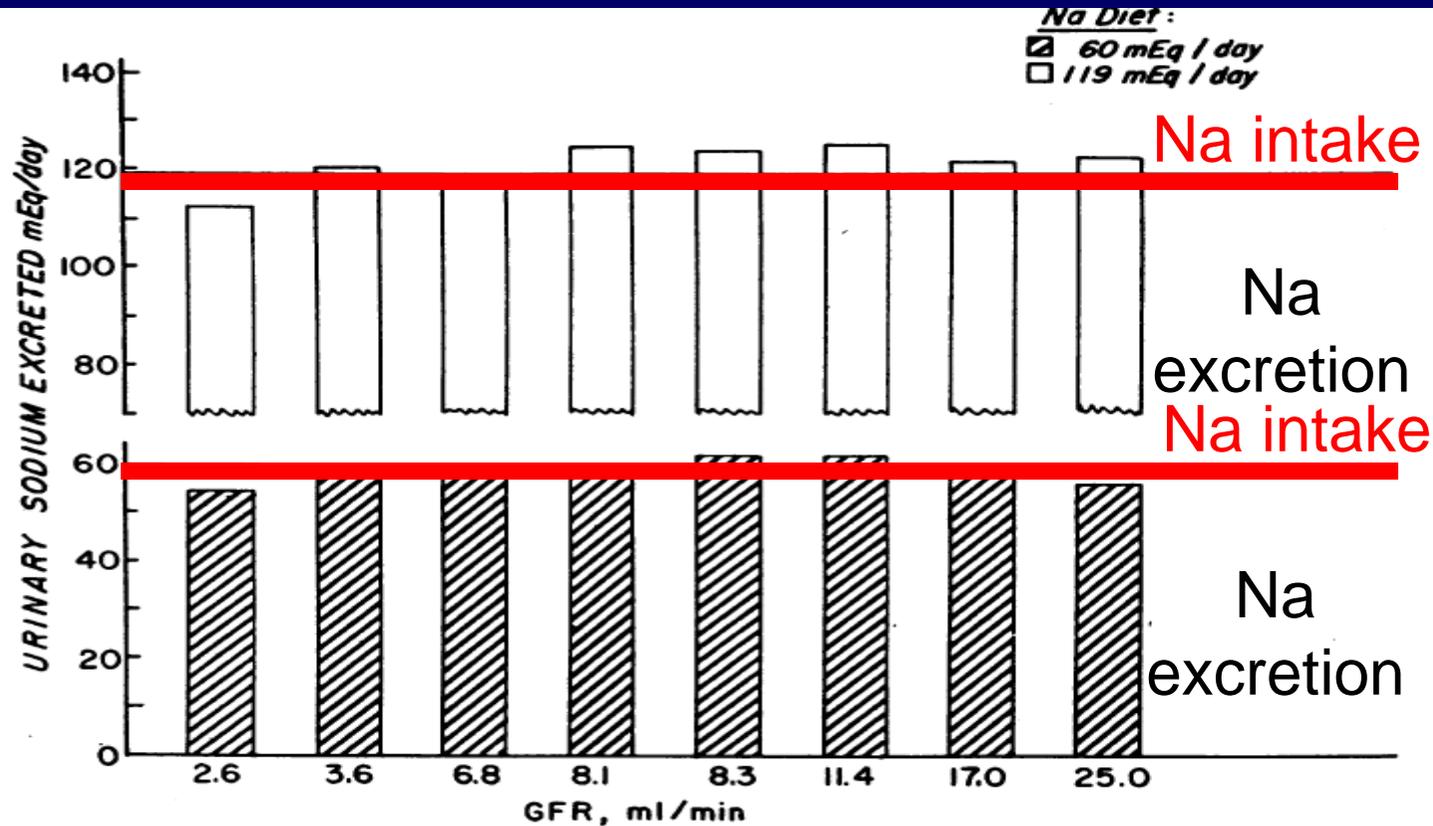


FIGURE 1 Sodium balance studies on 3.5 and 7.0 g salt diets. The horizontal lines represent sodium intake. The height of the vertical bars represents the mean of at least 2 24-hr sodium excretion rates. GFR, glomerular filtration rate.

# What This Means and Its Significance

- If edema is not occurring, then urinary Na excretion equals Na intake
- The FeNa rises as GFR falls to achieve this
- Something(s) is/are happening to achieve this
- Natriuretic factors are activated

# The Intact Nephron Hypothesis (3)

- Bricker's expansion with "The Trade-off Hypothesis"
  - NEJM 286:1093, 1972
- States simply that
  - As the remaining (intact, super) nephrons adapt to stimuli, the stimuli and the adaptations both carry consequences that may or may not be advantageous in the long run
  - Short term adaptations to accommodate a dysfunction (e.g. decreased phosphate excretion) result in adverse effects later (e.g. hyperparathyroidism, FGF-23 excess)

# The Intact Nephron Hypothesis (4)

- The body of evidence supports both the “intact nephron” and “trade-off” hypotheses
- Thus, it follows that if there is activation of compensations as kidney failure progresses, then the initiation of dialysis could “deactivate” the stimuli and consequently the adaptations themselves
- Dialysis compromises the diseased kidneys’ adaptations to nephron loss

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**The intact nephron adaptation is reversed**

# Sodium Excretion in Late Stage Chronic Kidney Disease

- Fractional excretion (FeNa) ~ 15%
- Dependent upon:
  - Increase in single nephron GFR
  - Suppression of aldosterone
  - Activation of numerous natriuretic peptides
- Dialysis ultrafiltration removes the stimuli for these adaptations

# Slow Versus Rapid Dialytic Removal of the Stimuli to the Adaptations

- As the adaptations developed slowly, their loss may occur slowly if the stimuli are allowed to remain in some lesser degree
  - Incremental dialysis
- In contradistinction to aggressive salvage dialysis which may entirely ablate the adaptive stimuli

# Preserved RKF With Incremental Dialysis over Full Dose

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# Does PD Slow the Rate of RKF Loss?

Ramon et al PDI 22:239, 2002

- 14/36 PD pts had almost monthly Cr Cl studies for > 12 months prior to PD and started this period with Cr Cl  $\geq 20$ , then followed on PD for > 6 months
- Mean rate of loss of RKF was less on PD for all pts
- Consistent with at least two rat model studies

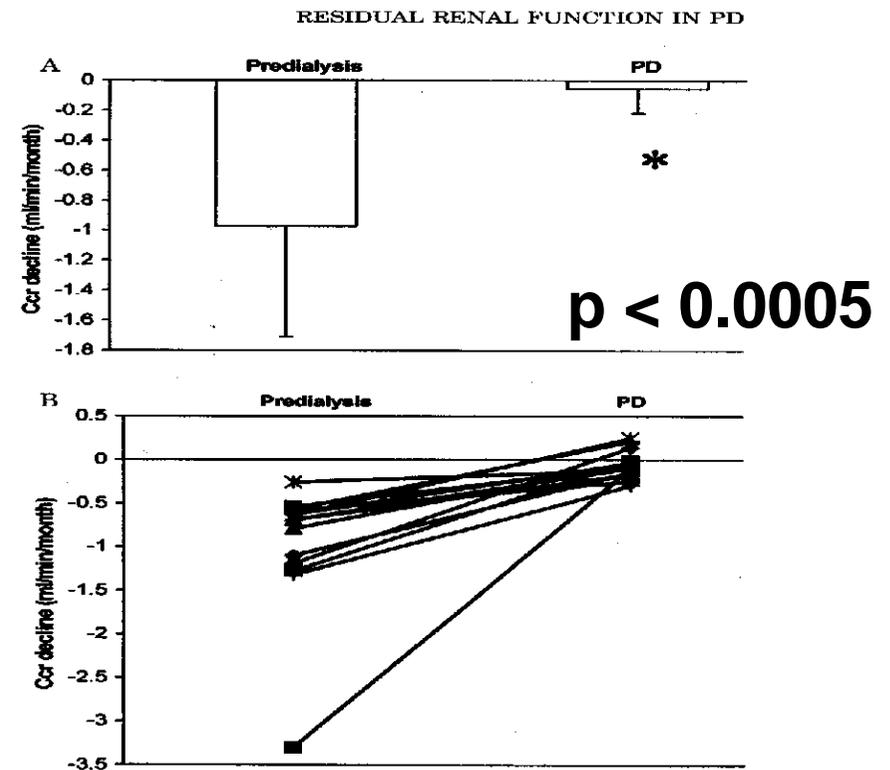


Figure 2 — Mean rate of decline in renal creatinine clearance (CCr) during the predialysis period and during the peritoneal dialysis (PD) period; mean  $\pm$ SD (A). A slower rate of decline in renal CCr was present in every patient (B).

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# Incremental Hemodialysis

- Less frequent sessions
  - Intermittent PD
- Less intensity per session
  - Shorter time
  - Smaller needles
  - Lower blood/and or dialysate flow rates
  - Smaller dialyzer size (surface area)

# Blood Flow Rate and AV Fistula Survival

Asano et al Nephron Clin Pract 124:23, 2013

- DOPPS 498 facilities 1,183 incident and 949 prevalent pts across Japan, North America, Europe Australia and New Zealand, adjusted for patient characteristics.
- AVF failure rates were higher in facilities with higher median blood flow rates
  - Hazard ratio 1.21 (95% CI, 1.05, 1.39)

# Seminars in Dialysis 29:476, 2016

MAKING DIALYSIS ADEQUATE – ADDRESSING ITS LIMITATIONS

## Incremental Hemodialysis: How I Do It

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### ABSTRACT

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Incremental hemodialysis (incrHD) is not widely used nor is it well understood. In addition, and perhaps with more impact, governmental regulations in the United States and their consequential influences on dialysis provider organizations have made the practice of incrHD more difficult than traditional thrice weekly in-center HD. IncrHD is critically dependent on the amount of residual kidney function (RKF) as well as the individualized goals of end-stage renal disease (ESRD) management. RKF has to be assessed frequently and dialysis adjusted accordingly.

Home HD lends itself to an incremental approach more so than in-center HD. This may be due to more experience of the provider, more knowledge of the therapy by the patient and family, the availability of dialysis platforms conducive to incrHD, and/or that its less onerous regulation by the government. I have had a long and successful experience performing incremental dialysis (both peritoneal and hemodialysis) and share here my practice strategies and approaches for incrHD.

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# Incremental Peritoneal Dialysis

By its very nature, PD is less intense than HD

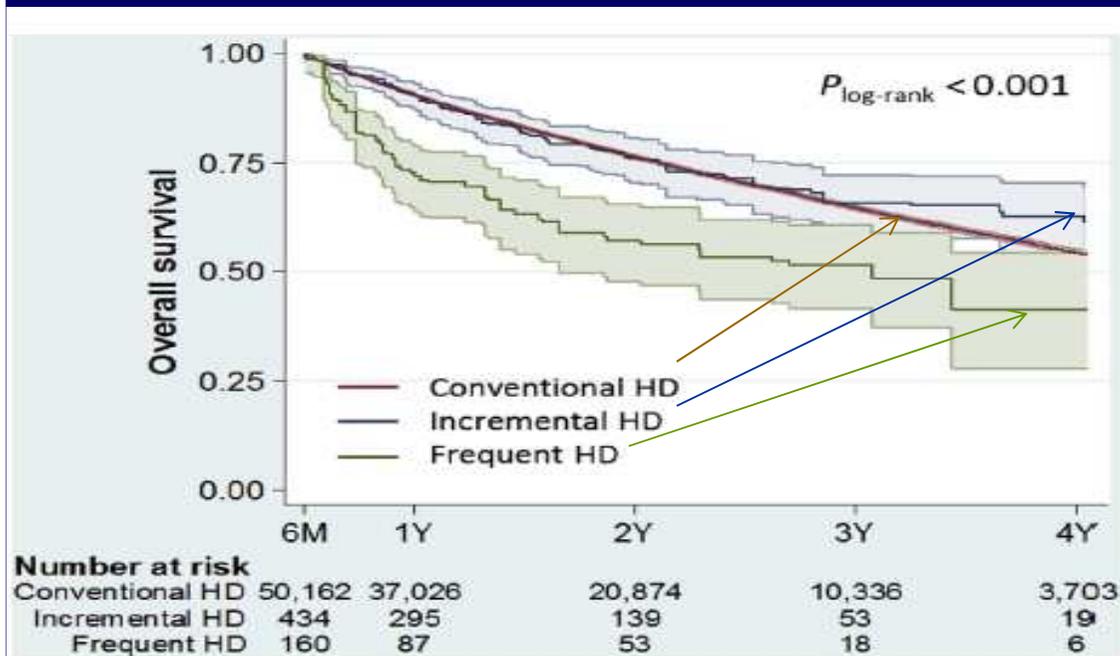
- Less frequent exchanges
  - Per 24 hours in CAPD
  - Per cycling at night
  - Cycling sessions per week
  - Dry periods
- Smaller fill volume
  - Each exchange
  - Ambulatory exchanges
  - Vary by exchange and activity

How well do patients do  
with incremental HD?

# Treatment Frequency and Mortality

Matthew et al KI, 2016 (in press)

doi 10.1016/j.kint.2016.05.028

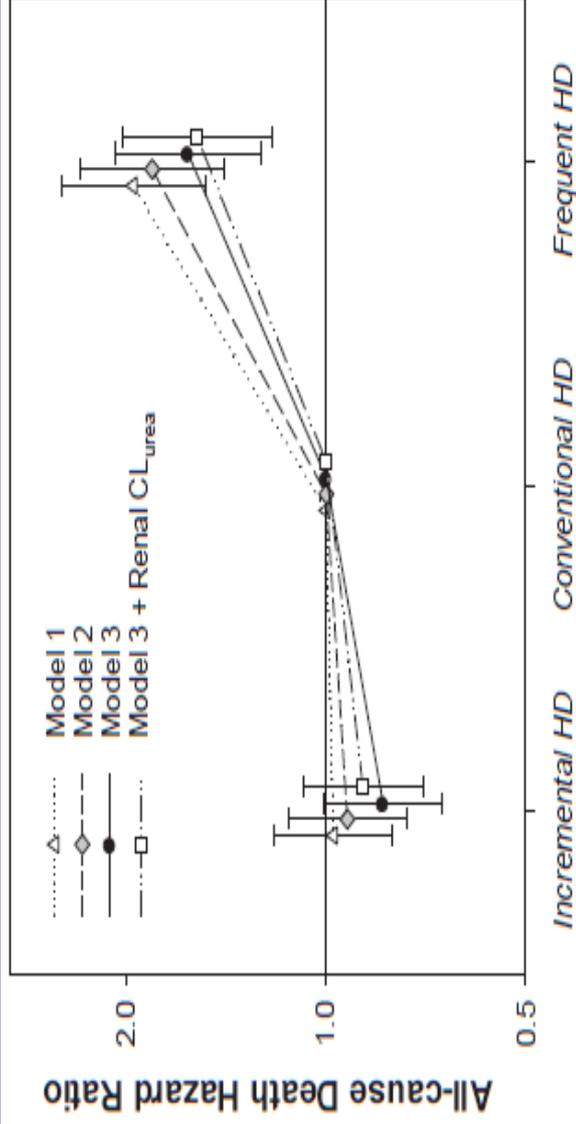


**Figure 2 | Kaplan-Meier survival estimates and 95% confidence intervals by initial hemodialysis (HD) regimen in the matched cohort ( $N = 50,756$ ). Weighted coarsened exact matching were used based on age, sex, race, central venous catheter as vascular access, and the Charlson Comorbidity Index.**

Demographic and comorbidity adjustments

Matched cohorts  
DaVita pts 2007-11

Still confounded by indication



**Figure 3 | Adjusted all-cause mortality risk of incremental and frequent hemodialysis (HD) in the matched cohort ( $N = 50,756$ ).** Weighted coarsened exact matching were used based on age, sex, race, central venous catheter as vascular access, diabetes, and the Charlson Comorbidity Index. Model 1 is the unadjusted model. Model 2 includes Medicare as primary insurance, single pool Kt/V, body mass index, hemoglobin, albumin, corrected calcium, iron saturation, bicarbonate, log-transformed ferritin, and intact parathyroid hormone (iPTH). Model 3 includes variables in Model 2, a history of fluid overload, interdialytic weight gain, creatinine, phosphorus. Data on laboratories were extracted during the first 91 days of dialysis, and those except for ferritin and iPTH were further restricted to the initial thrice-weekly HD period before starting infrequent or frequent HD. CL<sub>urea</sub>, urea clearance.

# DaVita Analysis Conclusions

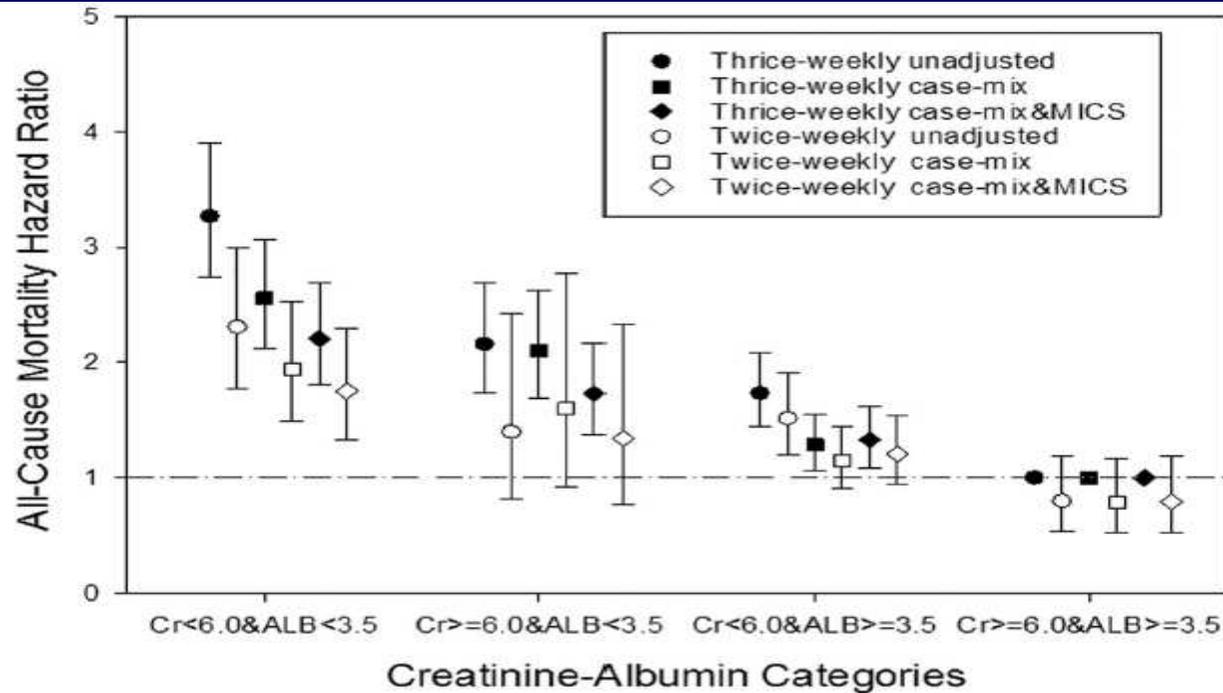
- Incremental initiation of HD does not appear to increase mortality
  - Population selected
    - Adequate residual function and IDWG
    - Low or moderate co-morbidity burden
- Only an RCT can eliminate confounding by indication

# Incremental HD Outcome By Creatinine and Albumin Levels

Wang et al J Renal Nutr  
doi10.1053/j.jrn.2016.07.001

- DaVita database
- 1,113 twice-weekly matched by 4,448 thrice-weekly, incident, 5 yr f/u (2007-11)
- Cr < 6 vs  $\geq 6$ ; alb < 3.5 vs  $\geq 3.5$
- Adjustments: demographic, co-morbidities, markers of malnutrition and inflammation
- $70 \pm 14$  yrs old, 48% female, 55% diabetic

# Incremental HD Outcome By Creatinine and Albumin Levels



**Figure 5.** Baseline survival hazard ratio over 5 years according to concurrence of serum creatinine (mg/dL) and albumin (g/dL) among after matched twice-weekly (n = 1,113) and thrice-weekly (n = 4,448) hemodialysis patients. The reference groups are categories in which creatinine  $\geq 6.0$  mg/dL and albumin  $\geq 3.5$  g/dL in thrice-weekly hemodialysis patients. See text for the list of covariates in multivariate adjustment. MICS, malnutrition-inflammation complex syndrome.

# Incremental HD Outcome By Creatinine and Albumin Levels

Wang et al J Renal Nutr  
doi10.1053/j.jrn.2016.07.001

- Conclusions:
  - 1. Surrogate markers of higher visceral protein (e.g serum albumin) and muscle mass (serum creatinine) combined may confer greatest survival in both twice-weekly and thrice-weekly groups
  - 2. Twice-weekly HD pts have similar survival according to the same levels of nutritional status and muscle mass when compared to thrice-weekly HD patients

# Caveats

# Does an Incremental Start Mean An Earlier Start?

- Not starting before it is needed, but starting at the correct time to ease the patient into the burden of transitioning into dialysis
- Circumstances where this may occur earlier than others:
  - Concern over the HD access functionality
  - Concern over the integrity of the peritoneum (e.g. surface area, hernias, membrane damage)

# When Not To Practice Incremental Dialysis

- When there is a failure of understanding that over time dialysis dose will need to be intensified by:
  - Patient and family
  - Staff
  - Dialysis organization
  - Oversight body
- Absence of an integrated ESRD care program

# Summary/Conclusions

- Chronic kidney failure and end-stage kidney disease are a continuum and should be treated as such
- Healthy start to dialysis and the incremental approach are practical and well tolerated
- Incremental dialysis may help preserve RKF longer with all the benefits derived from that
- The mechanism may well be the intact nephron hypothesis in reverse