



Time and Adequacy of Hemodialysis: Were the Data Really Negative?

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Disclosures

- Advisory boards:
 - Amgen
 - C.B. Fleet, Co
- Spouse employed by Genzyme

Take home message

- Hemodialysis treatments of <4 hours are associated with increased mortality.
- This association is constant across a number of populations and sub-populations, *including those patients in who Kt/V conforms to practice standards.*
- This suggests that 4 hours should be the requisite minimum dialysis treatment time.

Overview

- **The history of dialysis titration**
- Rationale for reconsidering time
- Associations between time and survival
- Potential Mechanisms
- Conclusions

Dialysis titration over time



National cooperative dialysis study

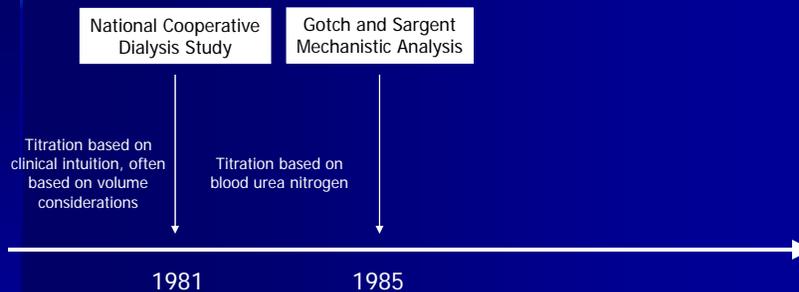
- Impetus:
 - Determine best way of addressing ongoing uremia
- Multicenter randomized trial; 2 X 2:
 - Time averaged BUN (50 vs 100 mg/dL)
 - Session length (2.5-3.5 versus 4.5-5 hours)
- 151 subjects
 - Mean age 51 years
 - No patients with diabetes, coronary disease, recurrent infections, cancer, anticipated survival <3 years
- Outcomes:
 - Primary: morbidity (medical drop out, hospitalizations)
 - Secondary: mortality

National cooperative dialysis study

- Trial stopped early by data safety monitoring board:
 - Median follow up 48 weeks
 - Primary analysis used week 26 data
- Results:
 - Urea concentration highly associated with hospitalization
 - Session length not associated with hospitalization ($p=0.056$)
 - No association of either with mortality

Lowrie EG, et al. N Engl J Med 305: 1176-1181, 1981

Dialysis titration over time

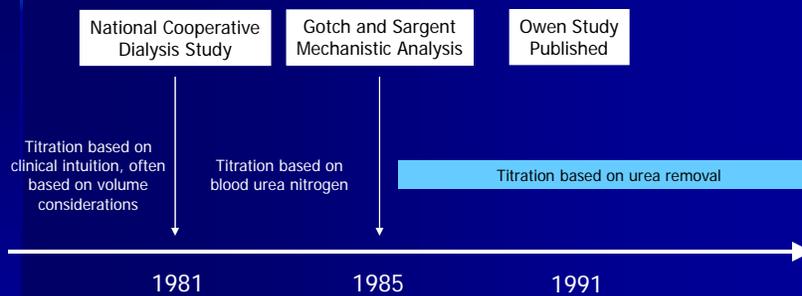


Mechanistic analysis

- Data taken from National cooperative dialysis study
- Demonstrated increased ability to predict “failure” when using Kt/V as opposed to time averaged BUN
 - Medical drop out
 - Medical drop out + hospitalization
- Did not consider mortality

Gotch FA, et al. Kidney Int 28: 526-534, 1985

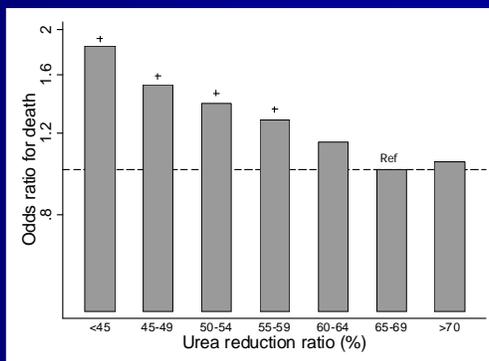
Dialysis titration over time



Identification of a urea removal target with respect to mortality

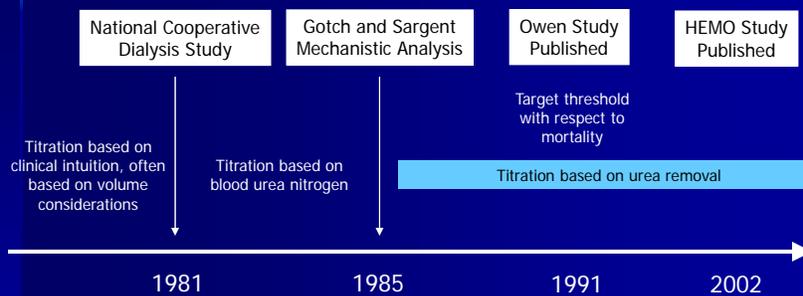
Retrospective analysis:

- 13,473 patients
- 6-month mortality Oct 90-Mar 91



Owen WF, et al. N Engl J Med 329: 1001-1006, 1993

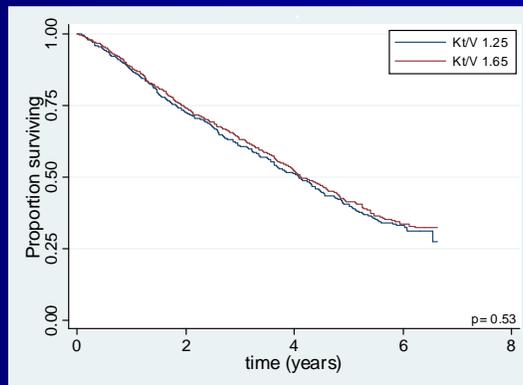
Dialysis titration over time



HEMO study

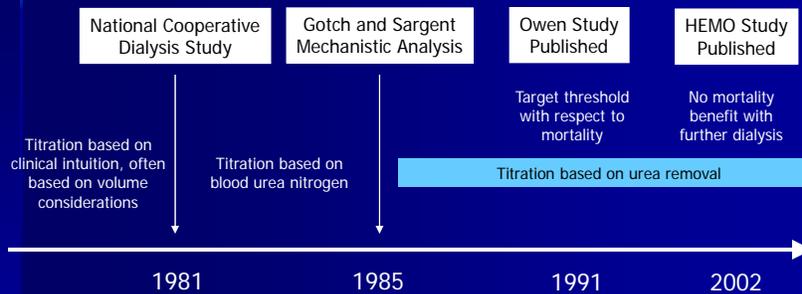
Randomized trial, 2X2:

- Flux
- Dose
 - Sp-Kt/V 1.25
 - Sp-Kt/V 1.65
- 1,846 subjects



Enkoyan G, et al. N Engl J Med 347: 2010-2019, 2002

Dialysis titration over time



Overview

- The history of dialysis titration
- **Rationale for reconsidering time**
- Associations between time and survival
- Potential Mechanisms
- Conclusions

Philosophical considerations

- There are (at least) three processes happening in parallel during dialysis:
 - Removal of small solutes
 - Removal of middle molecules
 - Removal of fluid
- Under a given paradigm, any of one (or more) of these may be survival-limiting
- If the paradigm changes, reevaluation is necessary

Technological developments

- Widespread introduction of high efficiency dialyzers.
 - Enable very rapid removal of small solutes
 - Fundamentally alter the implied relationship between urea kinetics and:
 - Middle molecule removal
 - Fluid removal
- If treatments are shortened in response to earlier attainment of Kt/V target, may leave insufficient time for these other goals.

Revisiting HEMO with an eye towards session length

- HEMO found “no adverse effects of shorter treatment times.”
- However...
 - “Study was not optimized to evaluate the effects of treatment time”
 - “Study was designed to allow to time to vary within [group]”
 - Dialysis was titrated to “the shortest treatment time consistent with the patient’s assigned dose”

Depner T, et al. *Kidney Int* 65: 1386-1394, 2004

Consider two patients:

- Patient A with fistula
- Patient B with catheter
 - Patient B has less effective blood flow reduced → session length extended
 - Patient B at greater risk for mortality due to catheter
- Confounding of the session length—mortality association

In essence...

There has not been a randomized trial of hemodialysis session length since the National Cooperative Dialysis Study.

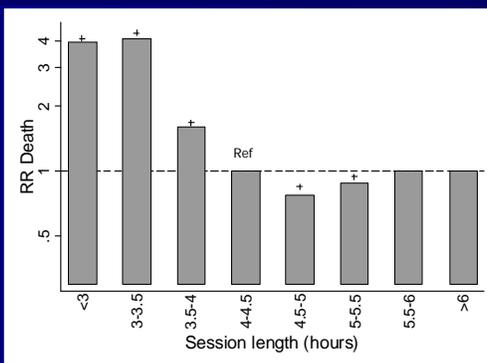
Overview

- The history of dialysis titration
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- **Associations between time and survival**
- Potential Mechanisms
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Studies of time

Retrospective analysis

- Japanese cohort 1993-94 (N=53,867)
- Session length assessed at baseline
- Outcome: adjusted risk of death at 1-year



Adjusted for: age, sex, diabetes, Kt/V, percent weight change, nPCR

Shinzato T, et al. Nephrol Dial Transplant 12: 884-888, 1997

Studies of time

Retrospective analysis

- Australia/ New Zealand cohort 1997-2004 (N=4,171; incident patients)
- Session length assessed at 12 months after dialysis initiation
- Outcome: all cause mortality

Session length	N	HR(95% CI)
<3.5 h	121	1.57 (1.14-2.17)
3.5-3.9 h	187	1.09 (0.81-1.46)
4-4.4 h	2091	1 (Ref)
4.5-4.9 h	753	0.80 (0.66-0.97)
≥ 5 h	1019	1.02 (0.85-1.22)

Adjusted for: age, sex, race, cause ESRD, late referral, creatinine clearance at initiation, access type, BMI, DM, CAD, PVD, CVD, CLD, HTN, smoking, Kt/V

Marshall MR, et al. Kidney Int 69: 1229-1236, 2006

Studies of time

Retrospective analysis

- Multinational DOPPS cohort 1997-2004 (N=16,333)
- Session length assessed at study entry
- Outcome: all cause mortality

Treatment time ≤ 240 min:

Adjusted HR 1.23; $p < 0.001$

Adjusted for: age, sex, race, ethnicity, vintage, 14 summary comorbid conditions, living status, height, weight, Kt/V, blood flow, residual renal function, catheter use, UFR

Saran R, et al. Kidney Int 69: 1222-1228, 2006

Studies of time

Retrospective analysis

- DaVita cohort 2001-06 (N=88,153)
- Session length time averaged
- Outcome: all cause mortality

Values approximate

Session length	N	HR(95% CI)
<3 h	6,000	1.12 (1.06-1.17)
3-3.4 h	25,000	1.02 (0.99-1.06)
3.5-3.9 h	27,000	1 (Ref)
≥ 4 h	25,000	1.01 (0.98-1.05)

Adjusted for: age, sex, race, ethnicity, DM, vintage, insurance, marital status, facility SMR, residual renal function, BMI, 11 laboratory surrogates of MICS, calendar quarter.

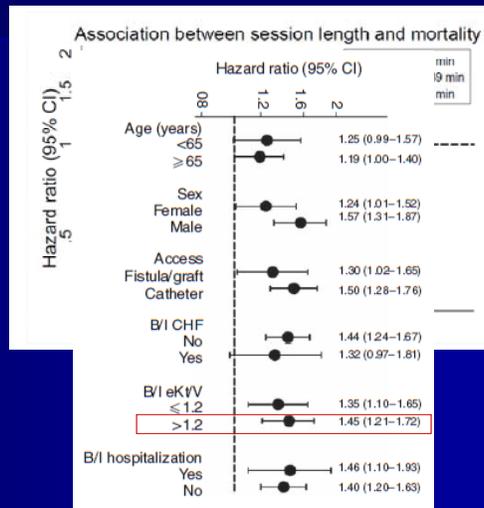
Effects of time more pronounced among women

Miller JE, et al. Am J Kidney Dis 55: 100-112, 2009

Studies of time

Retrospective analysis

- FMC cohort 2004-05 (N=8,552; incident patients)
- Session length time updated
- Outcome: all cause mortality
- Marginal structural modeling to adjust for time dependent confounding



Brunelli SM, et al. *Kidney Int* 77: 630-636, 2010

Why the dependency on time even when urea kinetics optimized?

- Indexing to body size (i.e., the "V" in Kt/V)
 - Smaller people require less Kt to achieve goal Kt/V and are also more likely to die
 - Kt associated with survival independent of body size; Kt/V not

Lowrie EG, et al. *Kidney Int* 66: 2077-2084, 2004

- Solute clearance beyond what is reflected by urea kinetics
 - Holding Kt/V experimentally constant (Genius system), longer treatment results in greater clearance of:
 - Creatinine
 - Phosphate
 - B2-microglobulin
 - Urea

Eloot S, et al. *Kidney Int* 73: 765-770, 2007

Why the dependency on time even when urea kinetics optimized?

- Though not entirely analogous, change to daily dialysis results in:
 - Improved phosphatemia
 - Despite decreased use of phosphate binders

Ayus JC, et al. Kidney Int 71: 336-342, 2007

- Do we need a new metric? biomarker?

Is ultrafiltration rate the culprit?

- Cardiovascular disease is the leading cause of death among HD patients
- Clinical intuition would suggest that UFR fits into a framework of CV mortality
 - Decreased circulating volume
 - Hypotension
 - Cardiac stunning
 - End-organ ischemic damage (troponin)
 - Inability to achieve “driest” weight
 - Cardiac remodeling → myopathy and arrhythmia risk
 - Vascular remodeling → arterial stiffness

Is ultrafiltration rate the culprit?

Retrospective analysis

- Multinational DOPPS cohort 1997-2004 (N=16,333)
- Session length assessed at study entry
- Outcome: all cause mortality

Treatment time ≥ 10 ml/h/kg:

Adjusted HR 1.09; p=0.02

Adjusted for: age, sex, race, ethnicity, vintage, 14 summary comorbid conditions, living status, height, weight, Kt/V, blood flow, residual renal function, catheter use, UFR

Saran R, et al. Kidney Int 69: 1222-1228, 2006

Is ultrafiltration rate the culprit?

- Prospective analysis
- Italian cohort 2001-05 (N=287)
- UFR considered at baseline
- Outcome: all cause mortality

UFR (per 1 ml/h/kg):

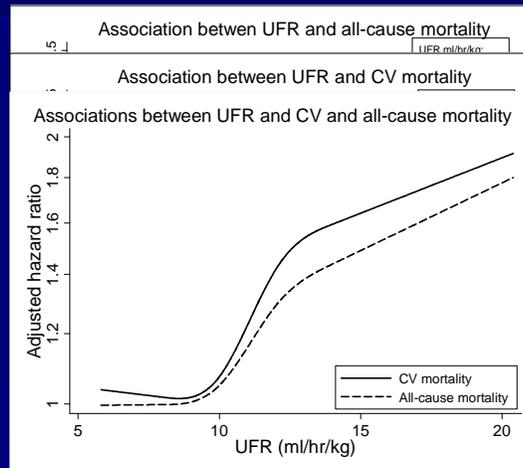
Adjusted HR 1.22 (1.16-1.28)

Adjusted for: age, sex, vintage, cardiovascular disease, DM, modality, weight, BMI, session length, IDWG, mean arterial pressure, pulse pressure, Kt/V, nPCR

Movilli E, et al. Nephrol Dial Transplant 22: 3547-3552, 2007

Is ultrafiltration rate the culprit?

- Post-hoc analysis
- HEMO Study data (N=1,846)
- UFR considered at baseline
- Outcomes: all cause and CV mortality



Flythe, et al. Unpublished

Is ultrafiltration rate the culprit?

- Again, though not entirely analogous, a change to daily dialysis results in:
 - Improvements in LV mass
 - Lower ultrafiltration volumes and rates

Ayus JC, et al. J Am Soc Nephrol 16: 2778-2788, 2005

Summary

- Shorter session lengths adversely affect survival even when current metrics of urea kinetics are optimized.
- This would imply a need to extend session length to at least 4 hours (and perhaps beyond).

Summary

- If this effect is mediated through augmented clearance of small or middle molecules, session length might be safely reduced upon eventual:
 - Identification/ monitoring of more appropriate:
 - Metrics of adequacy
 - Uremic biomarkers
 - Development of dialyzers that more efficiently clear offending toxins
- Some evidence suggests that this effect is mediated through the rate of fluid removal.
 - This would not be remediable through the above measures and necessitate strict adherence to longer dialysis (assuming IDWG cannot be curtailed).

Take home message

- Hemodialysis treatments of <4 hours are associated with increased mortality.
- This association is constant across a number of populations and sub-populations, *including those patients in who Kt/V conforms to practice standards.*
- This suggests that 4 hours should be the requisite minimum dialysis treatment time.

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 - NIDDK Data Repository

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 - Amgen
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