# The In-Center Hemodialysis Prescription as it Relates to Blood Pressure and Volume

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# DISCLOSURES

## Research funding

- National Institutes of Health
- Patient Centered Outcomes Research Institute

## Member, Data and Safety Monitoring Board

- National Institute of Diabetes and Digestive and Kidney Diseases
- Proteon Therapeutics

## Consulting

- GlaxoSmithKline

## Compensation

- National Kidney Foundation:  Deputy Editor, *American Journal of Kidney Diseases*

# Hemodialysis Prescription and BP / Volume Management: State of the Evidence

- Most of the data come from observational studies, small mechanistic studies, or small trials
- As a community, we are now in a position to more efficiently conduct large RCTs evaluating components of the hemodialysis prescription

# OUTLINE

- Target weight
- Ultrafiltration rate
- Treatment time
- Dialysate composition
- Dialysate temperature
- Residual kidney function



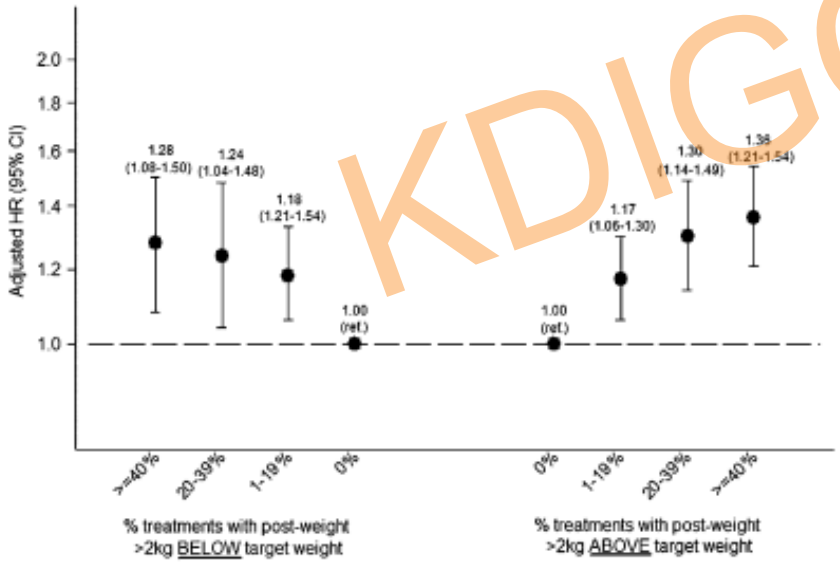
**I will *not* provide an exhaustive review of the literature or the issues**

# TARGET WEIGHT

Associations of Post-Hemodialysis Weights Above and Below Target Weight with All-Cause and Cardiovascular Mortality

~11,000 patients at a large US dialysis provider organization

All-Cause Mortality






Risk increases with proportion of sessions with post-dialysis weight >2 kg above or >2 kg below target weight

Flythe JE et al Clin J Am Soc Nephrol 10:808-816; 2015

# TARGET WEIGHT

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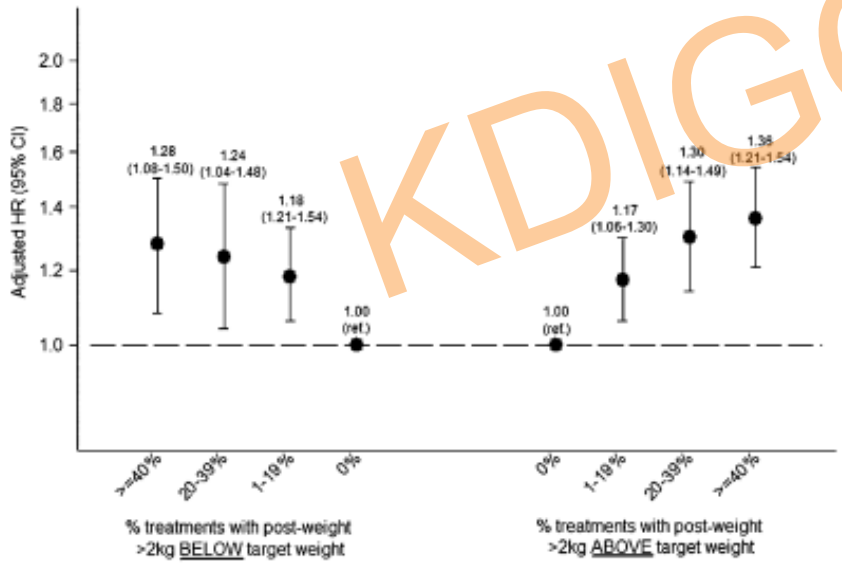
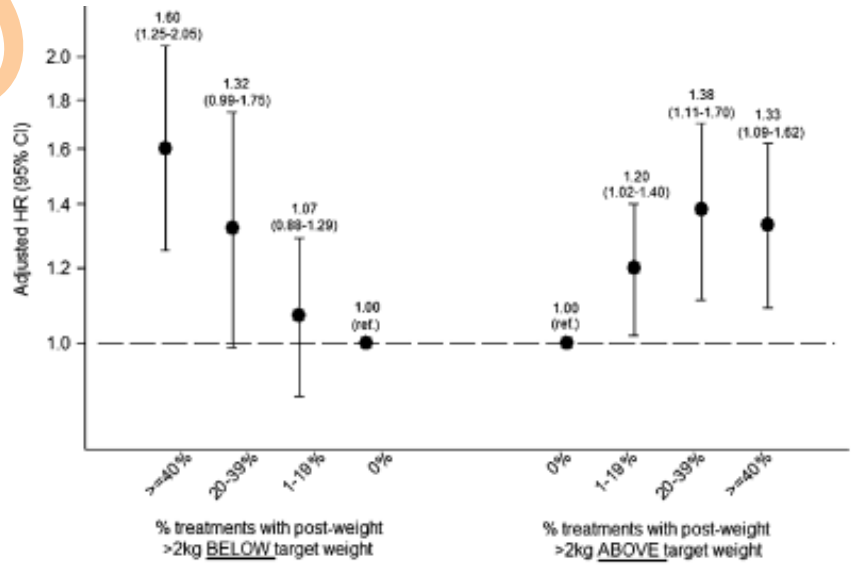



CV Mortality





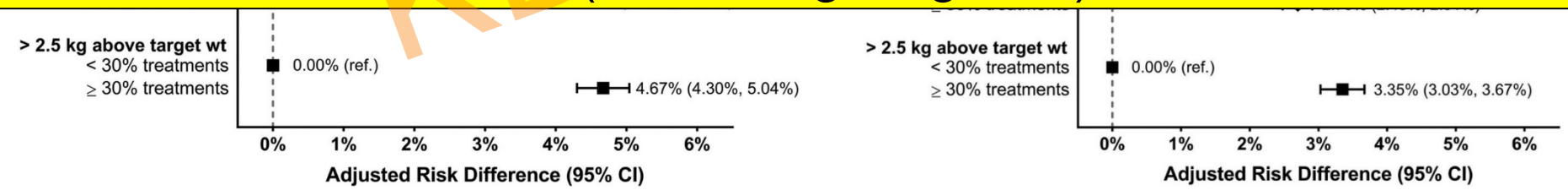

Flythe JE et al Clin J Am Soc Nephrol 10:808-816; 2015

# TARGET WEIGHT

Failed Target Weight Achievement Associates with Short-Term Hospital Encounters among Individuals Receiving Maintenance Hemodialysis

- ~114,000 pa
  from large U
  dialysis prov
- 180-day baseline;
  30-day exposure;
  30-day f/u

Is the high post-dialysis weight responsible for the outcome
OR
Is failure to meet the target (regardless of what it is) a marker of poor outcomes ("dose-targeting bias)?




- Risk higher if achieved post-dialysis weight > targeted post-dialysis weight in ≥30% vs <30% of sessions
- Risk difference increased as the difference in targeted and achieved weight increased.

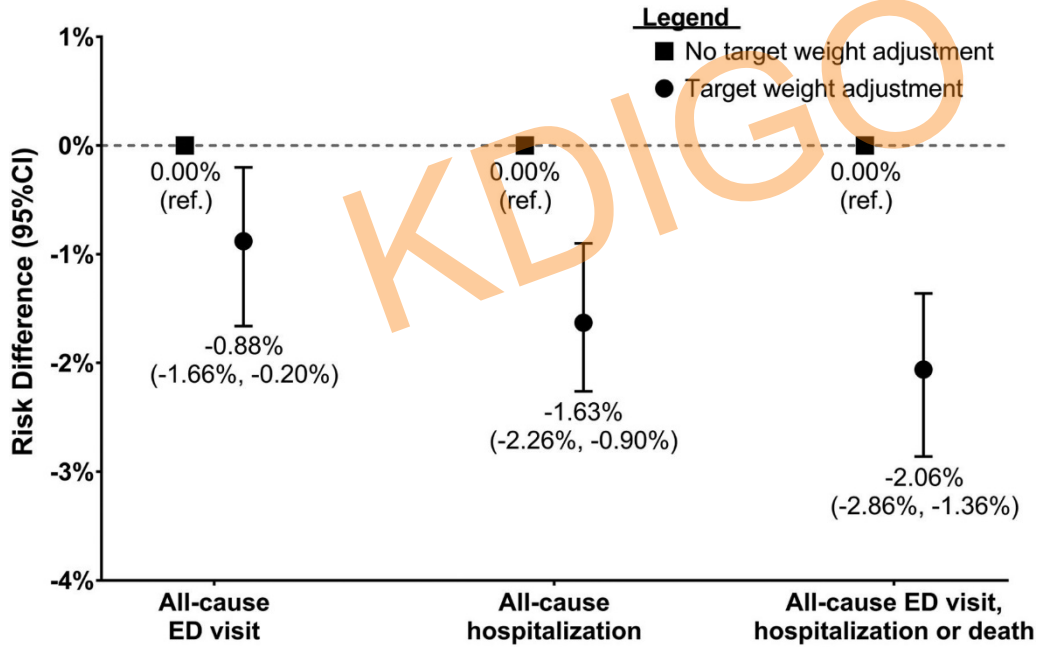
Assimon MM et

# TARGET WEIGHT

Failed Target Weight Achievement Associates with Short-Term Hospital Encounters among Individuals Receiving Maintenance Hemodialysis

- ~114,000 patients from large US dialysis provider
- 180-day baseline; 30-day exposure; 30-day f/u

Target Weight Adjustment Post-Hospital Encounter





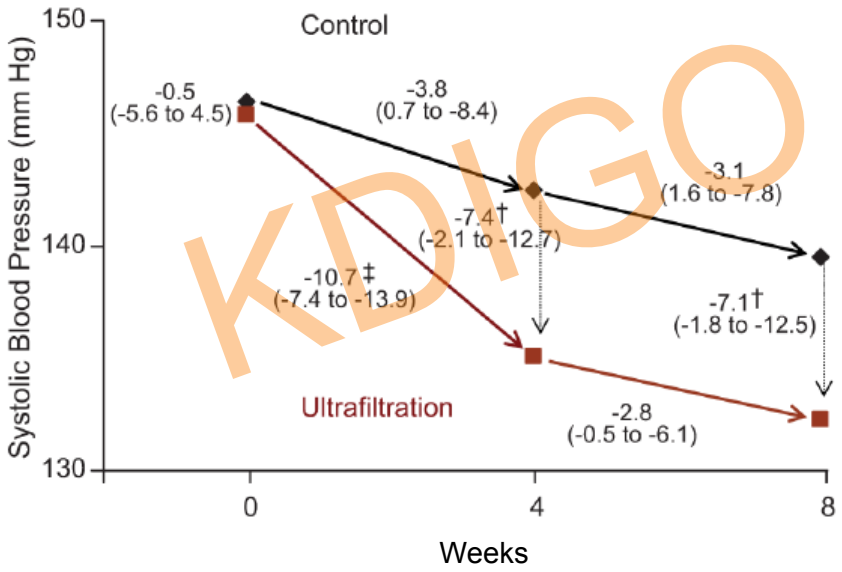

Lower risk if target weight was adjusted after the hospital encounter supports a causal relationship between achieved weight and ER visit or hospitalization

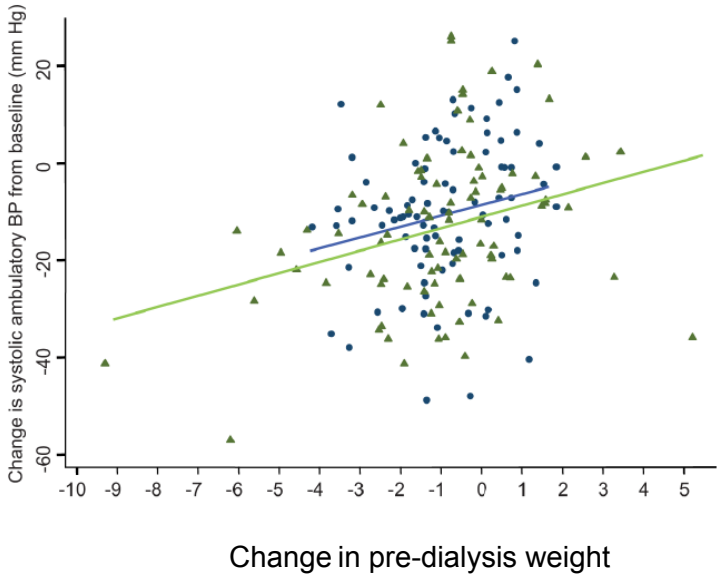
Assimon MM et al J Amer Soc Nephrol 29: 217802188; 2018

# TARGET WEIGHT: REDUCING "DRY" WEIGHT

Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP): A Randomized Controlled Trial

- Intervention: dry weight probing without increase in session duration or frequency
- 100 intervention; 50 control
- Run-in phase, then 8-week trial
- Primary outcome: change in systolic inter-dialytic BP



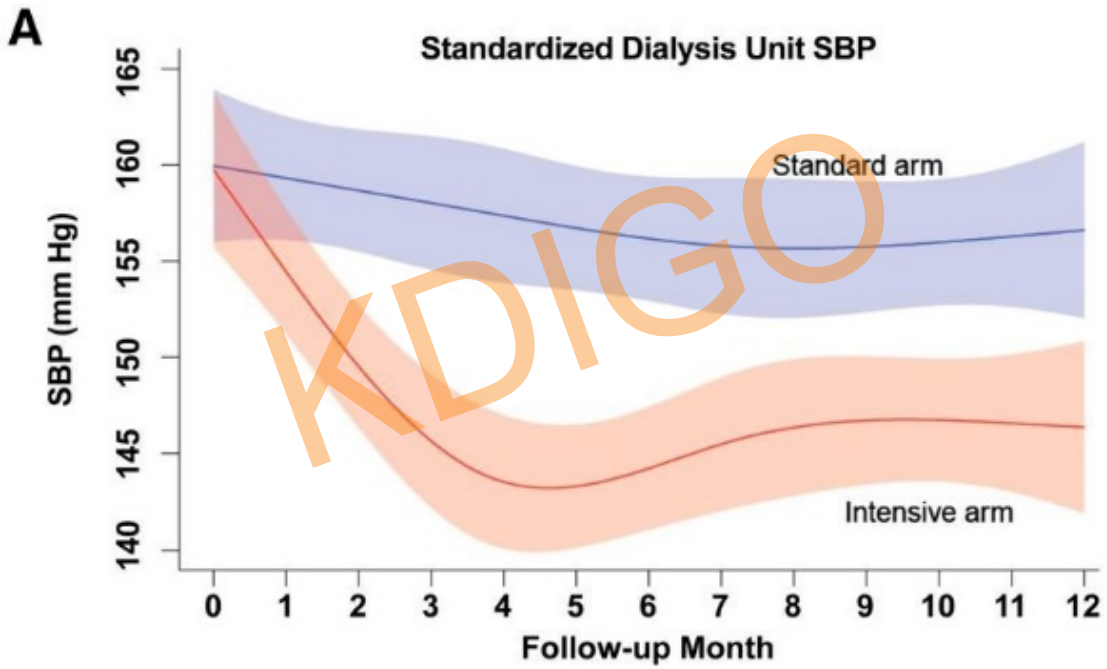

Intervention arm: 1 kg reduction in post-dialysis weight

Agarwal R et al. Hypertension; 53:500-507; 2009

# TARGET WEIGHT: REDUCING "DRY" WEIGHT

## BP in Dialysis: Results of a Pilot Study

- 126 hemodialysis patients
- Multiple centers in US
- Randomized to bp target 110-140 or 155-165 systolic
- Initial step to reduce BP was reduction in EDW





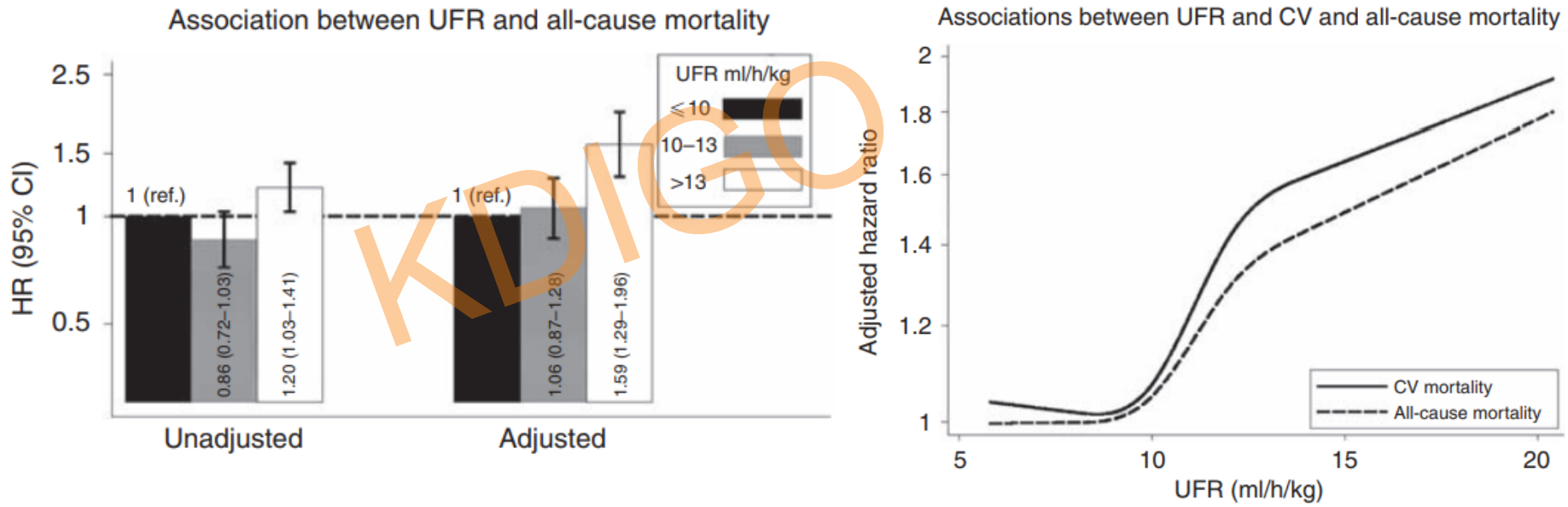

"Because many participants were intolerant to or refused these [dry weight] challenges, changes in antihypertensive medications were mainly responsible for achieving separation in SBP across treatment arms."

Miskulin DC et al. J Am Soc Nephrol 29:307-316; 2018

# ULTRAFILTRATION RATE

Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality

Post-hoc analysis of the HEMO Study (n=1846)






Flythe JE et al. Kidney Int 79:250-257; 2011

# Ultrafiltration Rate and Patient Experience

American Journal of Nephrology

Am J Nephrol 46:3-10; 2017

## Higher Ultrafiltration Rate Is Associated with Longer Dialysis Recovery Time in Patients Undergoing Conventional Hemodialysis

Hussein W.F.[a, b] · Arramreddy R.[a, b] · Sun S.J.[b] · Reiterman M.[b] · Schiller B.[a, b]



American Journal of Kidney Diseases

Volume 64, Issue 1, July 2014, Pages 86-94

## Recovery Time, Quality of Life, and Mortality in Hemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

Hugh C. Rayner MD, FRCP [1], Lindsay Zepel MS [2], Douglas S. Fuller MS [2], Hal Morgenstern PhD [2, 3, 4], Angelo Karaboyas MS [2], Bruce F. Culleton MD [5], Donna L. Mapes PhD [2], Antonio A. Lopes MD, MPH, PhD [6], Brenda W. Gillespie PhD [7], Takeshi Hasegawa MD [8], Rajiv Saran MD [7], Francesca Tentori MD [2, 9], Manfred Hecking MD [10], Ronald L. Pisoni PhD [2], Bruce M. Robinson MD [2, 7]

KDIGO Kidney Disease: Improving Global Outcomes

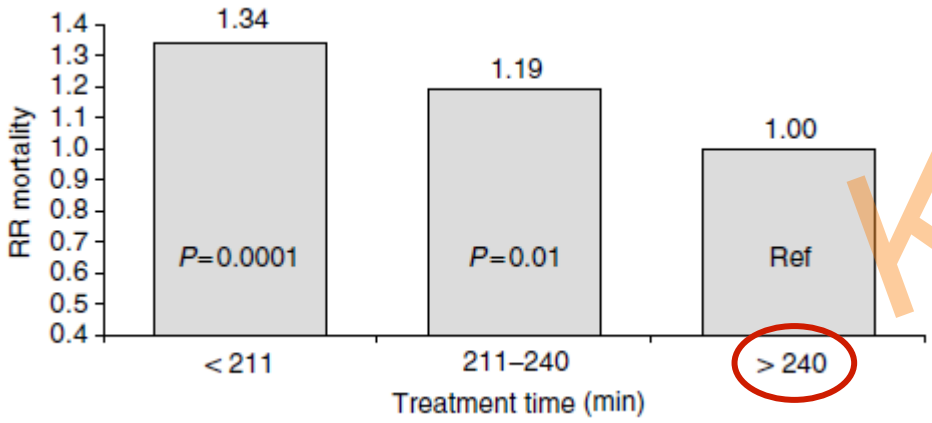
# Ultrafiltration Rate: Downsides of "Mandating" a Maximum UFR

- Two ways to reduce UFR: 1) lower inter-dialytic fluid intake
  2) increase treatment time
- Restricting fluid intake and increasing session duration are both burdensome to patients and may negatively affect quality of life
- Patients may leave dialysis volume overloaded
- Unpredictability of required session duration is logistically challenging for dialysis units

# SESSION DURATION

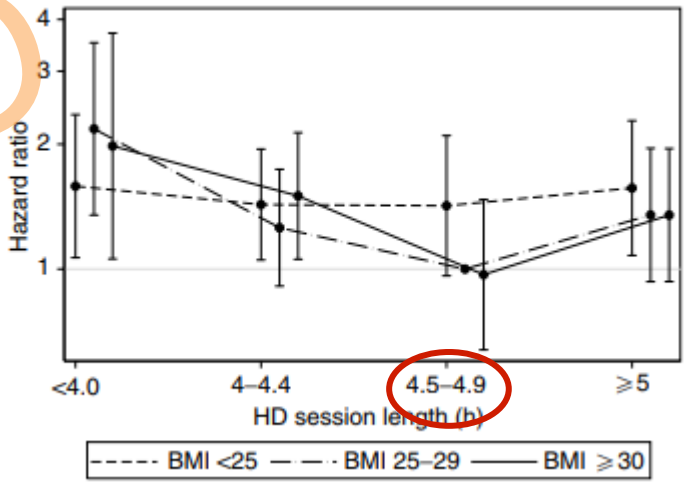
## Treatment time and mortality

### DOPPS




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

### ANZDATA Registry



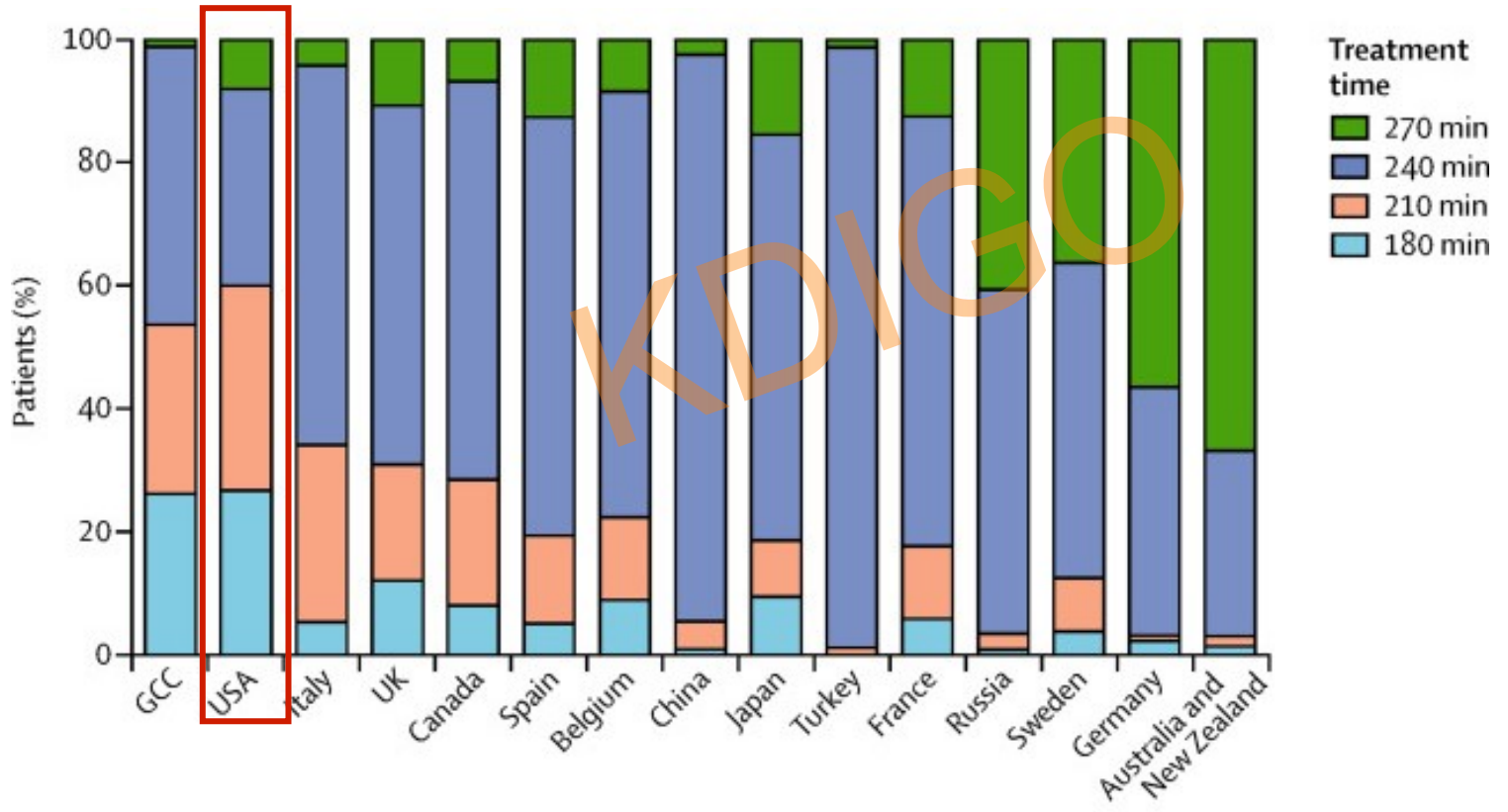

Marshall MR et al. Kidney Int 69:1229-1236; 2006

# Session Duration

| Reference | Source | Longer Treatment Time |
|---|---|---|
| Tentori et al NDT 2012 | DOPPS | Lower mortality |
| Flythe et al Kidney Int 2012 | DaVita | Lower mortality |
| Ramirez et al CJASN 2012 | CMS ESRD CPM Project | Higher mortality (trend) |
| Brunelli et al Kidney Int 2010 | Fresenius | Lower mortality or not different depending on analytic approach |
| Miller et al, AJKD 2010 | DaVita | Lower mortality but no difference beyond 3.5 hours |
| Saran et al Kidney Int 2006 | DOPPS | Lower mortality |
| Marshall et al Kidney Int 2006 | ANZDTA | Lower mortality |

# SESSION DURATION

DOPPS: Geographic variation in hemodialysis session duration





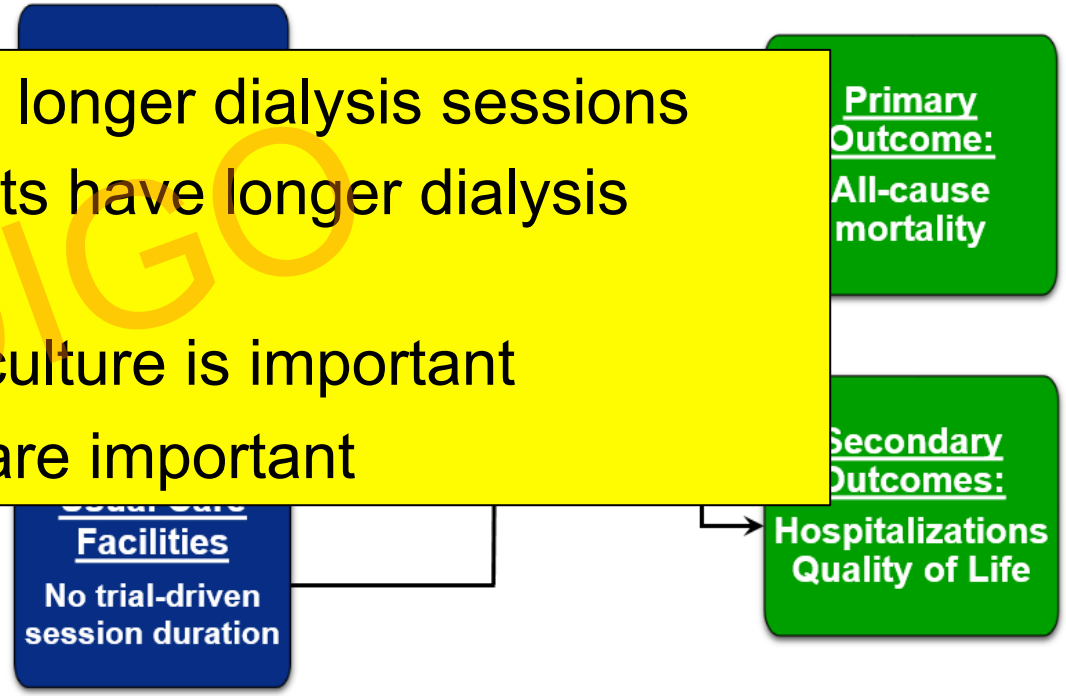

Robinson BM et al. The Lancet 388:294-306; 2016

# Session Duration

Time to Reduce Mortality in ESRD (TiME) Trial

- Pragmatic trial der
  project
- Cluster randomize
  embedded in clinic
  delivery
- 7035 patients; 266
  units

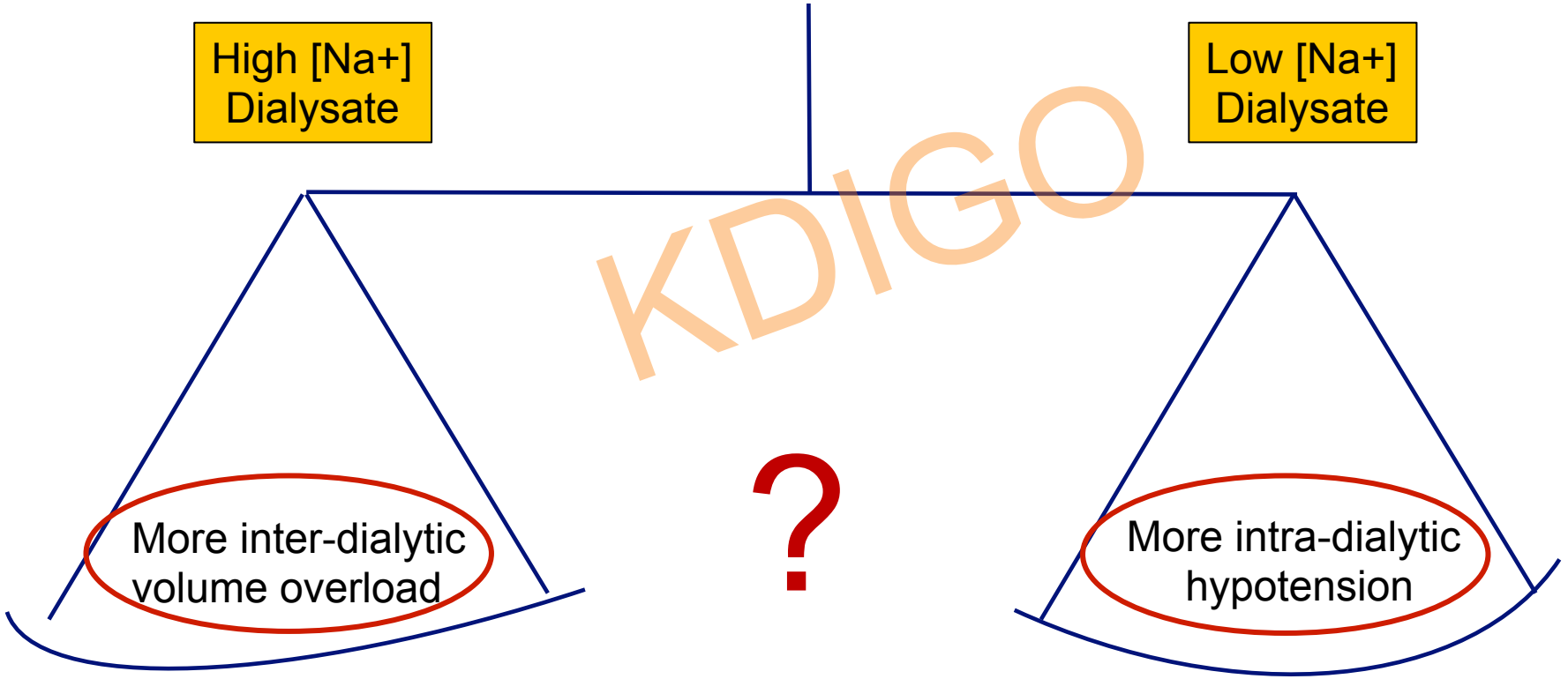
- Other countries have longer dialysis sessions
- Many US dialysis units have longer dialysis sessions
- Dialysis unit culture culture is important
- Patient preferences are important






ClinicalTrials.gov Identifier NCT02019225

# Dialysate Composition: [$Na^+$]



# Dialysate Composition: [$Na^+$]

High versus Low Dialysate Sodium Concentration in Chronic Haemodialysis Patients: A Systematic Review of 23 Studies

- N = 76,635
- 7 clinical trials (5 crossover, 3 randomized)
- High heterogeneity – intervention, f/u, outcomes
- “No clear evidence for superiority of low or high sodium dialysate on hard or surrogate outcomes”



Basile C et al. Nephrol Dial Transplant 31:548–563; 2016

# Dialysate Composition: [$Na^+$]

RESOLVE Trial: Randomized Evaluation of Sodium Dialysate Levels on Vascular Events

- Cluster randomized pragmatic trial of dialysate [$Na^+$] 137 vs 140 mEq/L
- Multinational: Australia, New Zealand, China, Canada, Germany, US
- Primary outcome: composite of MACE and all-cause mortality
- Target sample size: ~40,000 to detect 10% risk reduction

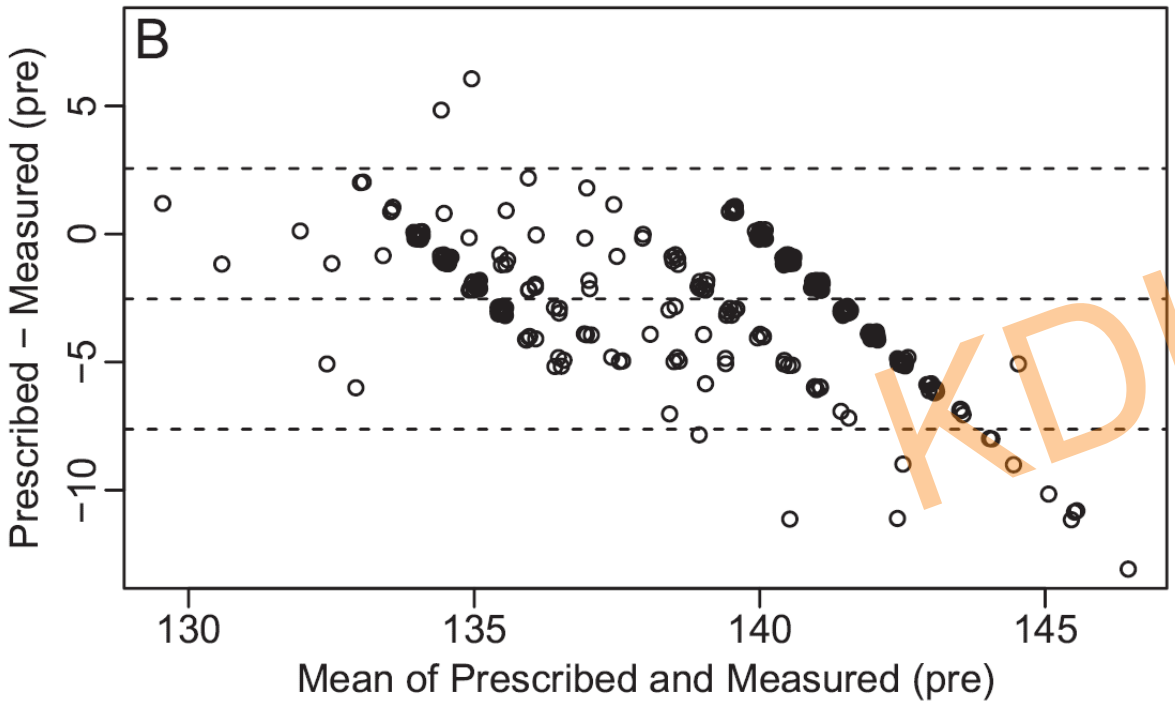


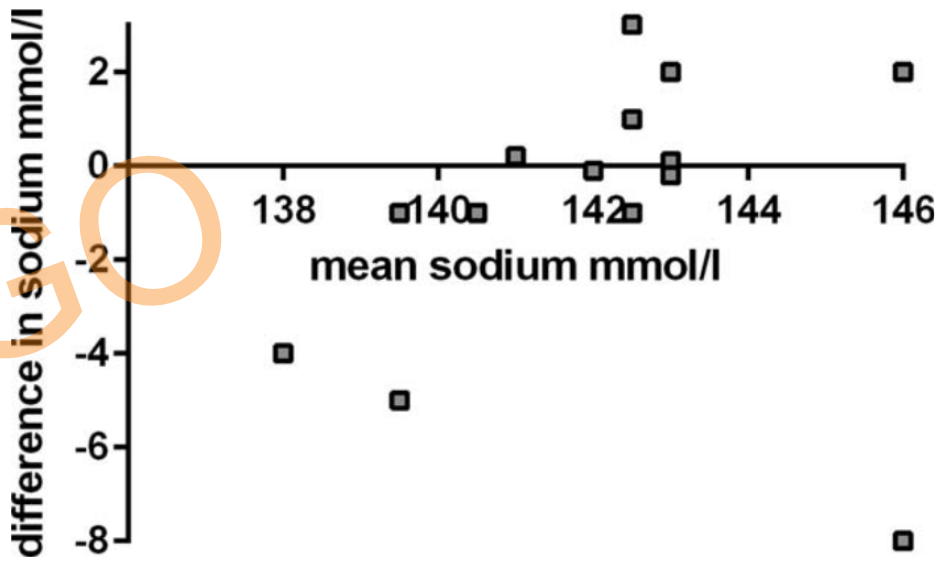
resolve
Randomised Evaluation of SOdium dialysate Levels on Vascular Events

THE GEORGE INSTITUTE for Global Health

ClinicalTrials.gov Identifier NCT02823821

# DIALYSATE COMPOSITION: [$NA^+$]






Gul A et al. Am J Kidney Dis 67:439-445; 2016

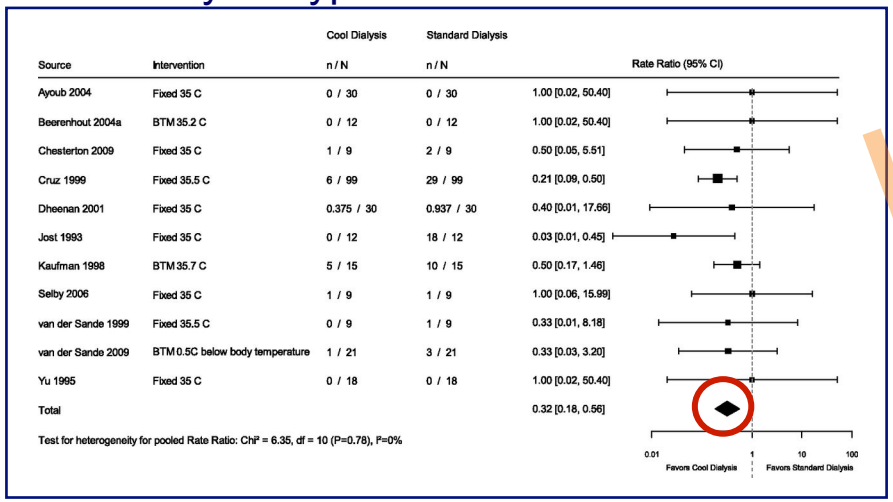
Ekbal NJ et al. Hemodialysis Int 20:S2-6; 2016

# DIALYSATE TEMPERATURE

Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis: A Systematic Review and Meta-Analysis

- 26 RCTs with 484 patients
- 17 included in meta-analysis

## Intra-Dialytic Hypotension



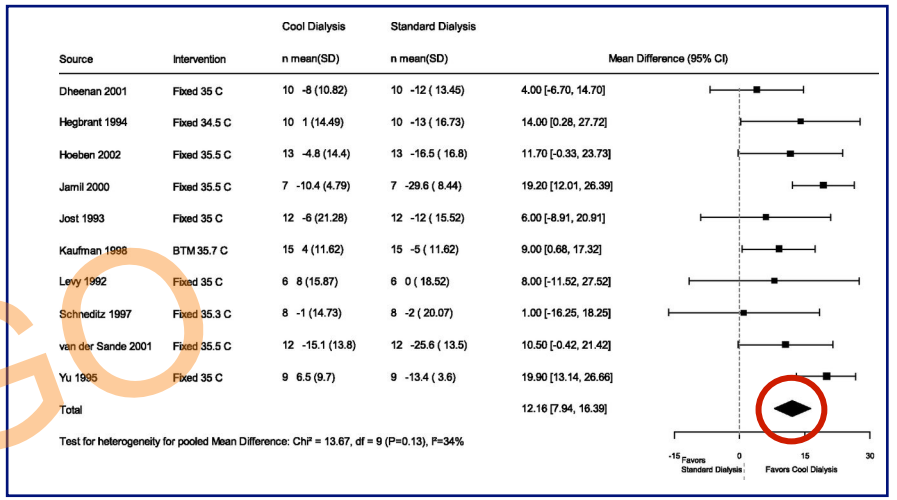
| Source | Intervention | Cool Dialysis n / N | Standard Dialysis n / N | Rate Ratio (95% CI) |
|---|---|---|---|---|
| Ayoub 2004 | Fixed 35 C | 0 / 30 | 0 / 30 | 1.00 [0.02, 50.40] |
| Beerenhout 2004a | BTM 35.2 C | 0 / 12 | 0 / 12 | 1.00 [0.02, 50.40] |
| Chesterton 2009 | Fixed 35 C | 1 / 9 | 2 / 9 | 0.50 [0.05, 5.51] |
| Cruz 1999 | Fixed 35.5 C | 6 / 99 | 29 / 99 | 0.21 [0.09, 0.50] |
| Dheenan 2001 | Fixed 35 C | 0.375 / 30 | 0.937 / 30 | 0.40 [0.01, 17.66] |
| Jost 1993 | Fixed 35 C | 0 / 12 | 18 / 12 | 0.03 [0.01, 0.45] |
| Kaufman 1998 | BTM 35.7 C | 5 / 15 | 10 / 15 | 0.50 [0.17, 1.46] |
| Selby 2006 | Fixed 35 C | 1 / 9 | 1 / 9 | 1.00 [0.06, 15.99] |
| van der Sande 1999 | Fixed 35.5 C | 0 / 9 | 1 / 9 | 0.33 [0.01, 8.18] |
| van der Sande 2009 | BTM 0.5C below body temperature | 1 / 21 | 3 / 21 | 0.33 [0.03, 3.20] |
| Yu 1995 | Fixed 35 C | 0 / 18 | 0 / 18 | 1.00 [0.02, 50.40] |
| Total | | | | 0.32 [0.18, 0.56] |

Test for heterogeneity for pooled Rate Ratio: Chi² = 6.35, df = 10 (P=0.78), I²=0%



Favors Cool

## Increase in MAP



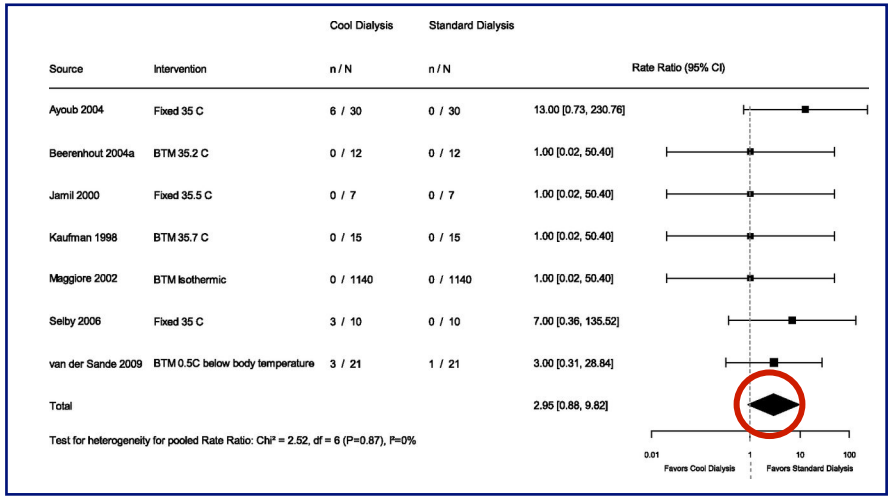
| Source | Intervention | Cool Dialysis n mean(SD) | Standard Dialysis n mean(SD) | Mean Difference (95% CI) |
|---|---|---|---|---|
| Dheenan 2001 | Fixed 35 C | 10 -8 (10.82) | 10 -12 ( 13.45) | 4.00 [-6.70, 14.70] |
| Hegbrant 1994 | Fixed 34.5 C | 10 1 (14.49) | 10 -13 ( 16.73) | 14.00 [0.28, 27.72] |
| Hoeben 2002 | Fixed 35.5 C | 13 -4.8 (14.4) | 13 -16.5 ( 16.8) | 11.70 [-0.33, 23.73] |
| Jamil 2000 | Fixed 35.5 C | 7 -10.4 (4.79) | 7 -29.6 ( 8.44) | 19.20 [12.01, 26.39] |
| Jost 1993 | Fixed 35 C | 12 -6 (21.28) | 12 -12 ( 15.52) | 6.00 [-8.91, 20.91] |
| Kaufman 1998 | BTM 35.7 C | 15 4 (11.62) | 15 -5 ( 11.62) | 9.00 [0.68, 17.32] |
| Levy 1992 | Fixed 35 C | 6 8 (15.87) | 6 0 ( 18.52) | 8.00 [-11.52, 27.52] |
| Schneditz 1997 | Fixed 35.3 C | 8 -1 (14.73) | 8 -2 ( 20.07) | 1.00 [-16.25, 18.25] |
| van der Sande 2001 | Fixed 35.5 C | 12 -15.1 (13.8) | 12 -25.6 ( 13.5) | 10.50 [-0.42, 21.42] |
| Yu 1995 | Fixed 35 C | 9 6.5 (9.7) | 9 -13.4 ( 3.6) | 19.90 [13.14, 26.66] |
| Total | | | | 12.16 [7.94, 16.39] |

Test for heterogeneity for pooled Mean Difference: Chi² = 13.67, df = 9 (P=0.13), I²=34%



Favors Cool

## Symptoms of Discomfort



| Source | Intervention | Cool Dialysis n / N | Standard Dialysis n / N | Rate Ratio (95% CI) |
|---|---|---|---|---|
| Ayoub 2004 | Fixed 35 C | 6 / 30 | 0 / 30 | 13.00 [0.73, 230.76] |
| Beerenhout 2004a | BTM 35.2 C | 0 / 12 | 0 / 12 | 1.00 [0.02, 50.40] |
| Jamil 2000 | Fixed 35.5 C | 0 / 7 | 0 / 7 | 1.00 [0.02, 50.40] |
| Kaufman 1998 | BTM 35.7 C | 0 / 15 | 0 / 15 | 1.00 [0.02, 50.40] |
| Maggiore 2002 | BTM Isothermic | 0 / 1140 | 0 / 1140 | 1.00 [0.02, 50.40] |
| Selby 2006 | Fixed 35 C | 3 / 10 | 0 / 10 | 7.00 [0.36, 135.52] |
| van der Sande 2009 | BTM 0.5C below body temperature | 3 / 21 | 1 / 21 | 3.00 [0.31, 28.84] |
| Total | | | | 2.95 [0.88, 9.82] |

Test for heterogeneity for pooled Rate Ratio: Chi² = 2.52, df = 6 (P=0.87), I²=0%



Favors Standard



Mustafa RA et al. Clin J Am Soc Nephrol 11:442-457; 2016

# Dialysate Temperature

MY TEMP: Major Cardiovascular and Other Patient-Important Outcomes with Personalized Dialysate Temperature

- Cluster randomized pragmatic trial of dialysate temperature 0.5°C lower than pre-dialysis body temperature vs standard care (36.5°C)
- Primary outcome: composite of all-cause mortality or MACE
- Target sample size: 7500 patients; 80 units
- Ontario, Canada



ClinicalTrials.gov Identifier NCT02628366

# RESIDUAL KIDNEY FUNCTION

J Am Soc Nephrol 12: 2158–2162, 2001

## Relative Contribution of Residual Renal Function and Peritoneal Clearance to Adequacy of Dialysis: A Reanalysis of the CANUSA Study

JOANNE M. BARGMAN,* KEVIN E. THORPE,† and DAVID N. CHURCHILL,‡ for the CANUSA Peritoneal Dialysis Study Group



CANUSA: solute clearance is associated with survival. However, residual renal function contribution to solute clearance is more important determinant of survival than is peritoneal clearance contribution.

# RESIDUAL KIDNEY FUNCTION

Residual Kidney Function Decline and Mortality in Incident Hemodialysis Patients

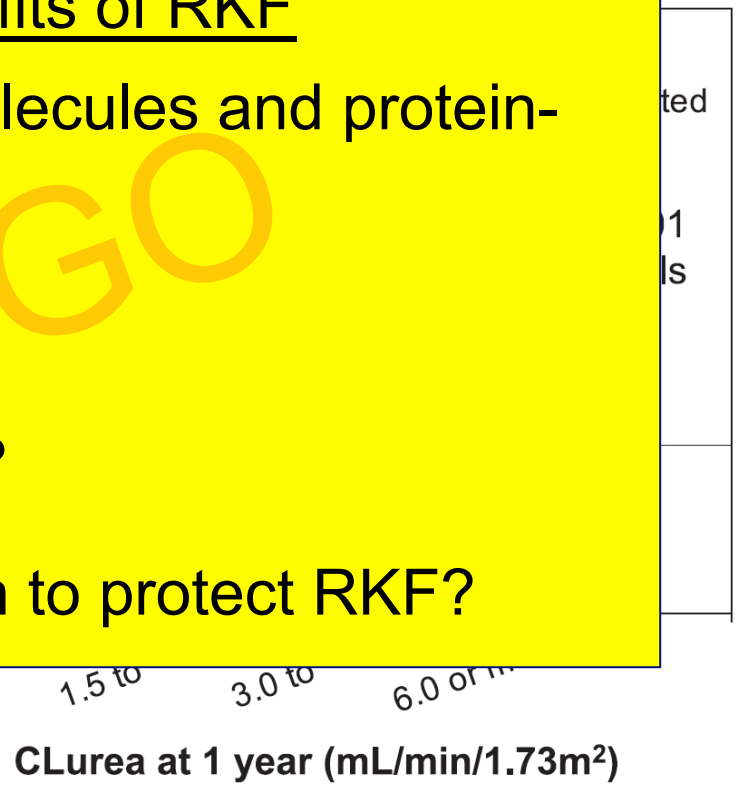
- 6538 inciden
  DaVita with r
  residual rena
  dialysis initia
  later (out of 4
  patients)

**Potential benefits of RKF**

- Clearance of middle molecules and protein-bound solutes
- Volume management
- Endocrine functions
- Inflammation reduction?

Are we doing enough to protect RKF?






Obi Y et al. J Am Soc Nephrol 27:3757-3768; 2016

# CHALLENGES

- Do we have sufficient data currently to weigh the advantages and disadvantages of dialysis prescription components? Which issues should be prioritized for RCTs?
- How do we individualize dialysis prescriptions to improve outcomes and to incorporate patient preferences and goals?
- How do we design rigorous clinical trials that incorporate individualization of treatment approaches?