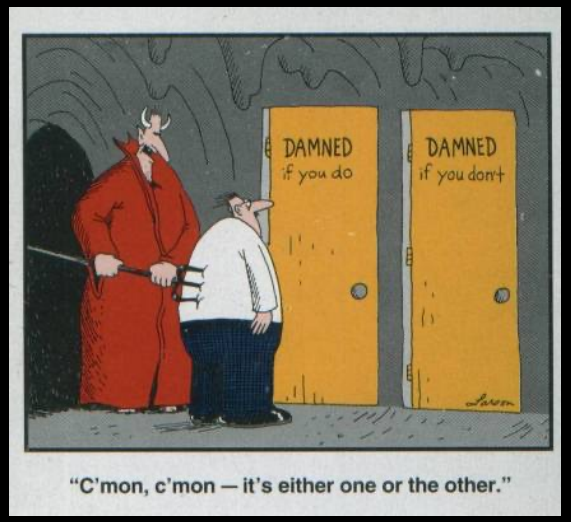
Between a Rock and a Hard Place: Intradialytic Hypotension in Volume Overloaded Hemodialysis Patients



Michael Shoemaker-Moyle, M.D.

Associate Professor of Clinical Medicine

University of Missouri

University of Missouri

Disclosures

- No conflicts of interest

Objectives

- Review the adverse outcomes in hemodialysis patients with volume overload and intradialytic hypotension
- Review the pathophysiology of intradialytic hypotension
- Discuss potential modifications to the hemodialysis prescription to mitigate intradialytic hypotension and assist ultrafiltration.
- Discuss potential modifications to the dialysis environment that can mitigate intradialytic hypotension and assist ultrafiltration.

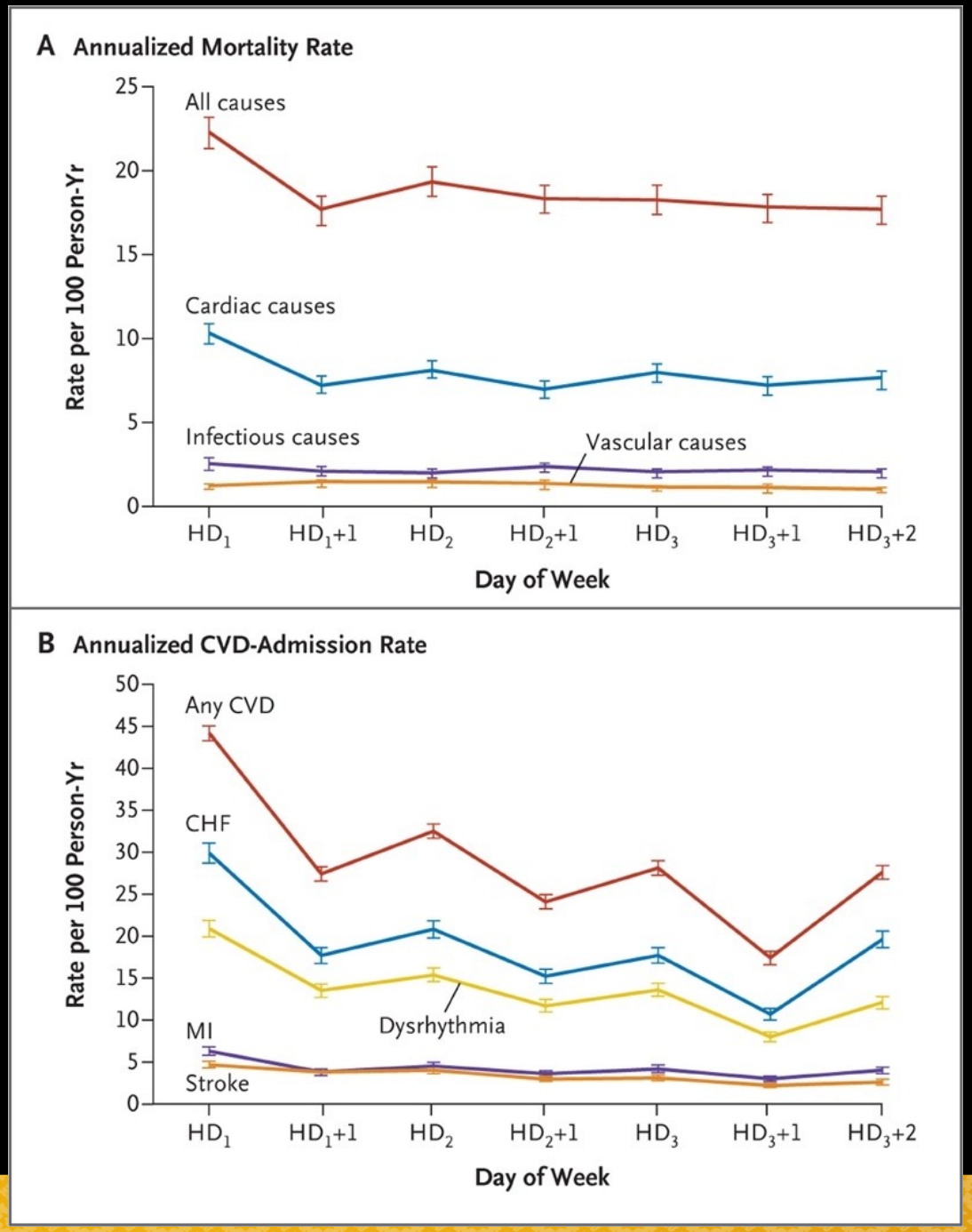
A typical case…

- 68 y/o man on intermittent hemodialysis for close to 3 years. His ESKD is secondary to long-standing, type II DM.
- Other past medical history includes HTN, coronary artery disease with a history of RCA stent 2 years, moderate, concentric LVH and diabetic retinopathy and peripheral neuropathy.
- Medications: metoprolol, lisinopril, sevelamer, and gabapentin.
- Dialysis prescription: Time: 4H, Bath: 2K, 2.5Ca, 138Na, 35HCO3. He has a left forearm AVF with QB = 400, QD = 600. spKt/V with this prescription was 1.4. Average Intradialytic wgt gain was 4kg, target wgt = 98.5kg. Dialysate temperature = 35.5 degrees C.

- He has chronic bilateral lower ext edema and has had a tendency to develop hypotension between 3 to 3.5 hours into his treatments. He complains of calf cramping and nausea with these episodes.
- His symptoms and BP improve with holding UF, and saline boluses.
- His EDW was increased with off dialysis complaints of DOE, worsening edema.
- His cardiologist has requested more aggressive ultrafiltration.

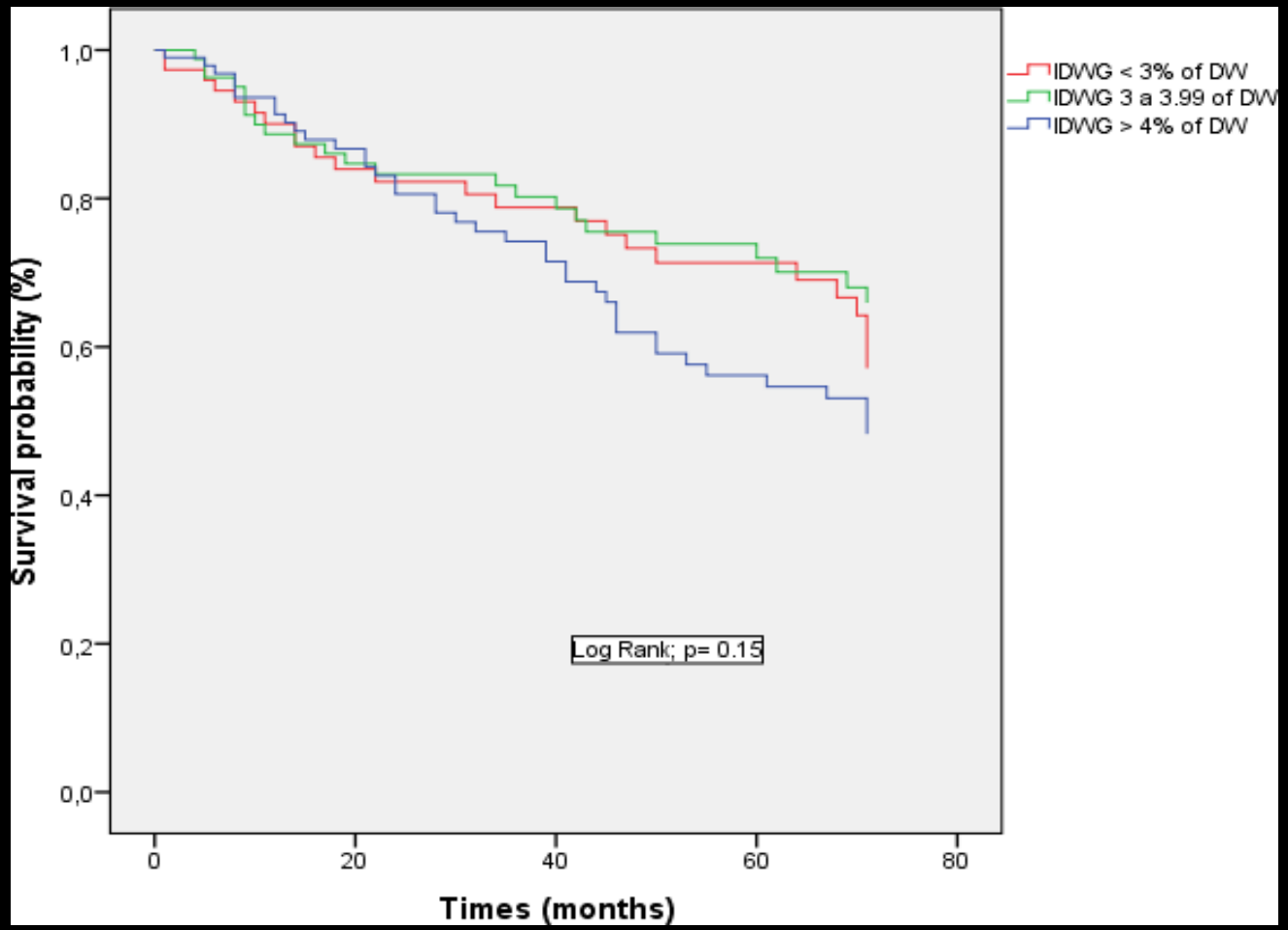
The danger of volume overload

- Cardiovascular disease is the etiology for over 50% of deaths in ESRD patients. CV mortality is 9 fold higher in this population.
- Risk of hospital admission for heart failure is 25-40% higher on the first dialysis day of the week.
- Volume overload is considered to be a major underlying etiology in these associations.
- Excessive intradialytic wgt gain and subsequent excessive ultra-filtration during dialysis treatment represent a cyclic CV stress.



Foley RN, et al. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl JMed 2011; 365:1099–1107

- Higher intradialytic weight gain is associated with higher pre-dialysis BP and higher average BP.
- Volume overload is the main pathogenic mechanism of hypertension in the ESKD population.
- The worldwide prevalence of HTN in dialysis patients is around 85%.
- Intermittent volume expansion may cause CV damage through alteration of arterial stiffness.
- The recurrent stretching of cardiac chambers with intradialytic weight gain between sessions results in long term cardiac chambers remodeling



IDWG ≥4% of DW was associated with a risk of cardiovascular mortality, with hazard ratio of 2.02 (CI 95% 1.17–3.49, $p = 0.012$).

BMC Nephrology **volume 20**, Article number: 402 (2019)

Measuring Volume Status

- The old way (that most of us are still using…): Clinical Assessment
  - History
  - Blood Pressure
  - Edema
  - JVP
  - Rales
  - Gallops

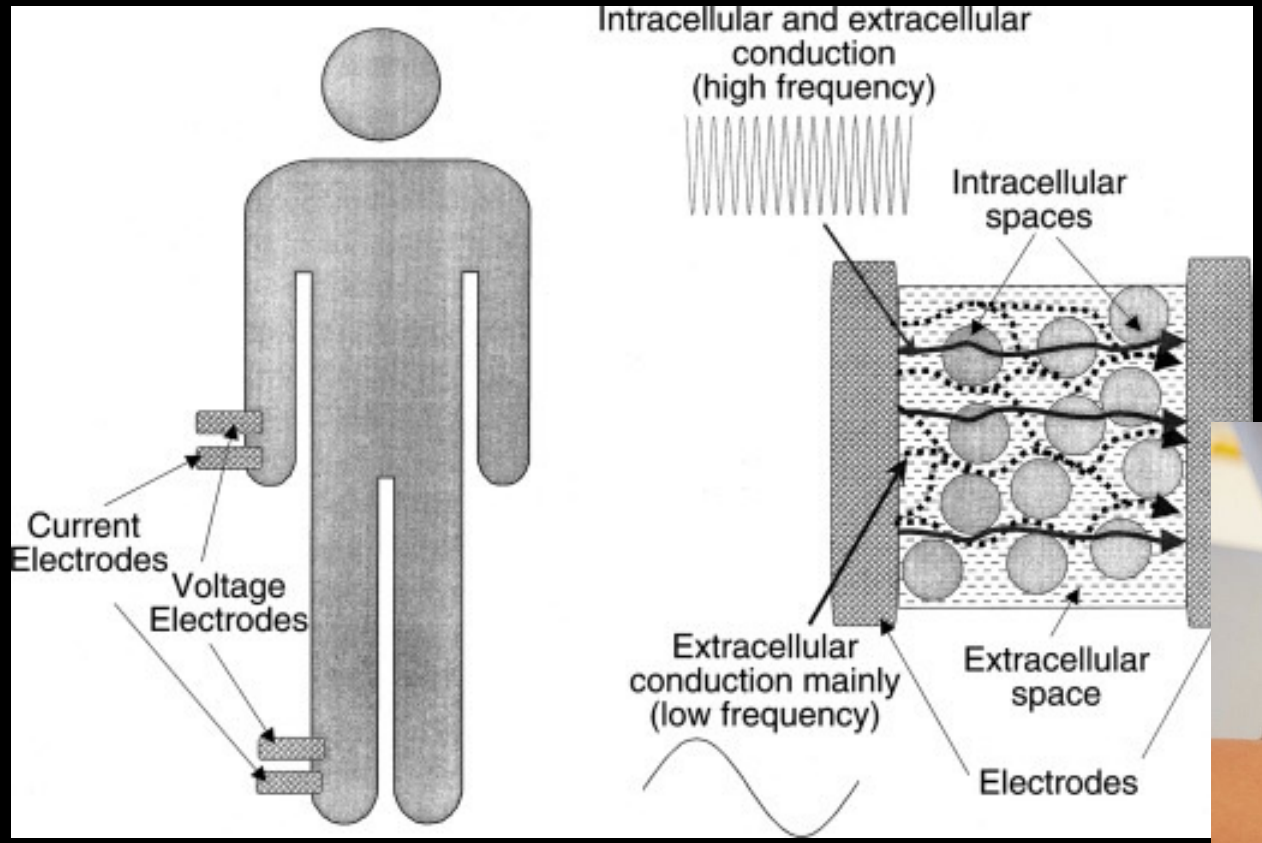
- How well do we do?

Not very well

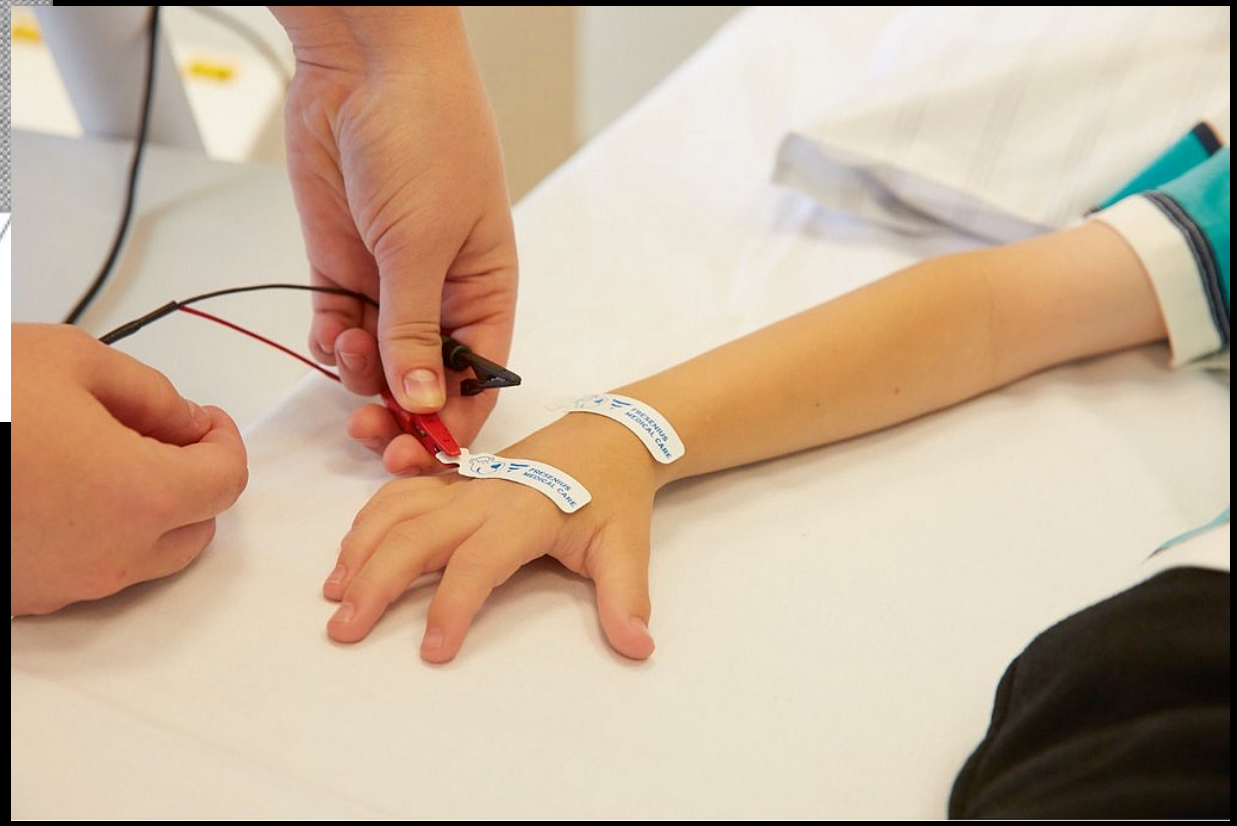
- Observer Dependent
- Non-specific
- The presence of edema correlates poorly with volume overload assessed by IVC diameter, pro-BNP, plasma renin and aldosterone levels. (Loutradis CN, Curr Vasc Pharmacol 2017; 16:54–60)
- Pre and post dialysis BP are frequently inconsistent when c/w bioimpedance as a measurement of hydration status.
- Rales correlate poorly with ultrasound assessment of pulmonary edema.

Is there a better way?

- Bioimpedance spectroscopy
- Lung Ultrasound
- IVC Diameter
- Biomarkers
- Real Time Hematocrit Monitoring
- LV Ejection Time (Flow Time)



Chamney, P. et al. Kidney International, Vol. 61 (2002), pp. 2250–2258



- A bioimpedance model of interpretation of resistance and reactance at 50 frequencies correlates well with volume assessment based on tracer dilution.
- A theoretical “overhydration” compartment can be determined by bioimpedance assuming lean muscle and adipose tissue vary little in volume overloaded states.
- There is increased mortality associated with volume overload identified by bioimpedance.
- Bioimpedance guided UF has been shown to reduce hypertension, LVH, rate of hospitalization but has not yet been shown to affect mortality.

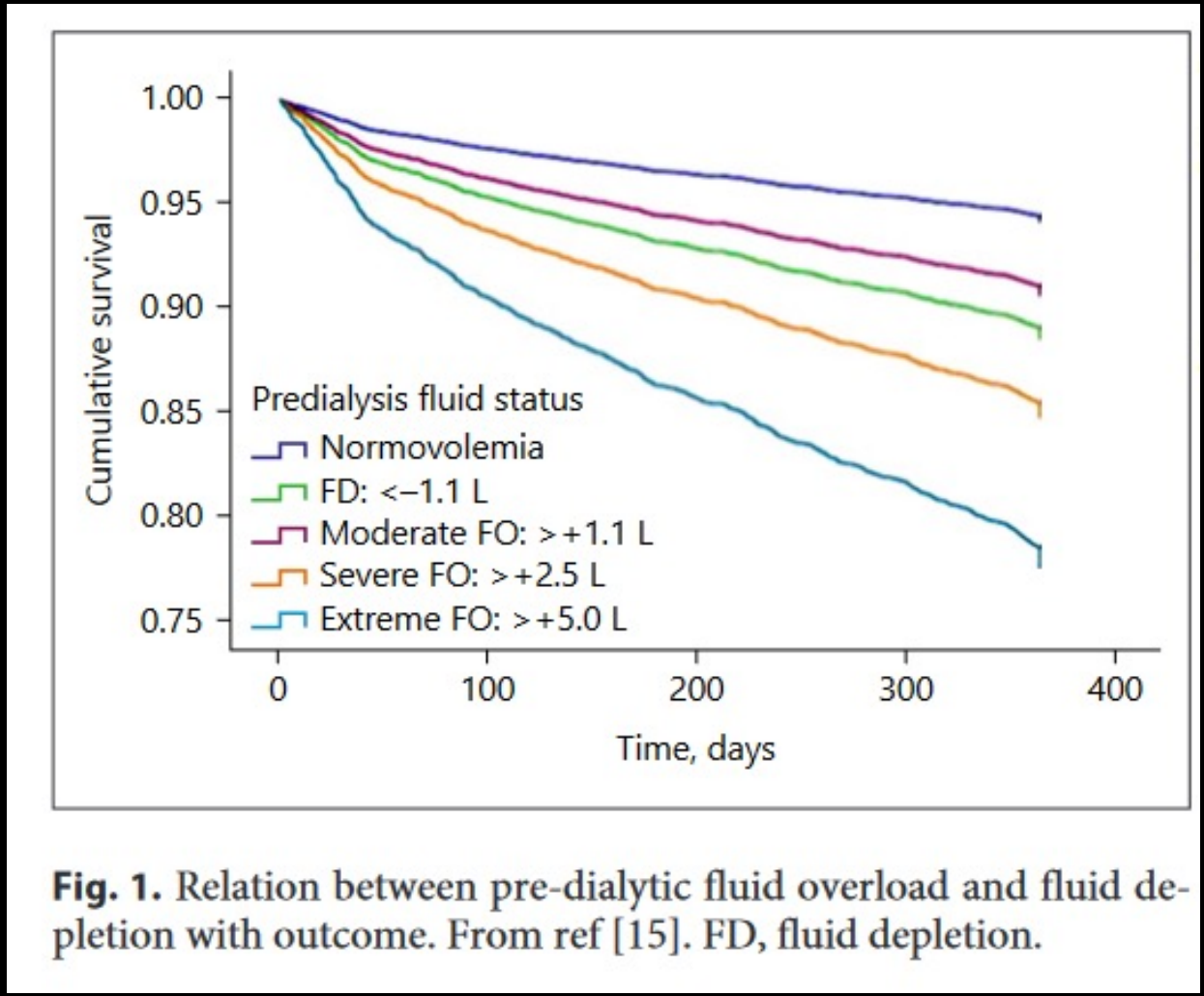


Fig. 1. Relation between pre-dialytic fluid overload and fluid depletion with outcome. From ref [15]. FD, fluid depletion.

Report from the MONDO consortium.

8883 ESRD patients

Blood Purif 2020;49:178–184

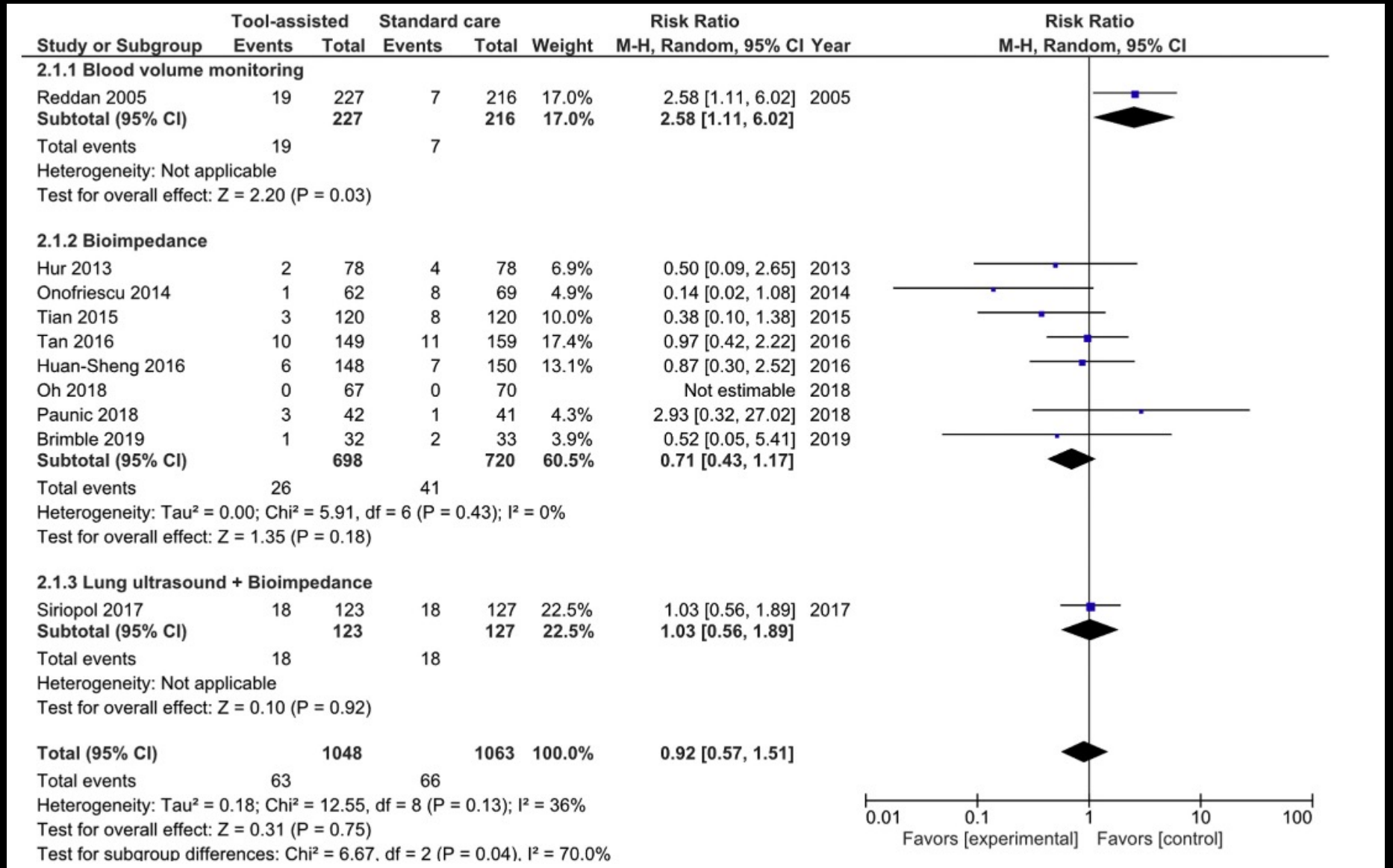


Figure 2. All-cause mortality and technology-assisted target weight adjustment. CI, confidence interval; M-H, Mantel-Haenszel.

Kidney International Reports (2019) 4, 1426–1434

The danger of intradialytic hypotension

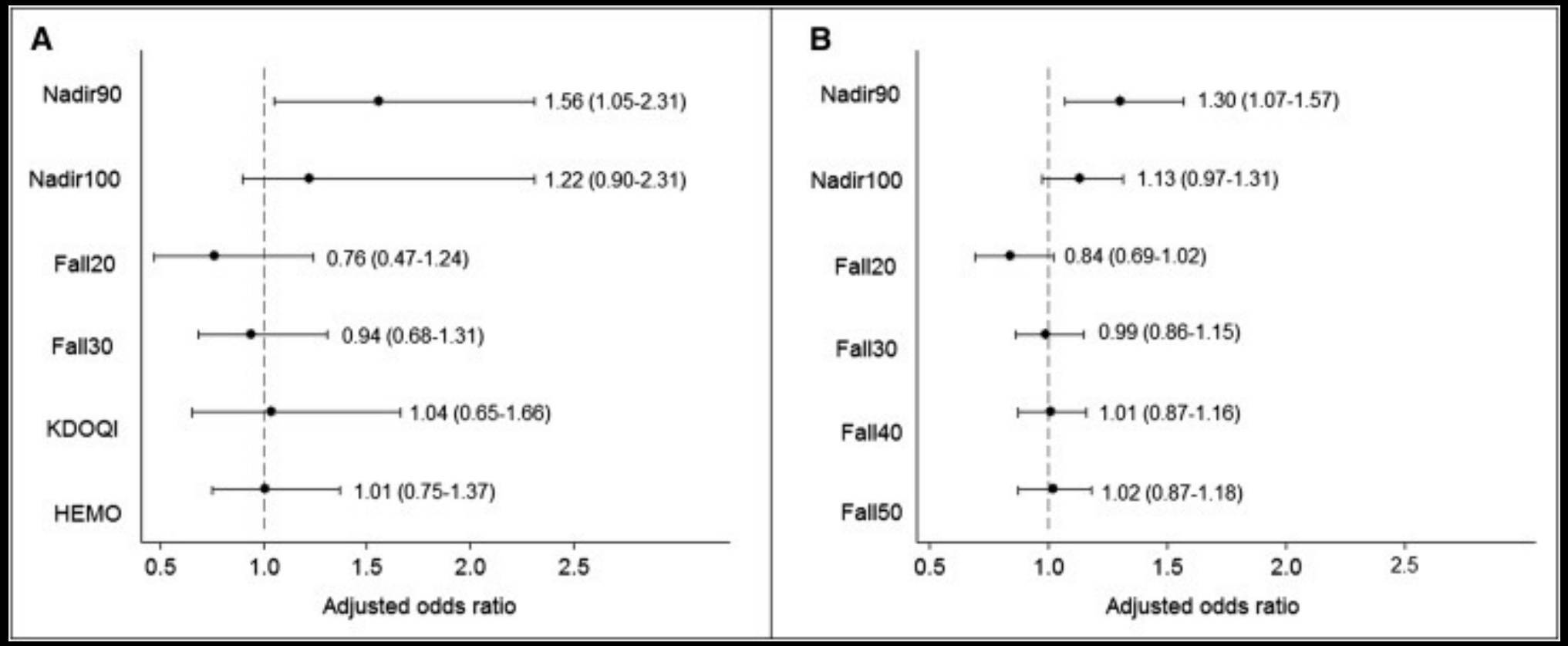
- The most common complication of outpatient hemodialysis
- Frequency: 10-12%
- Definition has been a problem:
  - Symptomatic hypotension requiring active management
  - Symptomatic or asymptomatic absolute/percentage fall in SBP
  - Fall in mean arterial BP
  - Absolute nadir SBP

TABLE 1 Clinical practice guideline definitions for intradialytic hypotension

Guideline (Year)	Intradialytic hypotension definition
K/DOQI Clinical Practice Guidelines (2002)[30]	A decrease in systolic BP ≥20 mm Hg or a decrease in MAP ≥10 mm Hg associated with symptoms that include: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety
European Best Practice Guidelines (2007)[32]	A decrease in systolic BP ≥20 mm Hg or a decrease in MAP ≥10 mm Hg associated with clinical events and need for nursing interventions
UK Renal Association Guidelines (2009)[33]	An acute symptomatic fall in BP during dialysis requiring immediate intervention to prevent syncope
Japanese Society for Dialysis Therapy Guidelines (2012)[31]	Symptomatic sudden drop systolic BP ≥30 mm Hg during dialysis or a decrease in the mean BP by ≥10 mm Hg

BP, blood pressure; K/DOQI, Kidney Disease Outcomes Quality Initiative; MAP, mean arterial pressure.

Assimon MM, et al. *Semin Dial.* 2017;30:464-472.



A. 1409 patients analysed from the HEMO Study
B. 10,392 patients analysed from a single large dialysis organization

Flythe JE, et al. *J Am Soc Nephrology.* 2015 Mar; 26(3): 724–734.

- In Patients with predialysis systolic BP<120 or 120–159 mmHg, an absolute nadir systolic BP<90 mmHg was most potently associated with mortality.
- Within the subgroup of patients with predialysis BP≥160 mmHg, nadir BP<100 mmHg was most potently associated with mortality.

Lets further complicate matters…

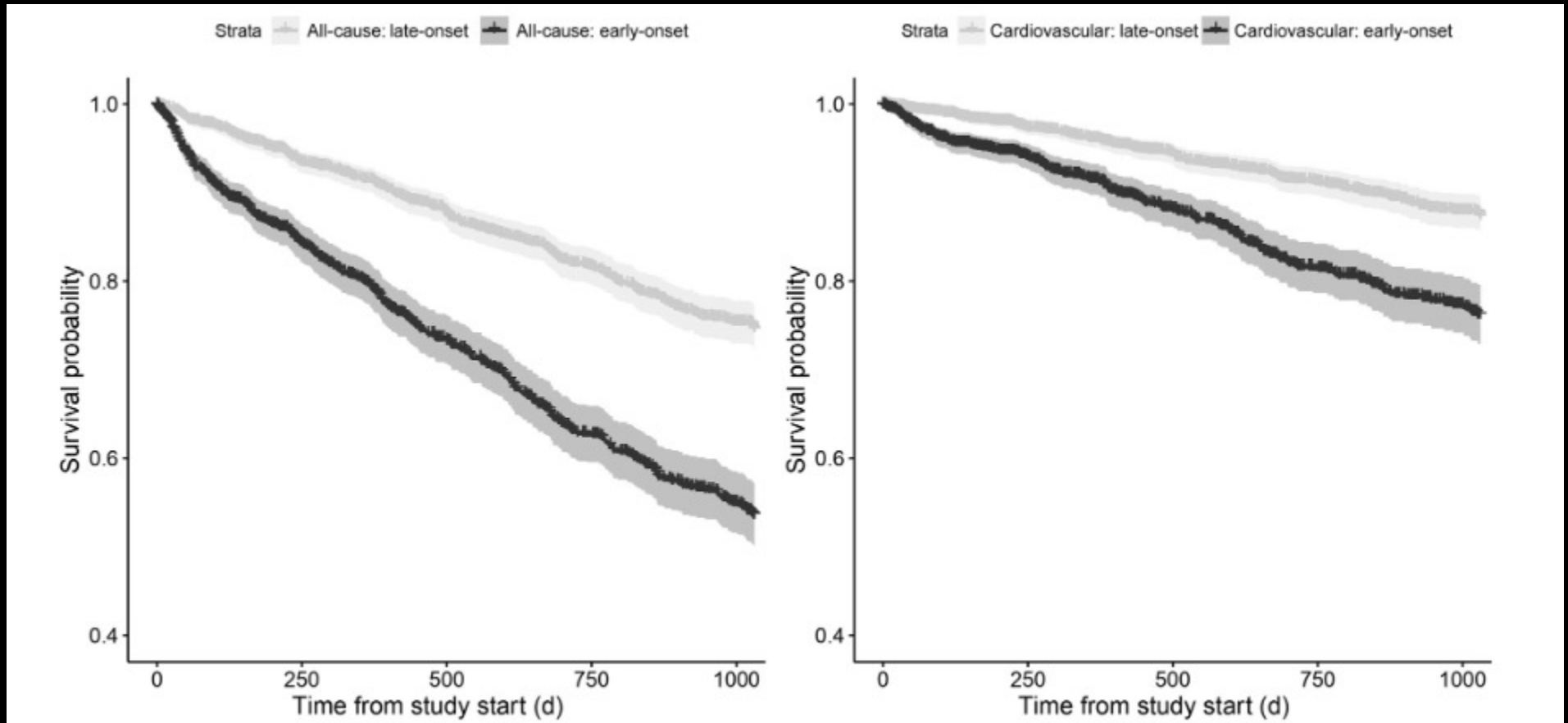
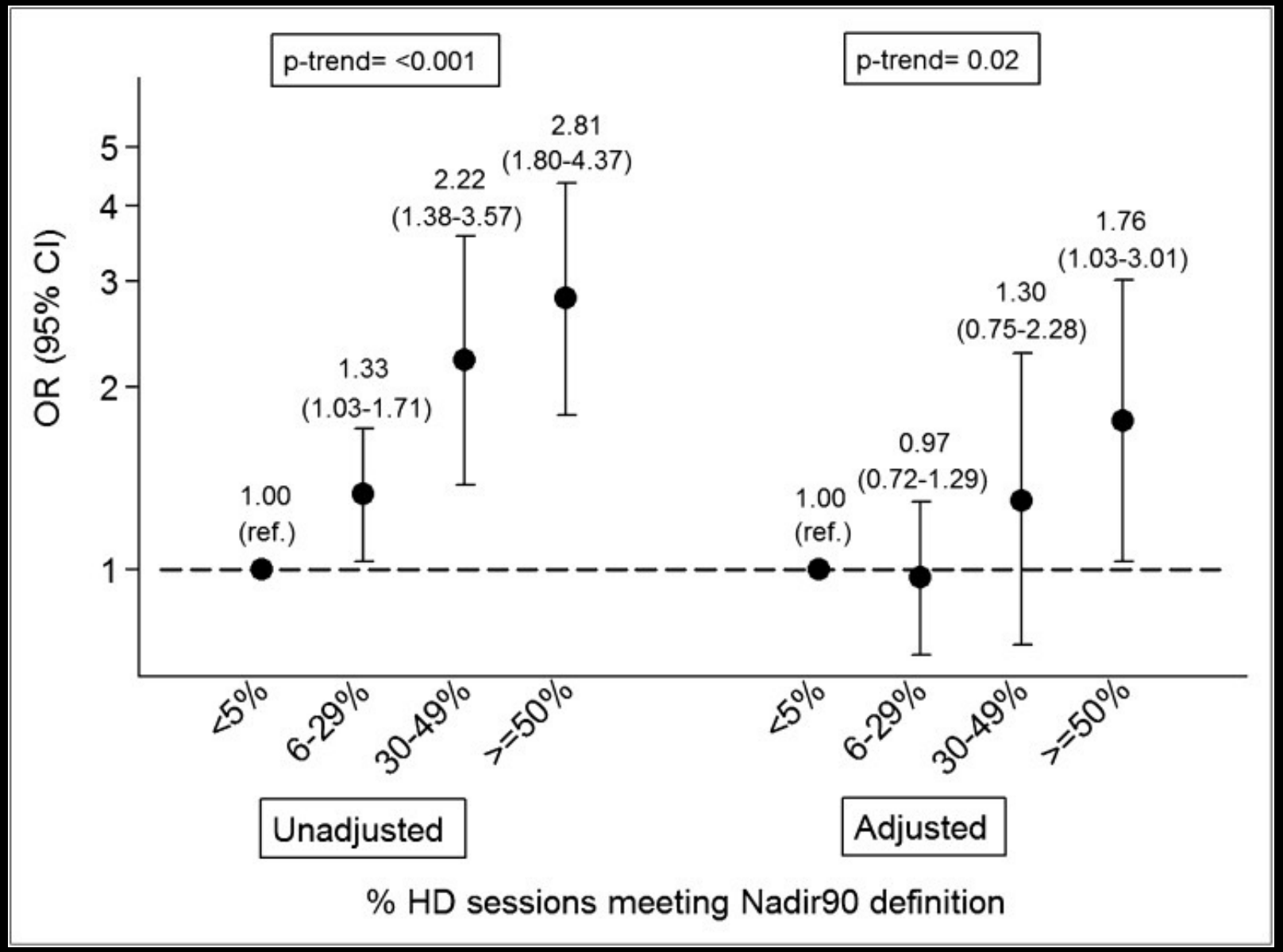


Figure 5 | Kaplan-Meier curves for patients who tended to have intradialytic hypotension (IDH) in the first half of a session compared with those who tended to have IDH in the second half of a session. Data presented for all-cause and cardiovascular mortality, with accompanying 95% confidence intervals.

Kidney International (2021) 99, 1408–1417

Now that we are a little closer to agreement on what we are talking about…

- Risk factors for IDH: patient factors, anti-hypertensive medication use, larger intradialytic wgt gain, dialysis prescription issues
- UF rates > 10-13 mL/hr/kg are highly predictive of cardiovascular and all cause mortality.
- IDH causes acute reversible myocardial hypoperfusion and contractile dysfunction (stunning). This has potential long-term consequences on myocardial contractility.
- IDH has non-cardiac hypoperfusion effects: stroke, gut ischemia resulting in endotoxin translocation and protein-energy wasting, reduced cerebral oxygenation.
- IDH increases the risk of access thrombosis and reduces quality of life measures.



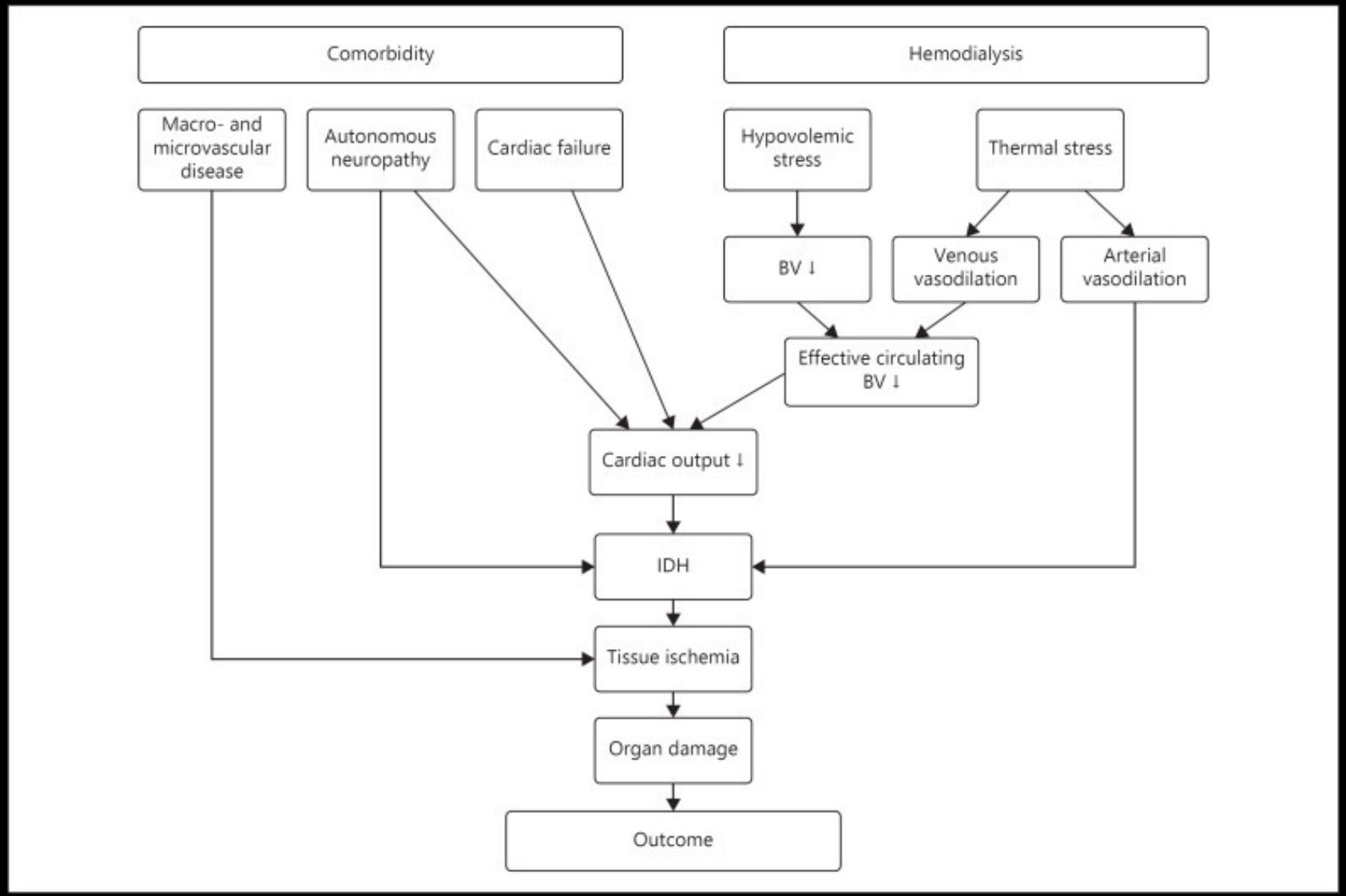
Mortality odds ratio in the HEMO study by percentage of treatments with IDH.

Adjusted for sex, age, ischemic heart disease, heart failure, access type, cerebrovascular disease, diabetes and other variables.

Flythe JE, et al. *J Am Soc Nephrology.* 2015; 26(3):724-734.

Pathophysiology

- How does dialysis provoke hypotension?
  - The rate of ultrafiltration exceeds the rate at which fluid mobilization can occur from extravascular compartments (the plasma refill rate) without adequate neurohumoral response.
  - Acute changes in serum osmolality
  - Dialysis patients usually have a need for regular ultrafiltration and often have compromised ability to tolerate it.
  - Anemia, low albumin
  - Impaired humoral responses: inappropriate vasopressin response to UF. Blunted dopamine, norepinephrine and epinephrine response.
  - Myocardial Stunning

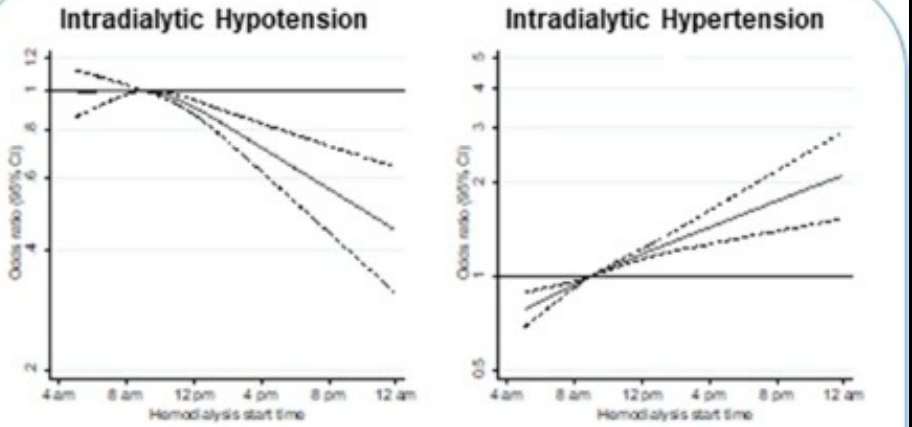


Blood Purif. 2020 Feb; 49(1-2): 158–167.

Time of Hemodialysis and Risk of Intradialytic Hypotension and Intradialytic Hypertension in Maintenance Hemodialysis

Two cohorts of **thrice-weekly maintenance HD**
- **The Hemodialysis Study** N=1,838 patients, n=64,503 sessions
- **Satellite Healthcare** N=3,302 patients, n=33,590 sessions

Random effects logistic regression examined the association of **HD start time** with **intradialytic hypotension**[1], and **intradialytic hypertension**[2]



Adjusted splines for the risk of adverse outcomes in the Hemodialysis Study
[1]***Intradialytic hypotension***: *nadir intradialytic SBP <90mmHg if pre-HD SBP <160mmHg, or <100mmHg if pre-HD SBP >=160mmHg.*
[2]***Intradialytic hypertension*** *SBP increase>=10 mmHg from pre-HD to post-HD*

- We observed a **monotonic lower risk of intradialytic hypotension** and **monotonic higher risk of intradialytic hypertension** with later dialysis start times.
- Whether HD treatment allocation to certain times of the day in hypotensive-prone or hypertensive-prone patients improves outcomes deserves further investigation

Alostaz, M., *et al.* Time of hemodialysis and risk of intradialytic hypotension and intradialytic hypertension in maintenance hemodialysis. *J Hum Hypertens* (2023).

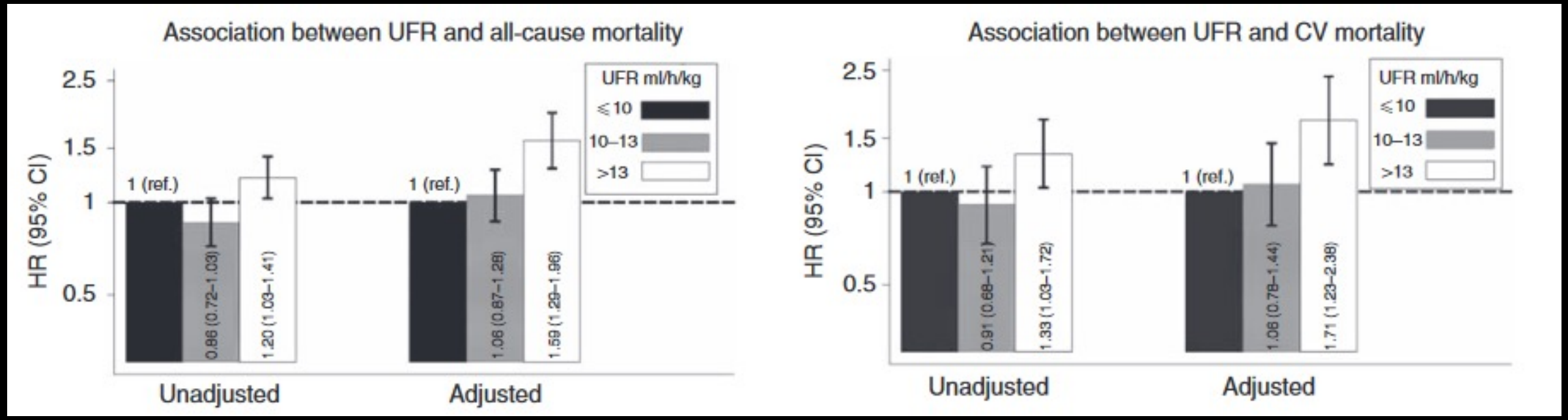
Interventions

- Establish an appropriate Target Weight
- Limit intradialytic weight gain---Sodium and Fluid Restrictions
- Attempt to limit UF Rate to accommodate plasma refill rate or adjust the timing of UF to optimize volume removal when the pt can tolerate it best
- Adjust dialysate composition to influence tonicity/vascular tone
- Adjust dialysate temperature

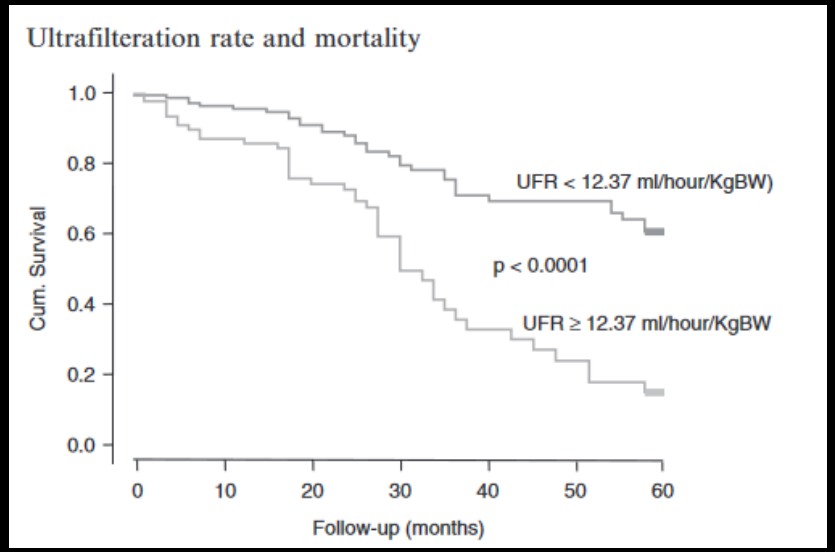
- Isolated Ultrafiltration
- Review and adjust timing of BP medications
- Limit eating in the dialysis unit
- Pharmacologic Vasoconstriction
- Make sure that there is not a alternate cause of hypotension

“Hey doc, would you cut my time by 15 min?”

- Longer, slower dialysis/ultrafiltration would seem an obvious intervention to reduce hypotension.
- Observation studies report an association between higher UF rates and intradialytic hypotension. Increasing time would decrease rates and allow more UF.
- The DOPPS study showed that a UF > 10 ml/h/kg is associated with a 1.3 RR of intradialytic hypotension (Clinical Kidney Journal, 2020, vol. 13, no. 6, 981–993)
- Practically difficult.



Flythe JE et al. Kidney International (2011) 79, 250–257



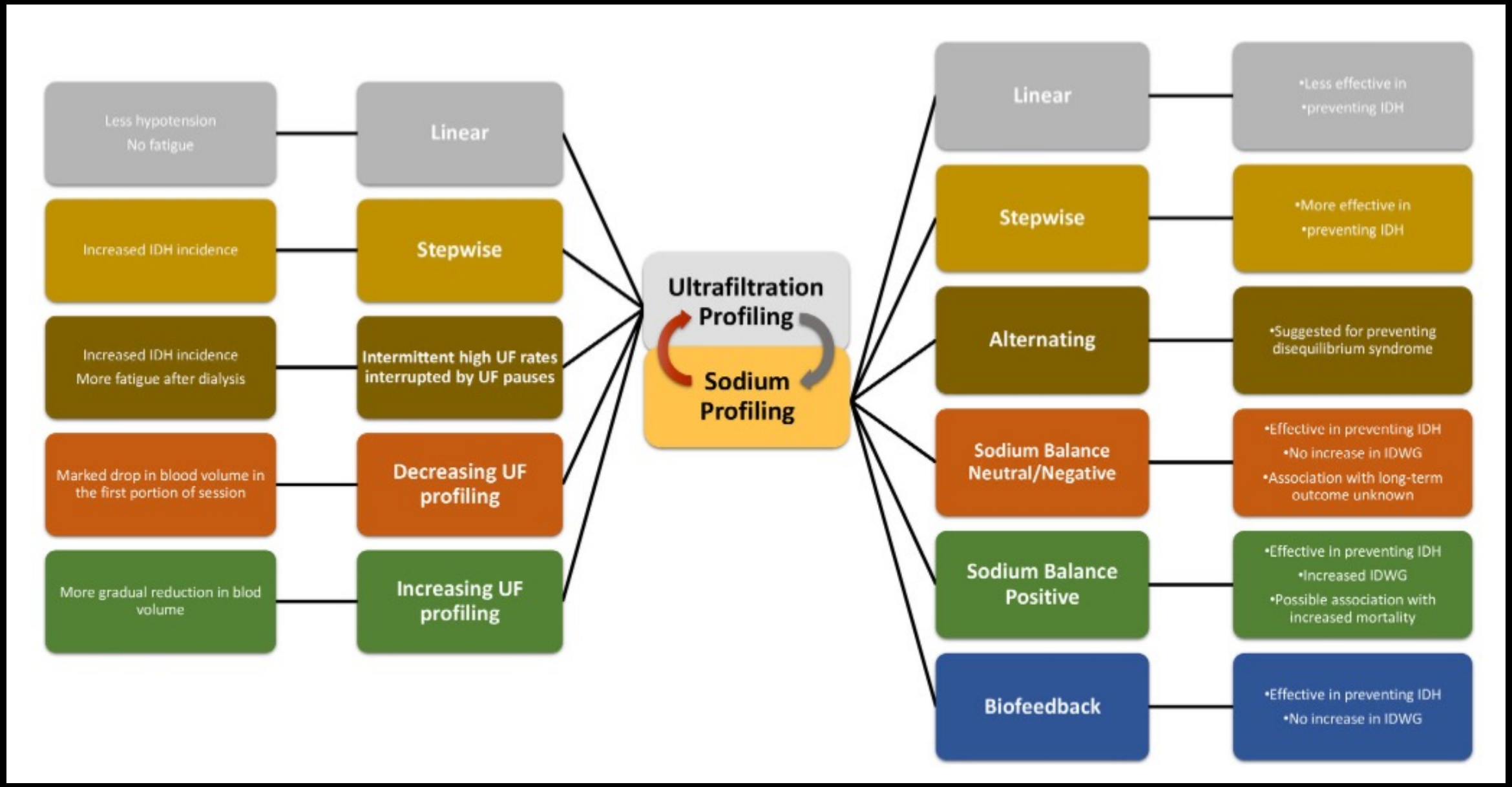
Movilli E. et al. Nephrol Dial Transplant (2007) 22: 3547–3552

Reduce Intradialytic Weight Gain

- Preserve residual urine output
- Dietary sodium restriction
- Fluid restriction
- Maximize urine output with diuretics

Sodium and Ultrafiltration Gymnastics

- Sodium profiling: adjust the dialysate sodium concentration to maintain intravascular volume. Higher sodium dialysate enhances the refill rate avoiding intradialytic hypotension and allowing for more UF.
- UF Profiling: maximize UF at the times during dialysis when the pt can best tolerate it.

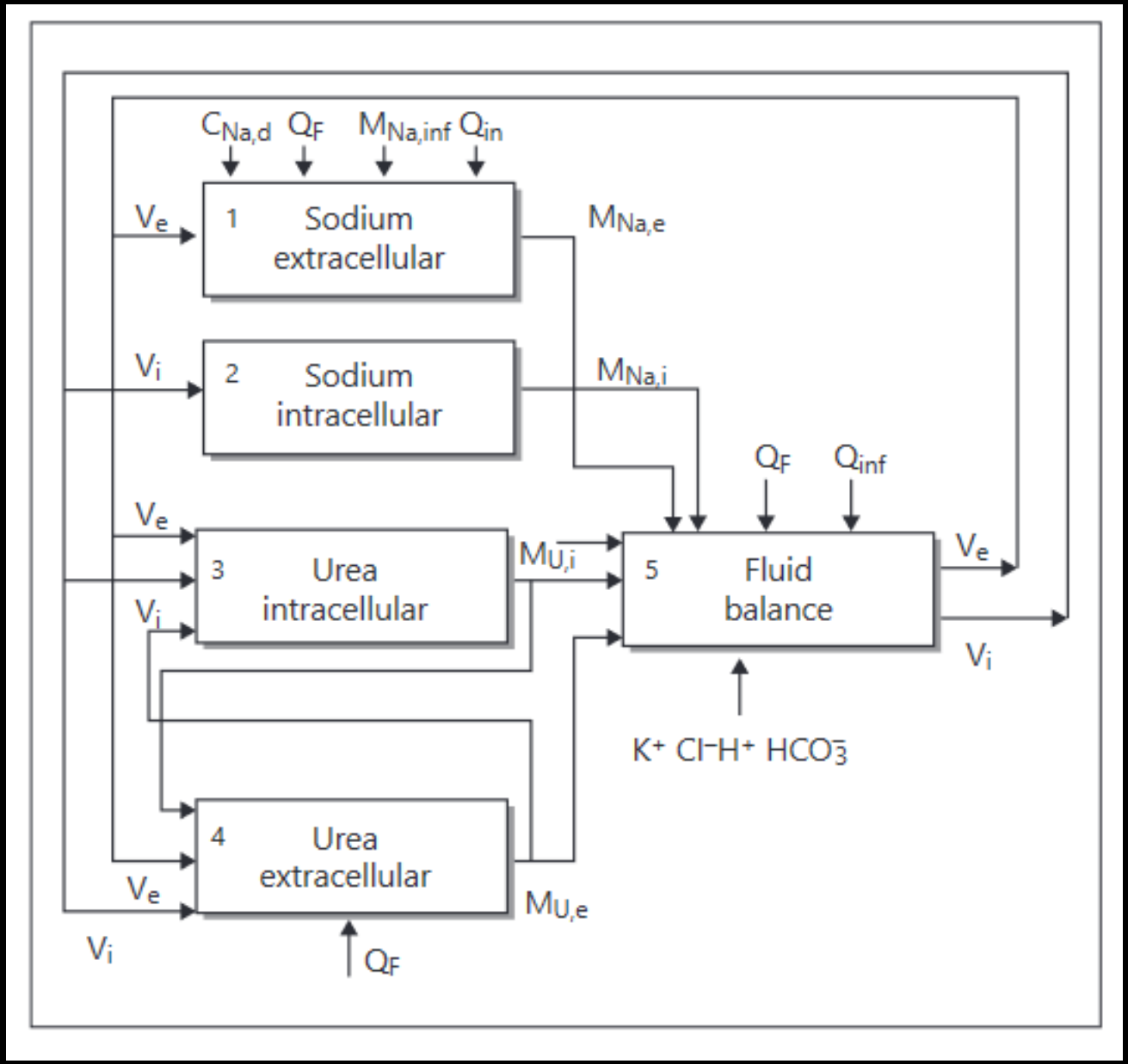


Hemodialysis International.2021;25:433–446

- Traditional linear and stepwise sodium profiling is associated with increased intradialytic weight gain.
- Limited evidence for improvement in quality of life and mortality.
- There may be advantages to individualizing sodium concentrations based on pre-dialysis sodium and biofeedback systems.
- Ideally one would be able to monitor real time patient parameters and continuously adjust accordingly.

We need to avoid giving patients sodium

- Increased mortality with > 2.5g sodium/day in the post hoc analysis of the HEMO study
- Dialysis treatments frequently create a positive sodium balance
- This leads to more intracellular to extracellular fluid shift, hypertension, thirst and greater intradialytic wgt gain
- And yet…less intradialytic hypotension, better tolerated dialysis



Blood Purif 2018;45:61–70

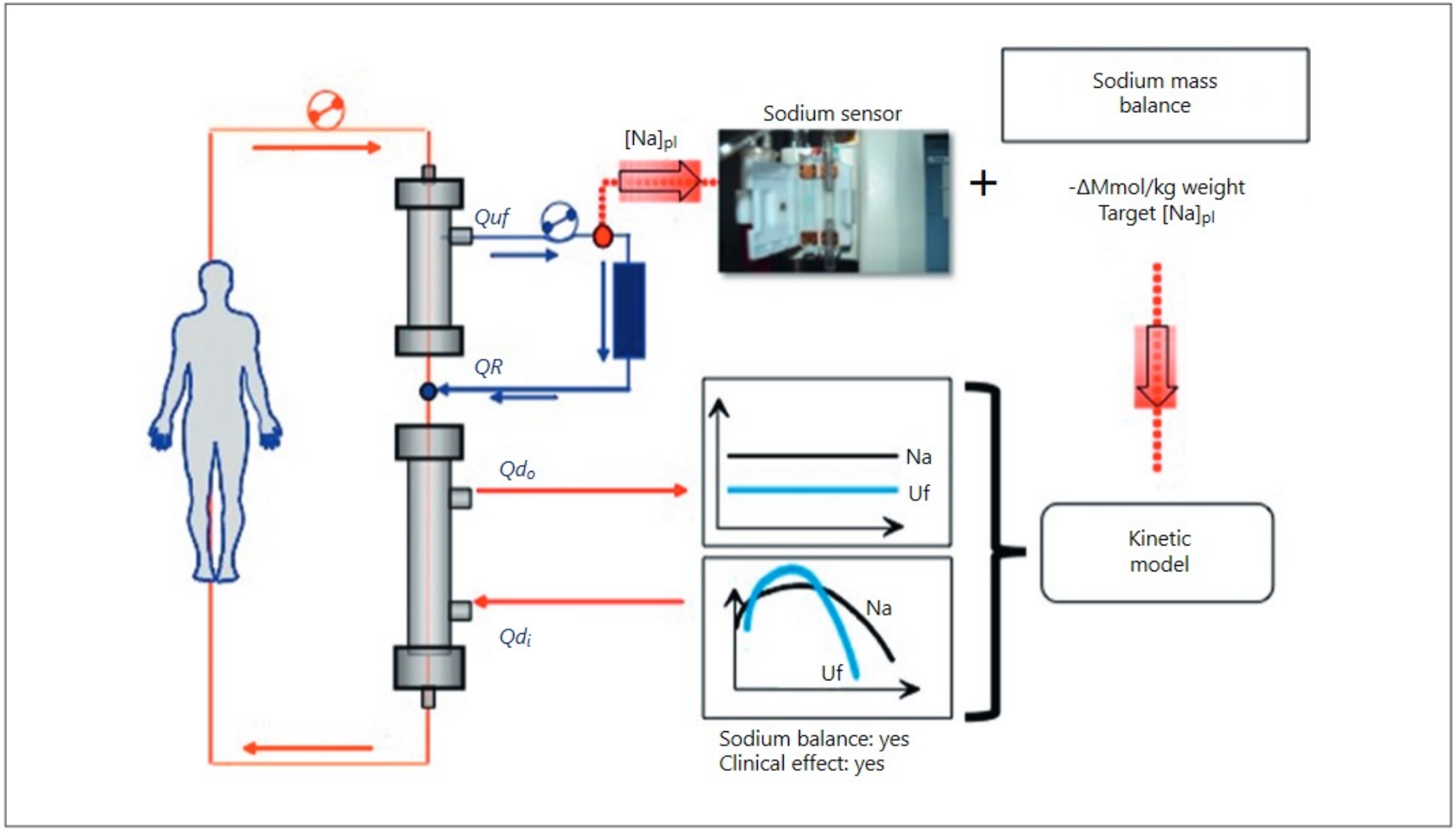
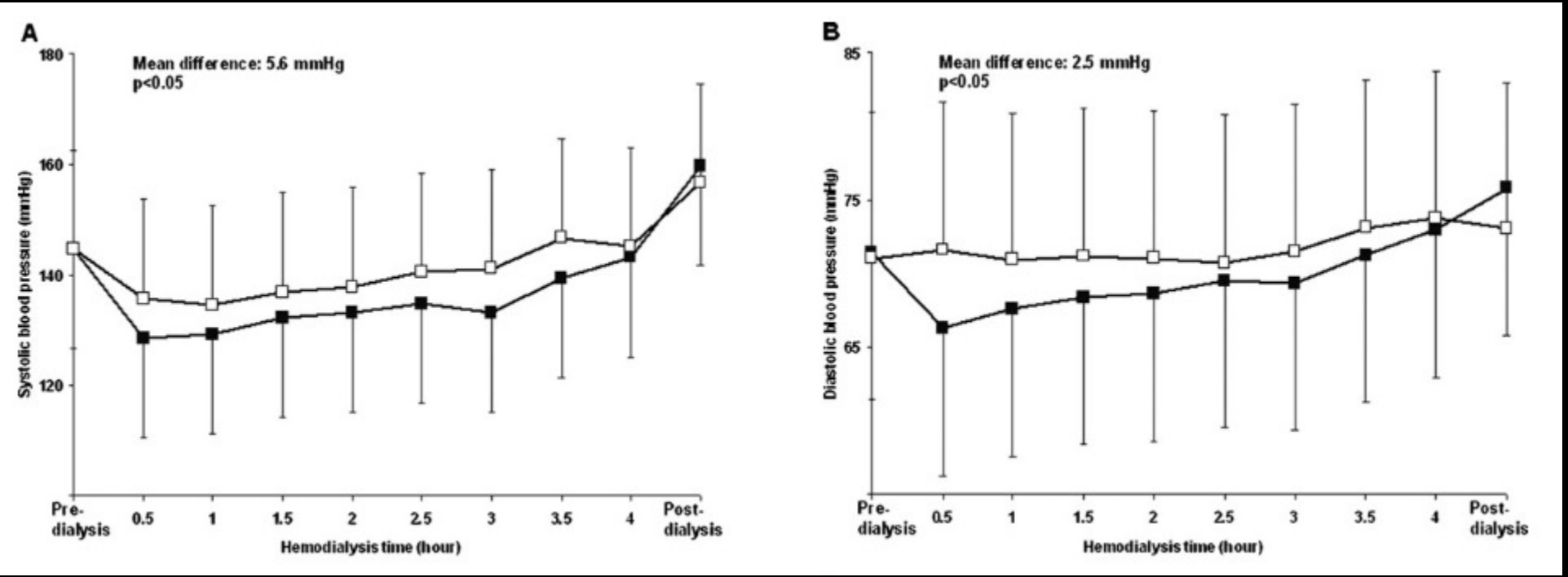


Fig. 2. Schematic diagram of HFR Aequilibrium.

Blood Purif 2018;45:61–70

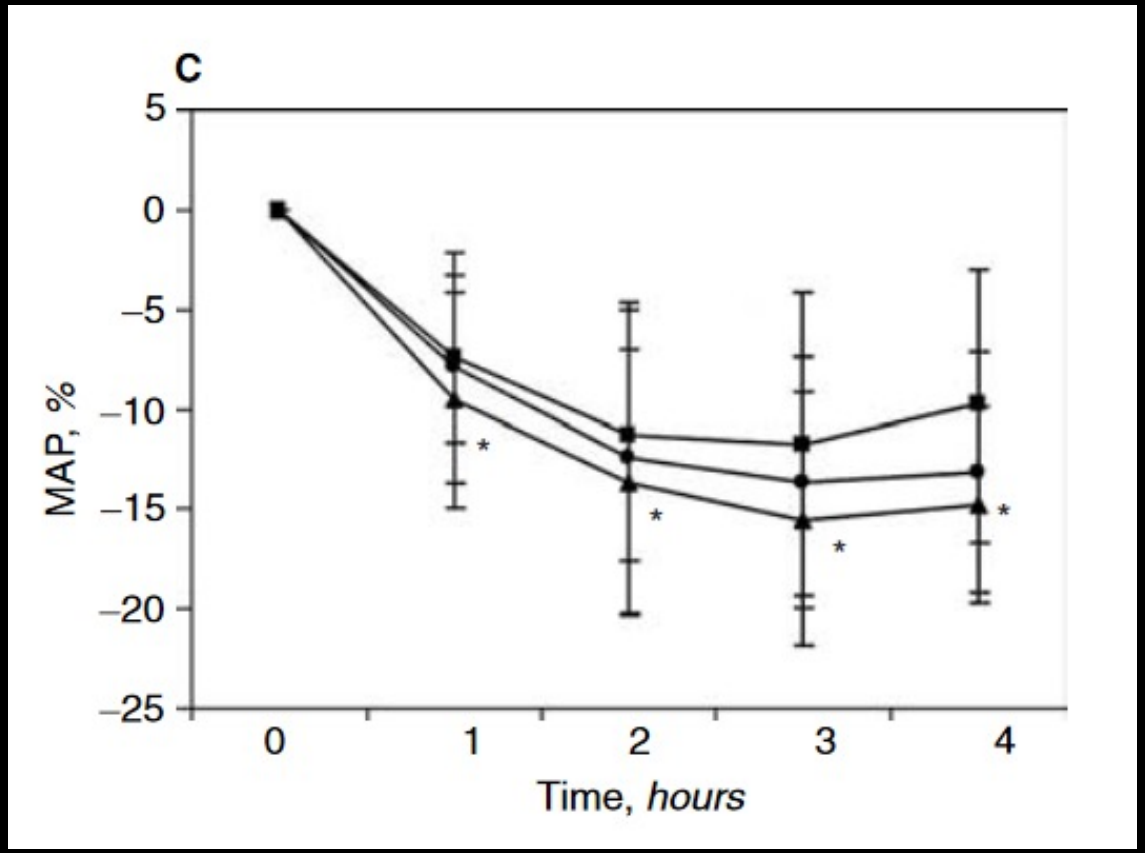
Other elements of Dialysate Composition

- Potassium concentration
  - Theoretically low dialysate potassium risks hypokalemic arrythmias
  - No studies examining the effect of dialysate potassium concentration on intradialytic hypotension
- Calcium concentration
  - KDOQI recommends (Opinion) a dialysate Ca concentration of 1.25 mmol/L
  - Some dialysis providers lower dialysate Ca concentration to avoid calciphylaxis
  - Calcium affects vascular tone: calcium administration induces vasoconstriction
  - Higher dialysis calcium is associated with reduced incidence of Intradialytic hypotension



■: Dialysate Ca = 1.5 mmol/L
□: Dialysate Ca = 1.25 mmol/L

Nephrol Dial Transplant (2009) 24: 973–981



Magnesium concentration:

Standard dialysate magnesium is usually 0.5 mmol/L---sub physiologic

Magnesium plays a role in cardiac myocyte action potential generation

Higher magnesium baths have been associated with less blood pressure decline during dialysis

■: 0.75 mmol/L Mg Dialysate
●: 0.5 mmol/L Mg Dialysate
▲: 0.25 mmoy/L Mg Dialysate

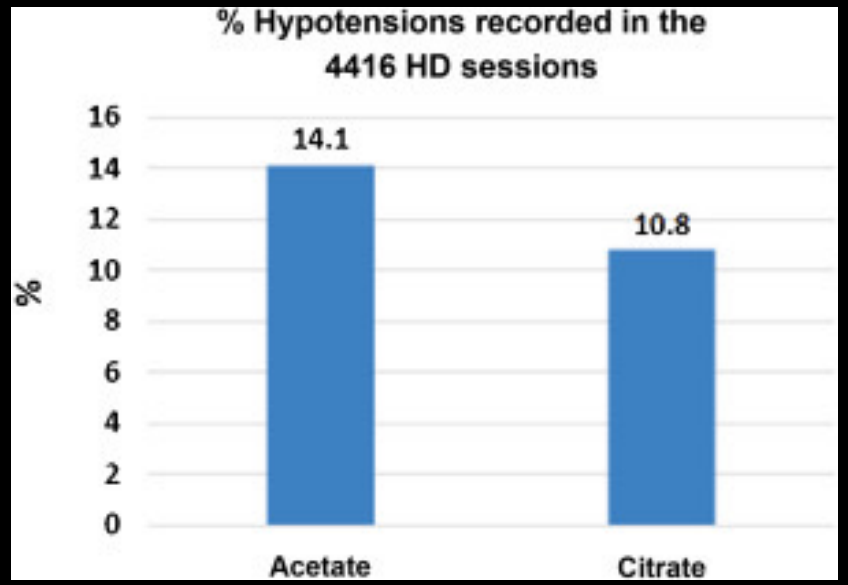
8 hemodialysis patients, single center study

Kidney International, Vol. 66 (2004), pp. 1221–1231

Acetate

- Acetate
  - Historically used as a dialysate buffer, prevents the precipitation of calcium and magnesium carbonate.
  - Associated with Intradialytic hypotension. Causes vasodilatation mediated by nitrous oxide.
  - Most current dialysates contain bicarbonate and a small amount of acetate (3-4mmol/L) though even this low concentration is substantially higher than acetate in plasma (0.1mmol/L).
  - Acetate-free biofiltration is available in Europe and acetate free dialysates (using low concentration citrate) are becoming available.

	ADF	CDF
Sodium, mEq/l	140	140
Potassium, mEq/l	1.5/2	2
Calcium, mmol/l	1.25/1.50	1.50/1.65
Magnesium, mmol/l	0.50	0.50
Chloride, mEq/l	109.5	106,5
Citrate, mmol/	0	1
Acetate, mEq/l 3 0	3	0
Bicarbonate, mEq/l	34	34

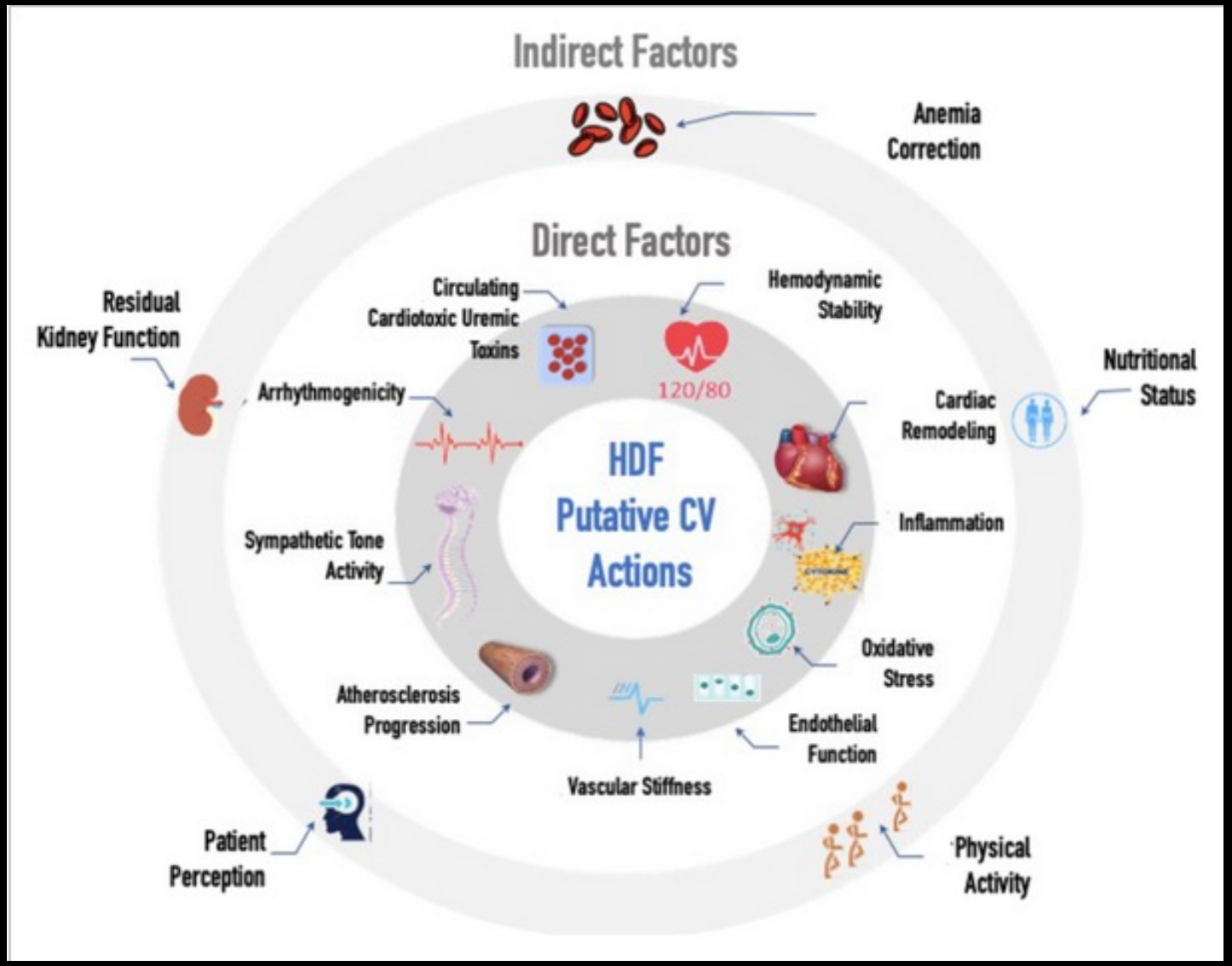


Open Label, 32 weeks, crossover study. Multicenter, 56 patients.

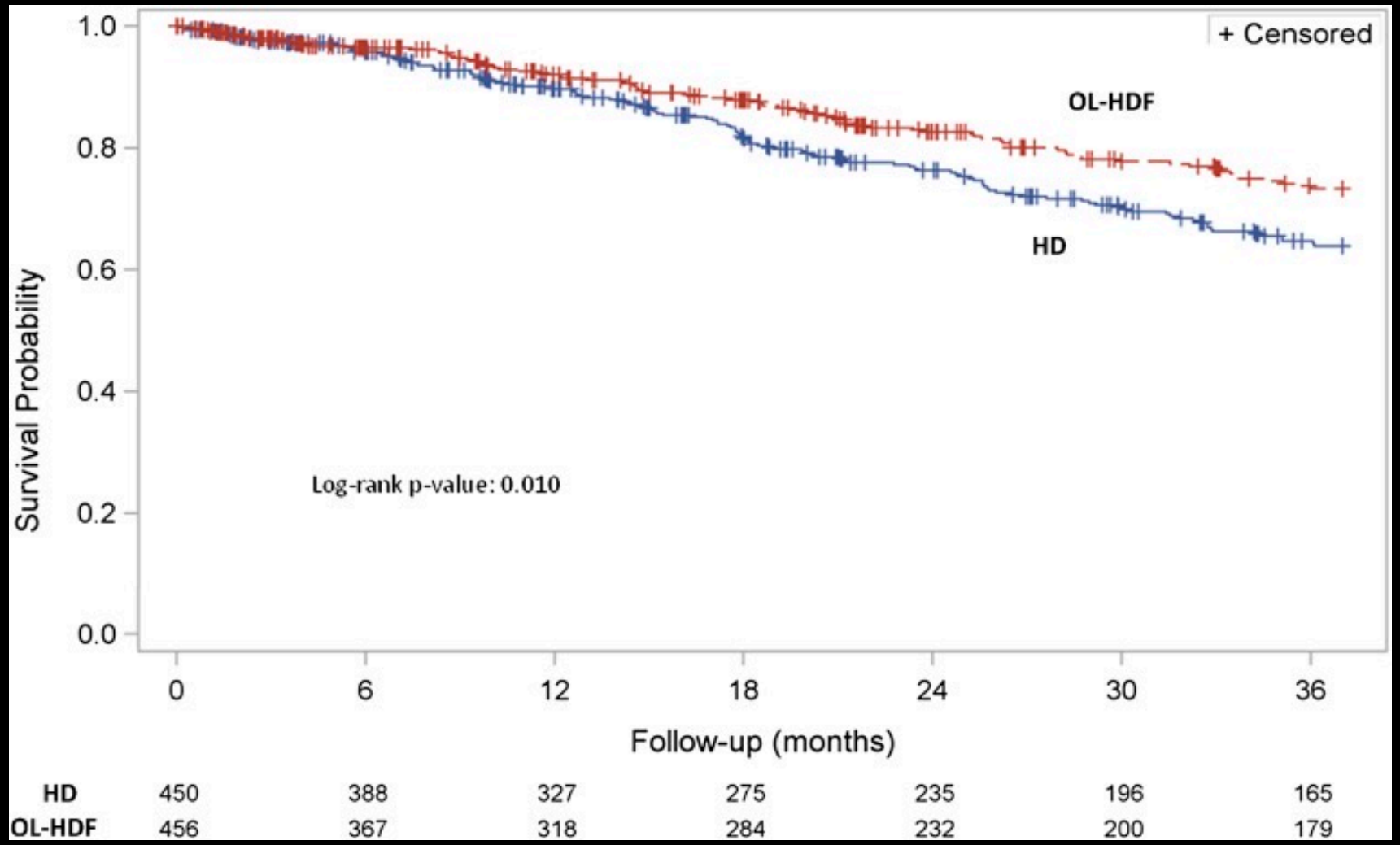
Nefrología (English Edition)Volume 42, Issue 3, May–June 2022, Pages 327-337

Hemodiafiltration

- Prevalent in Europe and Asia but only recently available in the US---slow approval of systems by the FDA
- Improved clearance of middle and large solutes
- Associated with improved mortality and CV outcomes in a meta-analysis on 2793 pts from four large European randomized controlled trials: 14% all cause survival benefit and 23% CV mortality benefit. (Dependent on convection volumes)
- Multiple studies have demonstrated a decrease in IDH with HDF vs conventional HD:
  - ESHOL: 908 patients: 27% risk reduction, RR: 0.72.
  - FRENCHIE: 381 patients: significantly fewer IDH events with HDF



Semin Dial.2022;35:117–128.



J am Soc Nephrol. 2013;24(3):487-497.

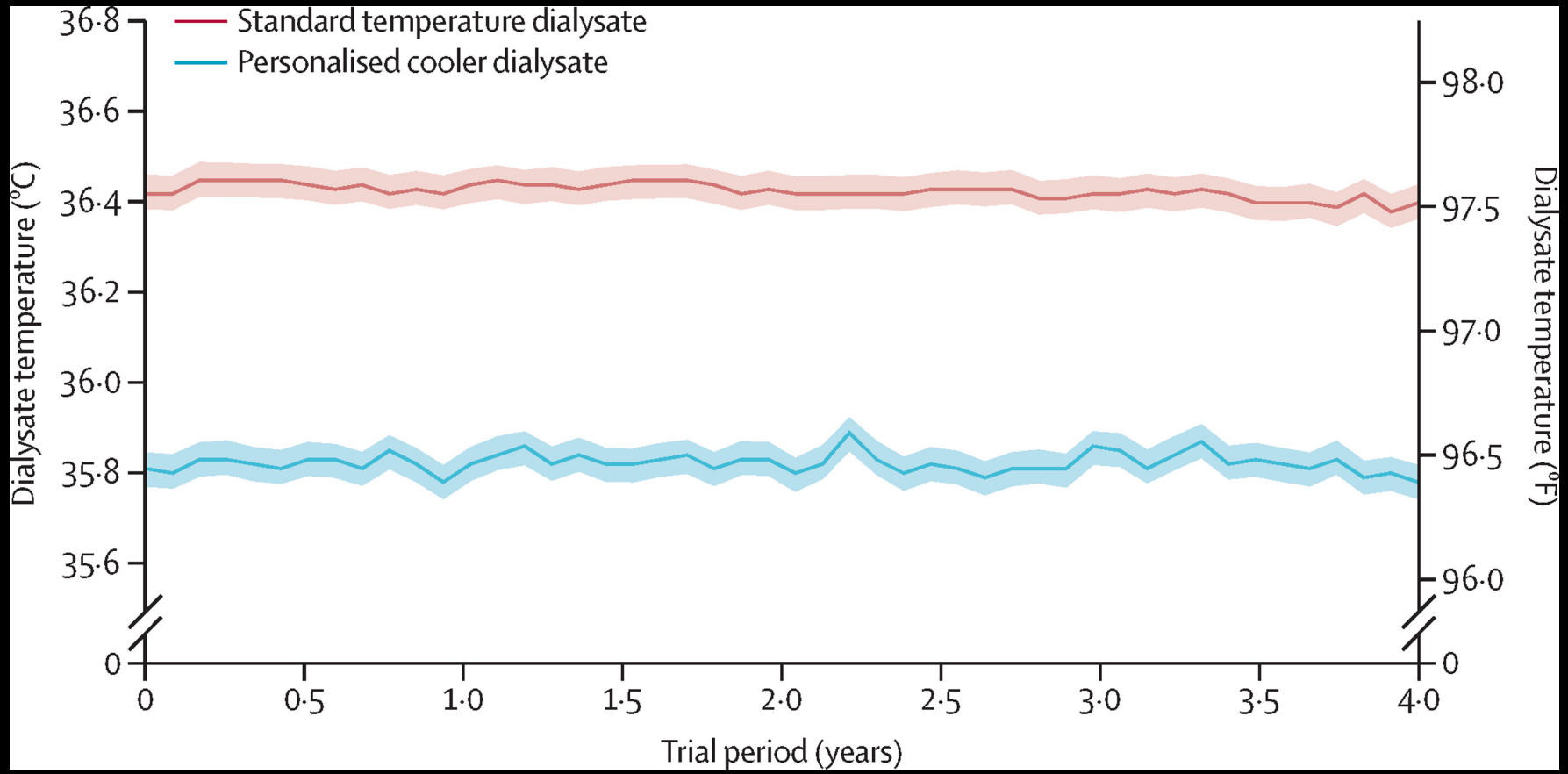
“Why do you keep it so cold in here?”

- Normal Human Body Temperature: 36.1 to 37.2 °C
- Dialysate temperature is often set at 37°C which often results in an increase in body temperature during the course of dialysis.
- Lowering dialysate temperature may increase peripheral vascular resistance, lowering the incidence of intra-dialytic hypotension.
- How low to go? Extant studies: < 36°C
- Should the temperature be fixed or varied during the dialysis session to align with patient temperature? Isothermic dialysis maintains a constant patient temperature utilizing the Blood Temperature Monitor (Fresenius, Bad Homburg, Germany)
- Cochran review published in 2019

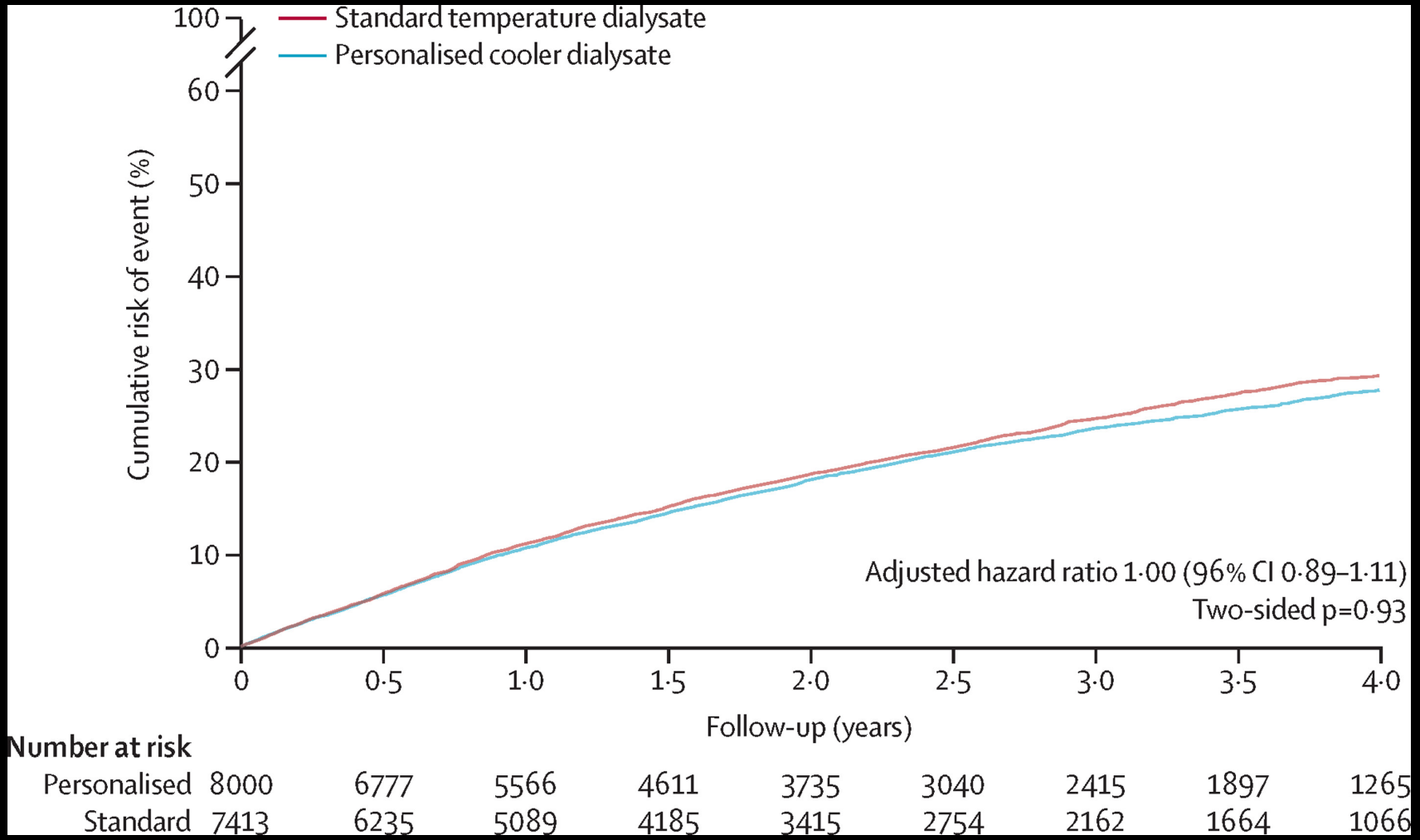
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard dialysate temperature	Risk with fixed reduction of dialysate temperature			
Intradialytic hypotension rate follow up: median 3 weeks	251 episodes per 1,000 person-dialysis session	131 episodes per 1,000 person-dialysis session (85 to 201)	RR 0.52 (0.34 to 0.80)	153 (8)	⊕⊖⊖⊖ VERY LOW [1,2]
Discomfort rate Follow up: median 4 weeks	25 episodes per 1,000 person-dialysis session	208 episodes per 1,000 person-dialysis session (47 to 928)	Rate ratio 8.31 (1.86 to 37.12)	81 (4)	⊕⊖⊖⊖ VERY LOW [1,2]
Dropout due to adverse events Follow up: median 3 weeks	Nine studies (268 participants) reported there were no dropouts due to adverse events		-	268 (9)	Not graded
Death (all causes)	No studies reported the outcome		-	-	-
Acute coronary syndrome	No studies reported the outcome		-	-	-
Stroke	No studies reported the outcome		-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

Tsujimoto Y, et al. Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis.Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD012598.



Lancet, The, 2022-11-12, Volume 400, Issue 10364, Pages 1693-1703



Lancet, The, 2022-11-12, Volume 400, Issue 10364, Pages 1693-1703

“But I’m so hungry and I have to be in this dialysis unit for so long.”

- Eating on dialysis can affect hemodynamics.
- Potential Mechanisms:
  - Splanchnic Vasodilation
  - Release of vasoactive substances during digestion
  - Reduced baroreceptor function
  - Blood sequestration
- And yet….dialysis patients are frequently protein malnourished and have reduced intake on dialysis days.

105 Hemodialysis patients in Croatia

4 weeks of eating during dialysis and 4 weeks of dialysis without meals

Intradialysis hypotension was defined by a 20 mmHg drop in systolic BP or 10mmHg drop in mean BP.

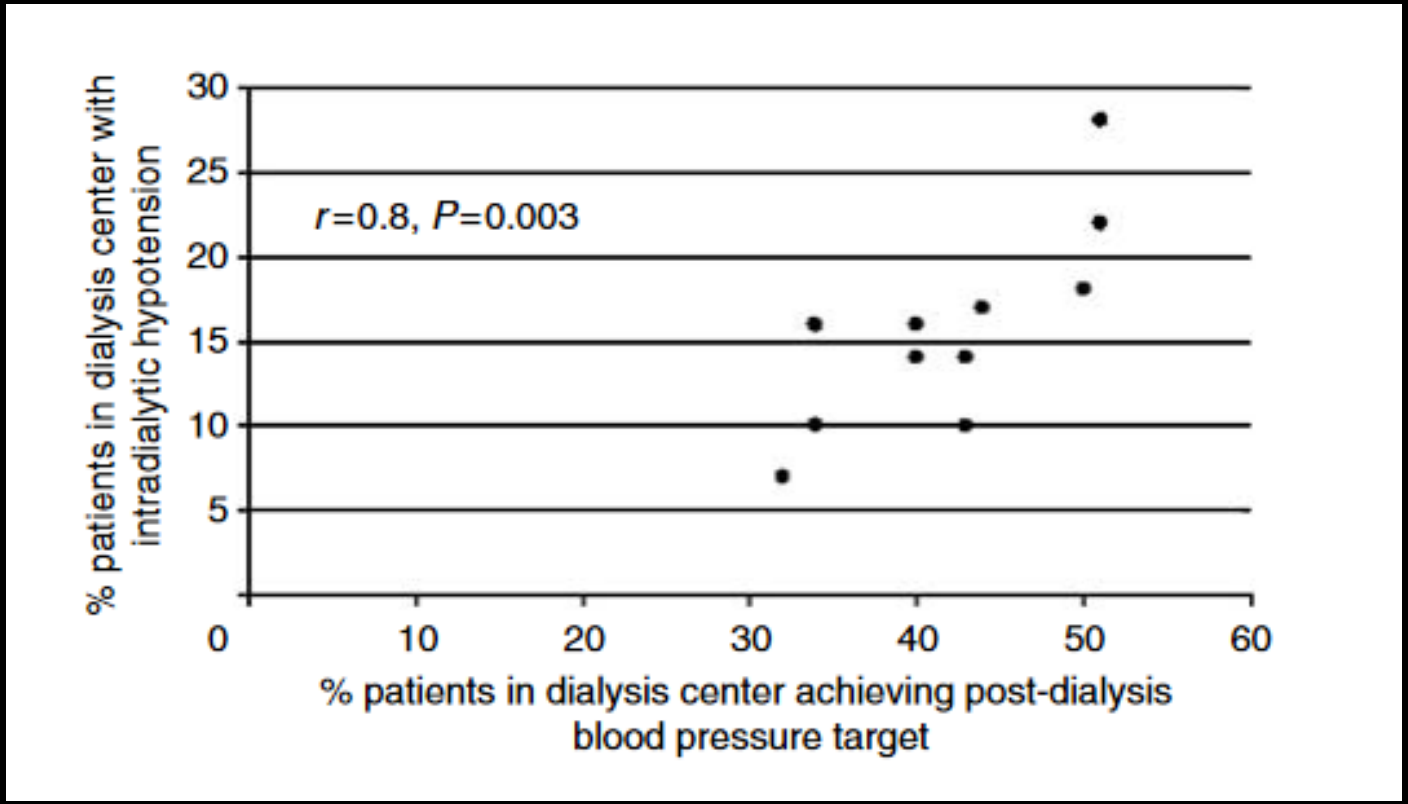
TABLE 1 Frequency of hypotensive events and cramping episodes in both periods

	With meal	Without meal	*p*
Hypotensive events	431	320	<0.001
Patients without hypotensive events	12	24	<0.001
Cramping episodes	32	12	0.035

HemodialysisInternational. 2021;25:333–337.

“My doctor says I have to take my medications every day!”

- Altering the timing of anti-hypertensive medications in an obvious way to avoid intradialytic hypotension
- But…HTN is associated with stroke, cardiovascular disease and mortality.
- K/DOQI and the UK Renal Association guidelines suggest that predialysis and postdialysis BPs should be < 140/90 and 130/80 mmHg respectively
- When these guidelines are met, intradialytic hypotension rates increase.
- Pre-HD and post-HD BP’s correlate poorly with interdialytic blood pressures.
- There is very limited evidence to guide recommendations for type of anti-hypertensive and timing of administration in dialysis patients.



Davenport A et al. Kidney International (2008) 73, 759–764

Compression Stockings

- Improve lower ext venous return
- Low risk intervention
- Patient tolerability may be an issue
- Very limited data to support use

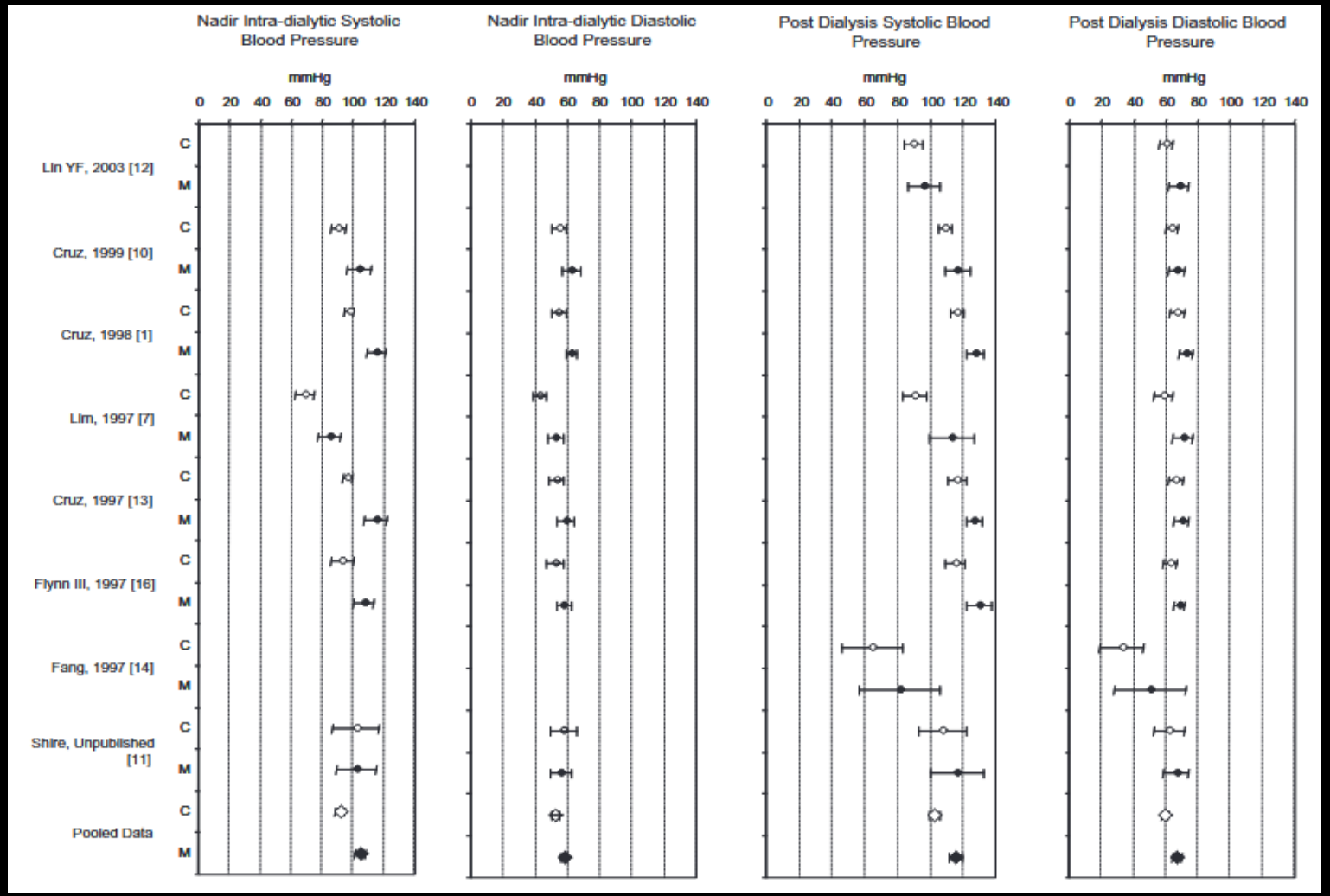
Midodrine

- Midodrine is a prodrug converted into desglymidodrine.
- An alpha-1 adrenergic receptor agonist: a vasoconstrictor, increases vascular resistance and venous return
- Approved for treatment of orthostatic hypotension but use for intradialytic hypotension is off label.
- Very few prospective studies on this intervention
- Midodrine is dialysable.

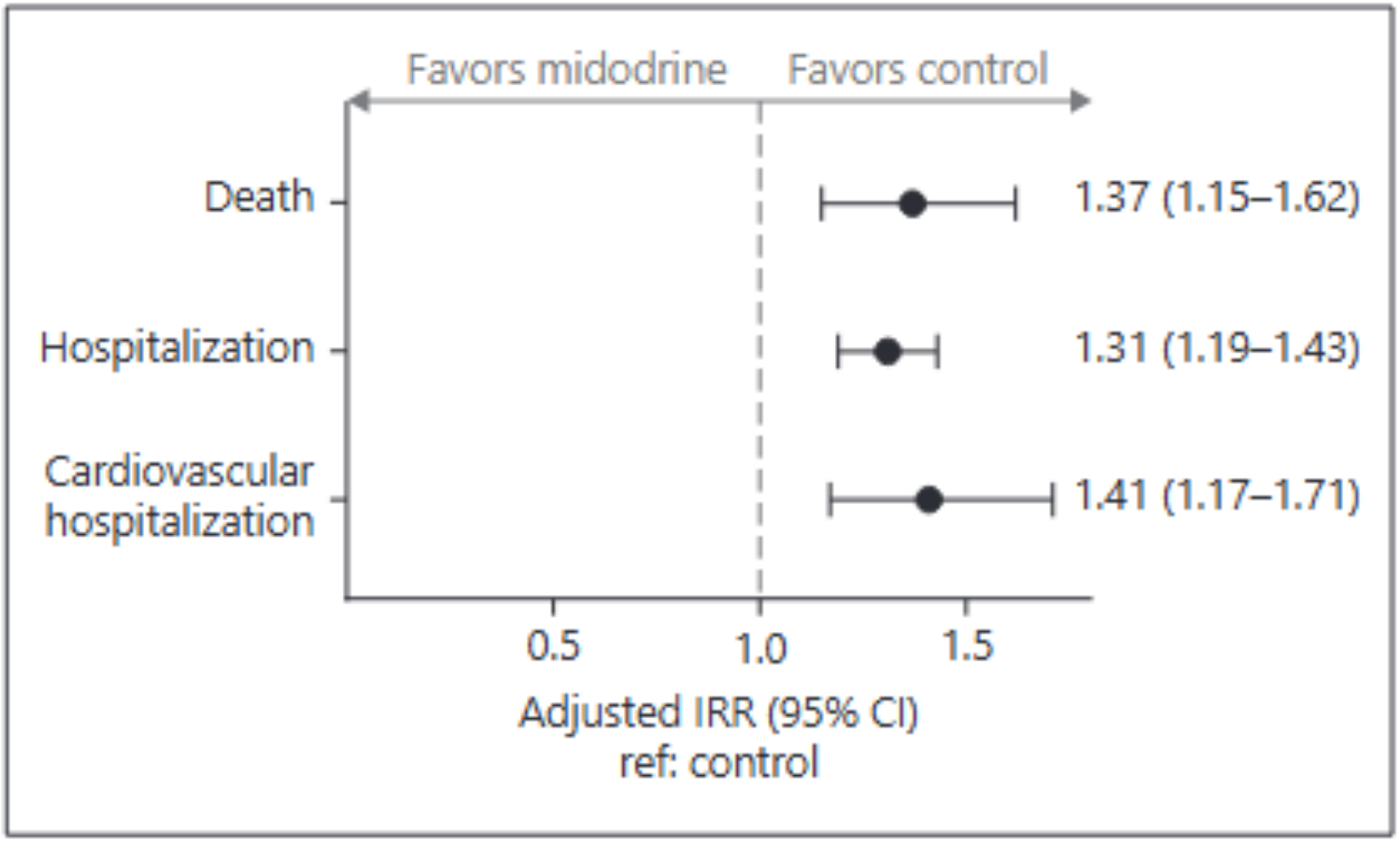
Meta analysis of studies with > 5 patients comparing intradialytic blood pressures with and without midodrine.

Primarily pre and post intervention studies. Very small pt numbers. No randomized controlled trials.

Seems to be a blunting of hypotension.



Nephrol Dial Transplant (2004) 19: 2553–2558



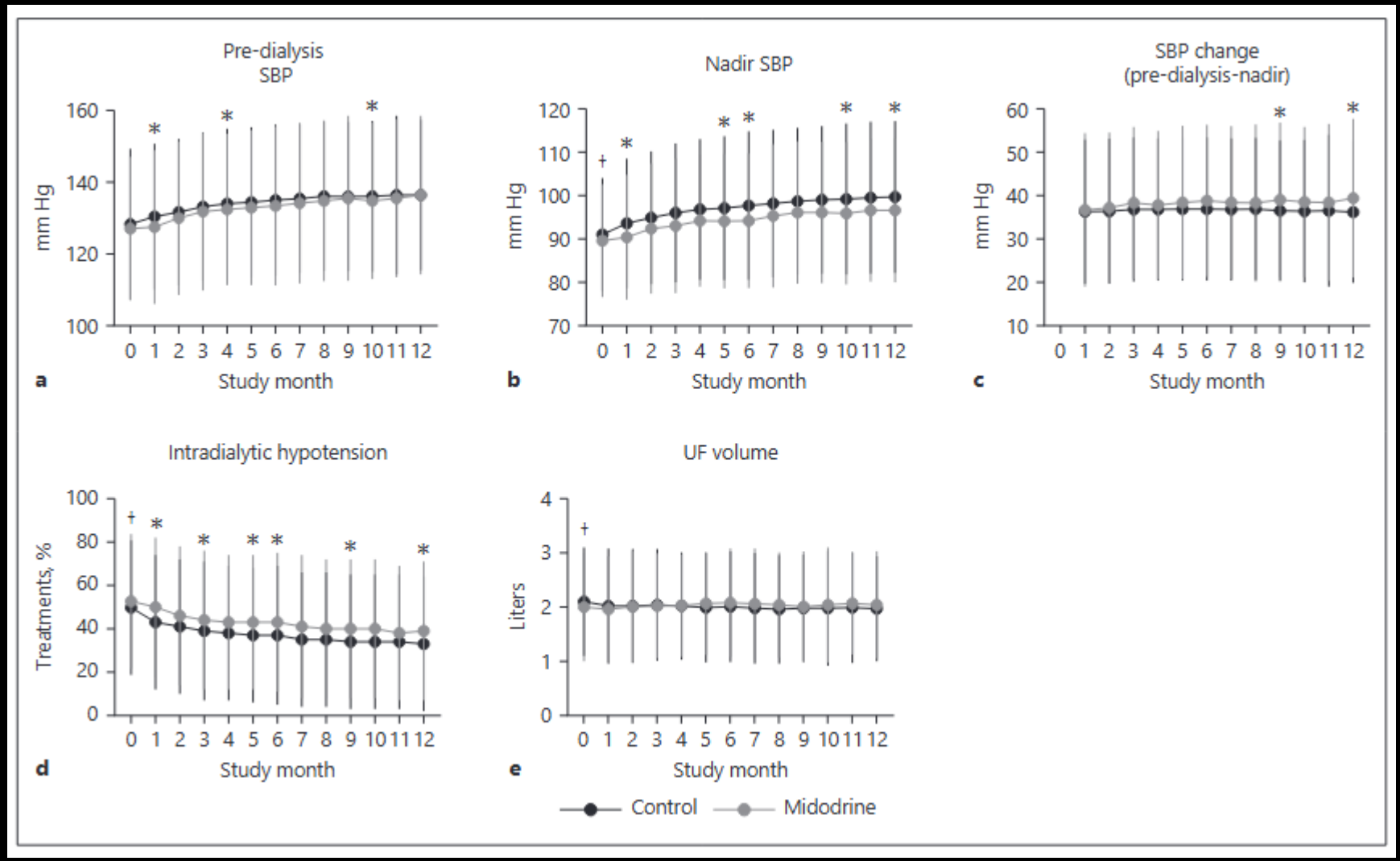
Retrospective, observational study comparing patients receiving midodrine to non-midodrine ESRD controls.

Midodrine pts n = 1046
Controls n = 2037

Time frame 7/2015 to 9/2016

Outcomes: mortality, all hospitalization, cardiovascular hospitalization, hemodynamic outcomes

Am J Nephrol 2018;48:381-388.

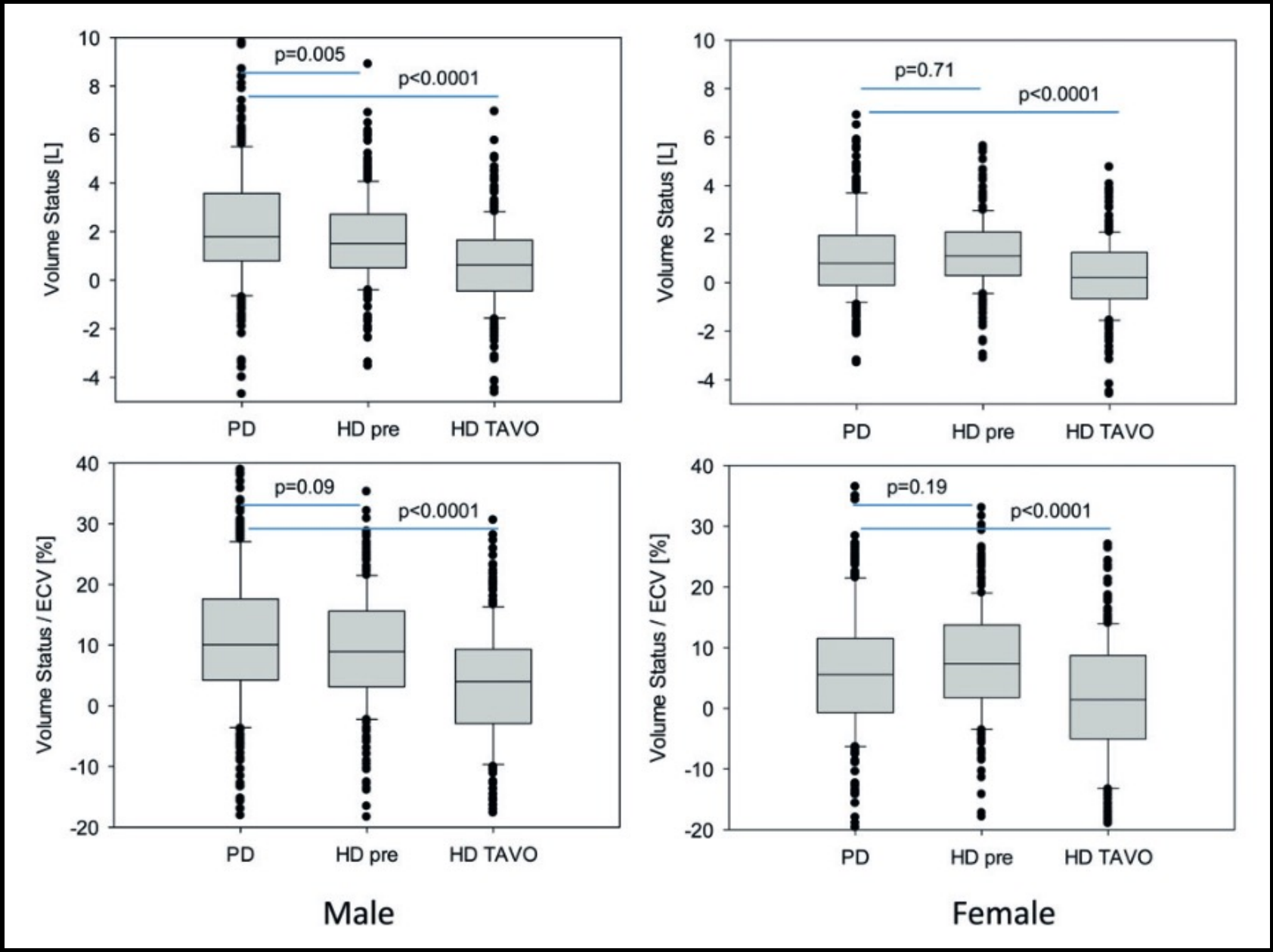


Does it really make that much of a difference?

Am J Nephrol 2018;48:381-388.

“I wish I didn’t have to come in here.”

- Switching to PD:
  - much slower UF
  - requires assumption of responsibility by the patient/caregivers.
- Home Hemodialysis
  - More flexibility in the frequency and duration of dialysis treatments.



Comparison of volume status using bioimpedance spectroscopy in patients on PD and HD.

van Biesen W, et al. Nephrol Dial Transplant 2013; 28: 2620–2628

Keep an open mind

- Bacteremia/Sepsis
- New Cardiac dysfunction: valvular disease, acute MI, pericardial effusion
- Hemorrhage
- Anaphylactoid reactions
- Inflammatory reactions to the extracorporeal circuit

Thank you for your attention!