What Is New in Iron Therapy of HD Patients?

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Indiana University School of Medicine
Annual Dialysis Conference
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Disclosures

- Advisory boards: Vifor Pharma, Rockwell Medical, AstraZeneca, Akebia
- Speakers bureau: AstraZeneca, Akebia

Outline

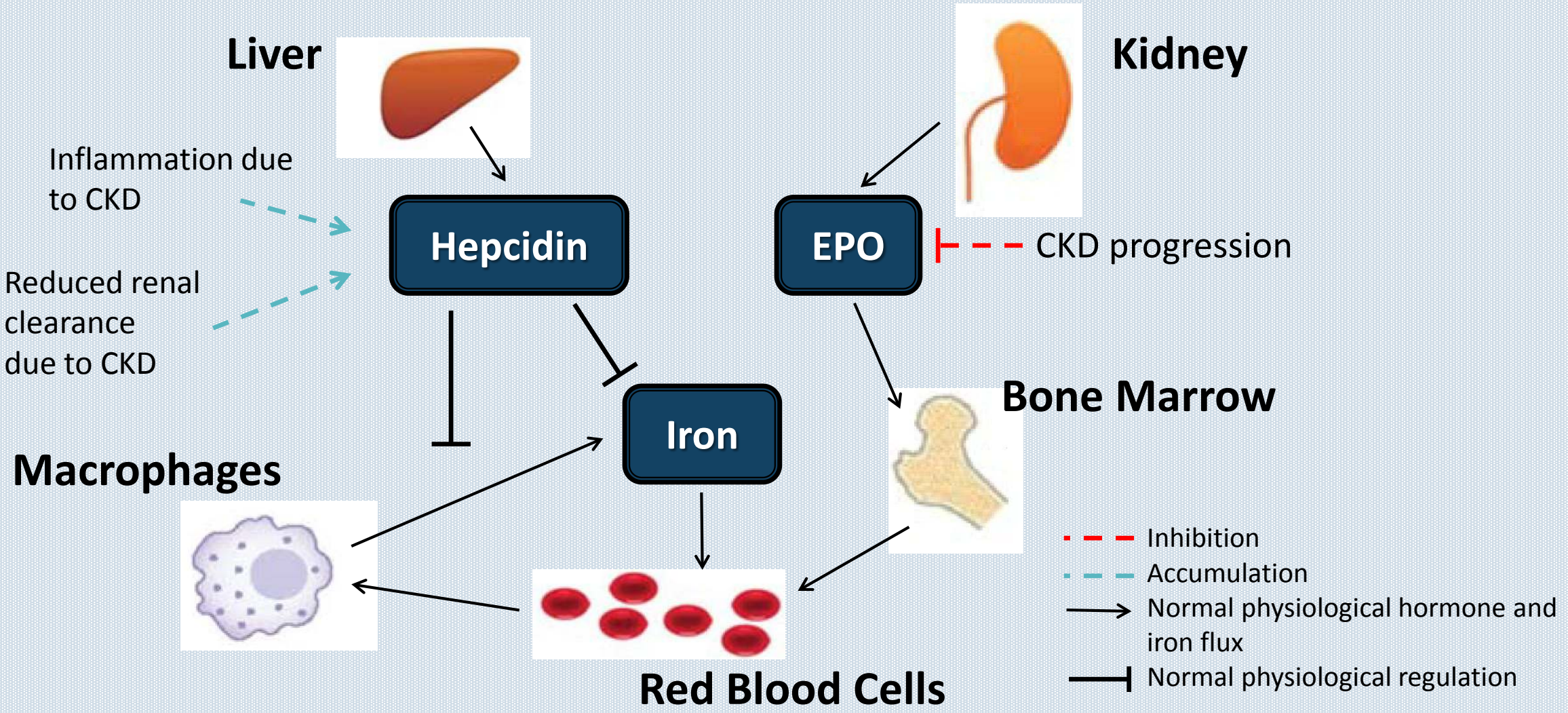
- Iron physiology in CKD
- Putting PIVOTAL in perspective
- IV ferric pyrophosphate citrate
- HIF prolyl hydroxylase inhibitors and iron
- Monoclonal antibody to IL-6

Hepcidin

- Hepcidin discovered in 2000
  - Peptide produced by liver
  - Key regulator of iron metabolism, use, recycling, and transport
  - Levels affected by iron stores, inflammation states, and erythropoietin (EPO)
- Hepcidin has been associated with anemia in CKD and resistance to ESA therapy
- Increased hepcidin in CKD
  - Caused by inflammation and reduced renal clearance
  - Leads to reduced circulating iron levels and impaired iron transport

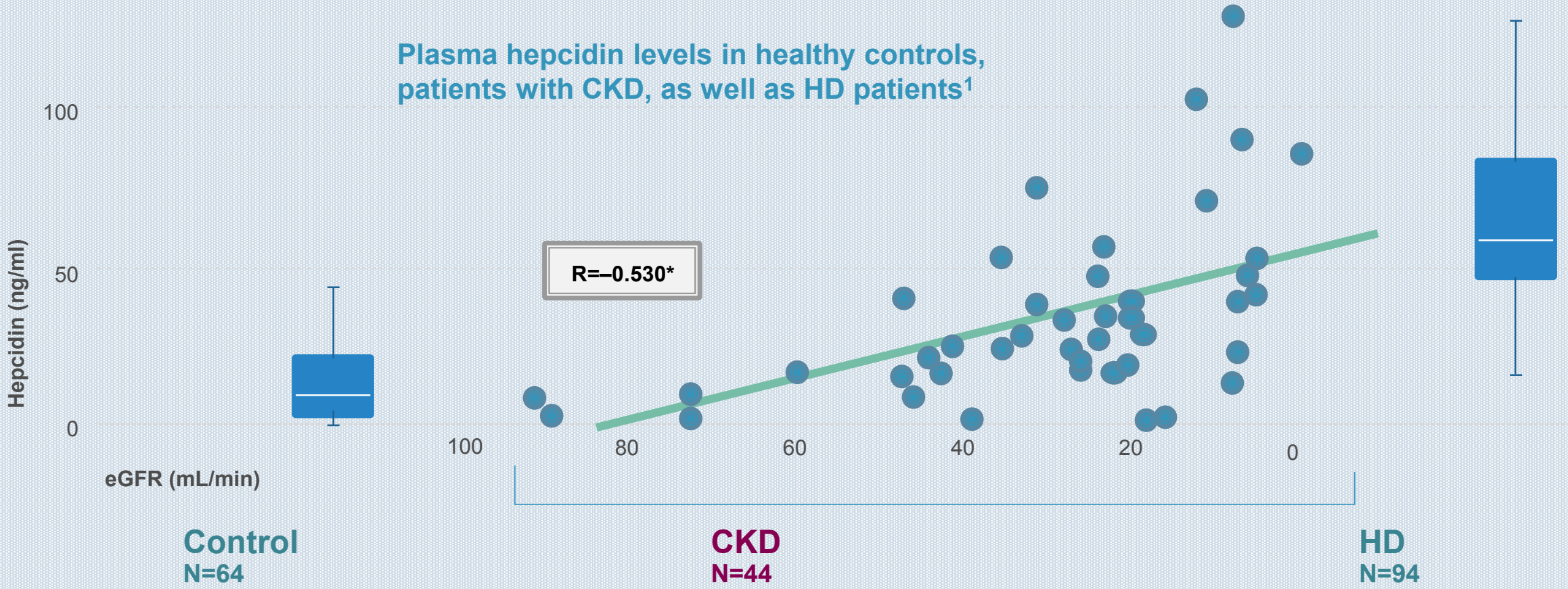
1. Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199. 2. Gaweda AE. *Hemodial Int*. 2017;21:S21-S27. 3. Atkinson MA, et al. *Pediatr Nephrol*. 2015;30(4):635-643.

Roles of EPO, Iron, and Hepcidin



Adapted from Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

Hepcidin Levels Increase as CKD Progresses to ESRD

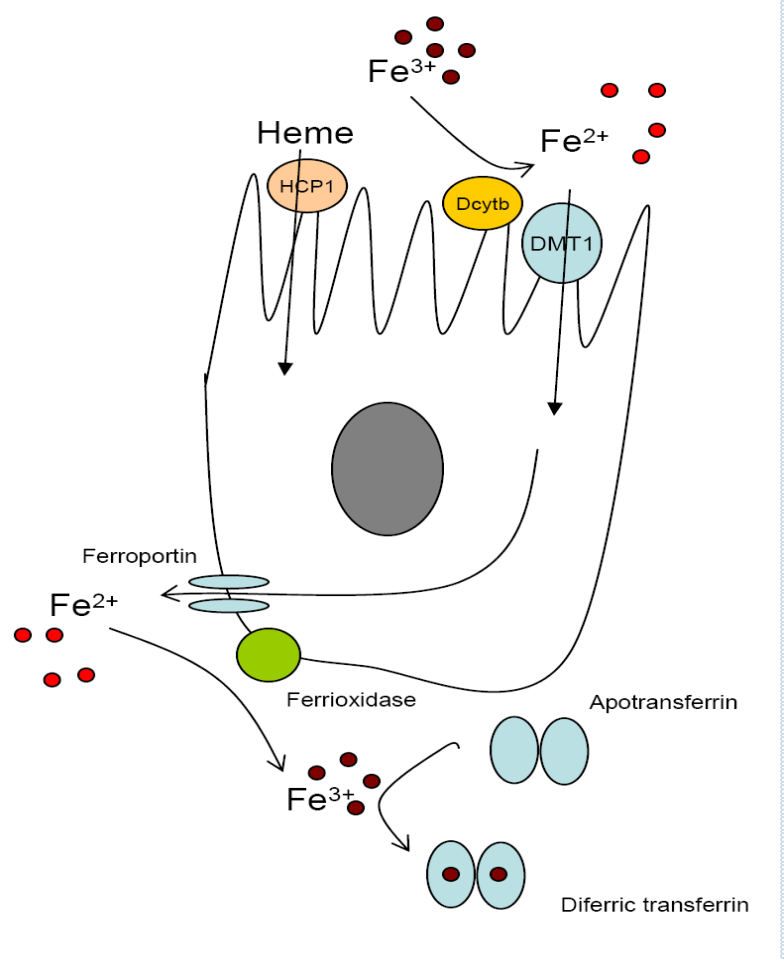


- **Hepcidin is a main cause of functional iron deficiency and iron-restricted erythropoiesis[2]**

1. Babitt JL, et al. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23:1631-1634.
2. Ashby DR, et al. Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease. *Kidney Int*. 2009;75:976-981.

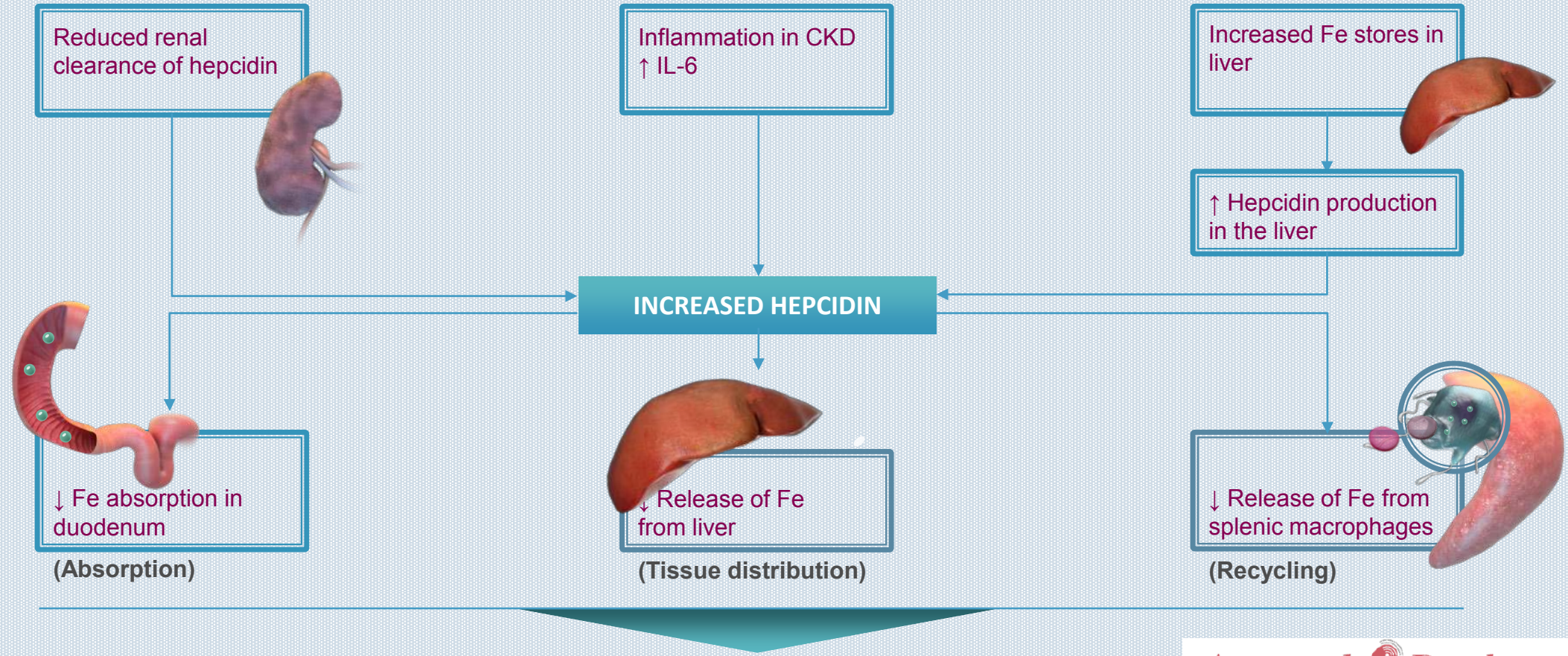
Iron Transport in the Duodenal Enterocyte

- Ferroportin regulates the amount of iron that leaves the duodenal enterocytes and goes into the circulation
- Ferroportin, in turn, is regulated by hepcidin
- Hepcidin internalizes ferroportin, preventing iron efflux from cells
- Higher hepcidin impairs
  - Iron absorption in the small intestine
  - Iron transport across the placenta
  - Iron release from macrophages



Andrews NC. Intestinal iron absorption: current concepts circa 2000. *Dig Liver Dis*. 2000;32:56-61.

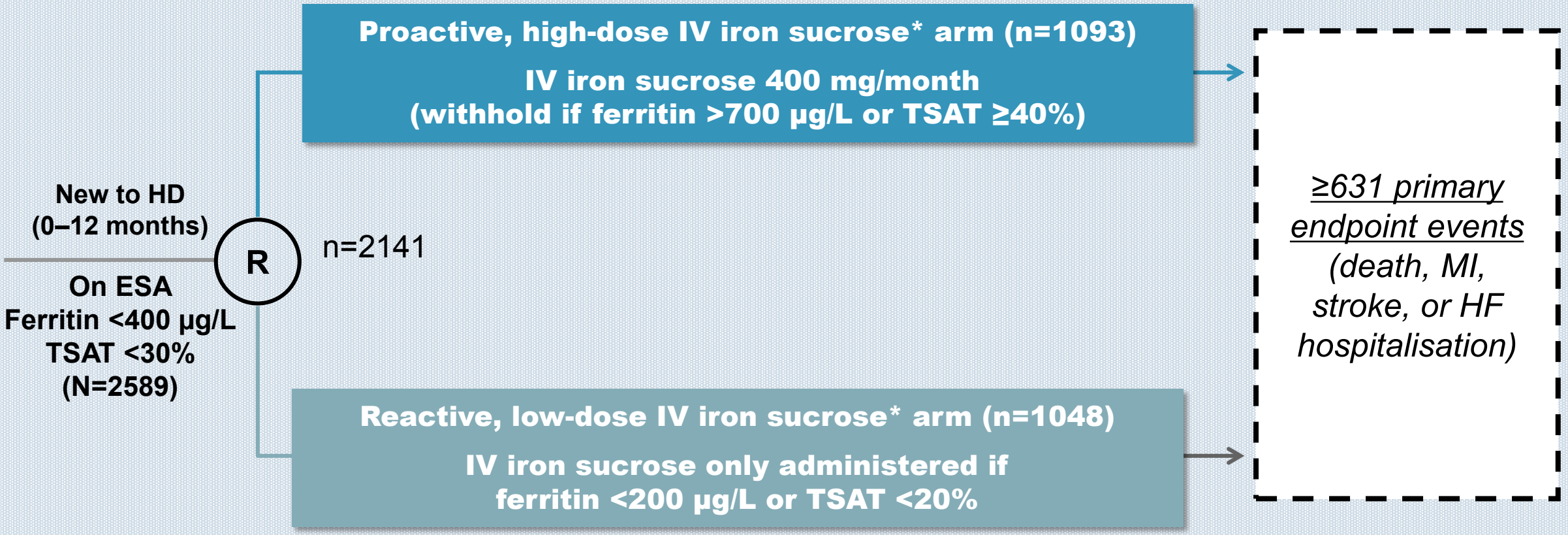
Hepcidin Regulates Iron Metabolism and Hepcidin Levels Are Often Elevated in CKD[1-3]



CKD = chronic kidney disease; Fe = iron; IL-6 = interleukin 6.

1. Babitt JL, et al. *J Am Soc Nephrol*. 2012;23:1631-1634. 2. Bergamaschi et al. *Haematologica*. 2009;94:1631-1633. 3. Kim YL. *Kidney Res Clin Pract*. 2012;31:1-3.

PIVOTAL Trial Design[1,2]

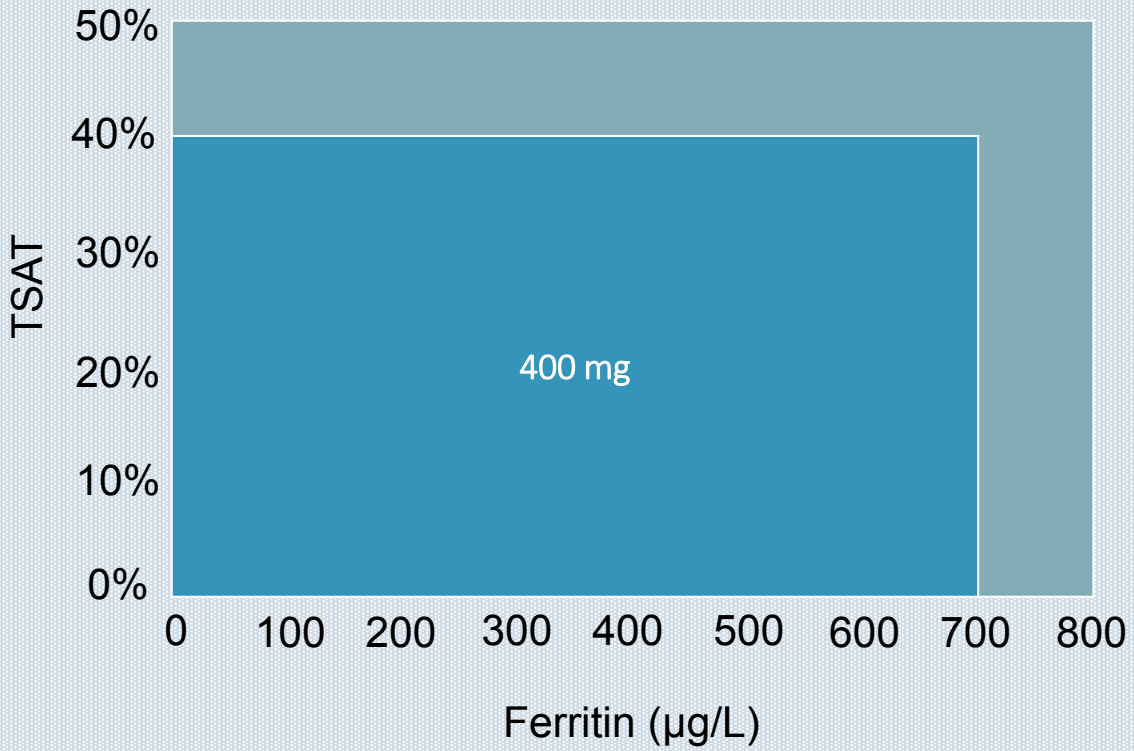


*IV iron sucrose used was Venofer®

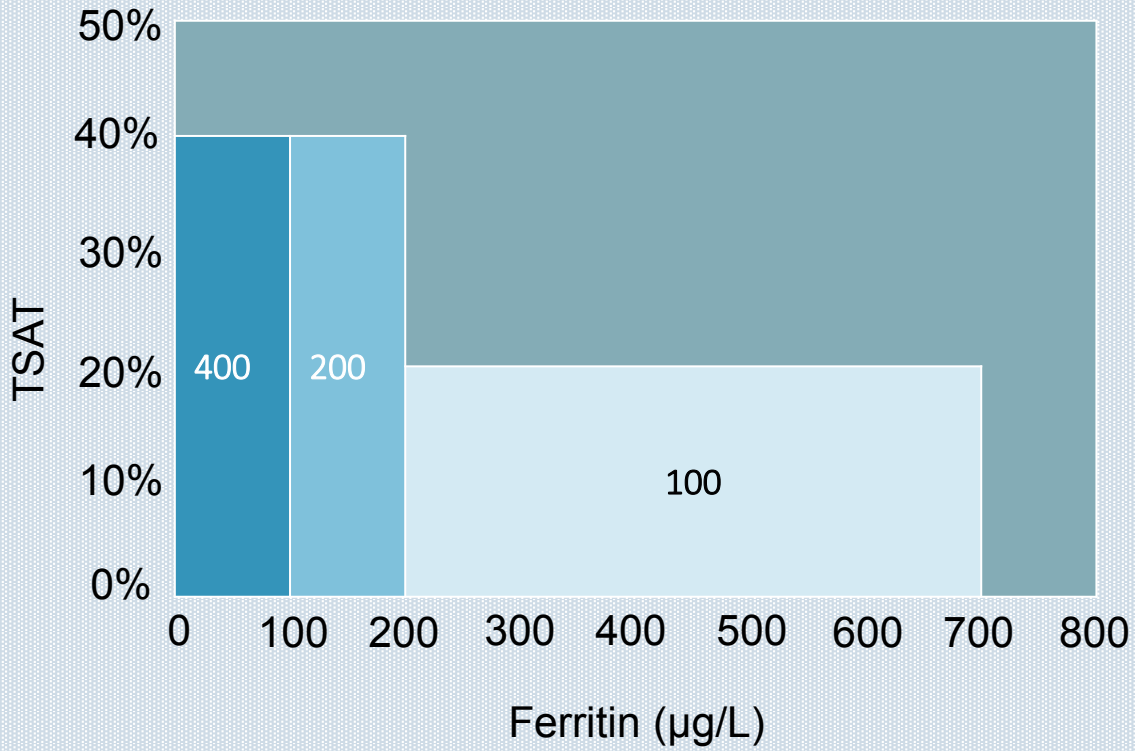
Adapted from Macdougall IC et al. *Am J Nephrol.* 2018;48(4):260-268.
1. Macdougall IC et al. *Am J Nephrol.* 2018;48(4):260-268; 2. Macdougall IC et al. *N Engl J Med.* 2019;380(5):447-458.

Monthly Iron Dosing Protocols[1,2]

Proactive, High-Dose IV Iron Sucrose[a,b]



Reactive, Low-Dose IV Iron Sucrose[a]



- [a]IV iron sucrose used was Venofer®.
- [b]In month 1, patients meeting criteria for iron administration received a total of 600 mg (200 mg administered during 3 sessions). All iron was to be administered during the week following the monthly blood tests (usually the second week of the calendar month).
- 400-mg monthly doses administered as 200 mg during each of the first 2 dialysis sessions of the week; other monthly doses administered during the first session of the week.
- 1. Macdougall IC et al. *Am J Nephrol.* 2018;48(4):260-268; 2. Macdougall IC et al. *N Engl J Med.* 2019;380(5):447-458.

PIVOTAL Trial Outcomes

Primary Endpoint

Composite of nonfatal MI, nonfatal stroke, hospitalisation for HF, or all-cause death, analyzed as time-to-first event

Components of the Primary Endpoint (Secondary Endpoints)

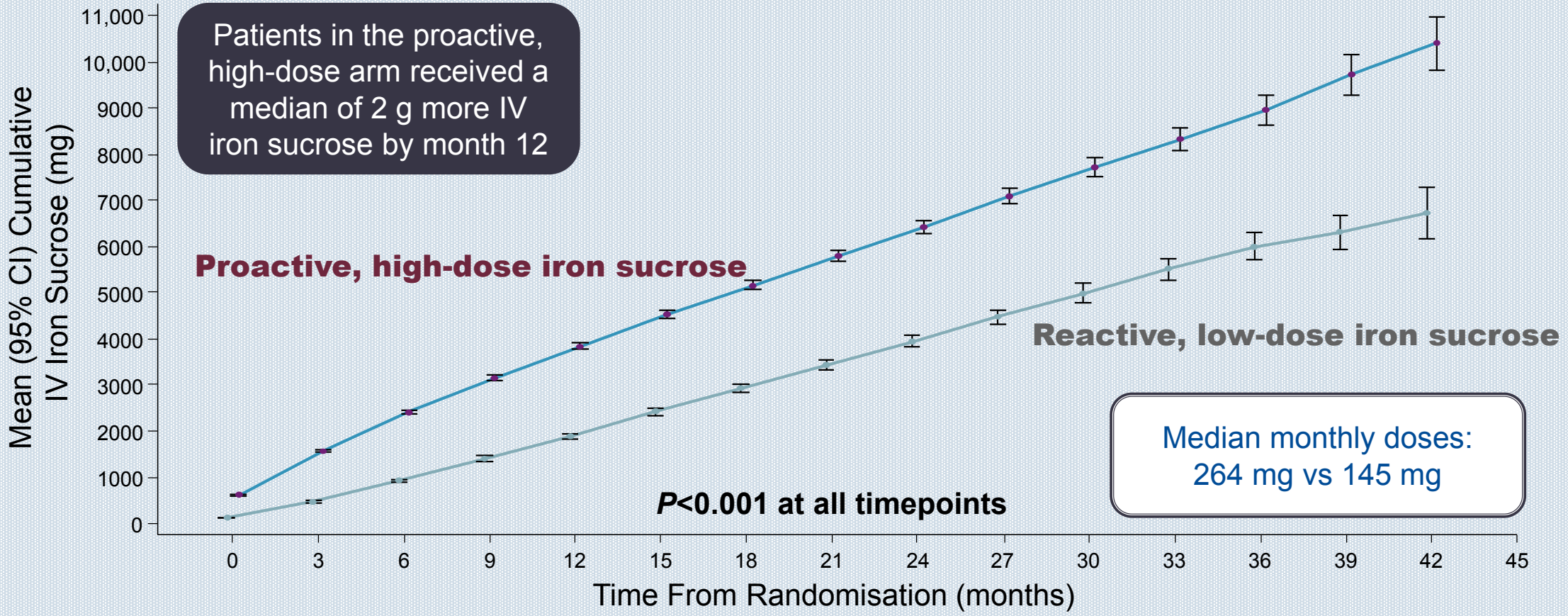
- All-cause death
- Composite of CV events (MI, stroke, and hospitalisation for HF [first event])
- MI (fatal or nonfatal)
- Stroke (fatal or nonfatal)
- Hospitalisation for HF

Recurrent Events (Secondary Endpoint)

MI, stroke, hospitalisation for HF, and deaths analysed as first & recurrent events

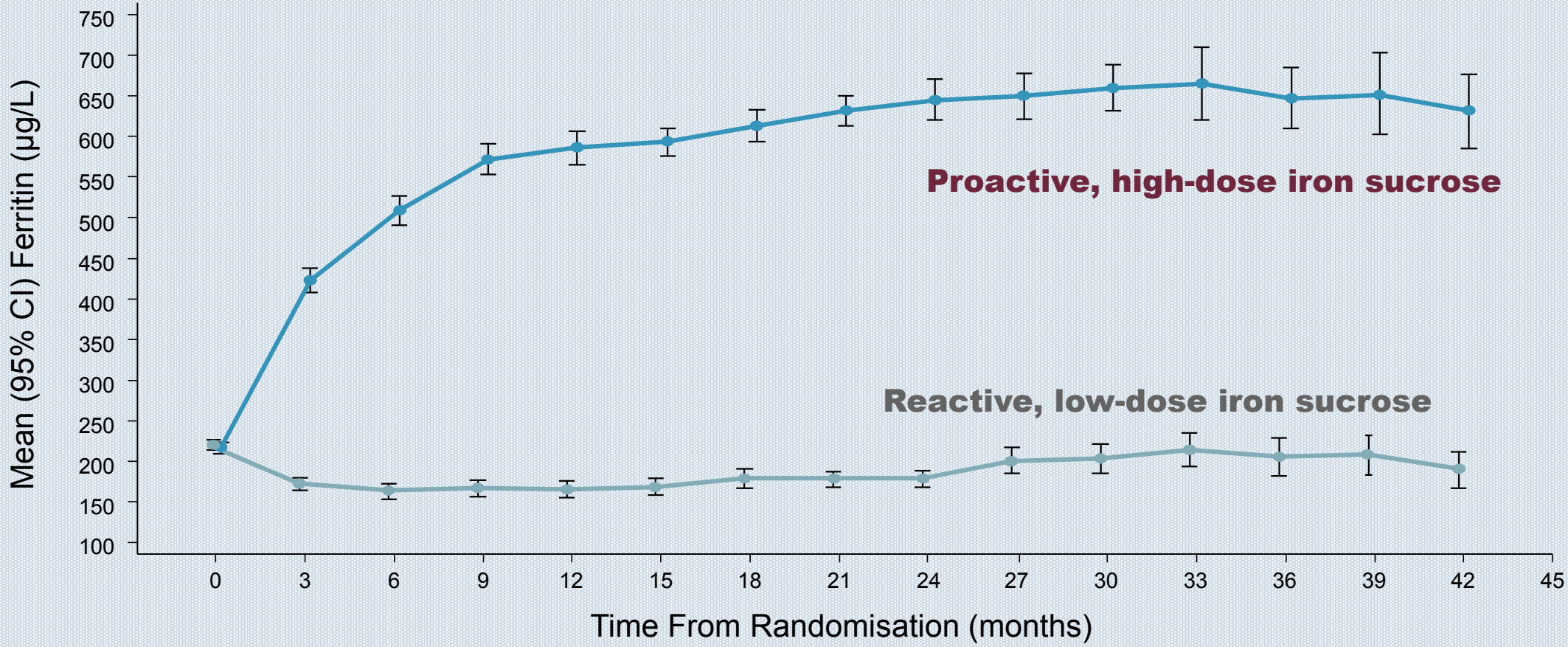
- Macdougall IC et al. *Am J Nephrol*. 2018;48(4):260-268.

Significantly More IV Iron Sucrose was Administered with the Proactive, High-Dose Regimen



- Data plotted 0 months reflect iron administered at first postrandomisation timepoints.
- From the *New England Journal of Medicine*, Macdougall IC et al., Intravenous iron in patients undergoing maintenance hemodialysis, [published online October 26, 2018]. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Macdougall IC et al. *N Engl J Med*. 2019;380(5):447-458.

Serum Ferritin Concentrations Rapidly Increased with Proactive, High-Dose IV Iron Sucrose



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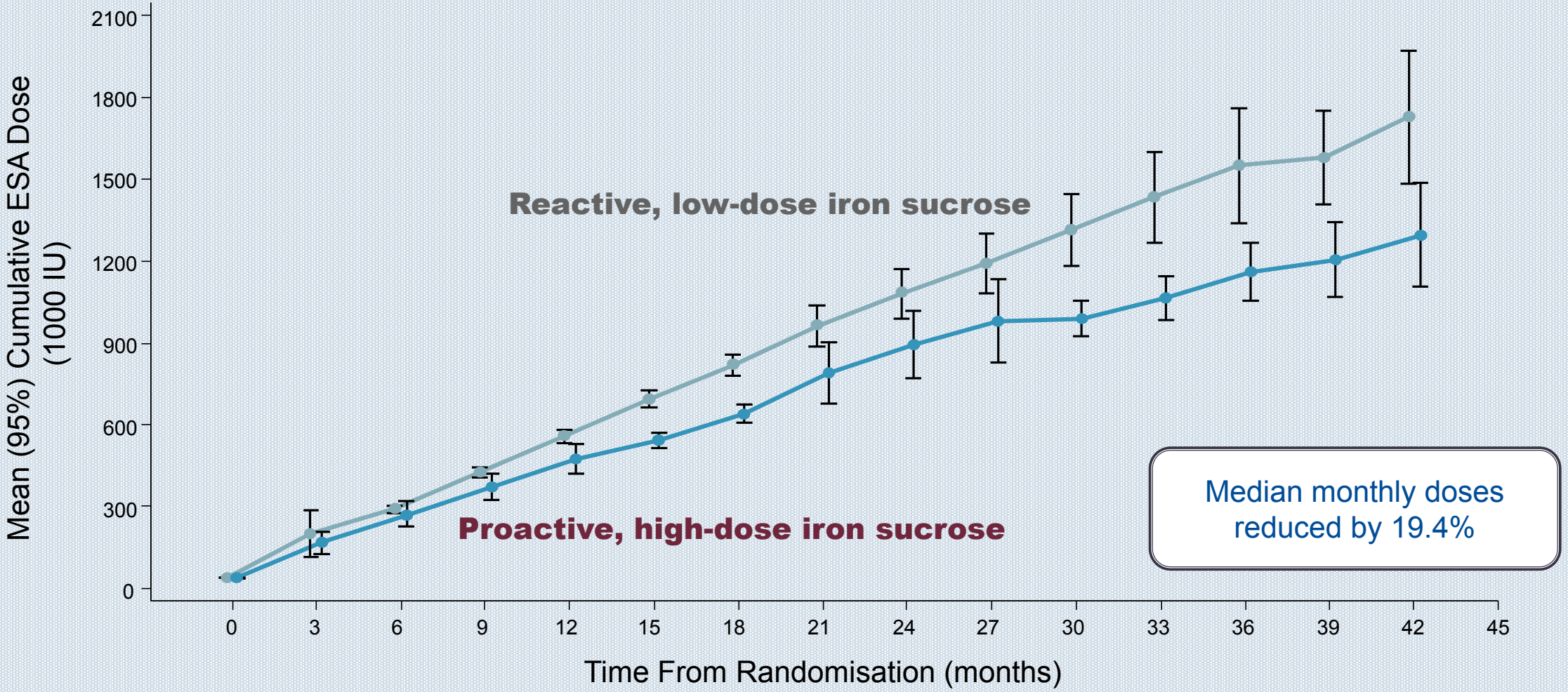
Cumulative ESA Dose



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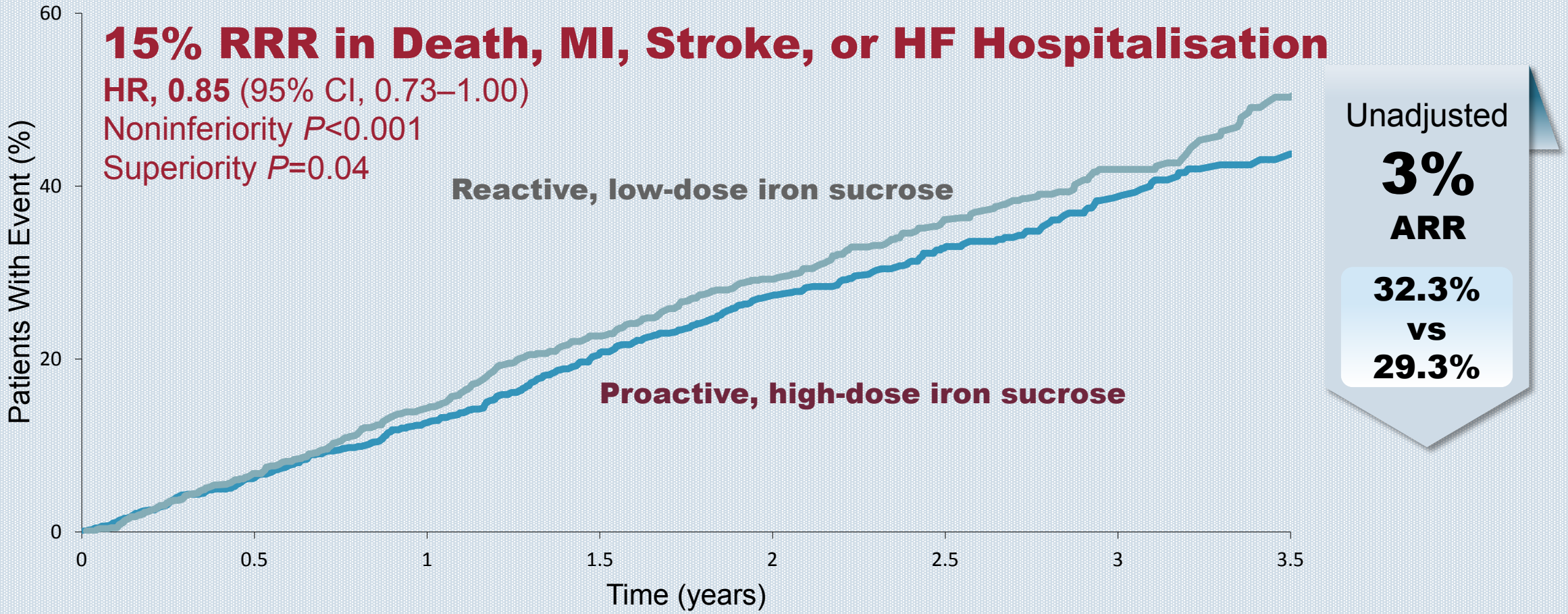
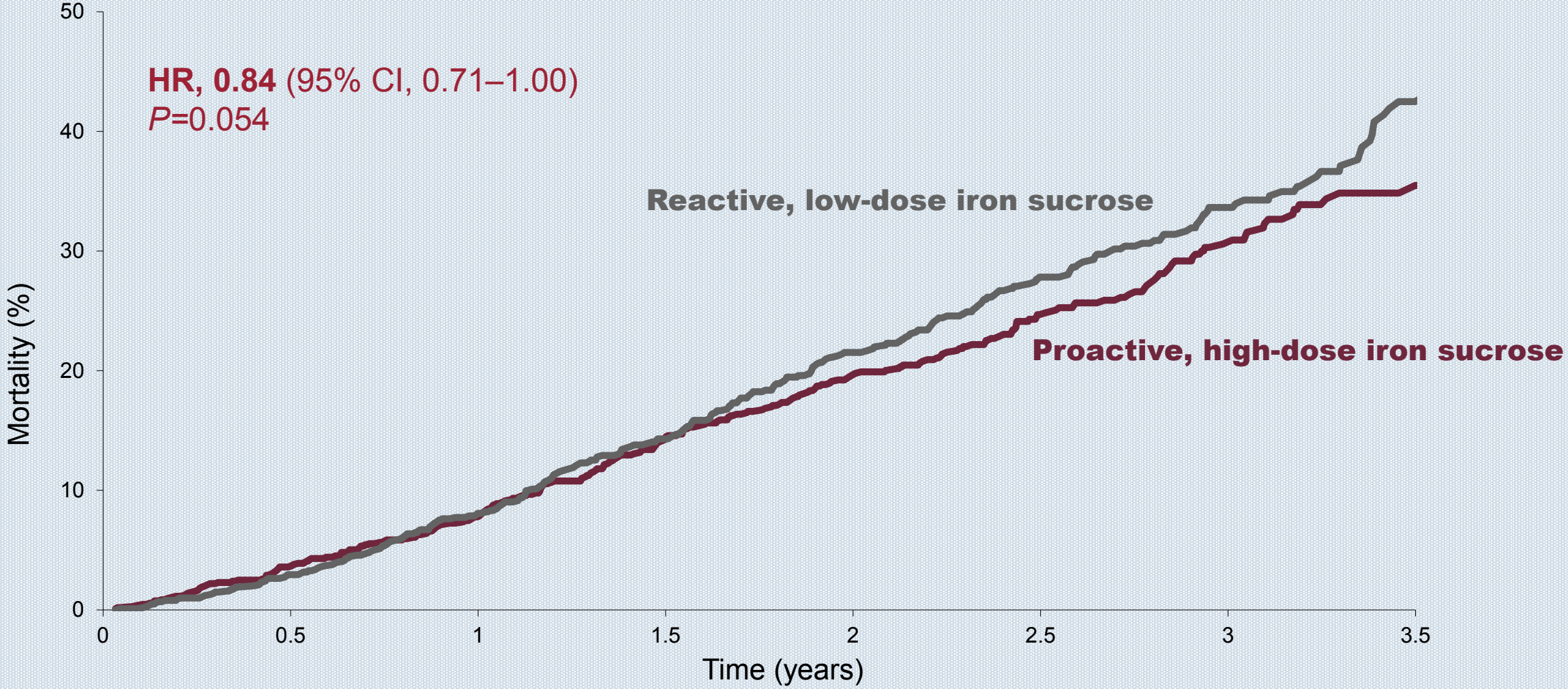
The High-dose Iron Sucrose Regimen was Associated with a Significantly Reduced Risk of **Death, MI, Stroke, or HF Hospitalization**



- ARR=absolute risk reduction; RRR=relative risk reduction.
  HR (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis; *P* value from Wald test.
  From the *New England Journal of Medicine*, Macdougall IC et al., Intravenous iron in patients undergoing maintenance hemodialysis, [published online October 26, 2018].

- Macdougall IC et al. *N Engl J Med*. 2019;380(5):447-458.

Death from Any Cause



- HR (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis.

- Macdougall IC et al. *N Engl J Med*. 2019;380(5):447-458.

The Risk of Cardiovascular Events was Lower Among Patients IN THE HIGH-DOSE ARM

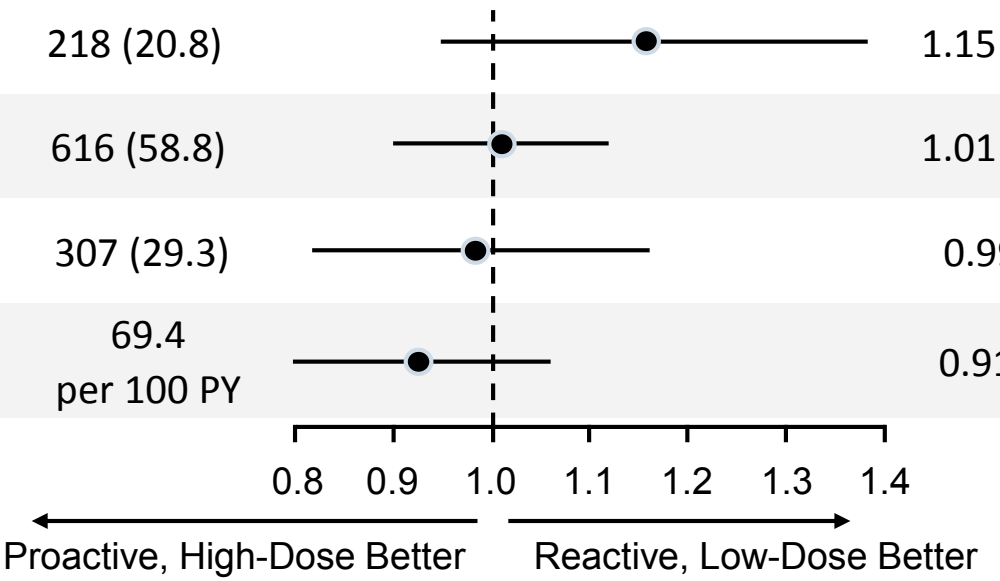
MI or Stroke or Hospitalisation for HF	20% RRR HR, 0.80 (95% CI, 0.64–1.00)	2.4% unadjusted ARR (16.0% vs 13.6%)
MI	**31% RRR** HR, 0.69 (95% CI, 0.52–0.93)	2.6% unadjusted ARR (9.7% vs 7.1%)
Stroke	HR, 0.90 (95% CI, 0.56–1.44)	N/A (3.3% vs 3.1%)
Hospitalisation for HF	**34% RRR** HR, 0.66 (95% CI, 0.46–0.94)	2.0% unadjusted ARR (6.7% vs 4.7%)

- HR (95% CI) adjusted for stratification variables: vascular access, diabetic status, and time on dialysis.

Macdougall IC et al. *N Engl J Med*. 2019;380(5):447-458.

The Safety Profile of Higher Doses of Iron was Similar to that of Low-Dose Iron

Endpoint	Proactive, High-Dose IV Iron Sucrose (N=1093) n (%)	Reactive, Low-Dose IV Iron Sucrose (N=1048) n (%)	Hazard or Rate Ratio (95% CI)	*P* Value
Vascular access thrombosis	262 (24.0)	218 (20.8)	1.15 (0.96–1.38)	0.12
All-cause hospitalization	651 (59.6)	616 (58.8)	1.01 (0.90–1.12)	0.90
Hospitalization for infection	323 (29.6)	307 (29.3)	0.99 (0.82–1.16)	0.92
Infection episodes	63.3 per 100 PY	69.4 per 100 PY	0.91 (0.79–1.05)	N/A



- N/A=not available.

Macdougall IC et al. *N Engl J Med*. 2019;380(5):447-458.

Questions Raised by PIVOTAL

- The ferritin ceiling in the low-iron group of 200ng/mL is lower than standard of care
  - KDIGO ferritin ceiling for IV iron is 500ng/mL
  - Many practitioners use ferritin ceilings higher than 500ng/mL
  - This may have led to iron deficiency in the control group which could have effects on cardiac performance and increased the number of cardiac events
  - IV iron supplementation in iron-deficient patients with HF (even without anemia) without ESRD leads to improved MACE outcomes
- Should the new ferritin ceiling for IV iron in HD patients be 700ng/mL?
  - This is lower than in many current practices
  - This is lower than the mean ferritin level among HD patients in the US

Dialysate Ferric Pyrophosphate Citrate (FPC)

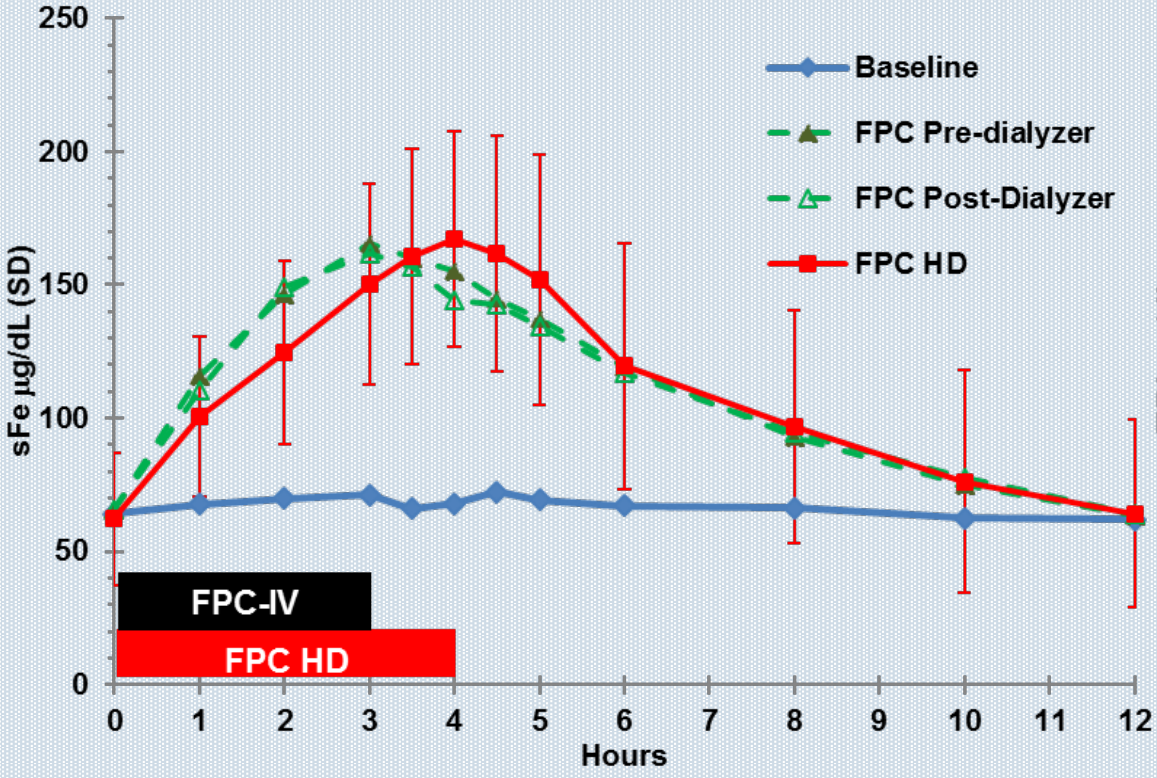
- A dialysate-based iron supplement designed to administer around 7mg iron per treatment, approximately equal to the iron lost with each hemodialysis
- Designed to maintain iron balance, reduce the need for IV iron supplementation, and avoid iron-restricted erythropoiesis
- Approved by the FDA in 2016 after phase 3 studies confirmed decreased IV iron and ESA requirements and AEs = placebo
- Added to bicarb mix in central delivery system or bicarbonate jug at dialysis station
- Adoption by dialysis facilities has been modest due to concerns regarding growth of siderophilic microorganisms in dialysate lines and red staining; cannot be used in machines with solid bicarbonate

IV Ferric Pyrophosphate Citrate (AVNU)

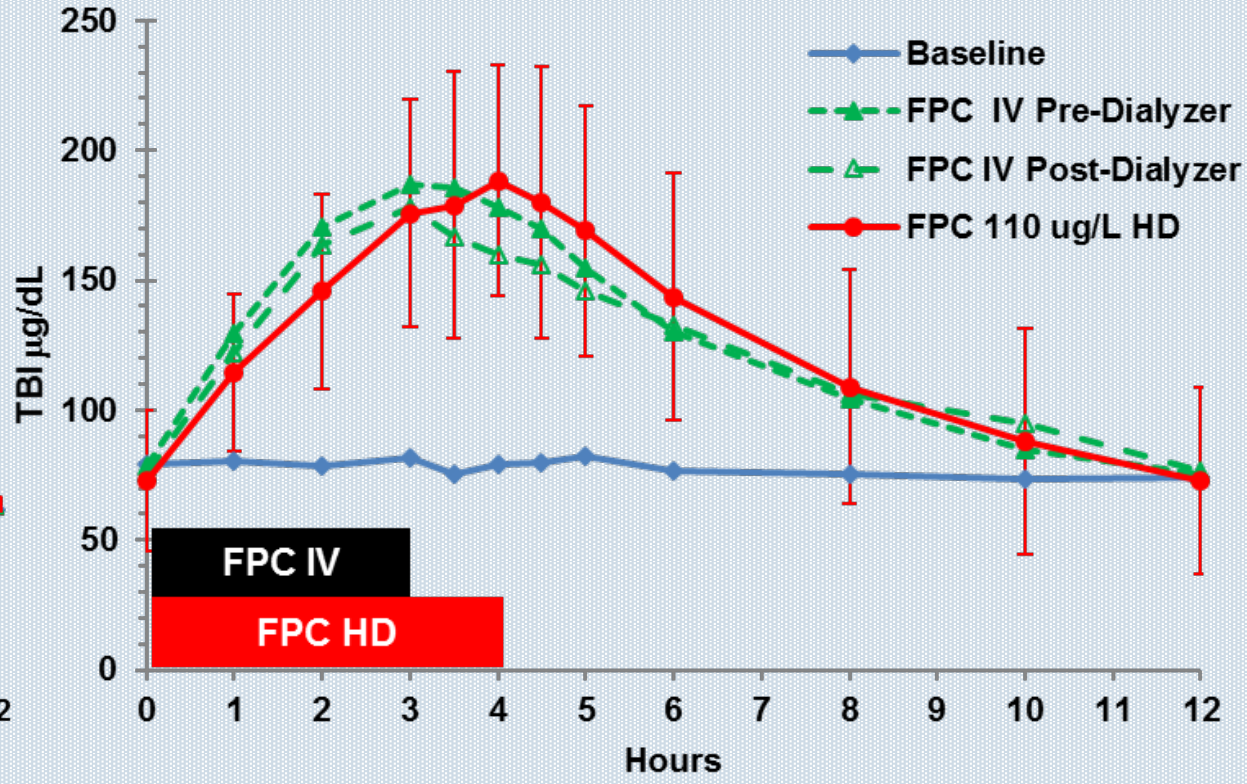
- Infused IV over the course of the dialysis treatment (can be pre- or post-membrane
- Provides 6.75mg iron per prefilled syringe
- Can use infusion pump or heparin pump on the machine
- If patient is receiving heparin infusion can be safely mixed with the heparin

Bioequivalence Studies of Dialysate FPC vs. IV FPC

Plasma Iron



Transferrin Bound Iron



Ferric Pyrophosphate Citrate Injection: No Clinical Drug Interaction with Unfractionated Heparin in Hemodialysis Patients

Raymond D Pratt, MD FACP

Rockwell Medical Inc. Wixom MI USA

Introduction

Ferric pyrophosphate citrate (FPC) is a unique iron (Fe) replacement product indicated to maintain Fe balance and hemoglobin (Hgb) concentration in adult hemodialysis patients. FPC can be administered via the dialysate (HD) or as a newly approved intravenous (IV) preparation (Triferic AVNU; 6.75 mg Fe/4.5 mL for IV administration). A clinical study of the effects of unfractionated heparin (UFH) mixed with FPC was conducted.

Methods

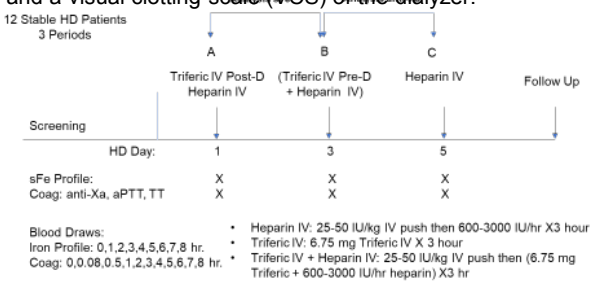
A preliminary In-vitro study of FPC and UFH was conducted to assess any FPC impact on the pharmacodynamic activity over 24 hours.

A prospective, open-label, randomized 3-period, crossover trial, investigated the effects of IV delivery over 3 hours of dialysis of FPC mixed with (UFH) compared with delivery of UFH and FPC by separate routes in 12 subjects.

The primary endpoint was the Anti-Xa activity of UFH + FPC compared to UFH alone and UFH and FPC administered IV separately at pre-and post-dialyzer sites. Secondary endpoints were the activated prothrombin time (aPTT), thrombin time (TT) and serum iron profile (sFe).

Bioequivalence parameters of area under the concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}).

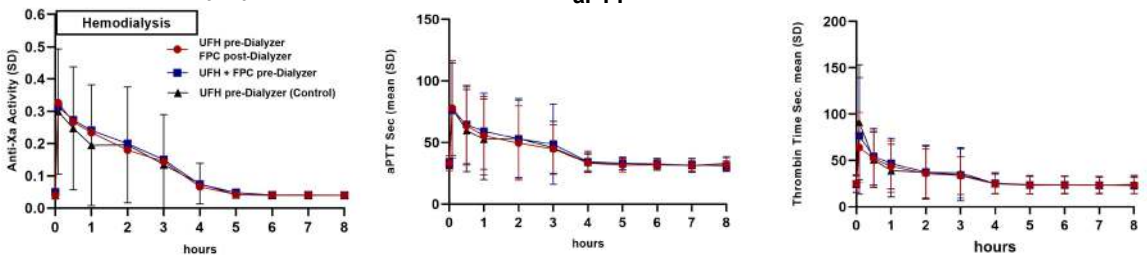
Safety was assessed by recording adverse events (AE) and a visual clotting scale (VCS) of the dialyzer.



Results

- In-vitro studies demonstrate that FPC mixtures with UFH have no change in pharmacodynamic activity of heparin for 24 hours at ambient room temperature and lighting. UFH has no effect on FPC stability for 24 hours under the same conditions.
- The Anti-Xa activity, aPTT and TT activity vs time results of the clinical study are presented in the graphs below. All HD treatments lasted for 4 hours. FPC and UFH were administered for the first 3 hours of HD.

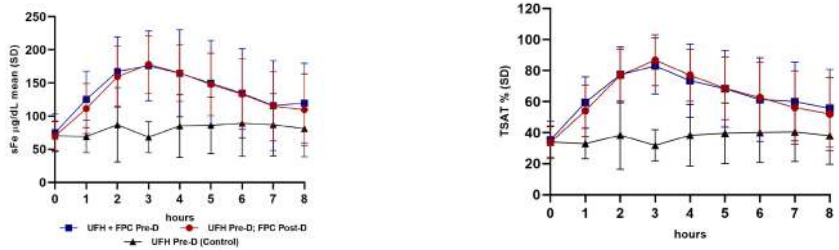
Anti-Xa **aPTT** **TT**



Ratios of Anti-Xa activity demonstrate the lack of effect of FPC mixed with UFH.

Parameter	Treatment	N	Geometric LSM	Treatment Comparison	Ratio of Geometric LSM	90% CI for Ratio
AUC_{0-4}	A (reference)	12	0.581	B/C	1.11	(0.972, 1.28)
	B (test)	12	0.600	B/A	1.03	(0.900, 1.18)
	C (reference)	12	0.538			
AUC_{0-t}	A (reference)	12	0.775	B/C	1.09	(0.977, 1.21)
	B (test)	12	0.798	B/A	1.03	(0.924, 1.15)
	C (reference)	12	0.733			
C_{max}	A (reference)	12	0.256	B/C	0.89	(0.758, 1.04)
	B (test)	12	0.279	B/A	0.918	(0.782, 1.08)
	C (reference)	12	0.288			

Serum iron profiles show no Drug-Drug Interaction when FPC is delivered as a mixture with UFH.



Summary

- The FPC +UFH mixture had no impact on the AUC_{0-t} values for Anti-Xa, aPTT or TT. The concentration-time profiles for sFe and TSAT were comparable across all treatments. No differences in transferrin, ferritin, or TIBC concentrations were observed.
- There was no effect of co-administration of a mixture of UFH and FPC on the serum iron profile or TSAT values compared to separate administration.
- FPC was well tolerated with no reported adverse events.
- No detectable clotting of the dialyzer was observed. None of the subjects required additional UFH for anticoagulation during any treatment.

Conclusions

- FPC for IV administration was well tolerated.
- No detectable drug-drug interaction between UFH and FPC *in-vitro* or *in-vivo* in HD patients
- Iron delivery by FPC administered IV shows no interaction with UFH
- FPC is stable for up to 24 hours alone or admixed with heparin when stored in a syringe at ambient room temperature and light conditions.

Acknowledgements

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Thomas Marbury, MD, the Staff and Patients from Orlando Clinical Research Center, Orlando FL.
Mark Bush and Scott Brantly, Nuventra Inc. Durham NC.
PK analysis and datasets

Contact

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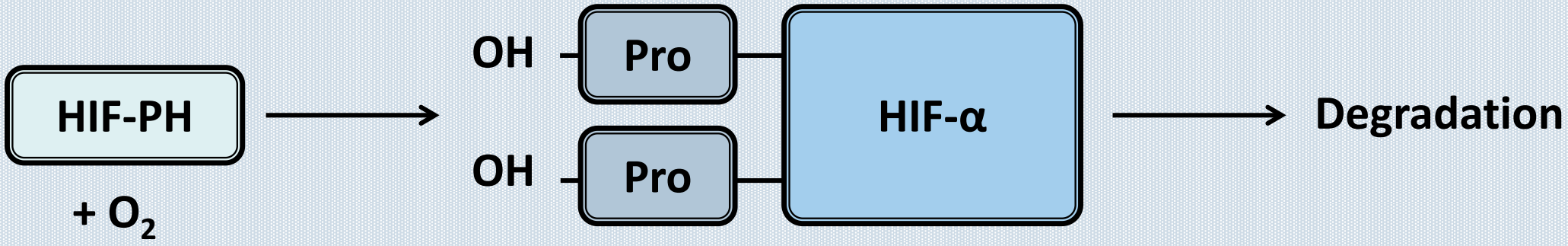
The HIF Pathway

- Hypoxia-inducible factors (HIF)
  - Family of oxygen-sensitive proteins that regulate the cell's transcriptional response to hypoxia
- Central regulator of erythropoiesis in response to hypoxia
  - EPO production
  - **Indirect suppression of hepcidin** by promotion of erythropoiesis
  - Augmentation of enteric iron absorption and transport
  - Mobilization of endogenous iron stores to erythroid marrow

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

HIF Intracellular Distribution: Normoxia

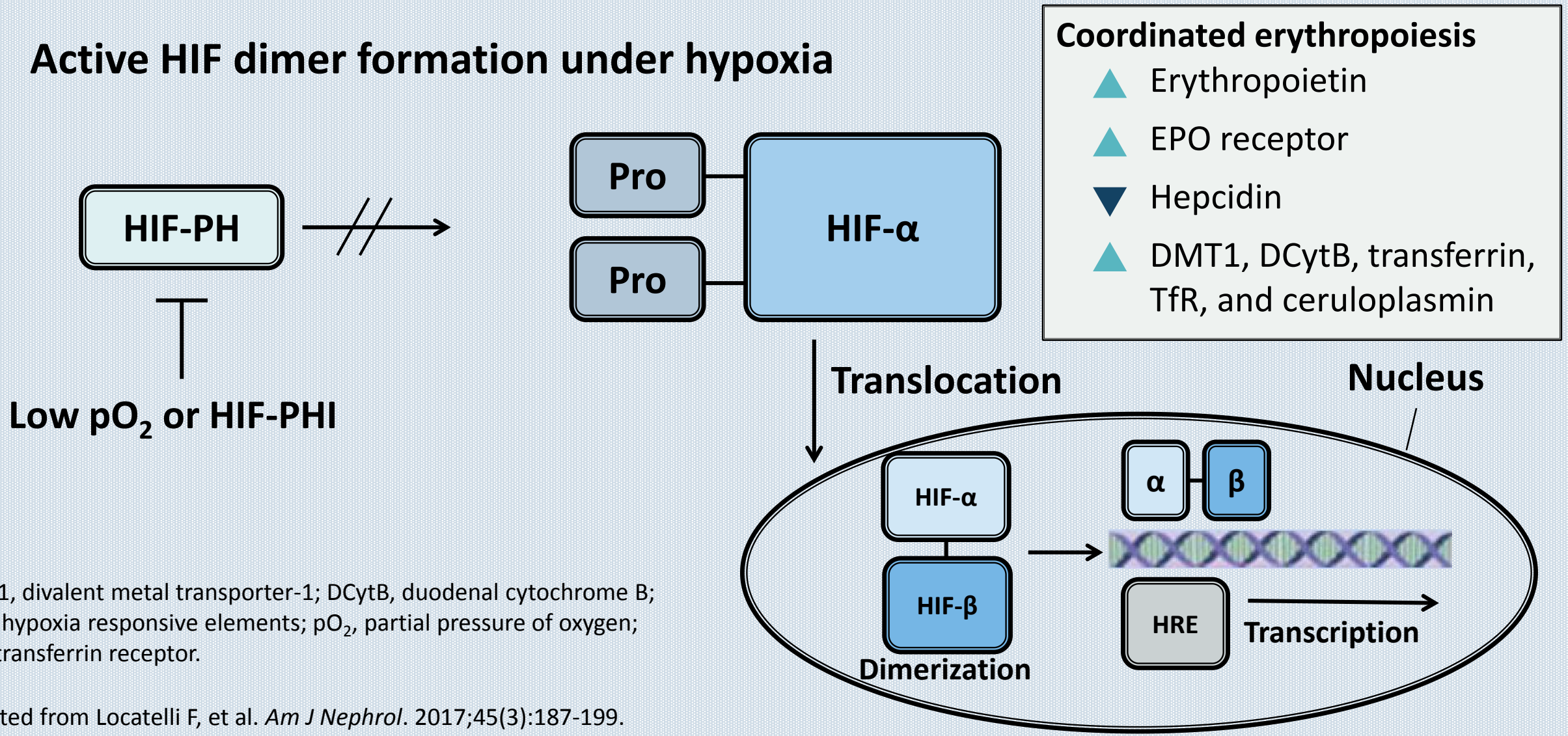
HIF-α degradation under normoxia



Pro, proline.

Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

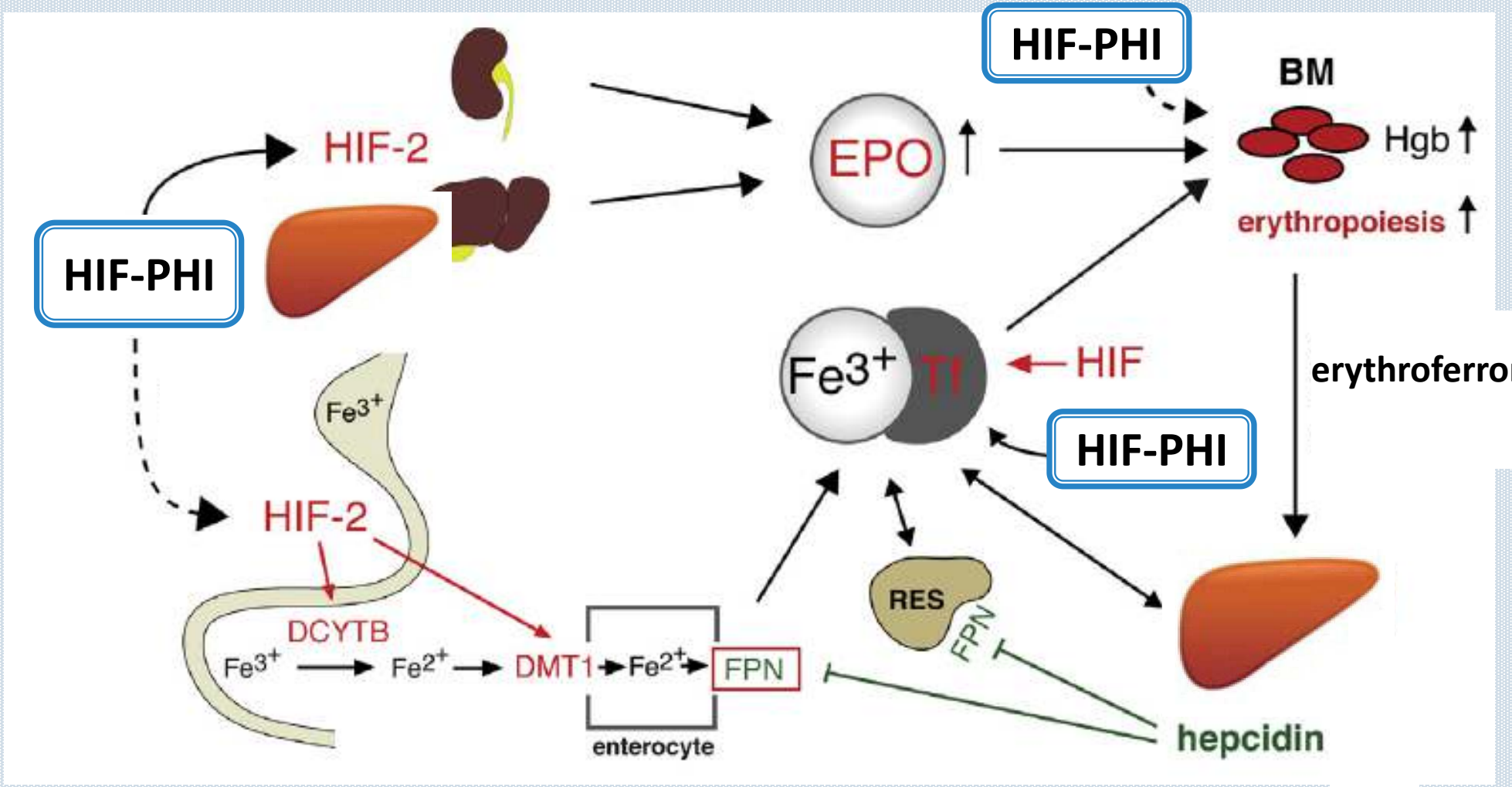
HIF Intracellular Distribution: Hypoxia



DMT1, divalent metal transporter-1; DCytB, duodenal cytochrome B; HRE, hypoxia responsive elements; pO_2, partial pressure of oxygen; TfR, transferrin receptor.

Adapted from Locatelli F, et al. *Am J Nephrol*. 2017;45(3):187-199.

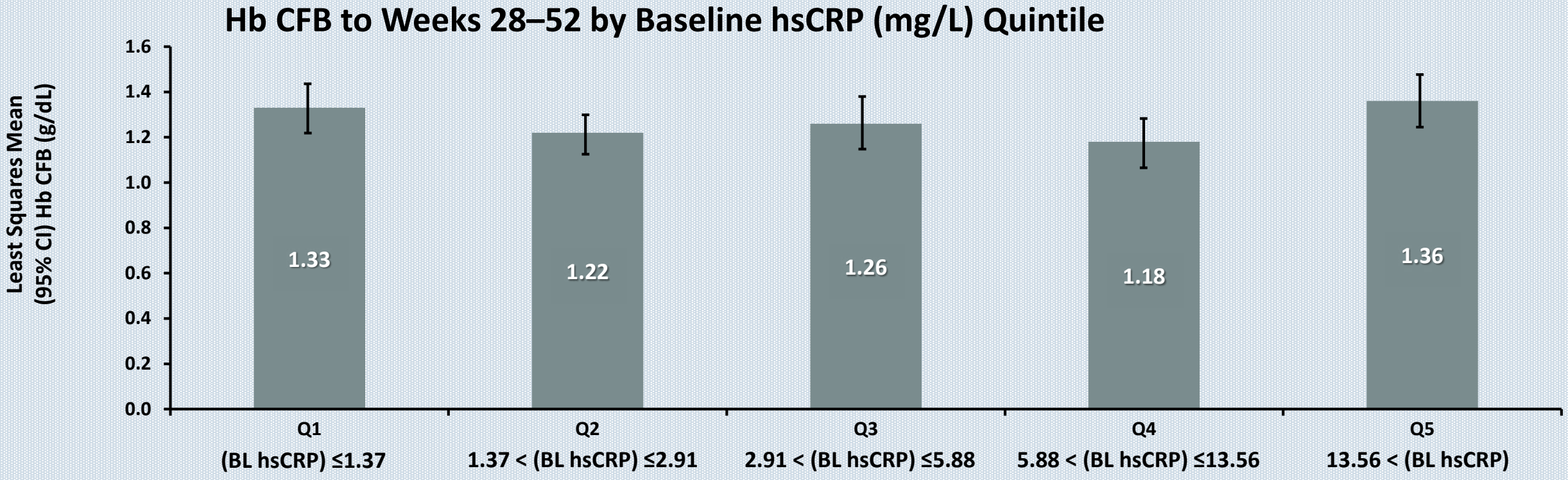
HIF-PHIs: Overview of Potential/Known Mechanisms



BM, bone marrow; FPN, ferroportin; GDF15, growth differentiation factor 15; RES, reticuloendothelial system; TF, transferrin; TIBC, total iron binding capacity.

Sanghani NS and Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

Roxadustat Efficacy in DD-CKD: Hb Response Independent of Inflammation in Pooled Global Phase III Studies

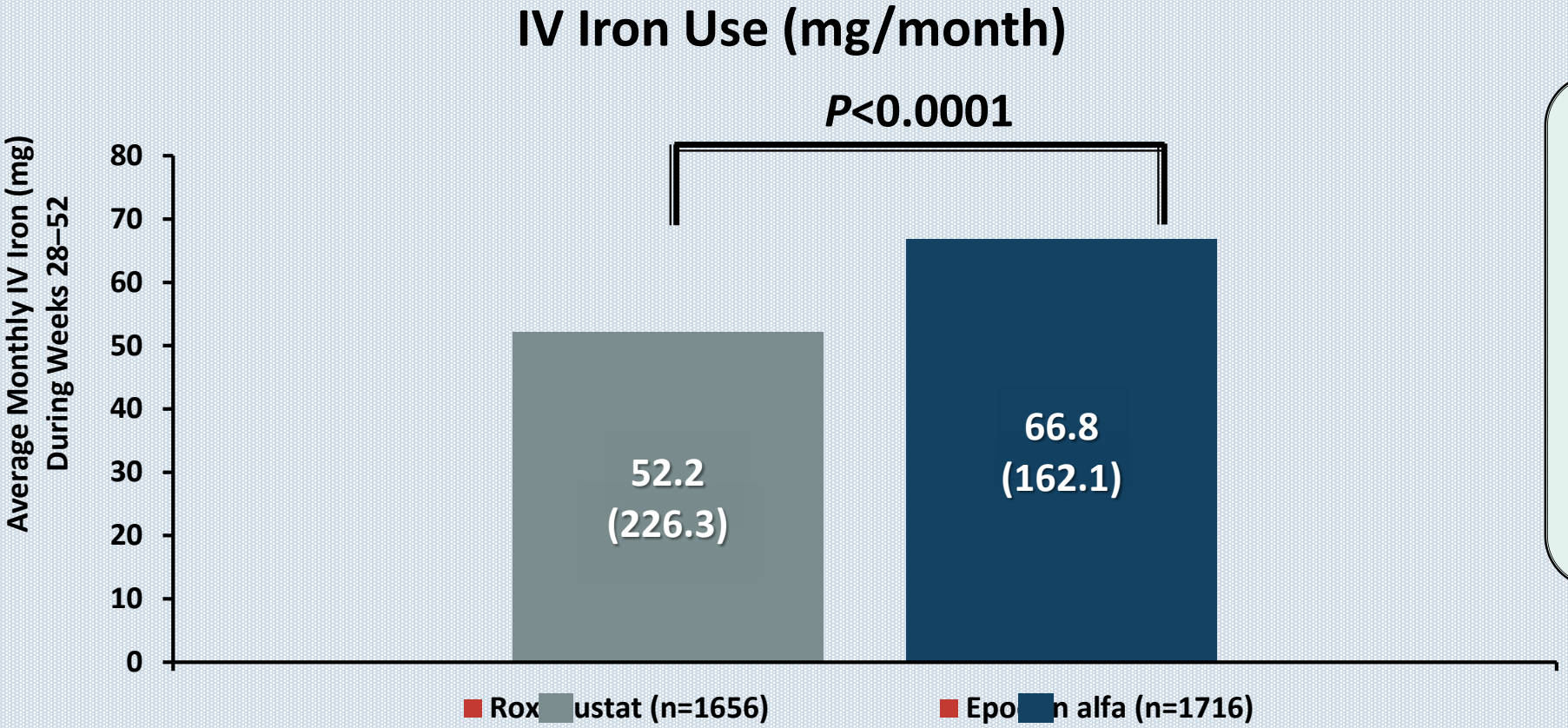


	Q1 (BL hsCRP) ≤1.37	Q2 1.37 < (BL hsCRP) ≤2.91	Q3 2.91 < (BL hsCRP) ≤5.88	Q4 5.88 < (BL hsCRP) ≤13.56	Q5 13.56 < (BL hsCRP)
N	314	326	285	317	296
Mean BL Hb (g/dL)	9.49	9.57	9.54	9.66	9.62
Mean weekly roxadustat dose at Week 24 (mg/kg)	3.9	3.4	3.5	3.3	3.6

Hb, hemoglobin, CFB, change from baseline; hsCRP, high sensitivity C-Reactive protein; BL, baseline.

El-Shahawy et al. ASN 2020 Kidney Week PO0265

Roxadustat Efficacy in DD-CKD: Iron Use in Pooled Results from Global Phase III Trials



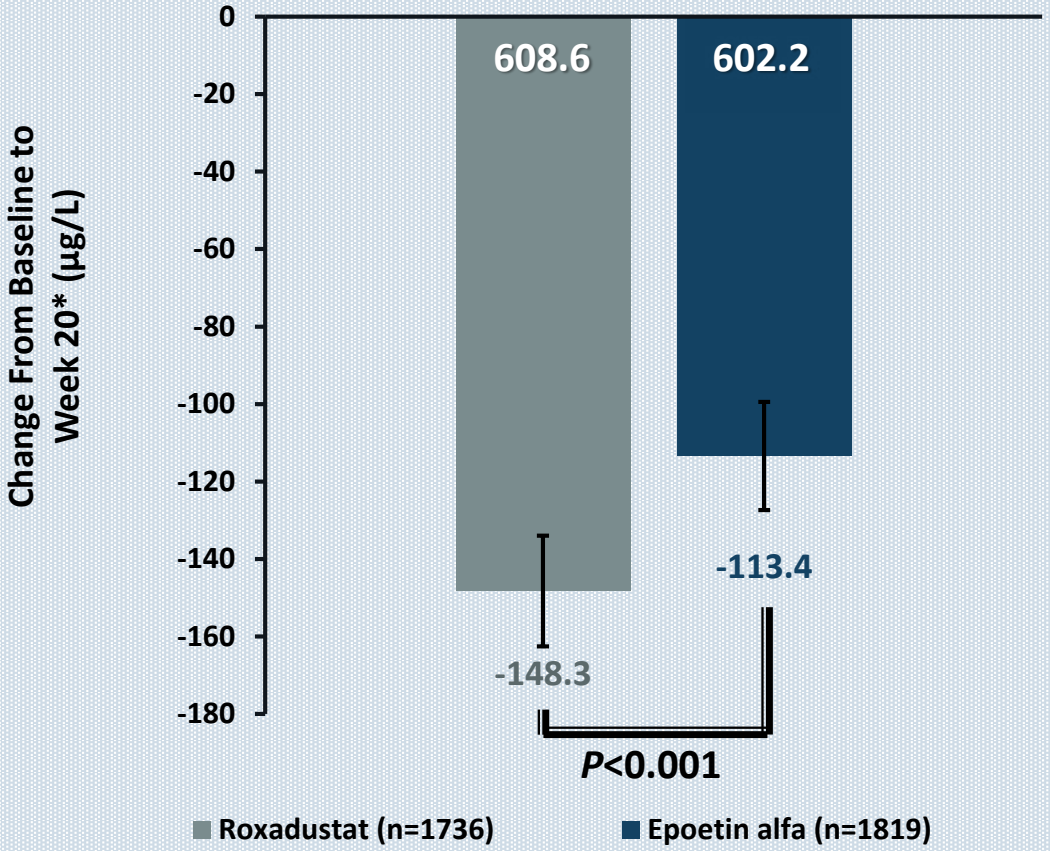
Roxadustat-treated patients ***used less IV iron*** *than epoetin alfa treated patients in pooled global phase III studies of* ***DD-CKD patients***

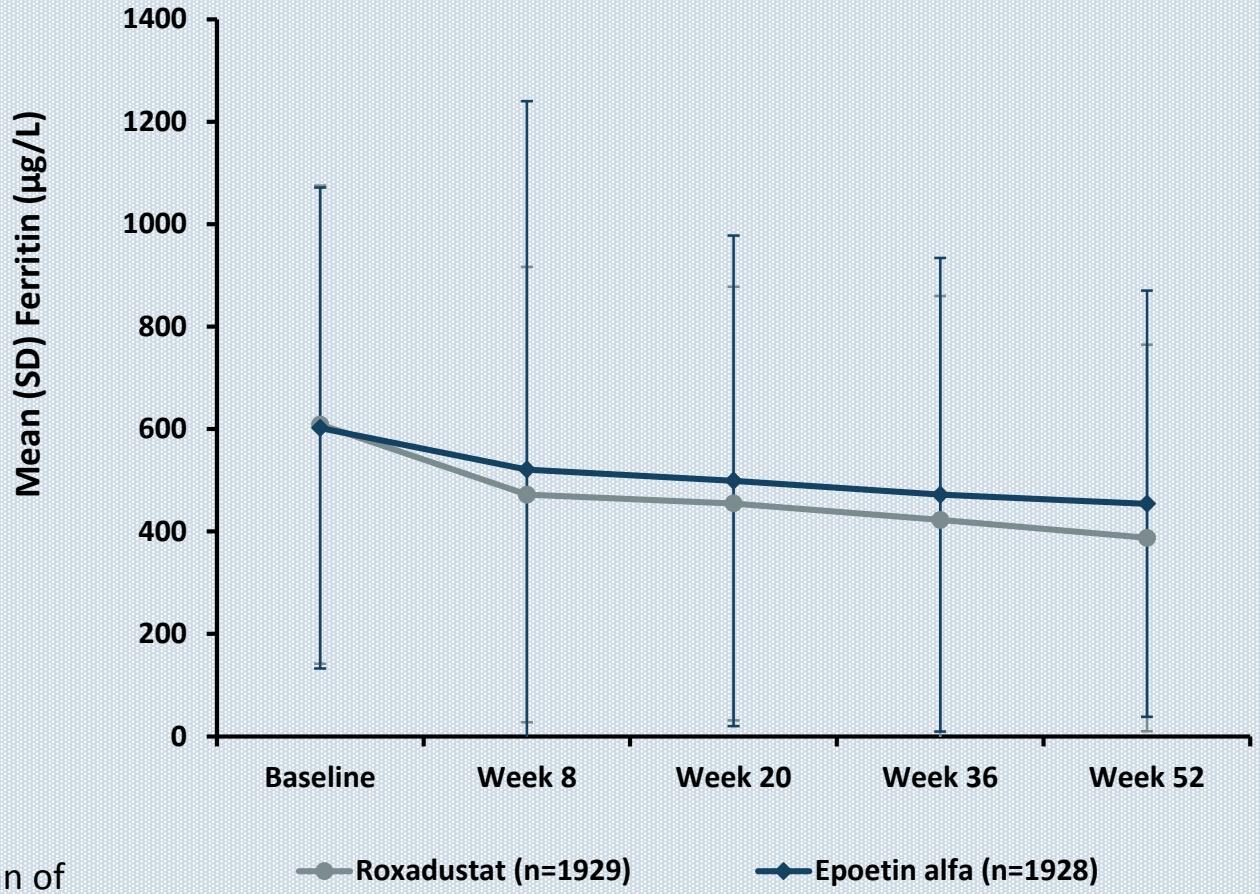
Full analysis set. Data are mean (SD); *P*-value is from Wilcoxon Rank-Sum Test.
SD, standard deviation; IV, intravenous.

Pergola et al. ASN 2020 Kidney Week TH-OR06

Roxadustat Efficacy in DD-CKD: Ferritin Reduction in Pooled Results from Global Phase III Trials

Roxadustat reduced ferritin to a greater extent than epoetin alfa in DD-CKD.

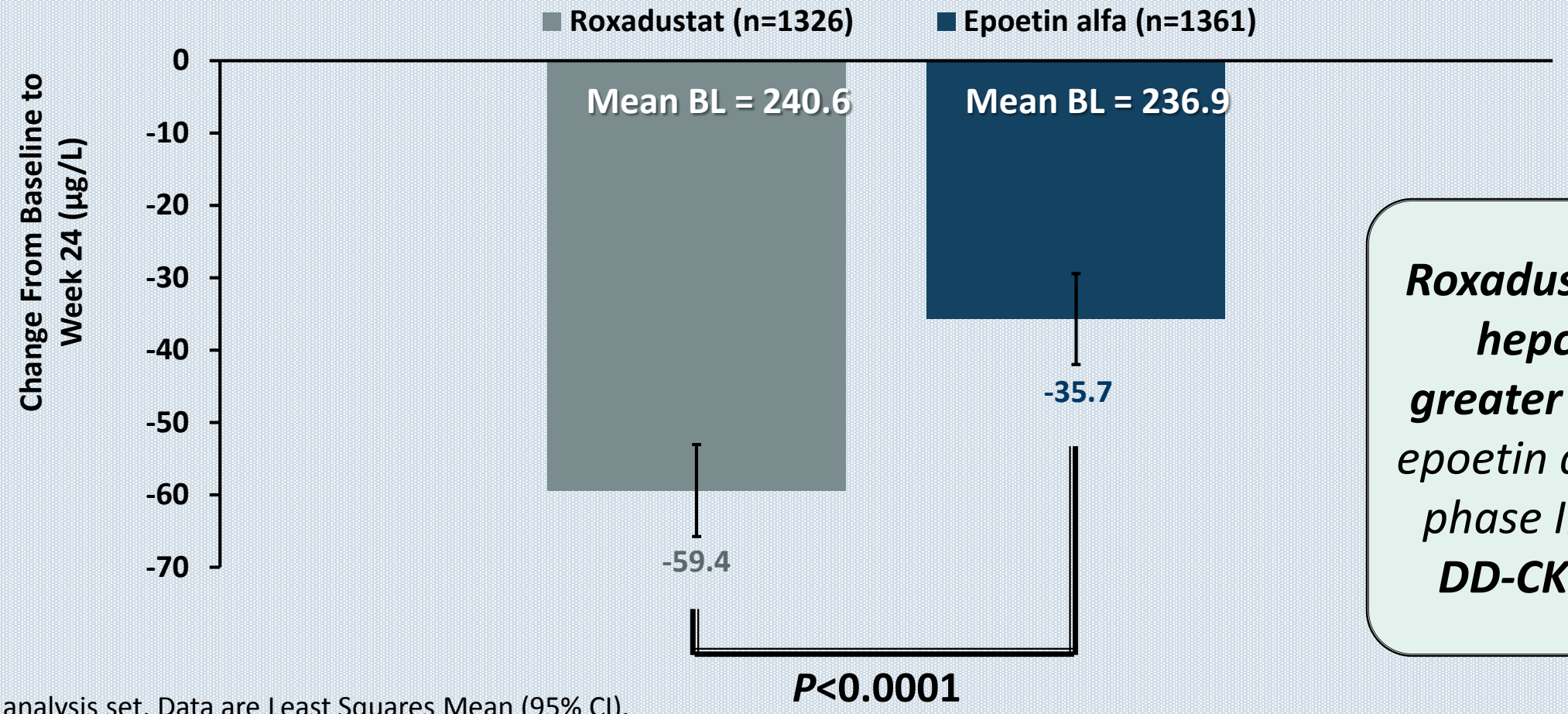




Full analysis set. *Data are Least Squares Mean (95% CI). Week 20 = the mean of Weeks 12–28. BL, baseline; CI, confidence interval.

Pergola et al. ASN 2020 Kidney Week TH-OR06

Roxadustat Efficacy in DD-CKD: Hepcidin Reduction in Pooled Results from Global Phase III Trials



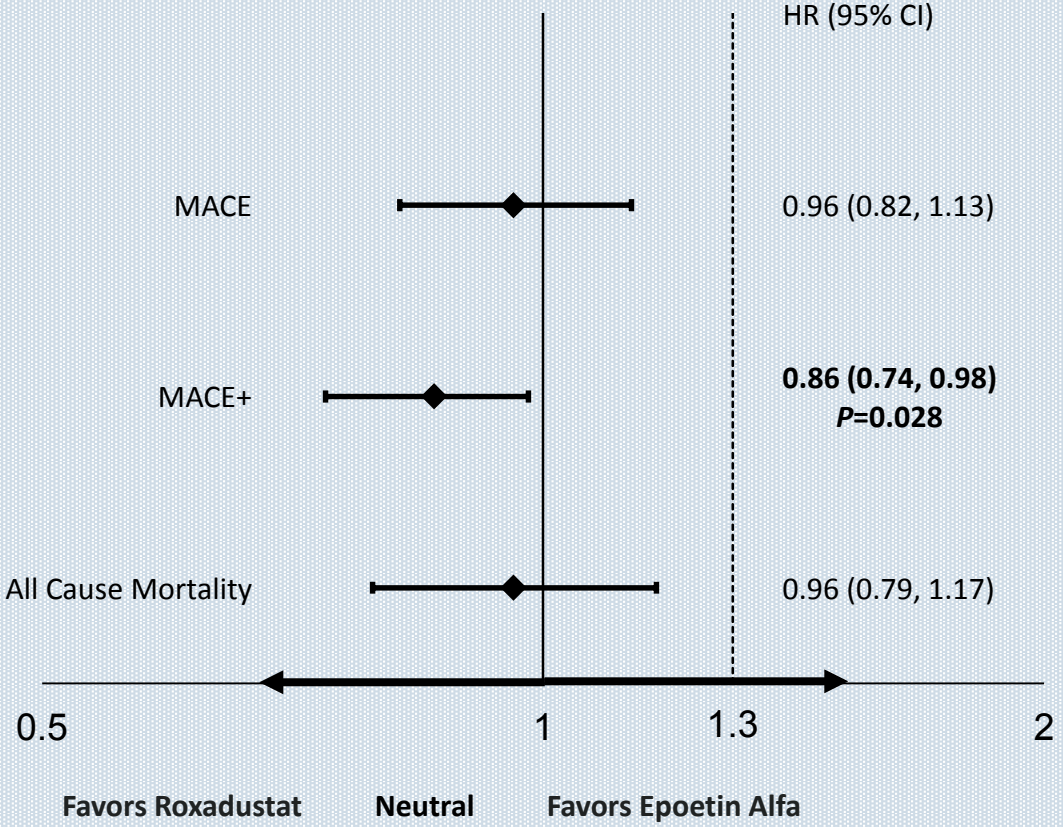
Roxadustat reduced hepcidin to a greater extent *than epoetin alfa in global phase III studies of* ***DD-CKD patients***

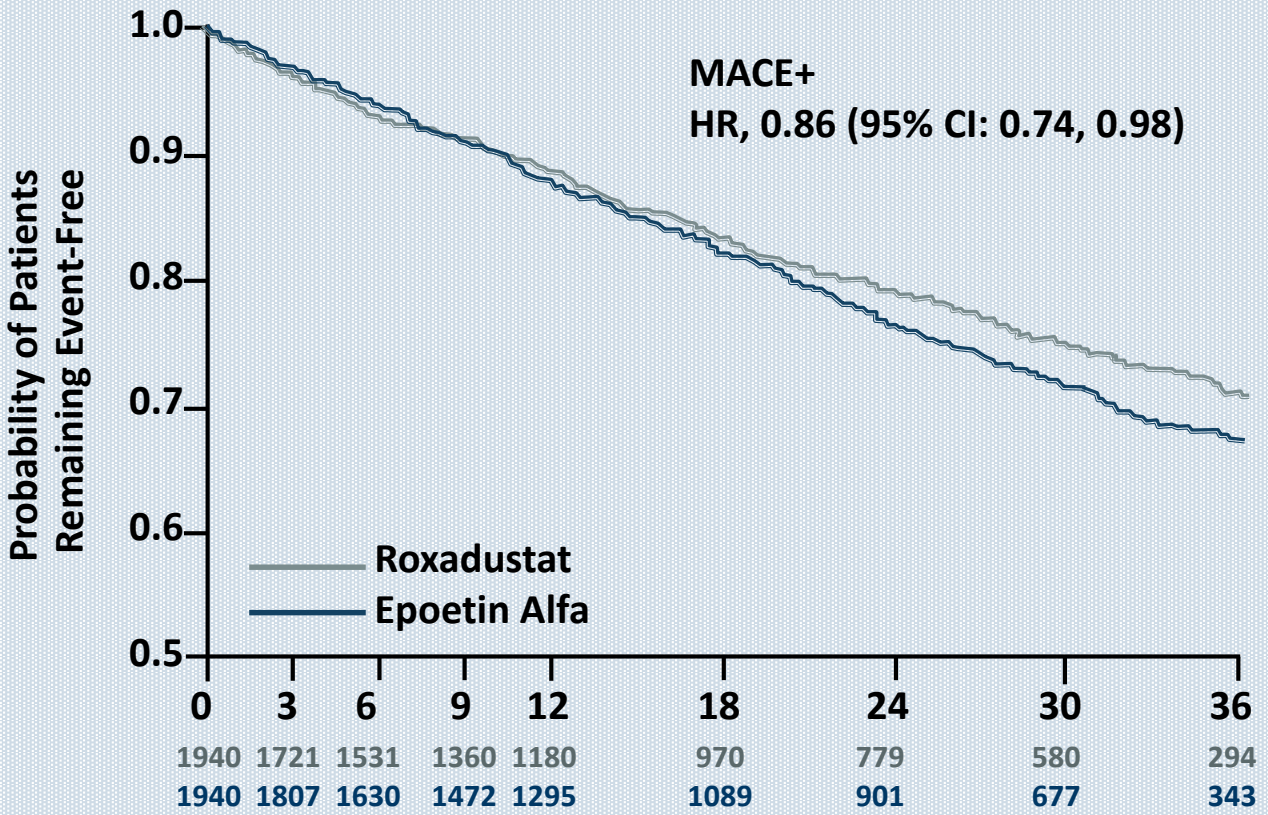
Full analysis set. Data are Least Squares Mean (95% CI).
BL, baseline; CI, confidence interval

Pergola et al. ASN 2020 Kidney Week TH-OR06

Roxadustat Safety in DD-CKD: Pooled Results from Global Phase III Trials

Time to event endpoints using Cox model, DD (ROCKIES, HIMALAYAS, SIERRAS), N=3880





Provenzano R, Fishbane S. ASN 2019 Kidney Week FR-OR131

Ziltivekimab for Treatment of Anemia of Inflammation in Patients on Hemodialysis

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

12 Sep 2016 – 11 Dec 2018

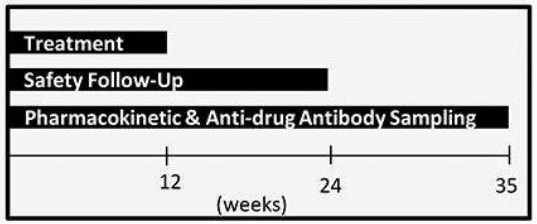
61 patients

- Hemodialysis
- TMPRSS6+
- Inflamed (IL-6 > 4 pg/mL)
- HgB ≥ 8.5 and ≤ 11.0 g/dL
- ESA hyporesponsive

double-blind
biweekly dosing

Intravenous

Ziltivekimab
(2 mg, 6 mg, 20 mg)
vs.
Placebo



OUTCOME

Markers of Inflammation

	PBO	2 mg	6 mg	20 mg
hsCRP (mg/L)	-0.6	-3.9	-10.6	-10.5
SAA (mg/L)	0.0	-6.1	-7.2	-17.0
Fibrinogen (mg/dL)	4.6	-87.3	-161	-216

Markers of Iron Metabolism

	PBO	2 mg	6 mg	20 mg
Hemoglobin (g/dL)	-0.1	0.8	1.0	0.8
ERI (U/kg per g/dL hemoglobin)	0.4	-5.6	-5.8	-10.5
Hepcidin (ng/mL)	-19.5	-42.7	-66.5	-88.8

Safety:
No patient experienced a dose-limiting toxicity. Twenty patients experienced an SAE during the trial, 3 (25%) in placebo, 4 (25%) in 2 mg, 7 (43.8%) in 6 mg, and 6 (35.3%) in 20 mg. Four patients died during the study. Two (12.5%) on 6 mg and 2 (11.8%) on 20 mg. Two of the deaths were due to sepsis. Neither patient experienced neutropenia during the trial. The other two deaths were cardiovascular.

Conclusion

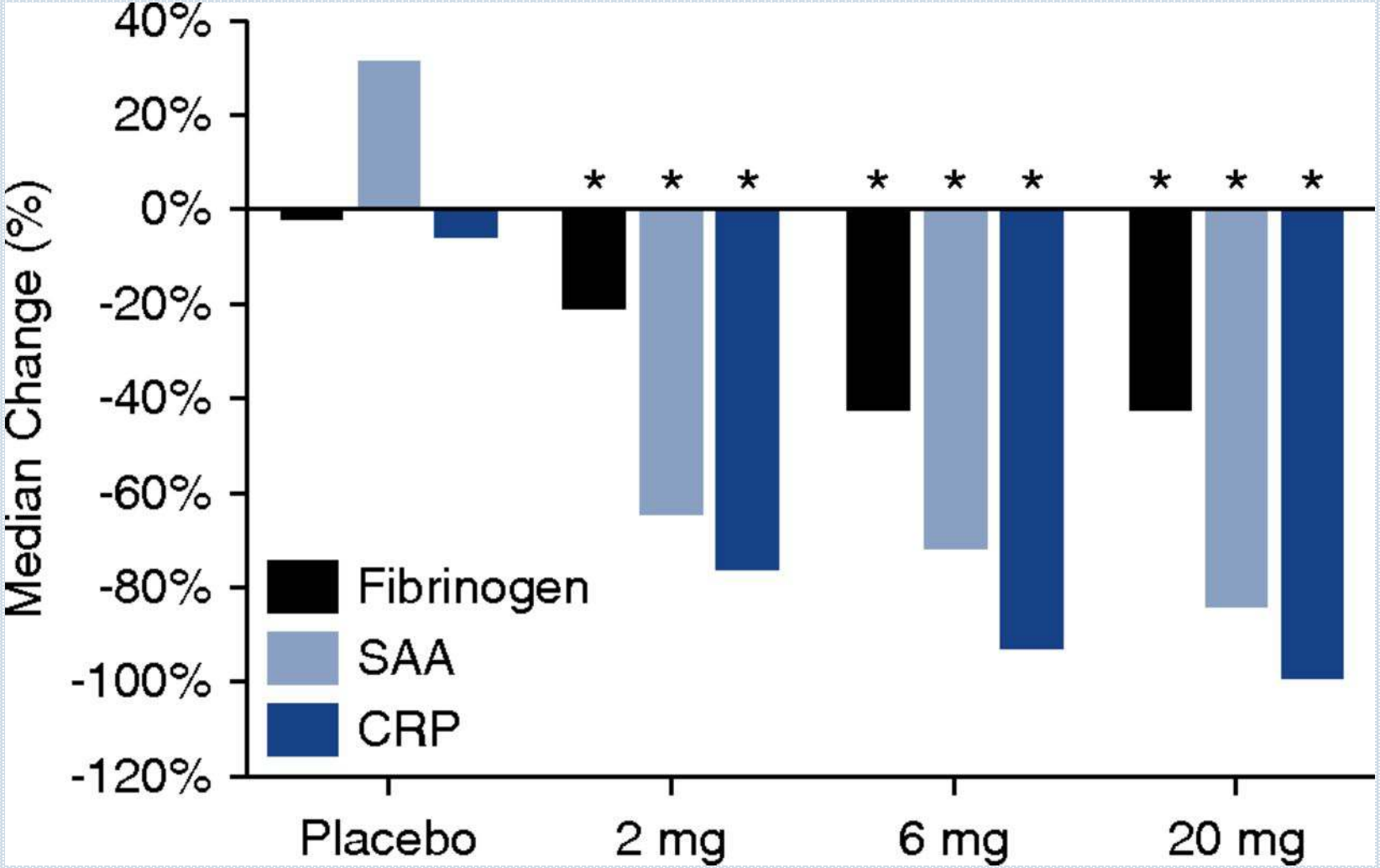
Ziltivekimab significantly improved markers of inflammation and iron metabolism in patients on hemodialysis with inflammation and hyporesponsive to ESA therapy. No patient experienced a dose-limiting toxicity during the trial.

doi: 10.1681/ASN.2020050595

Pablo E. Pergola et al. JASN 2021;32:211-222

JASN Journal of the American Society of Nephrology

Median percentage changes from baseline to end of treatment in hsCRP, SAA, and fibrinogen concentrations among patients undergoing hemodialysis receiving placebo or 2-, 6-, and 20-mg ziltivekimab (n=53). *P<0.05 versus placebo.

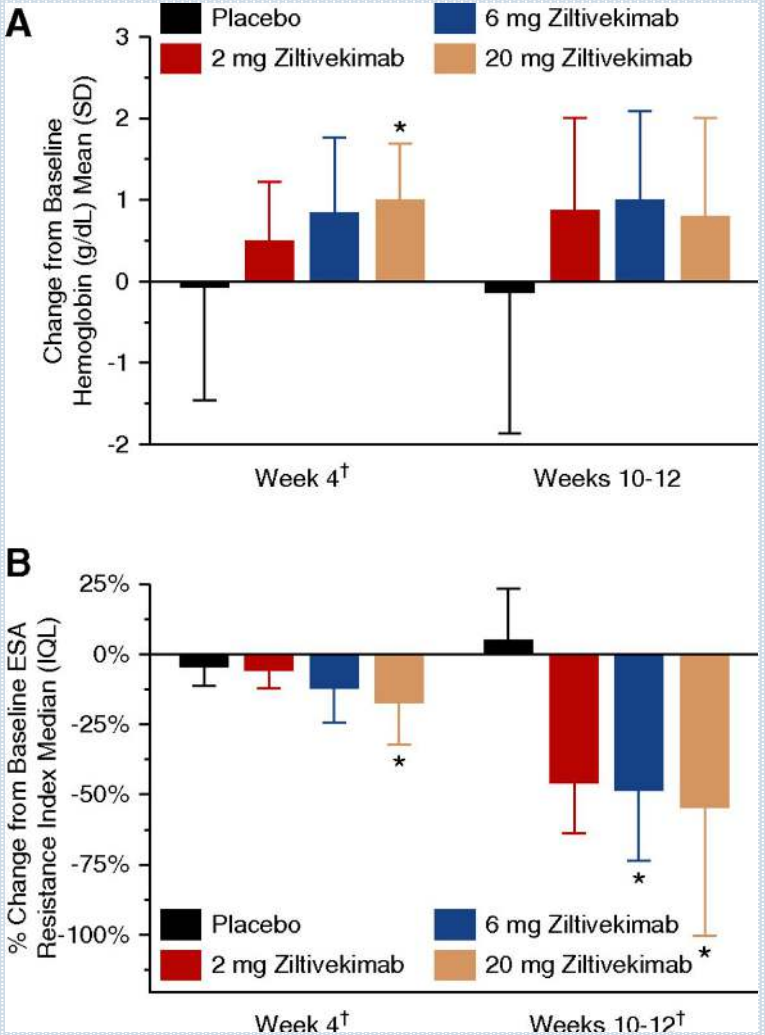


Pablo E. Pergola et al. JASN 2021;32:211-222

SAA – serum amyloid A

JASN Journal of the American Society of Nephrology

Changes in hemoglobin concentrations and percentage changes in the ERI from baseline to week 4 and weeks 10–12 among patients undergoing hemodialysis receiving placebo or 2-, 6-, and 20-mg ziltivekimab (n=53).



Pablo E. Pergola et al. JASN 2021;32:211-222

ERI – erythropoietin resistance index

JASN Journal of the American Society of Nephrology

Summary and Conclusions

- High hepcidin levels secondary to inflammation produce functional iron deficiency in HD patients by inhibiting GI absorption and macrophage release of iron
- The PIVOTAL study demonstrated improved outcomes with a proactive vs. reactive approach to IV iron therapy in HD patients
- HIF-PHIs increase transcription of genes related to iron absorption and transport, indirectly decrease hepcidin levels, thereby overcoming functional iron deficiency; lower IV iron requirements were demonstrated among HD patients receiving HIF-PHI vs. ESA
- Intravenous ferric pyrophosphate citrate, like the dialysate form, provides 7mg iron per treatment and may safely decrease requirements for other forms of IV iron and ESAs
- Monoclonal antibodies to IL-6 and other promotors of hepcidin synthesis offer a novel therapeutic approach to functional iron deficiency

Thank you.
Questions?

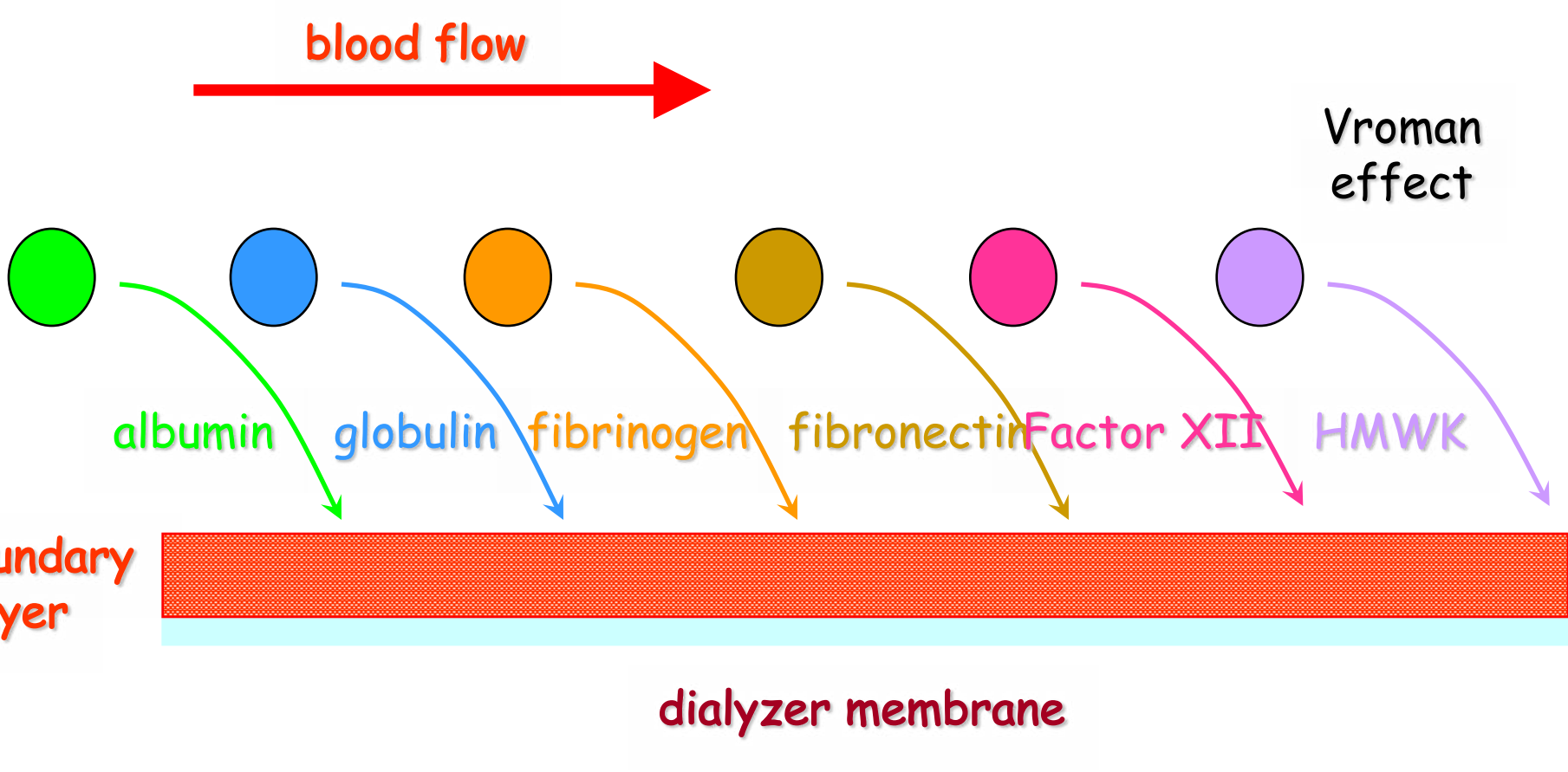
Haemodialysis for the patient at risk of bleeding

Andrew Davenport

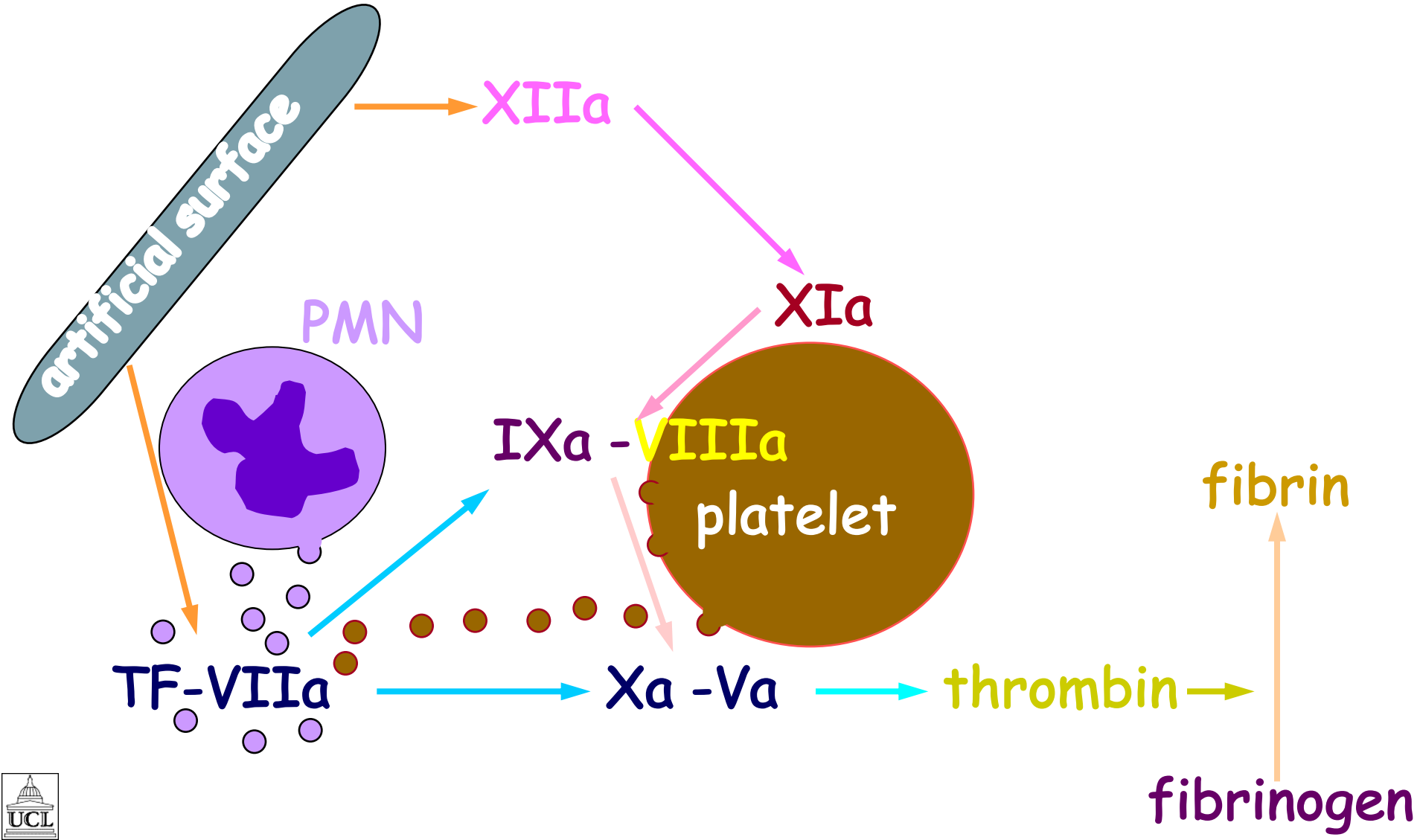
UCL Department of Nephrology

Contact pathway activation

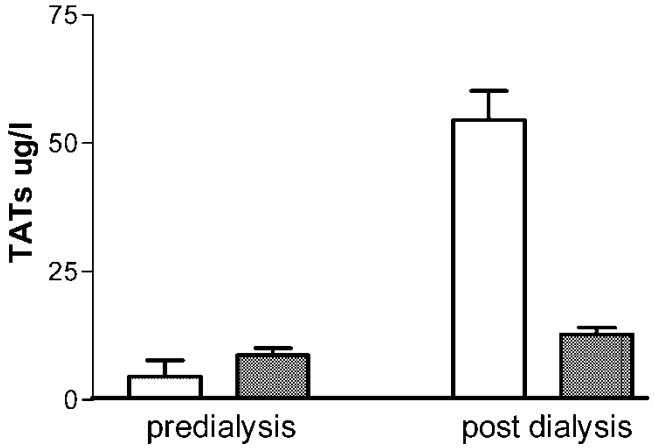
Vroman et al Blood 1980

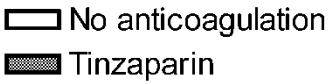


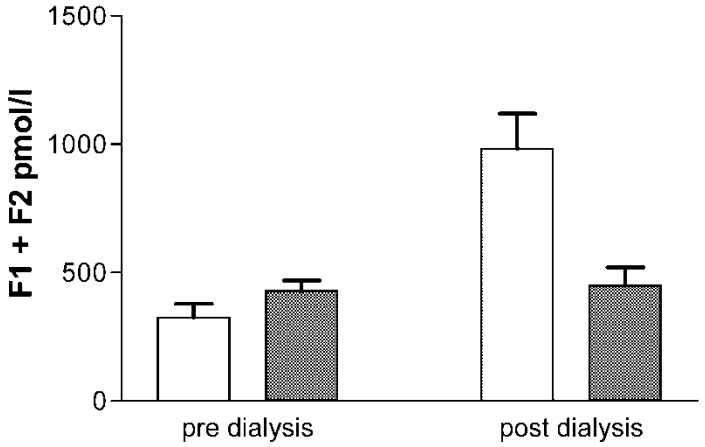
Coagulation during haemodialysis

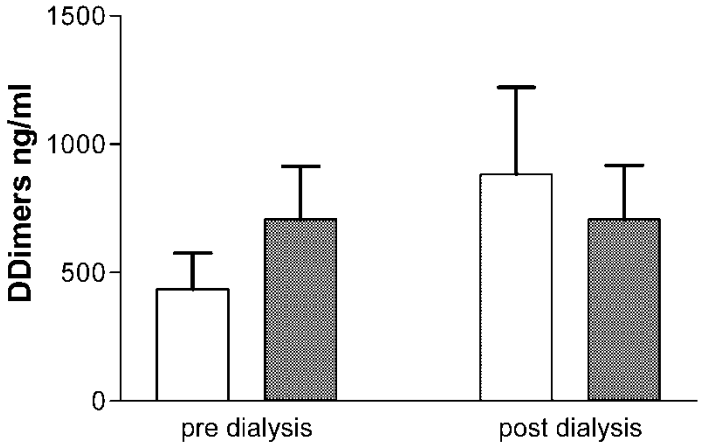


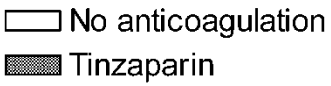
What normally happens with dialysis ?

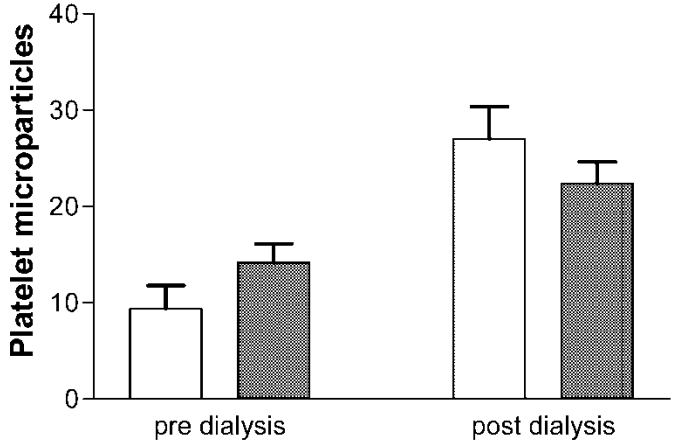






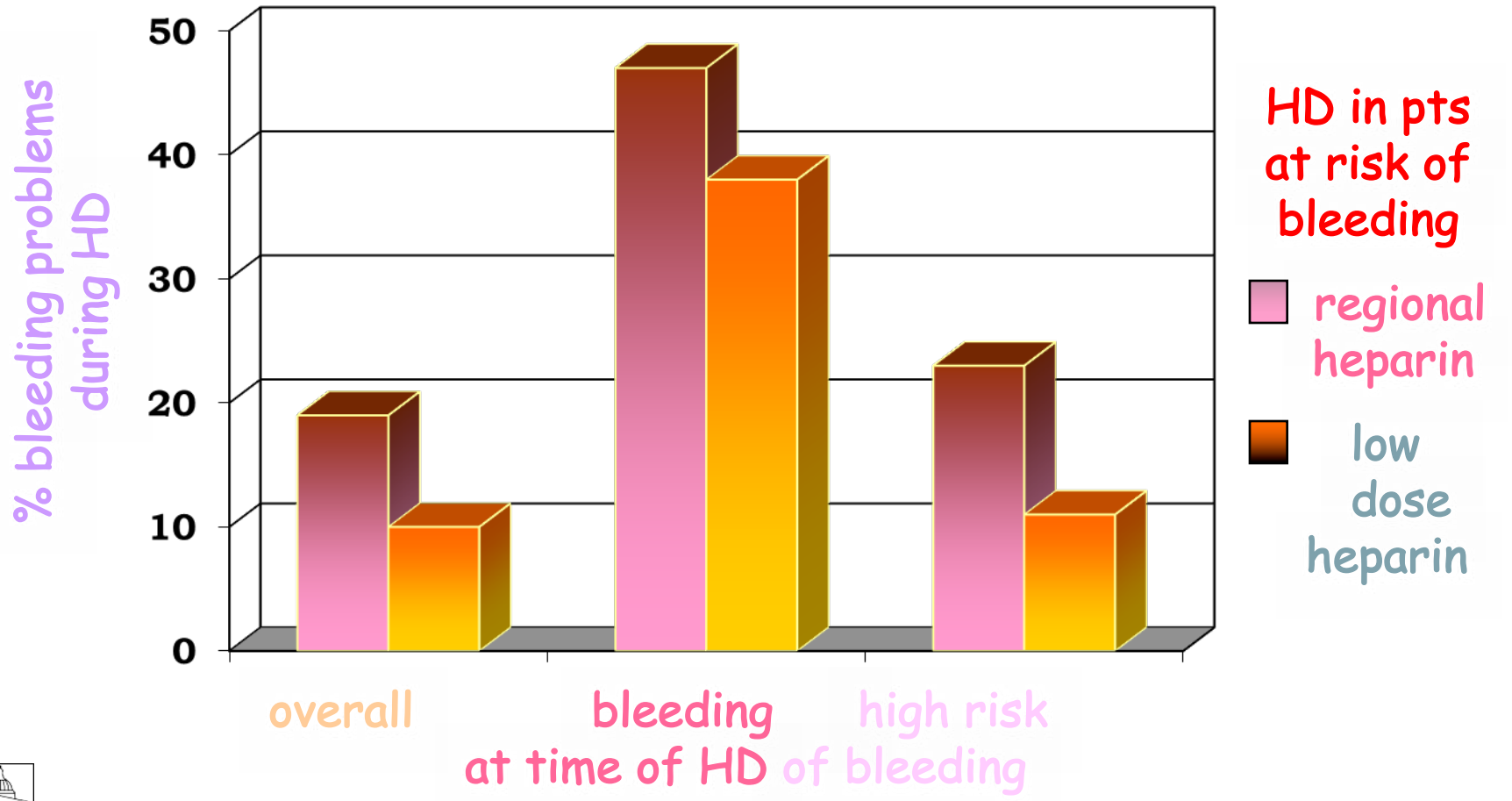






Extracorporeal anticoagulation

Swartz & Port kid Int 1979



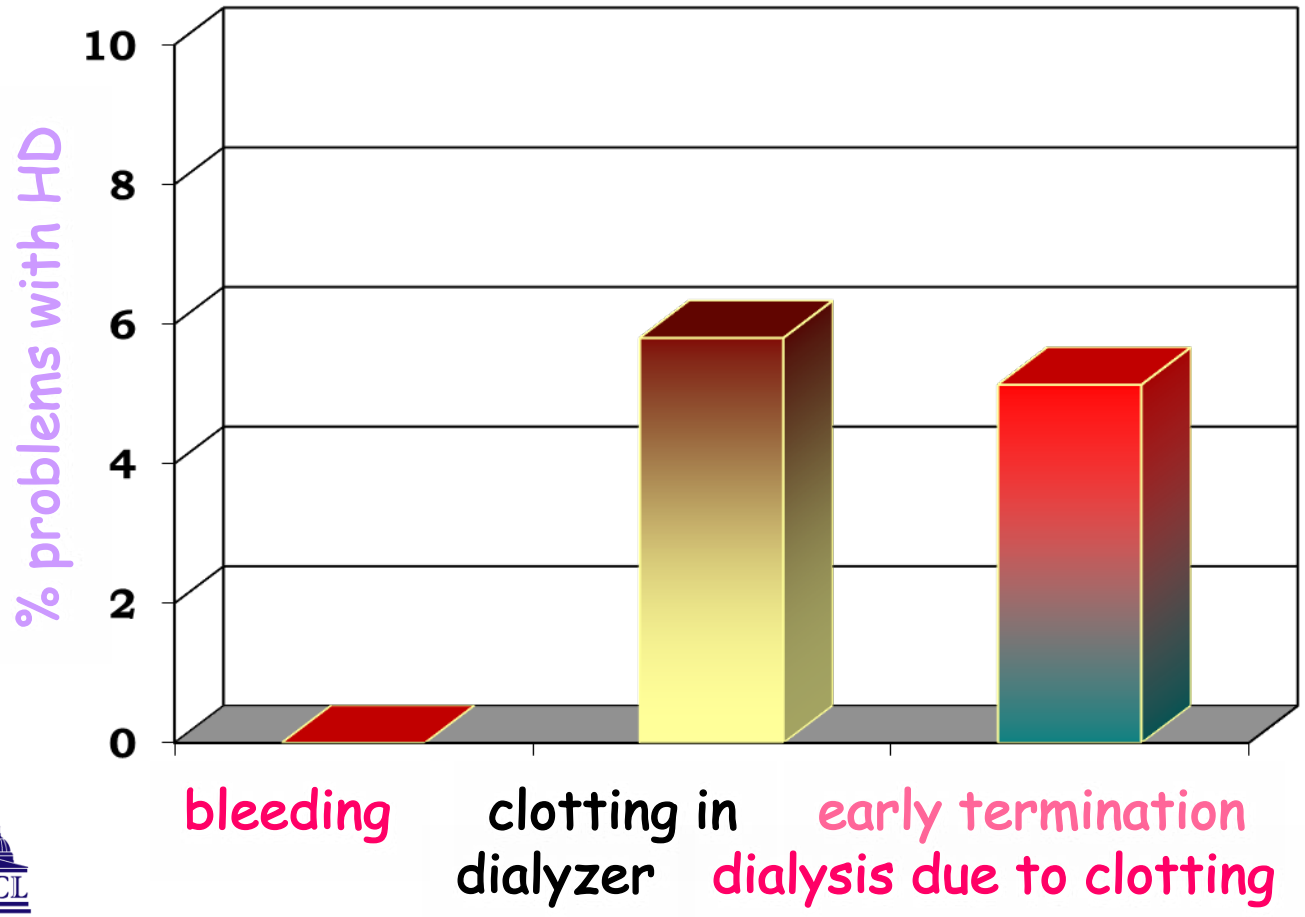
Patient at risk of bleeding

Options

- No anticoagulant
- Heparin priming
- Heparin bonding
- Regional anticoagulation
  - citrate
  - prostanoids
  - nafamostat
- Circuit design
- Dialysis prescription

Anticoagulant free HD

Sanders et al Am J Kid Dis 1985



University Alabama
28 HD pts
at risk
hemorrhage
156 HD Rxs
No aggravation
of bleeding

Heparin priming

Sanders et al Am J Kid Dis 1985

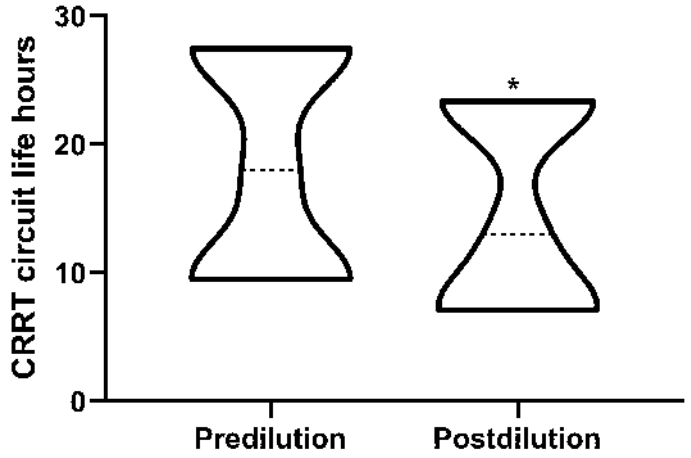
Hemodialysis

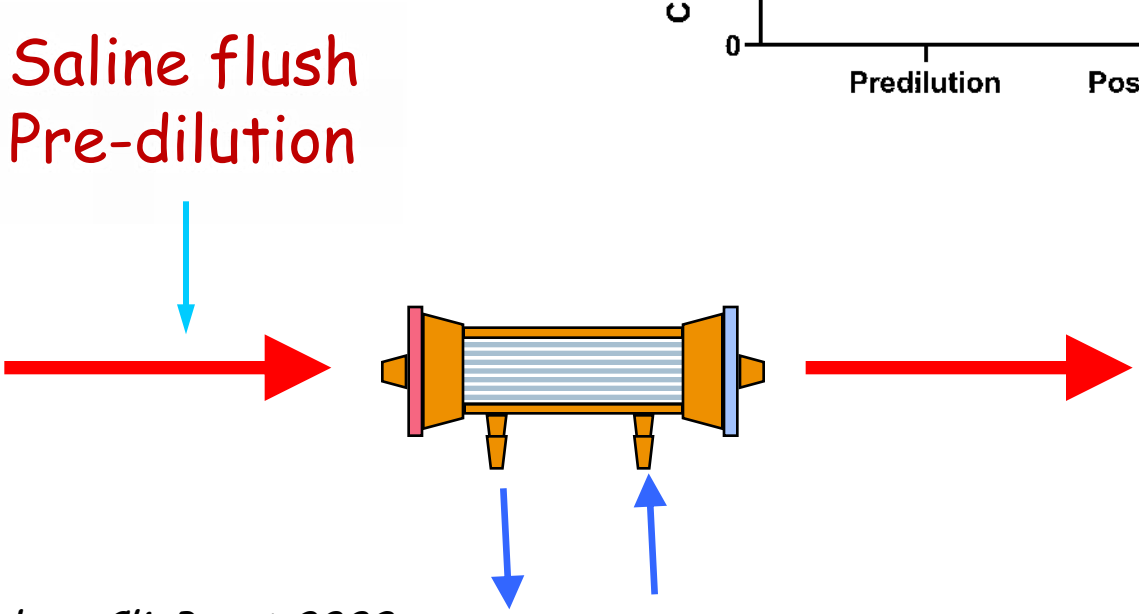
- **Patients at risk of hemorrhage**
  - ***priming***
    - 3000 IU heparin in 1.0 L 0.9%-saline
    - rinsed 0.9%-saline
  - *dialysis*
    - Qb 280 – 300 ml/min
    - 100 ml 0.9%-saline every 20 – 30 min

Patient at risk of bleeding

No anticoagulation

- Saline flushes
- Pre-dilution

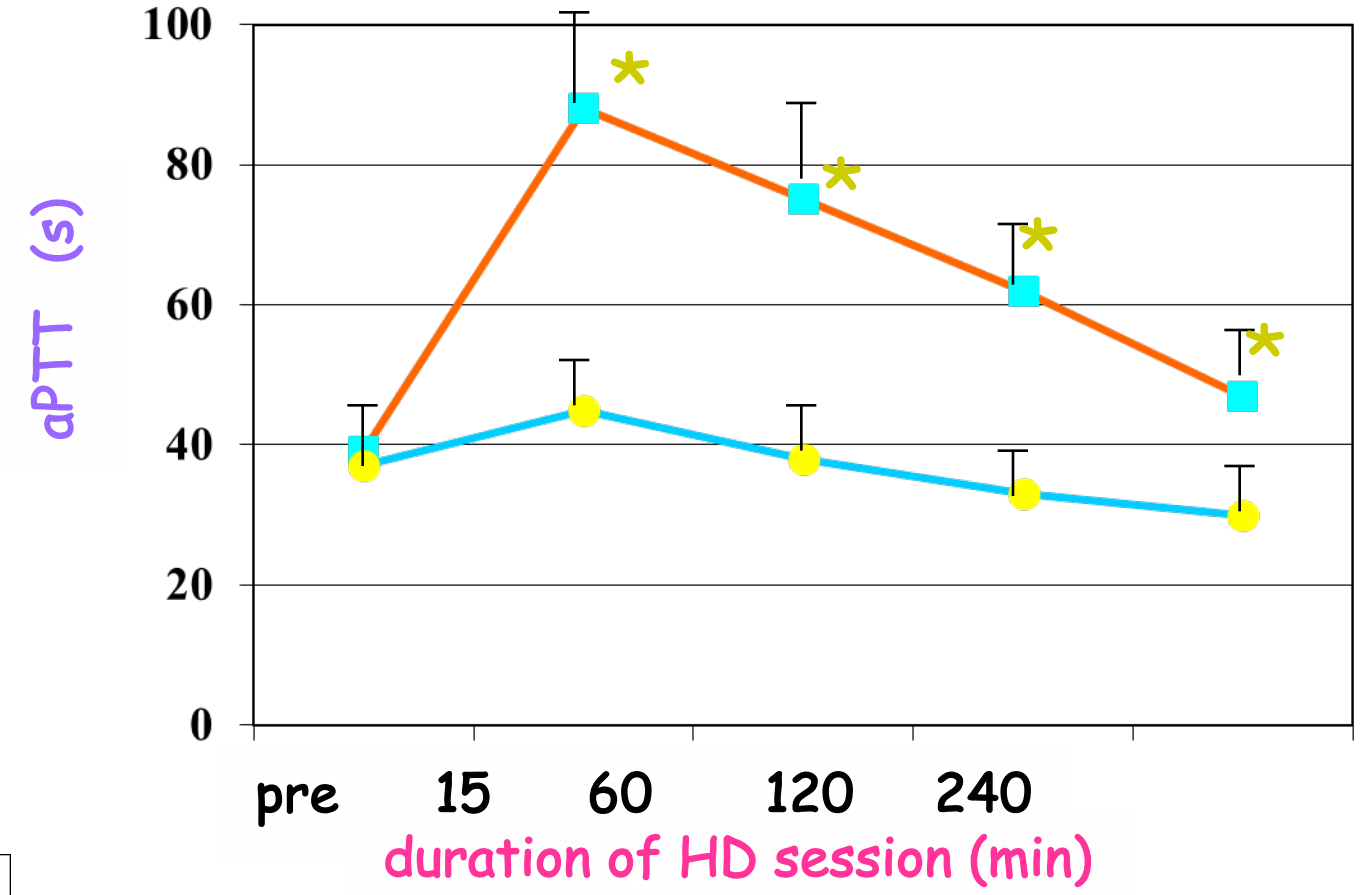




Uchino et al NephronClinPract 2003

Heparin free dialysis ?

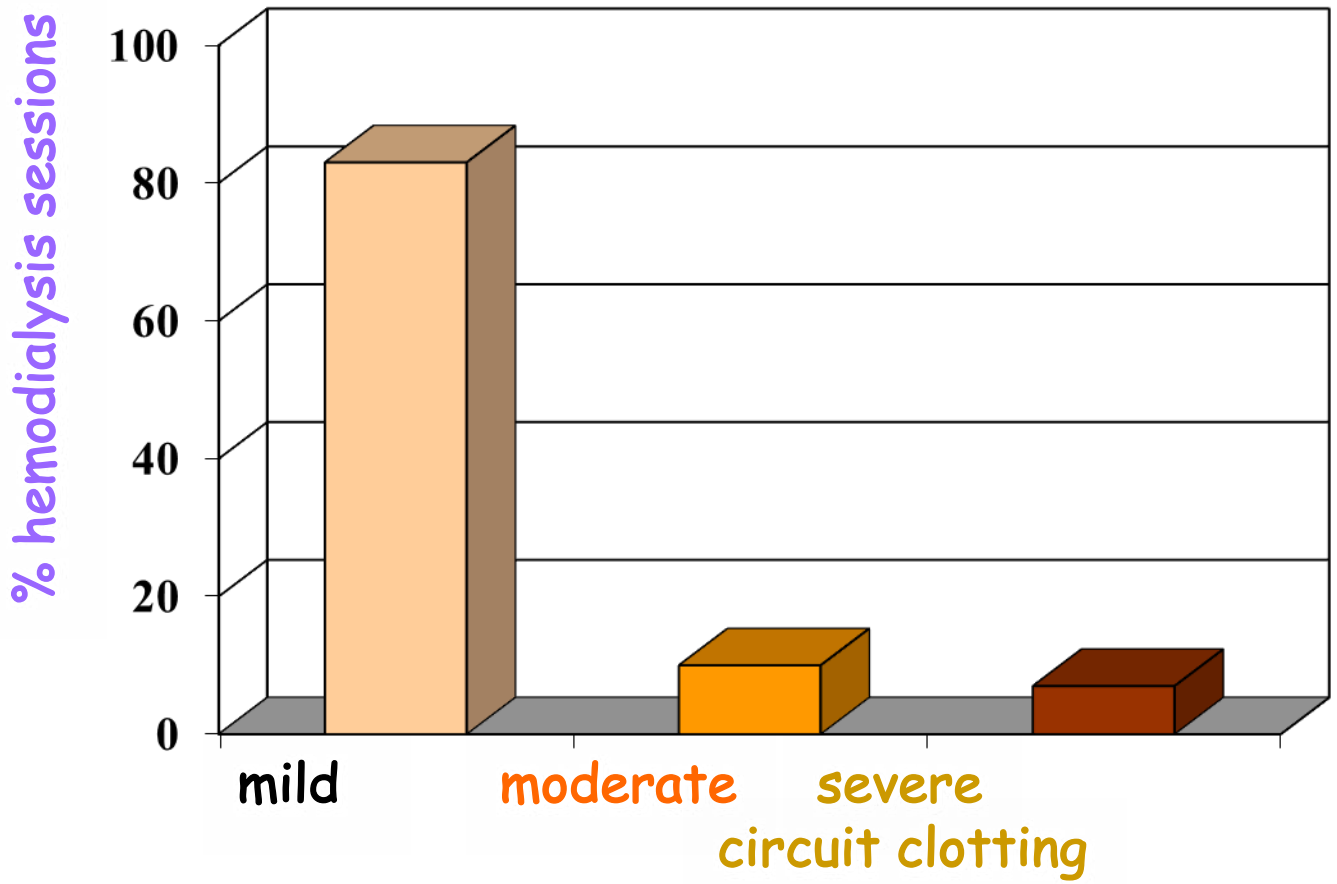
Kyu-Beck et al Nephron 2004



Samsung MC
Seoul
28 HD Rx
hemophan
20000 IU
Low dose H
1000-2000 IU
Infusion
500-1500 IU/h
Mean (SD)
* p <0.05

Heparin free dialysis ?

Kyu-Beck et al Nephron 2004

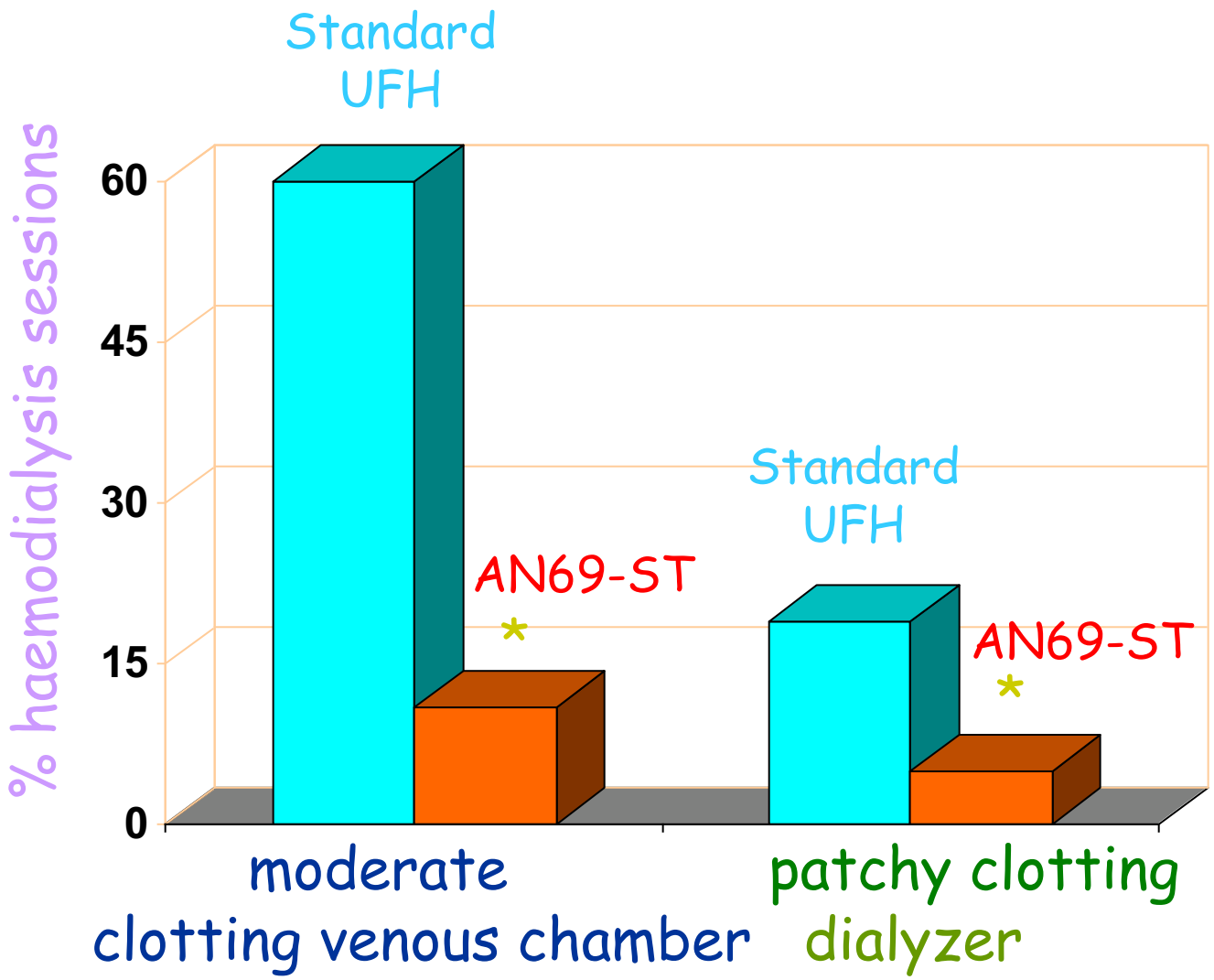


Samsung MC
Seoul
1057 HD Rx
hemophan
20000 IU

Clotting
dialyzer head
arterial/venous
chamber

Heparin coated dialyzer AN69-ST

Chanard et al NephrolDialTransplant 2008



170 HD pts

Bolus

75-100 IU/kg

3000-5000

2nd bolus 2nd h

vs

Prime 2 L

UFH 10000

AN69-ST

50% dose vs

PS/PMMA/CTA

* p <0.05

HepZero study

Visual Clotting Scale

Rossingnol et al KidInt 2014

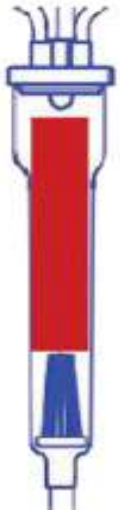
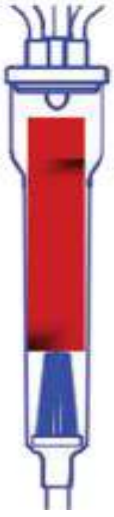
Grade 1:
No detectable clotting

Grade 2:
Minimal clot formation (fibrinous ring)

Grade 3:
Clot formation (up to 5 cm) but dialysis still possible

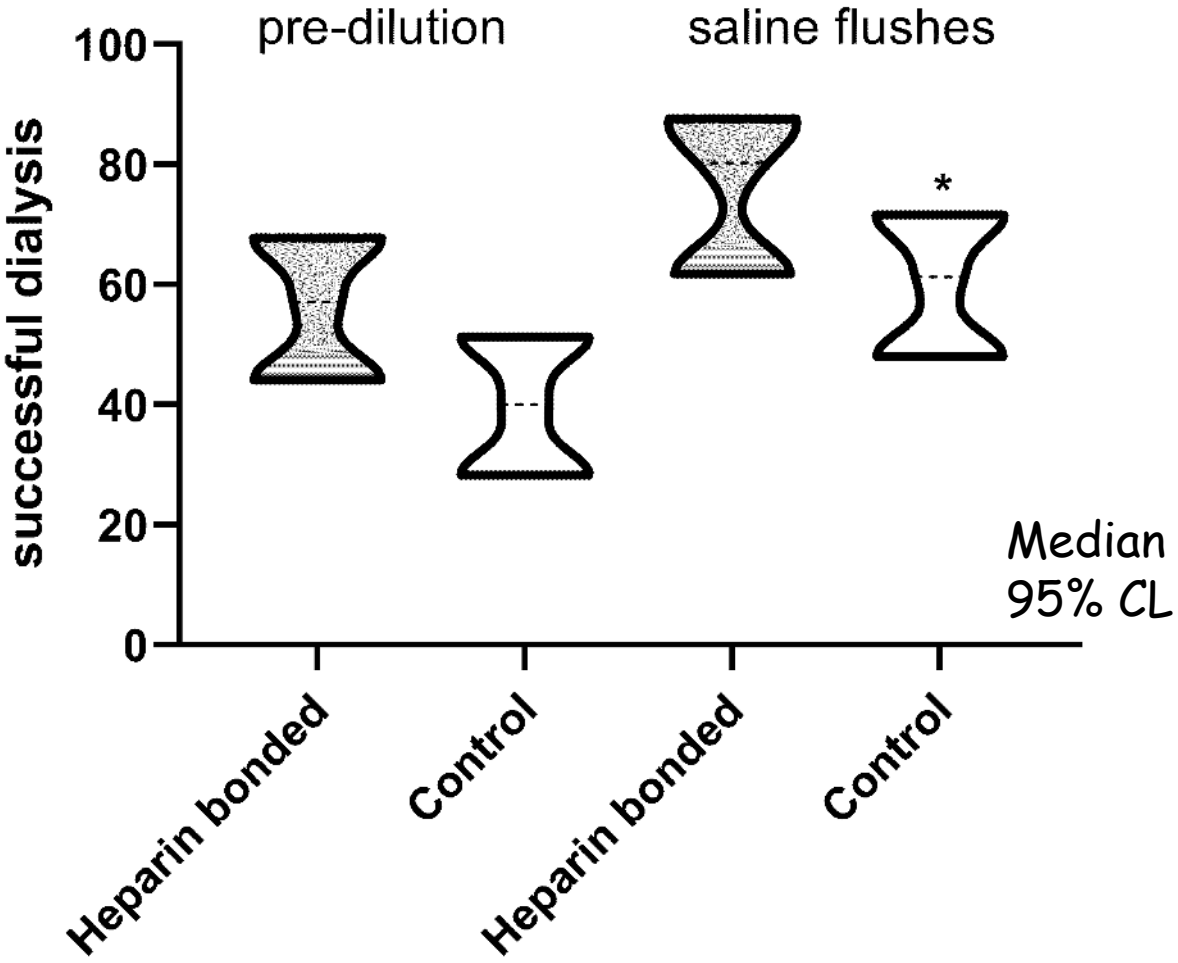
Grade 4:
Complete occlusion of air traps or dialyzer rendering dialysis impossible



Heparin free heparin-coated dialysis membrane (Evodial) vs standard care (saline flushes)

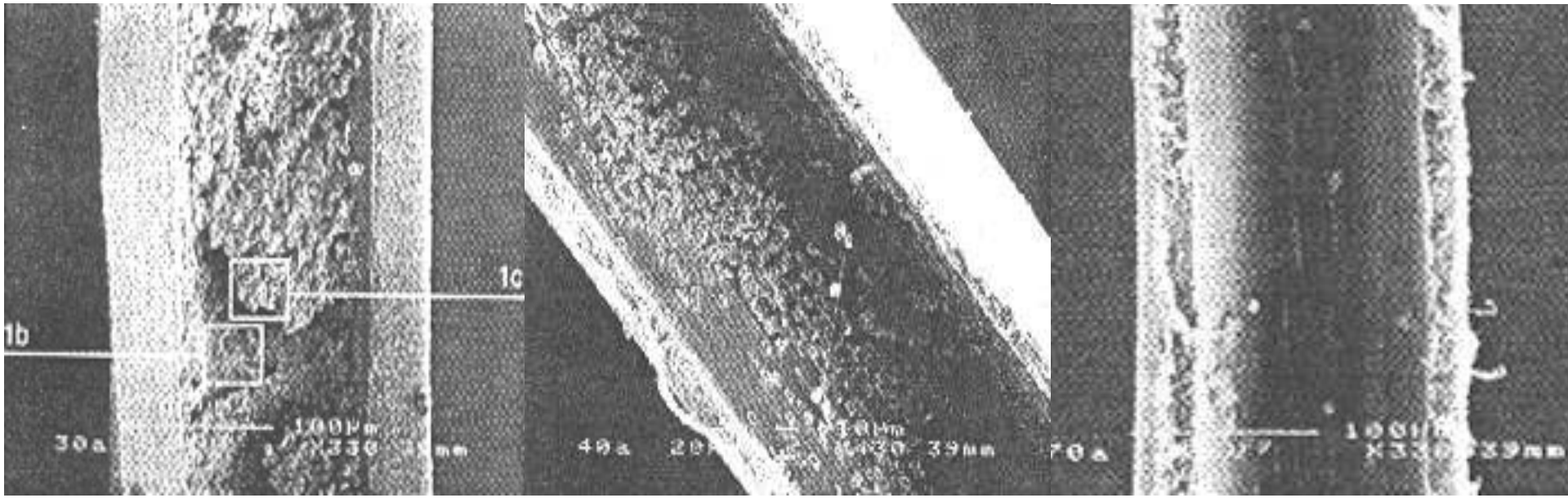
HEP-ZERO study



Laville et al KidInt 2014

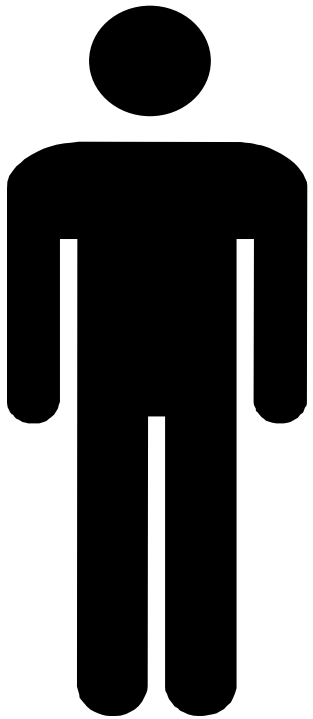
Dialyzer fiber post dialysis

Hoffbauer et al. Kidney Int. 1999



UFH LMWH Citrate

Citrate



Step 1

Citrate infused according to Qb citrate chelates free Ca^{2+}.

as ionised Ca^{2+} → 0.2 mmol/L
bleeding time → infinity

Step 2 alternatives

1..25-1.35 Ca^{2+} fresh dialysate

Step 2

0 Ca^{2+}

fresh dialysate

spent dialysate

Step 3

Post Filter ion Ca^{2+} is monitored and used to titrate citrate rate to assure anticoagulation

Step 4

Ca^{2+} is infused replace Ca^{2+} lost in dialysate, normalizing Ca^{2+} and preventing systemic anticoagulation.

Step 5

Citrate is metabolized primarily in the liver to HCO_3^- bound Ca^{2+} is released

Citrate

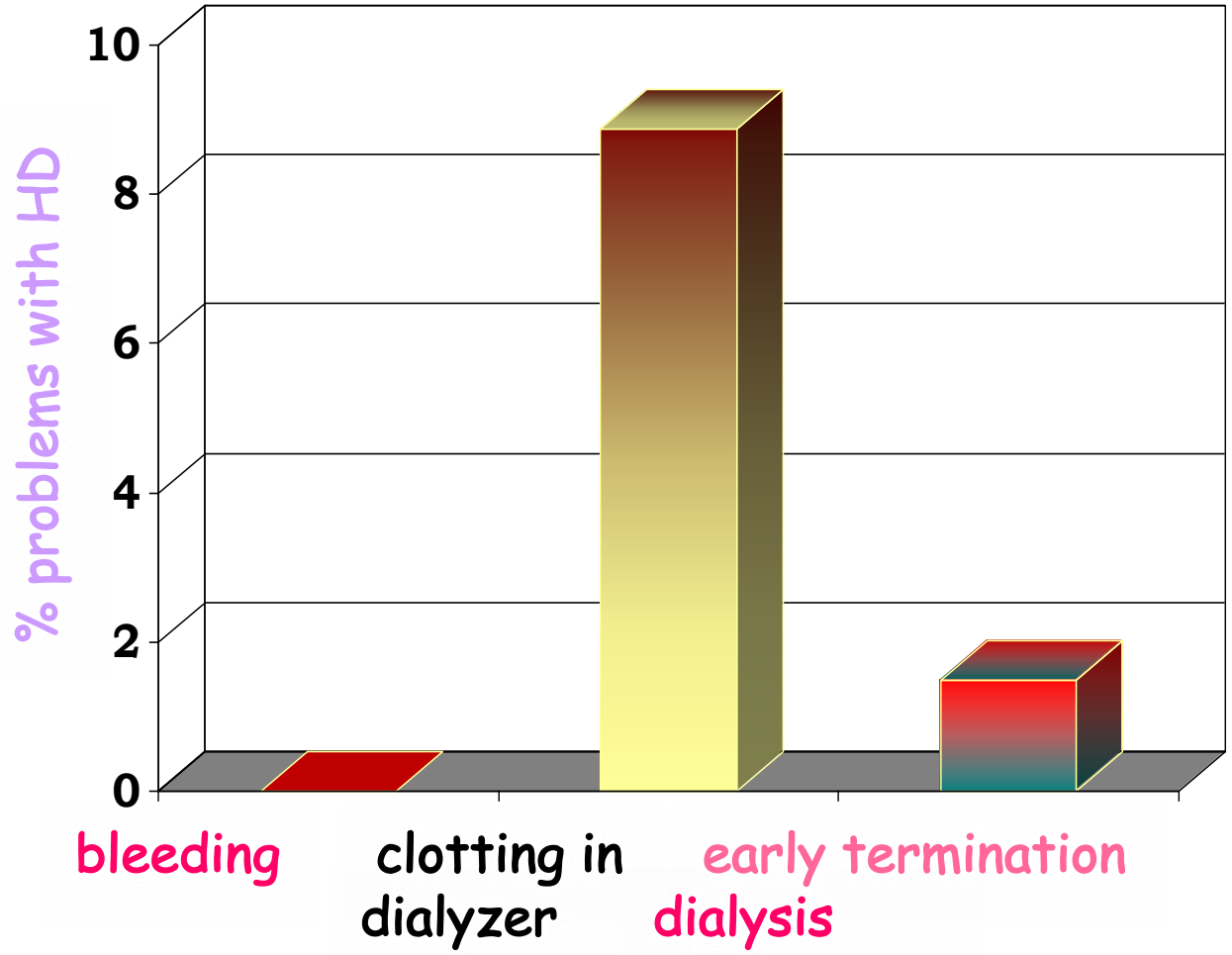
Requirements

- Citrate - ACD-A solution (3%)
  - Rate ~ Qb
  - 3% citrate rate (ml/h) ≈ blood flow rate (ml/min) × 2
- dialysate
  - Calcium free
  - low Mg
- calcium infusion
  - 10% calcium gluconate
  - initial rate ≈ blood flow rate (ml/min)/4

Kreuze et al PediatrNephrol 2010

Citrate anticoagulation

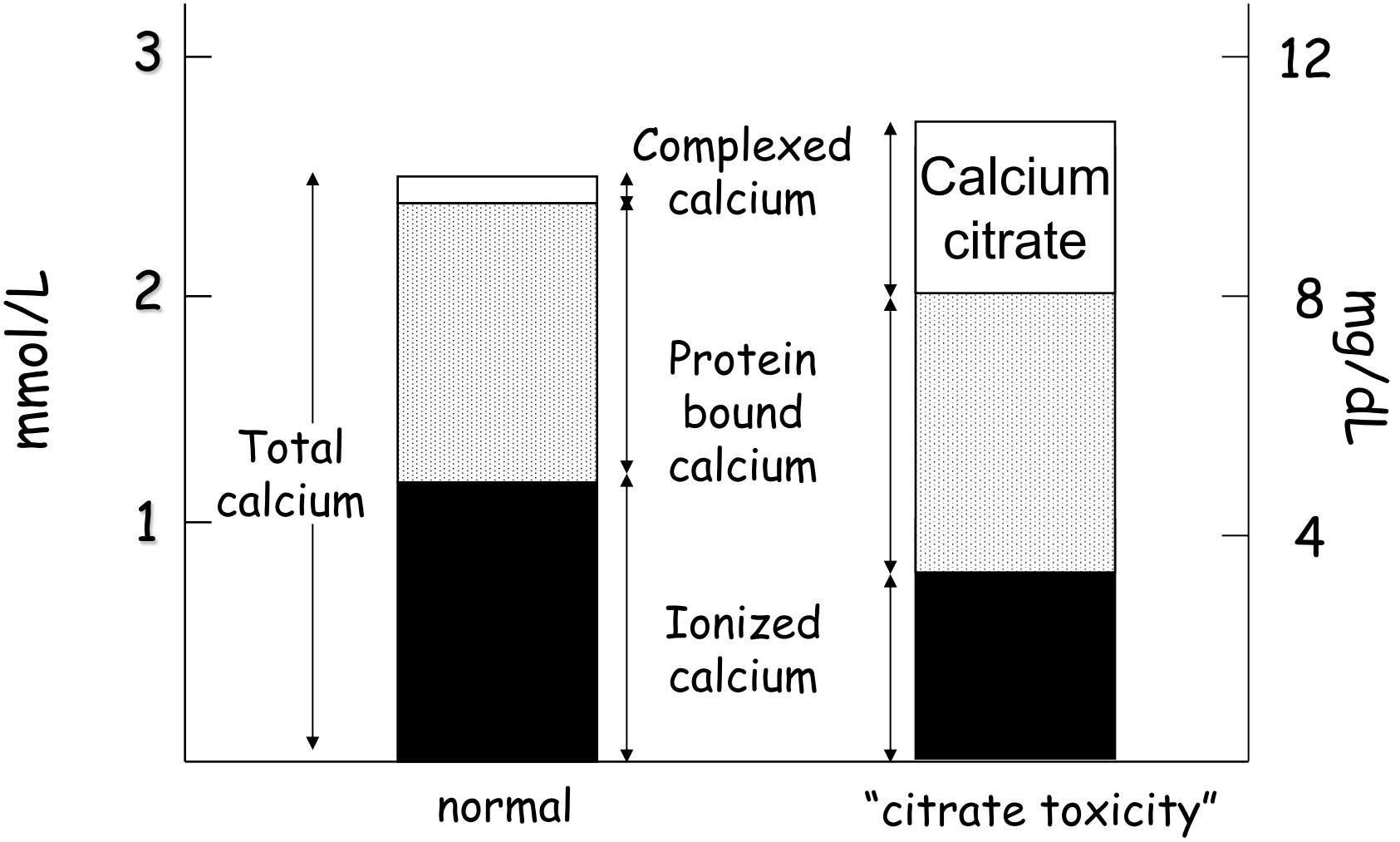
Evenepoel et al Am J Kid Dis 2002



University Hosp Leuven
45 HD pts
at risk hemorrhage
TCA
Ca++ dialysate
203 HD Rx

Citrate

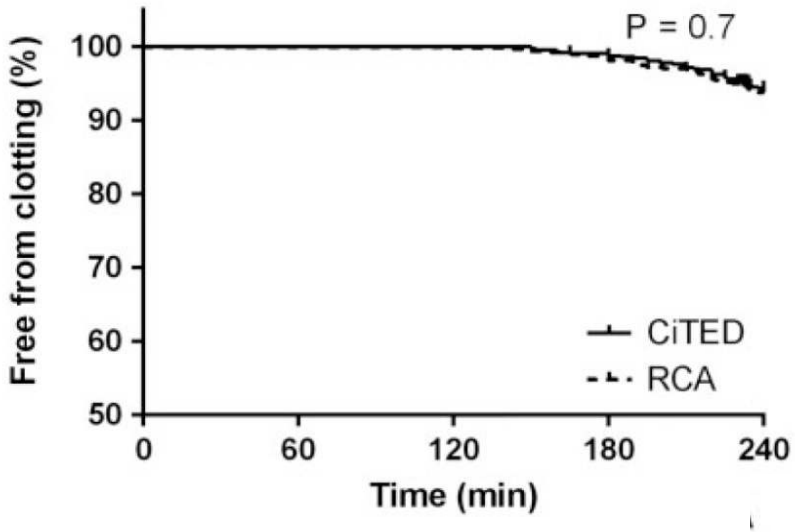
Suspect citrate toxicity when ratio of total calcium to ionised calcium > 2.5



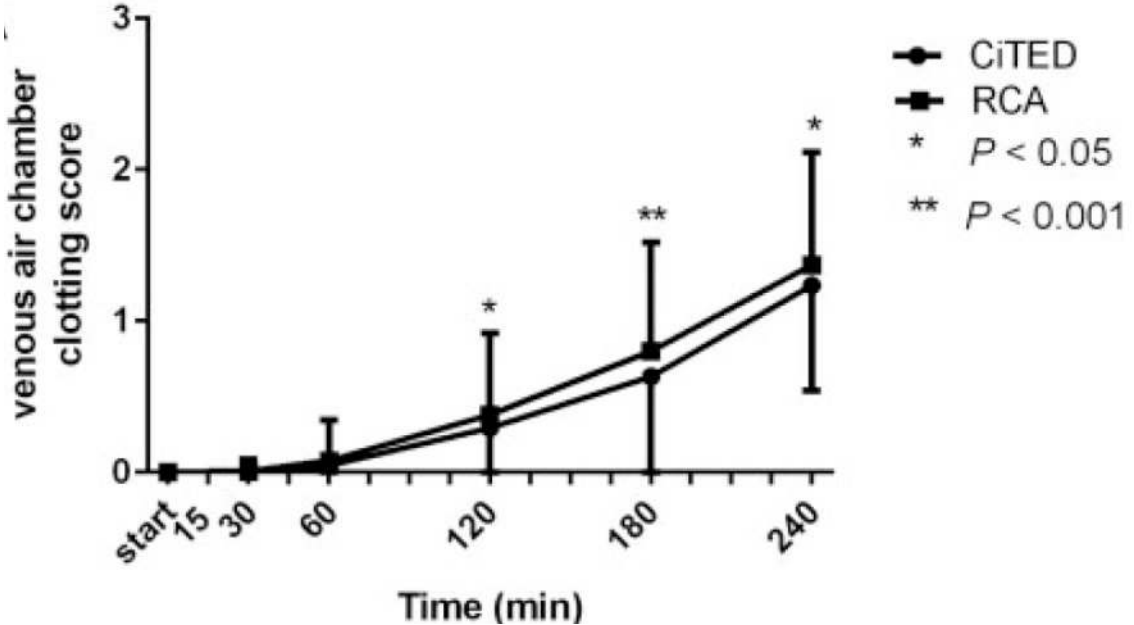
Combined with Citrate in dialysate

Chemical	Measure	Citrate Dialysate	Acetic Acid Dialysate
Sodium	mmol/L	138,0	138,0
Calcium	mmol/L	1,25	1,25
Magnesium	mmol/L	0,5	0,5
Potassium	mmol/L	2,0	2,0
Chloride	mmol/L	105,0	105,3
Acetate	mmol/L	0.3	4.0
Citrate	mmol/L	0.8	-
Glucose	g/L	1,0	1,0
Bicarbonate	mmol/L	35.2	34.2

CiTED study



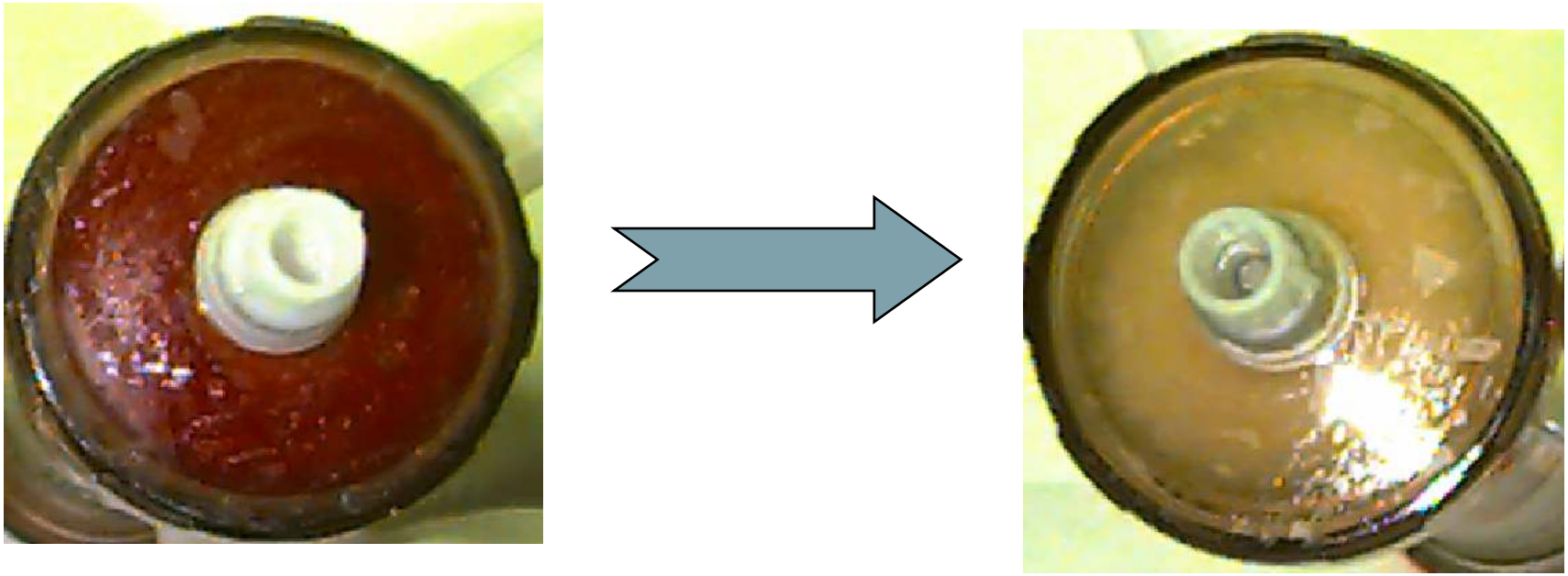
Regional citrate
vs
Heparin bonded
Dialyzer and
Citrate containing
dialysate



Meijers et al NDT 2017

Combination therapy

- 25% -50% reduction in UFH usage



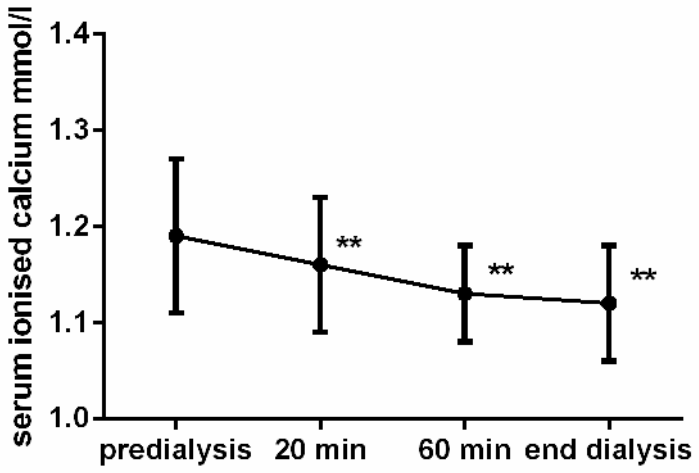
Citrate dialysate

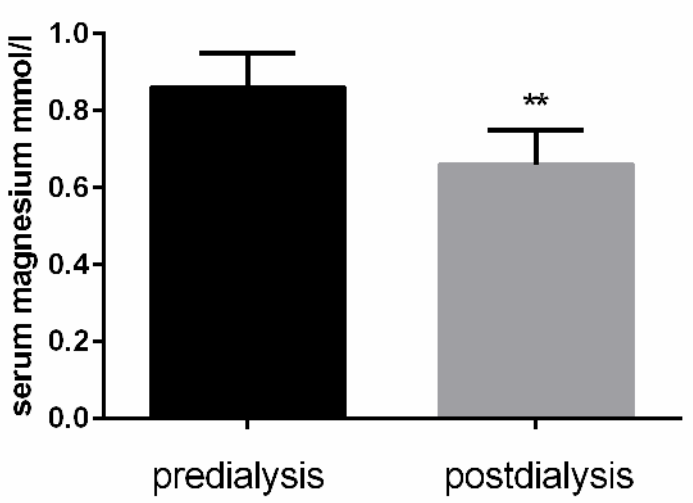
- Citrasate®
  - 81 treatments
  - some clotting in 21 (23.5%)
  - mild 28.5%, moderate38%, severe 33.3%
- combined with UFH
  - Reduced dose
  - 3.6 to 15 U/kg/h

Hanevoldet al Hemodial Int 2010

magnesium options

Chemical	Measure	Citrate Dialysate	Acetic Acid Dialysate
Calcium	mmol/L	1,25	1,25
Magnesium	mmol/L	0,5	0,5
Acetate	mmol/L	0,3	4,0
Citrate	mmol/L	0,8	-
Glucose	g/L	1,0	1,0
Bicarbonate	mmol/L	35,2	34,2



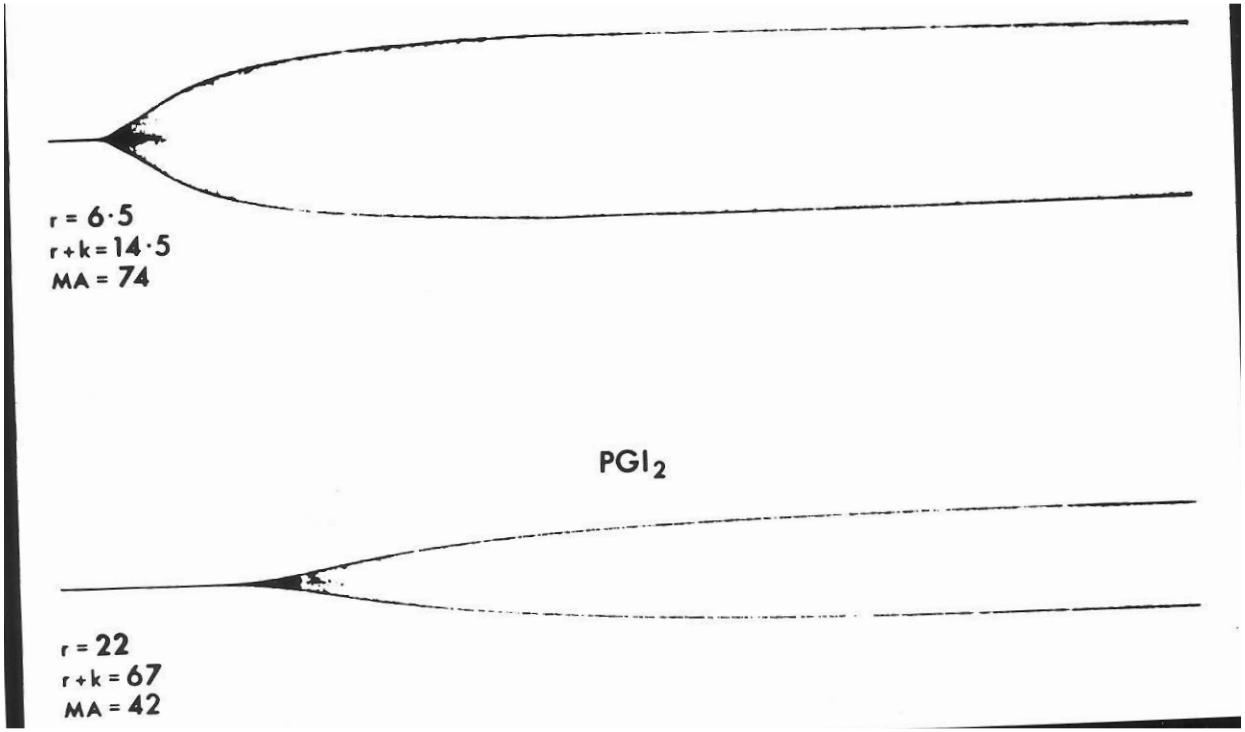


UCL MEDICAL SCHOOL

Prostanoids

- priming
  - variable
- prostaglandin E1 or E2
  - 10 - 20 ng/kg/min
- prostacyclin
  - 3-10 ng/kg/min
- iloprost
  - 0.5 - 2.0 ng/kg/min

Prostacyclin

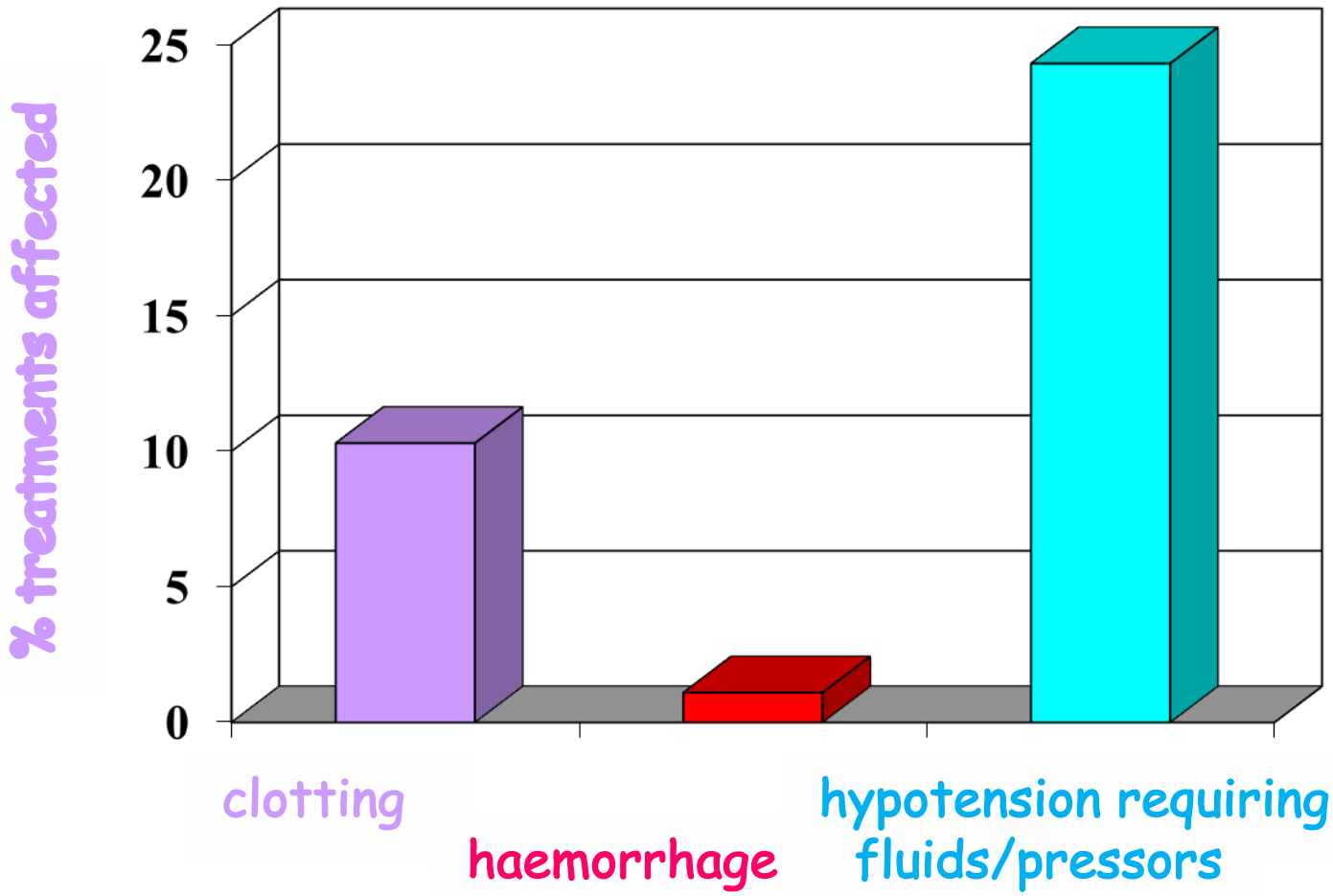


pre

PGI_2
5 ng/kg.min

PGI_2 for SLED

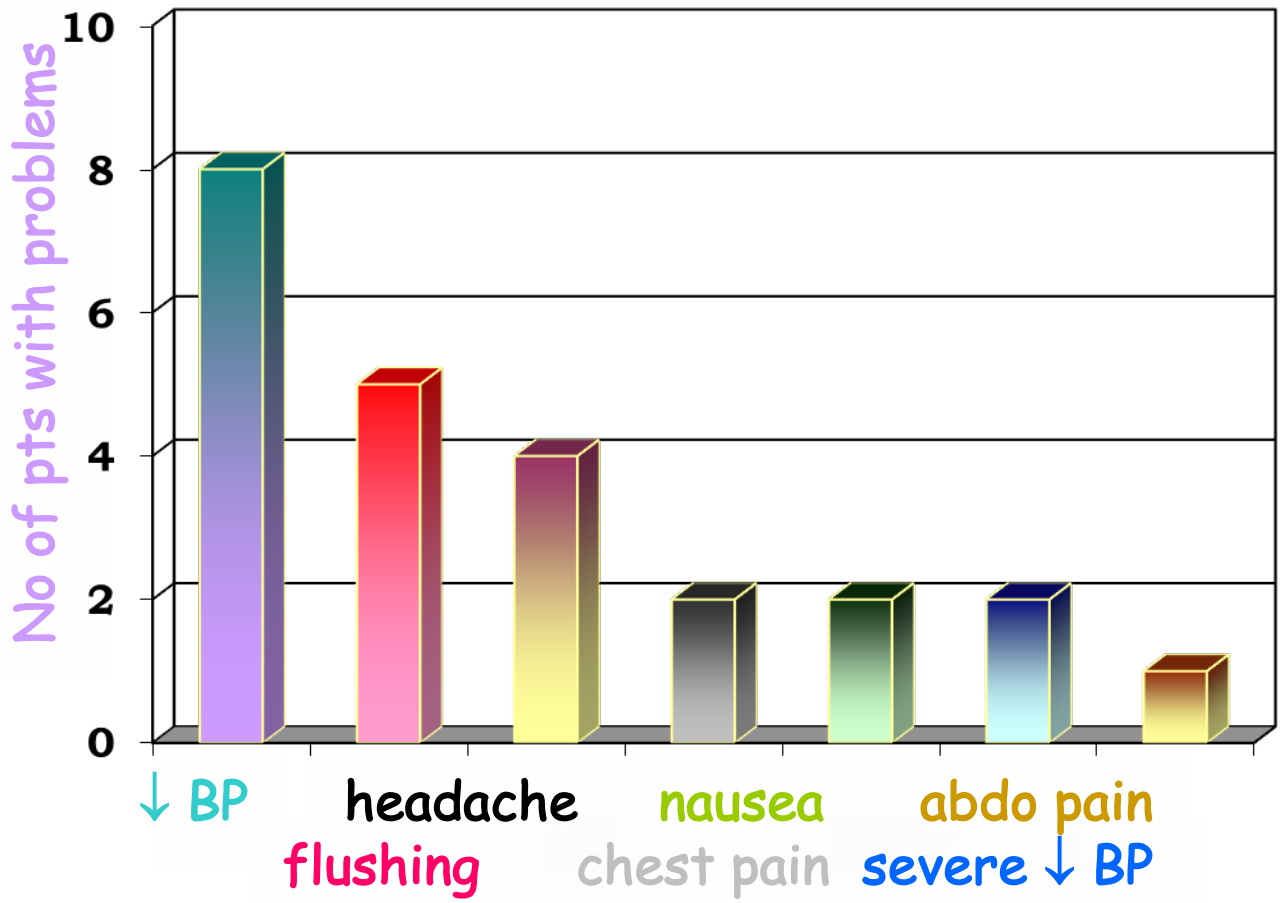
Fiacadori et al NephrolDialTransplant 2007



Parma
35 ICU pts
185 SLED
Start
3 ng/kg.min
iv Then
6 ng/kg.min
into circuit

Prostacyclin anticoagulation

Zusman et al N Engl J Med 1981



Mass Gen Hosp
Boston
10 HD pts
at risk
hemorrhage
Prostacyclin
423±91 ng/kg
4 h HD
no bleeding
no clotting

Nafamostat anticoagulaton

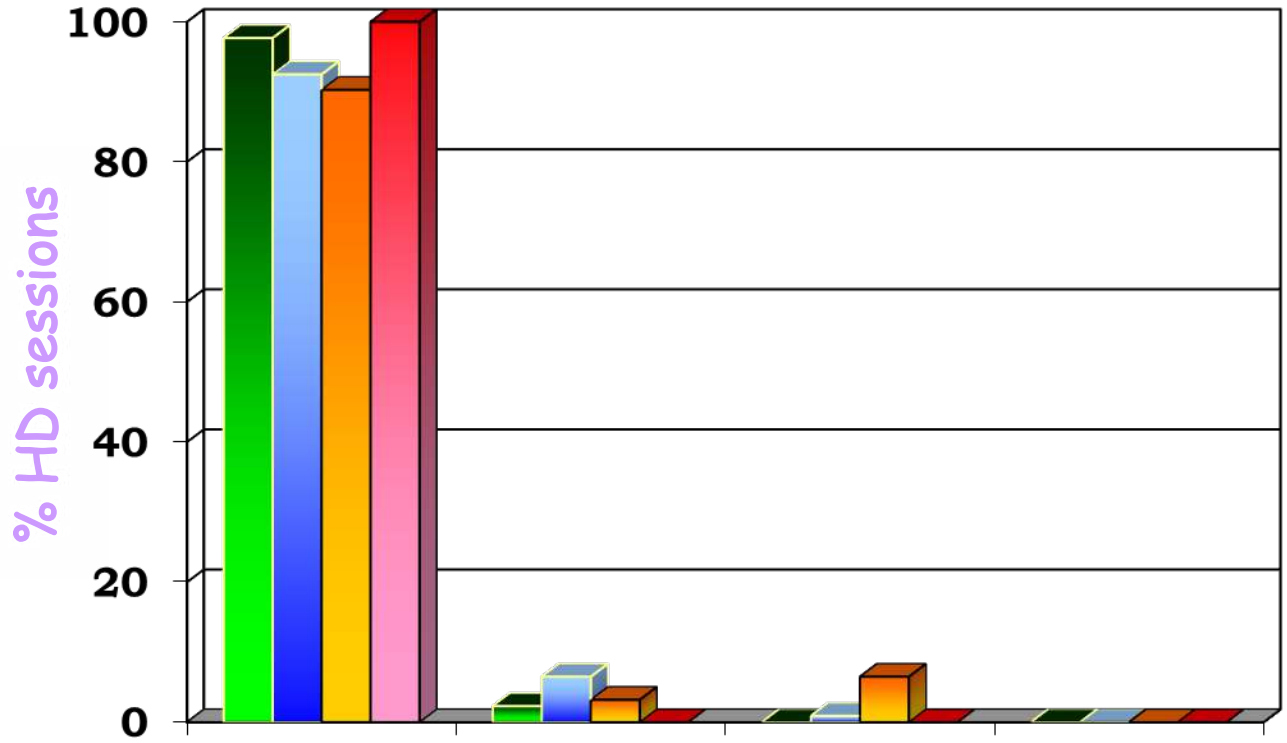
Akizawa et al Nephron 1993

Haemodialysis

- **Patients at risk of hemorrhage**
  - ***priming***
    - 20 mg in 1.0 L 0.9%-saline
  - ***initial infusion***
    - 40 mg /h

Nafamostat anticoagulaton

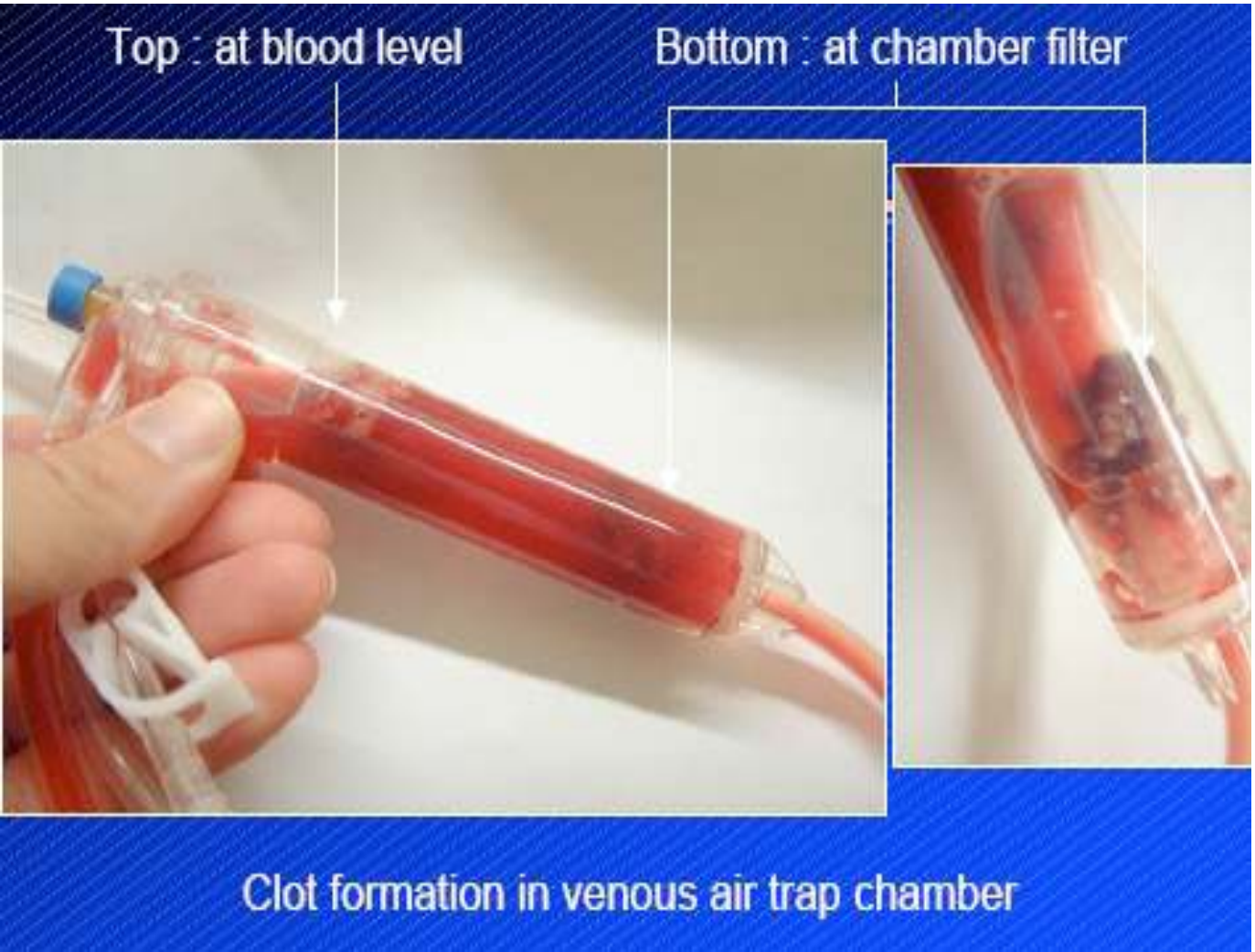
Akizawa et al Nephron 1993



Showa Uiv
Fujigaoka Hosp
Yokohama
107 HD pts
at risk
hemorrhage
573 HD Rxs
Pre HD status

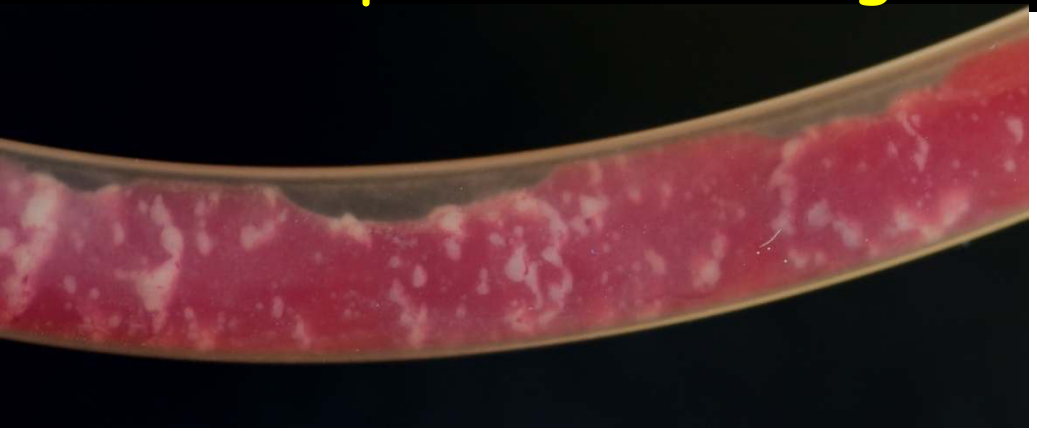
- Severe risk
- Moderate risk
- Mild risk
- No haemorhage

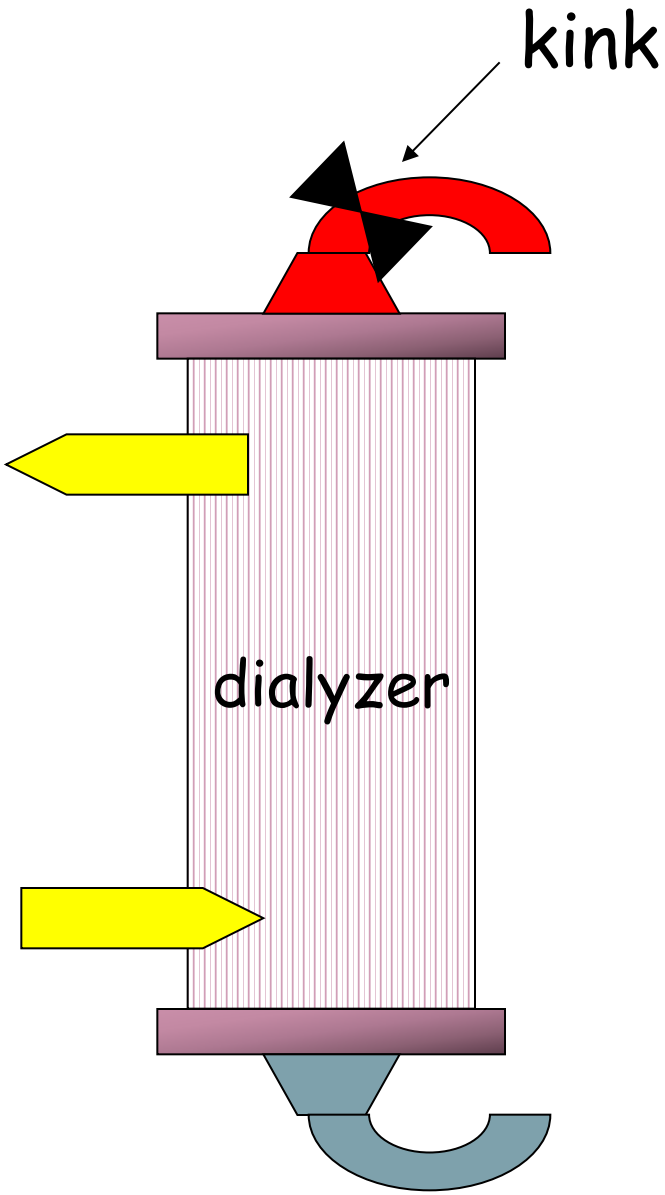
Sites of clot initiation during dialysis



- ✓ access
- ✓ blood-air interface
- ✓ dialyzer
- ✓ blood pump

Heat and plastics causing dialyzer clotting





Priming & circuits

No venous air detector

Can we reduce clot formation during haemodialysis ?

UCL

circuit design

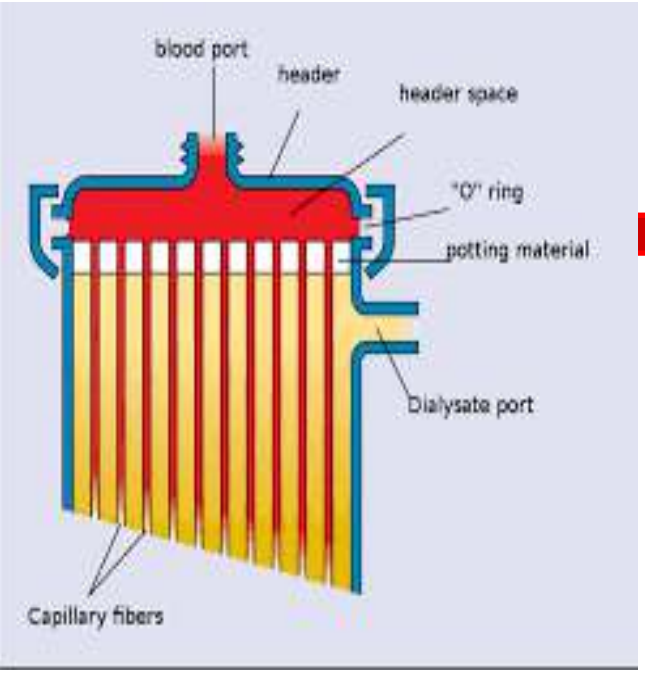
- arterial expansion chamber

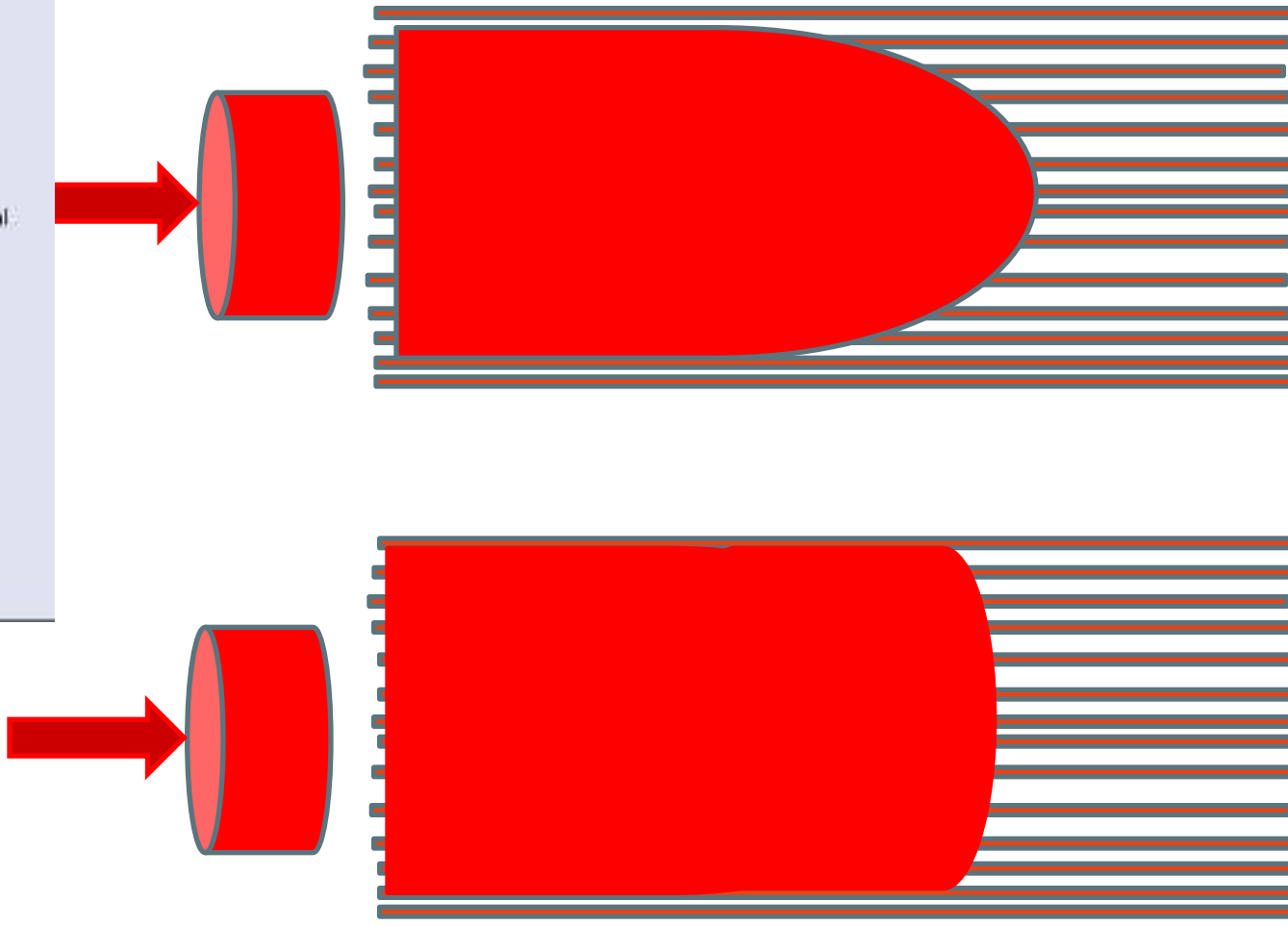
blood-air interfaces

UCL

Improving blood flow distribution

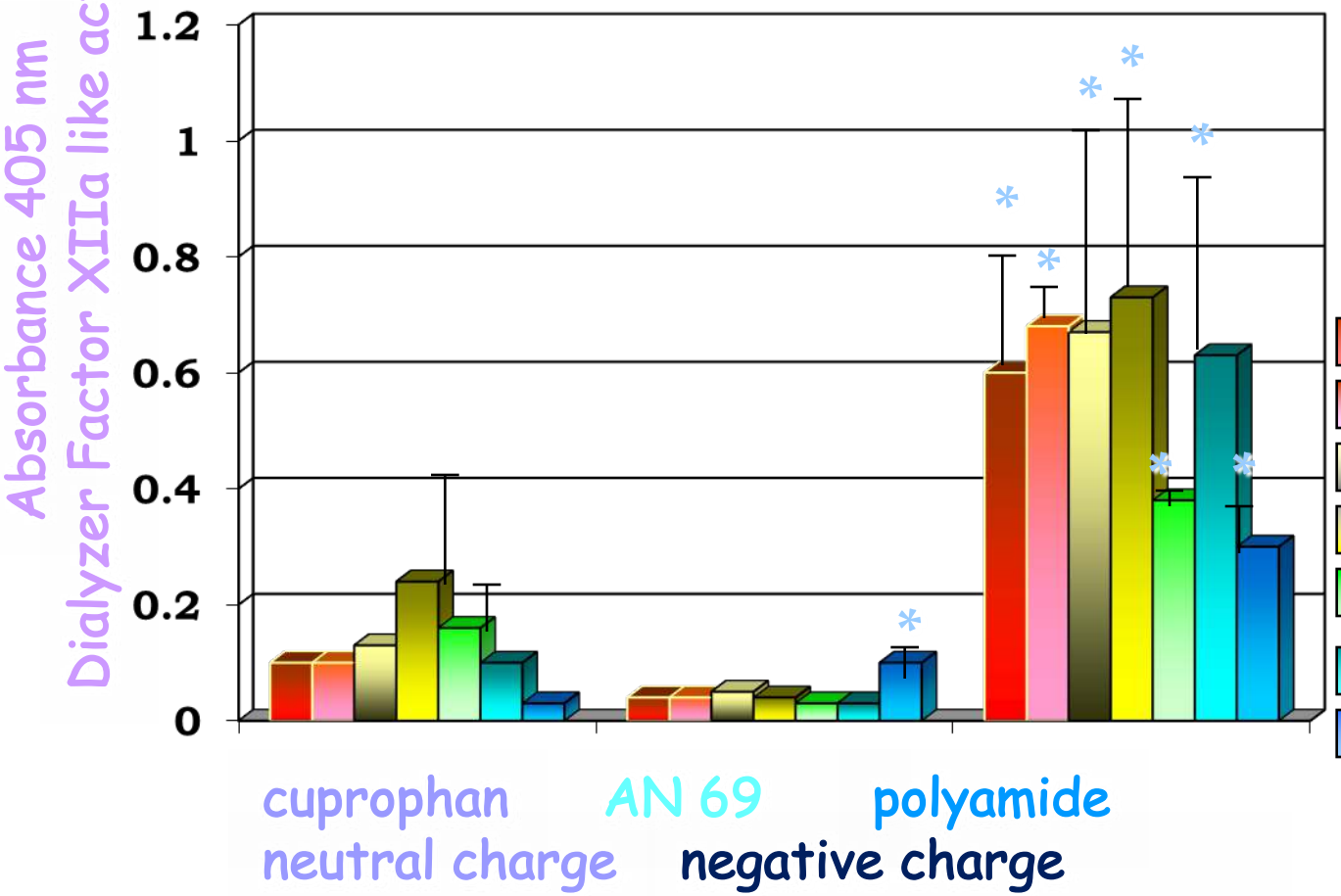
header





Contact phase activation

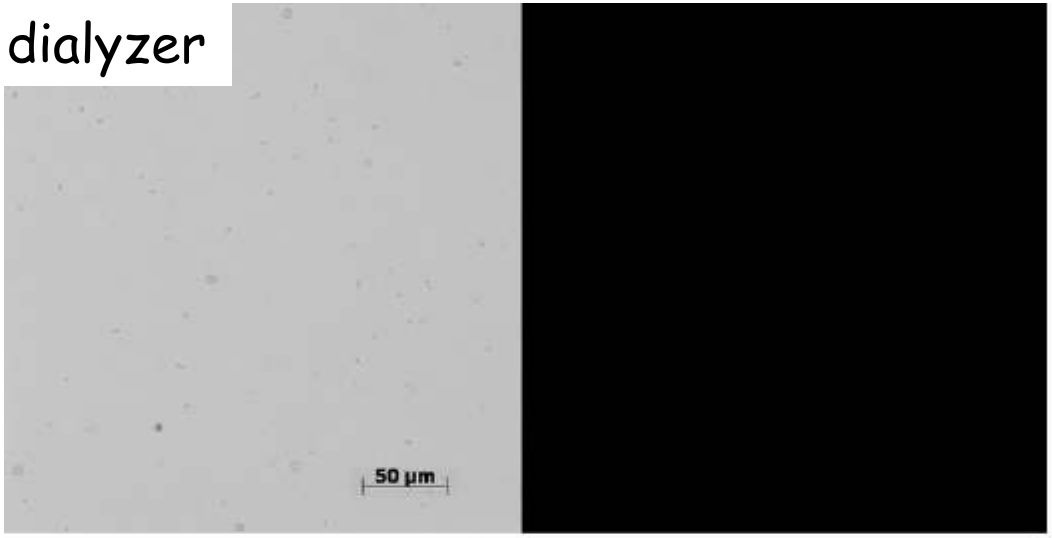
Matata et al Biomaterials 1995



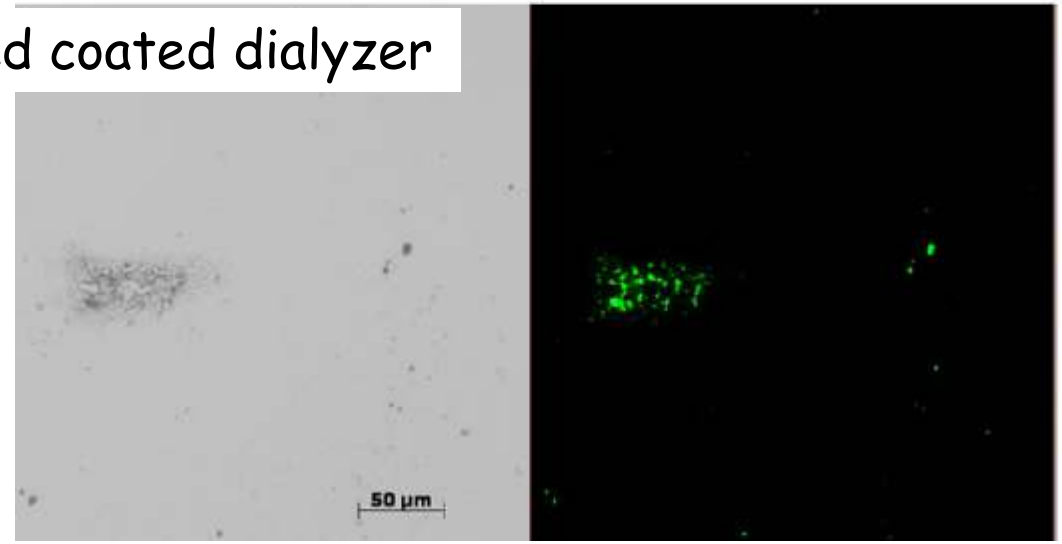
Platelet adhesion to Vitamin E coated dialyzers

Tsuakao et al JArtifOrgans 2013

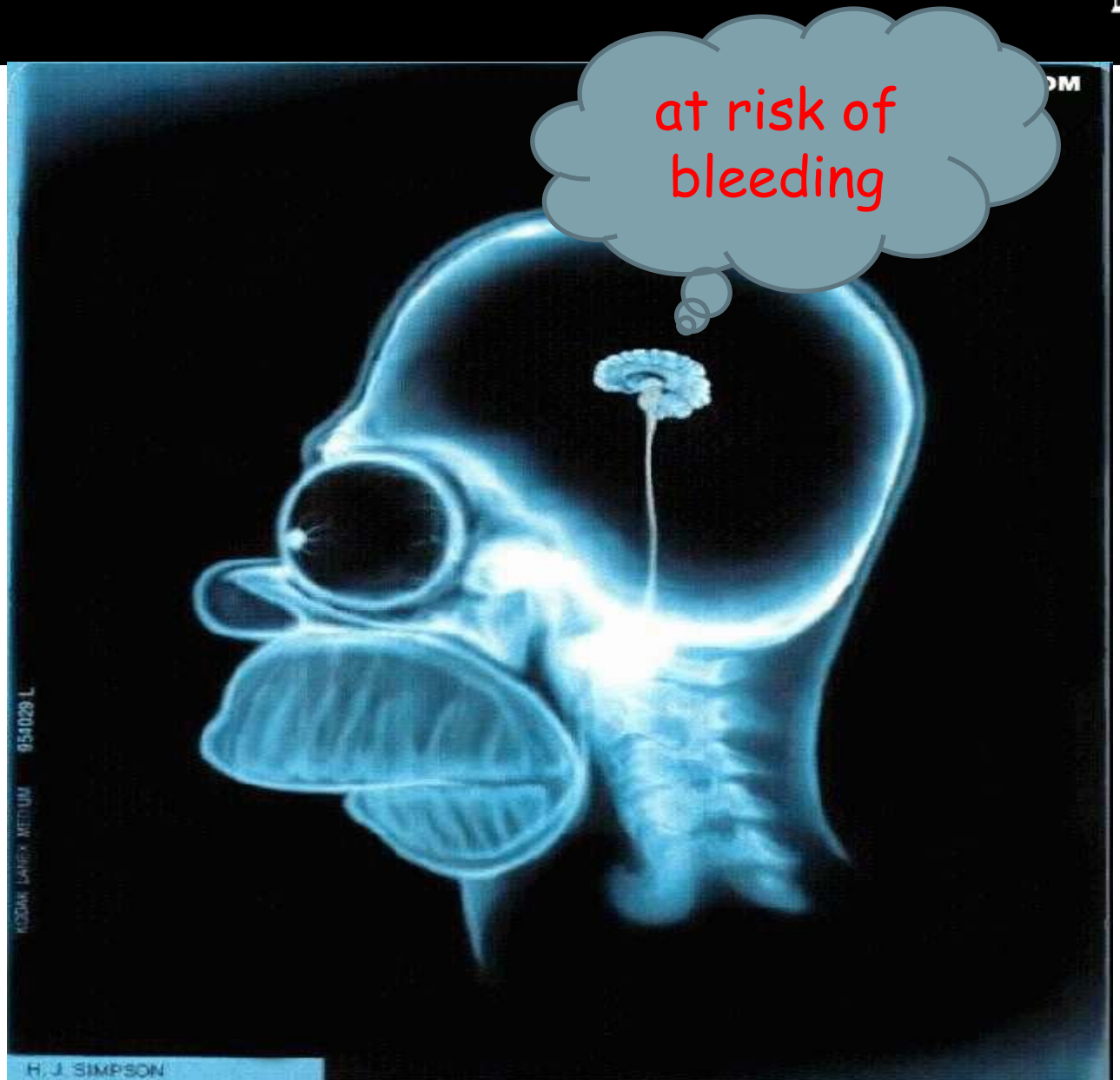
Vitamin E coated dialyzer



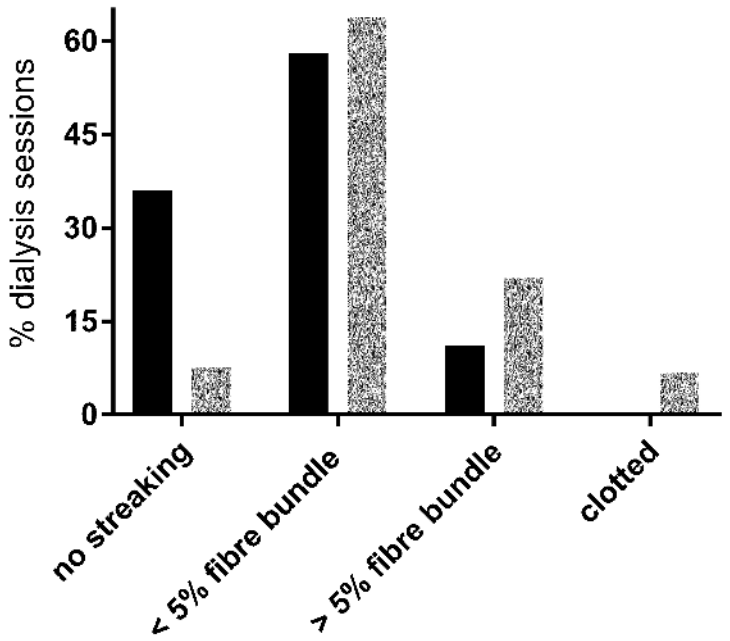
Vitamin E oxidised coated dialyzer



Dialysis prescription

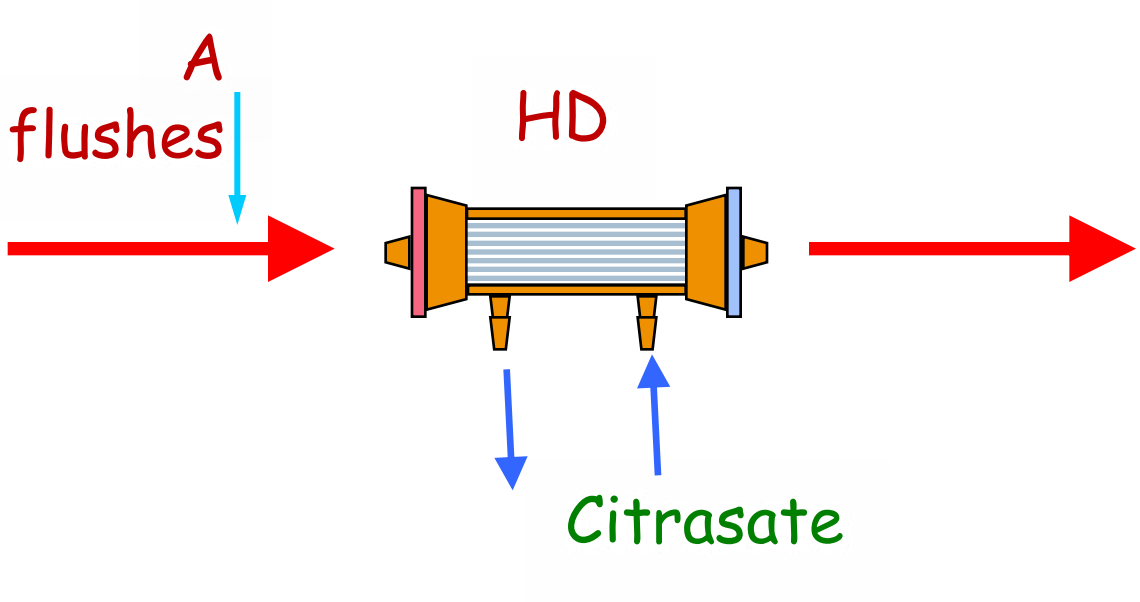


Haematocrit

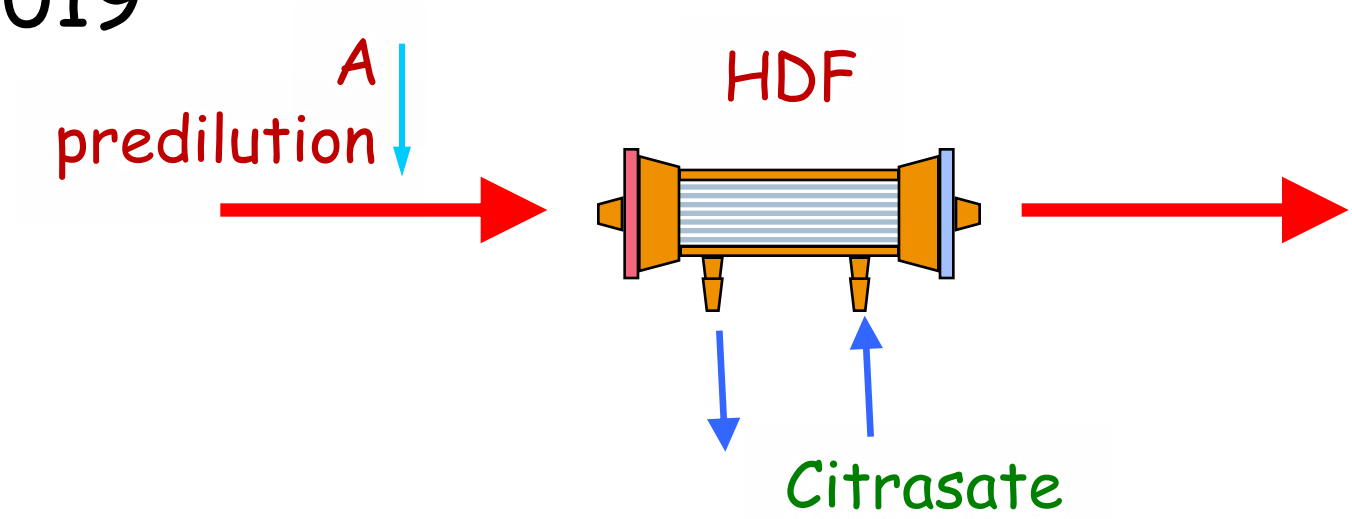


What do we do ?

< 2019



> 2019



Summary

Alternatives to systemic anticoagulation

- No anticoagulation
  - Pre-dilution
  - Heparin priming
  - Heparin bonded dialyzers
  - Short session times

- Regional anticoagulants – around the world
  - Citrate
    - citrate infusion
    - dialysate
  - Prostanoids
  - Nafamostat

Thank you for your attention

UCL

UCL MEDICAL SCHOOL

Ultrafiltration in hemodialysis:
Not so fast…

DRAFT

Annual Dialysis Conference
March 5, 2021

Jennifer E. Flythe, MD, MPH
Associate Professor of Medicine
University of North Carolina School of Medicine

Disclosures

- **Funding**: NIH/ NIDDK, NIH/ NHLBI, PCORI, Robert Wood Johnson Foundation, and Renal Research Institute (a subsidiary of Fresenius Medical Care)

- **Speaking Honorarium**: Fresenius Medical Care, American Society of Nephrology, National Kidney Foundation, multiple universities

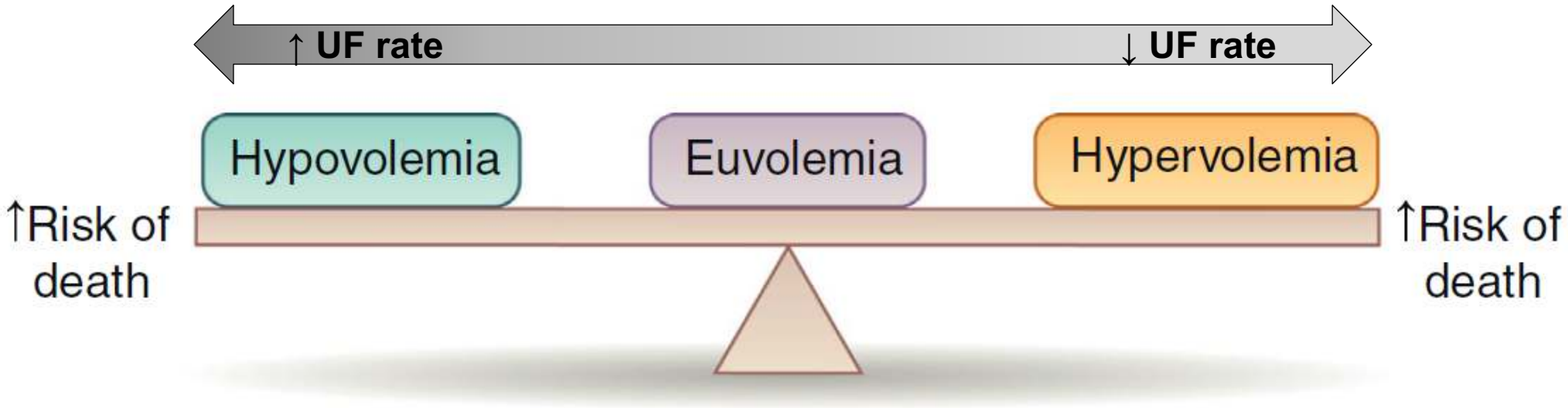
- **Consulting:** Fresenius Medical Care, AstraZeneca, NxStage Medical

Outline

- Volume management: the conundrum
- *Existing* opportunities to improve volume management
- *Future* opportunities to improve volume management

Volume management: the conundrum

Tension in managing volume status



Hypotension, access thrombosis, cramping, fatigue	Shorter-term risks	Hypertension, edema, dyspnea, fatigue
End-organ ischemia, faster loss of RKF	Longer-term risks	Cardiac remodeling, heart failure

Flythe. Kid Int, 2020.

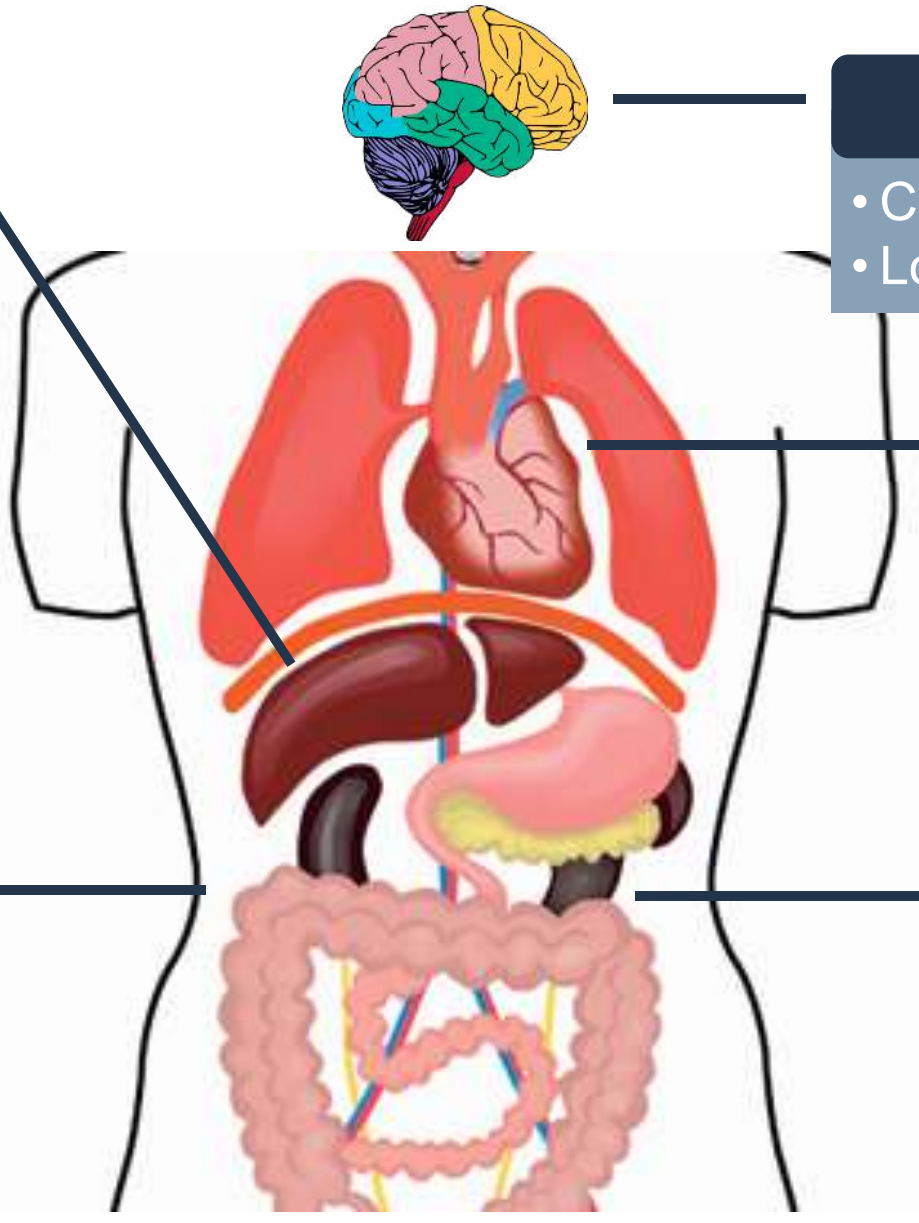
↑ Ultrafiltration rate → death

- U.S. cohort (N=118,394)

UF rate (mL/h/kg)	All-cause mortality Adjusted HR (95% CI)
<6	1.00 (reference)
6-8	1.03 (1.00-1.07)
8-10	1.09 (1.06-1.12)
10-12	1.15 (1.12-1.19)
12-14	1.22 (1.18-1.27)
>14	1.43 (1.39-1.48)

Assimon/ Flythe. Am J Kid Dis, 2016.

Impact of hypovolemia (ischemia) on organs



Brain

- Cognitive dysfunction
- Long-term ischemic damage

Liver

- Altered drug metabolism

Heart

- Myocardial stunning
- LVH
- Heart Failure
- Conduction abnormality

Gut

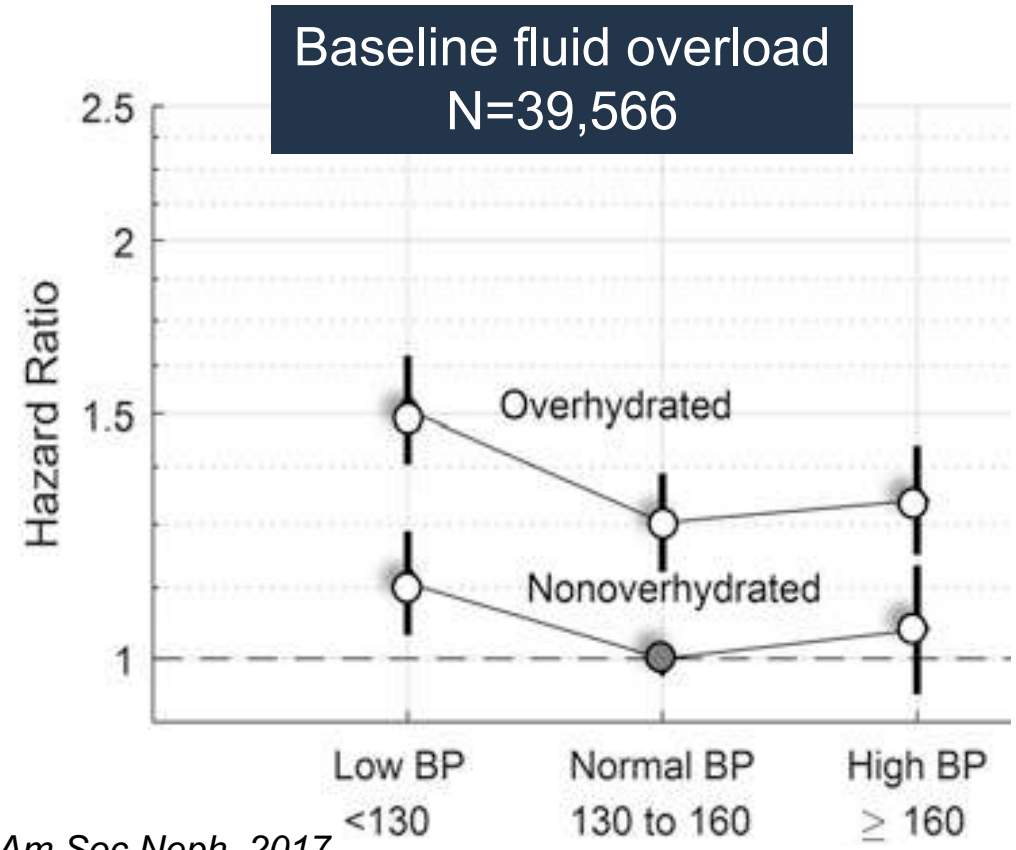
- Bacterial translocation
- Endotoxin release
- ↑ Inflammation

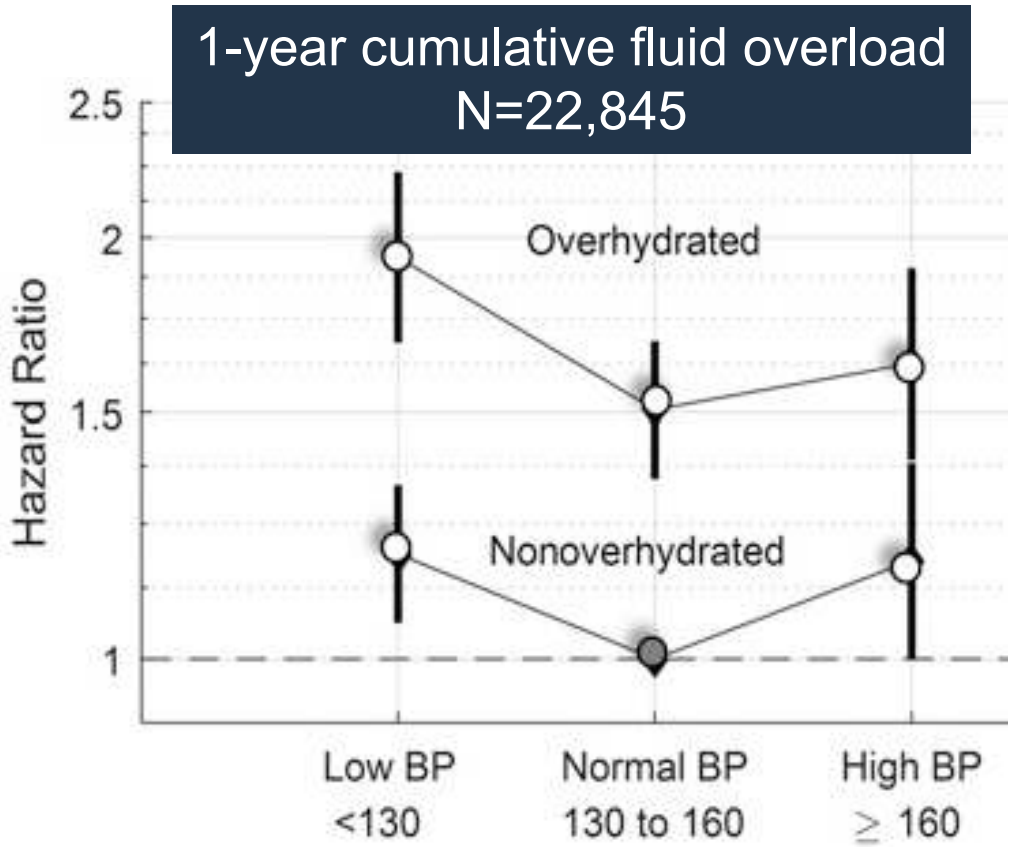
Kidneys

- ↓ residual kidney function

Extracellular volume overload → death

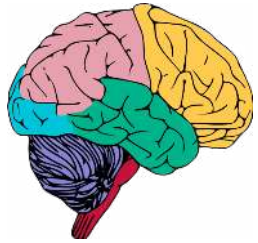
- 26 country cohort
- Volume status by multi-frequency bioimpedance





Zoccali. J Am Soc Neph, 2017.

Impact of hypervolemia on organs

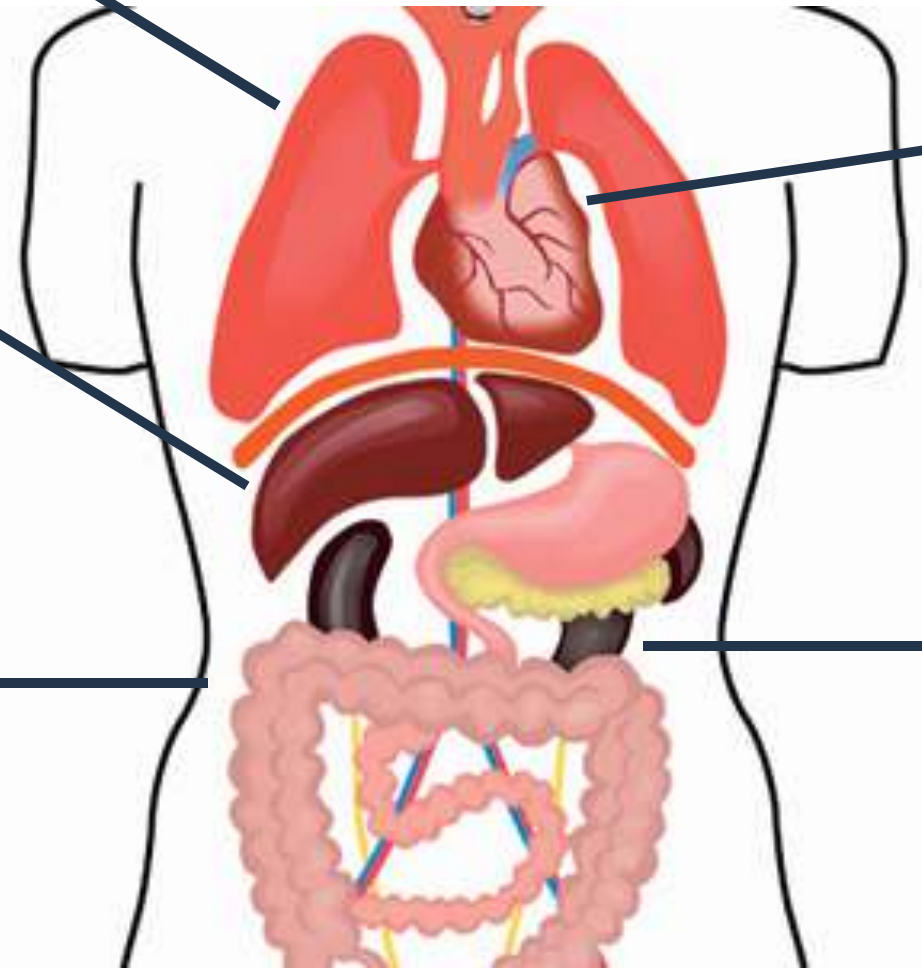


Brain

- Cognitive dysfunction

Lungs

- Pulmonary edema
- Impaired gas exchange
- ↓ Compliance



Heart

- Myocardial edema
  - Impaired contractility
- Left ventricular hypertrophy
- Heart failure
- Conduction disturbance

Liver

- Hepatic congestion
- Cholestasis

Gut

- Gut edema
- Malabsorption
- Ileus

Kidneys

- ↑ Interstitial pressure
- ↓ residual kidney function

They said [cramps] are close to what a man feels like having a baby. If that's the way it is, boy, I wouldn't want to have one. [60y M]

It feels terrible because sometimes I'll be gasping for breath. I start crying because I can't breathe. It's like my own lungs is shutting down and I just can't get the breath that I need. [49y F]

As soon as the cramps start, I'm yelling'. You never die, but it's so painful that you think that you do. [55y F]

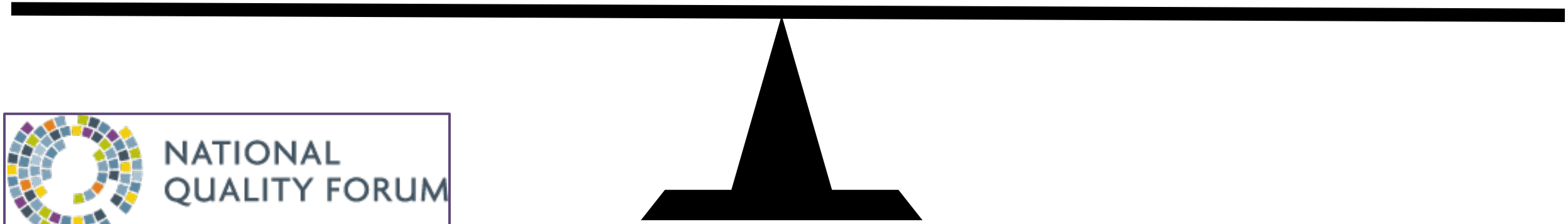
I just kind of panic when I can't get a deep breath. It's like I feel like I'm going to smother. [76y F]

Flythe. Neph Dialysis Trans, 2018.

Fluid-related clinical quality measures (2014)

Fluid Removal Rate Measure
% of patients in the clinic with average **fluid removal rate ≥13 mL/h/kg**

Euvolemia Measure
% of patients in the clinic with average **post-HD weight ≥1 kg above or below the prescribed target weight**



NATIONAL QUALITY FORUM

CMS.gov
Centers for Medicare & Medicaid Services

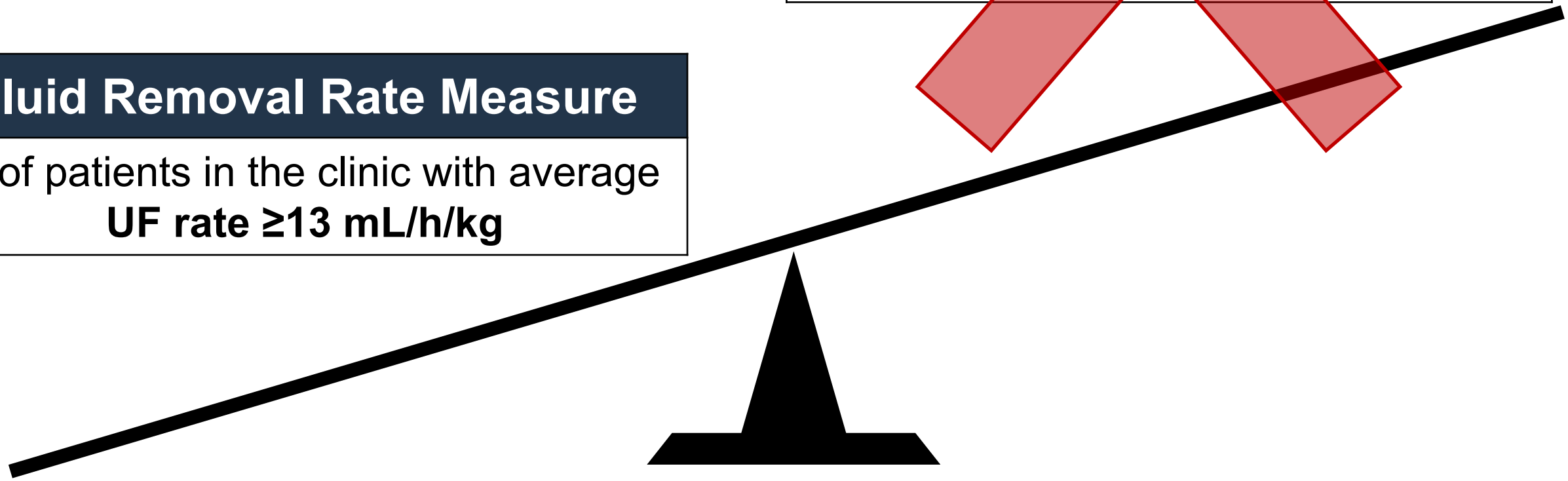
2020 ESRD QIP Reporting Measure

Euvolemia Measure

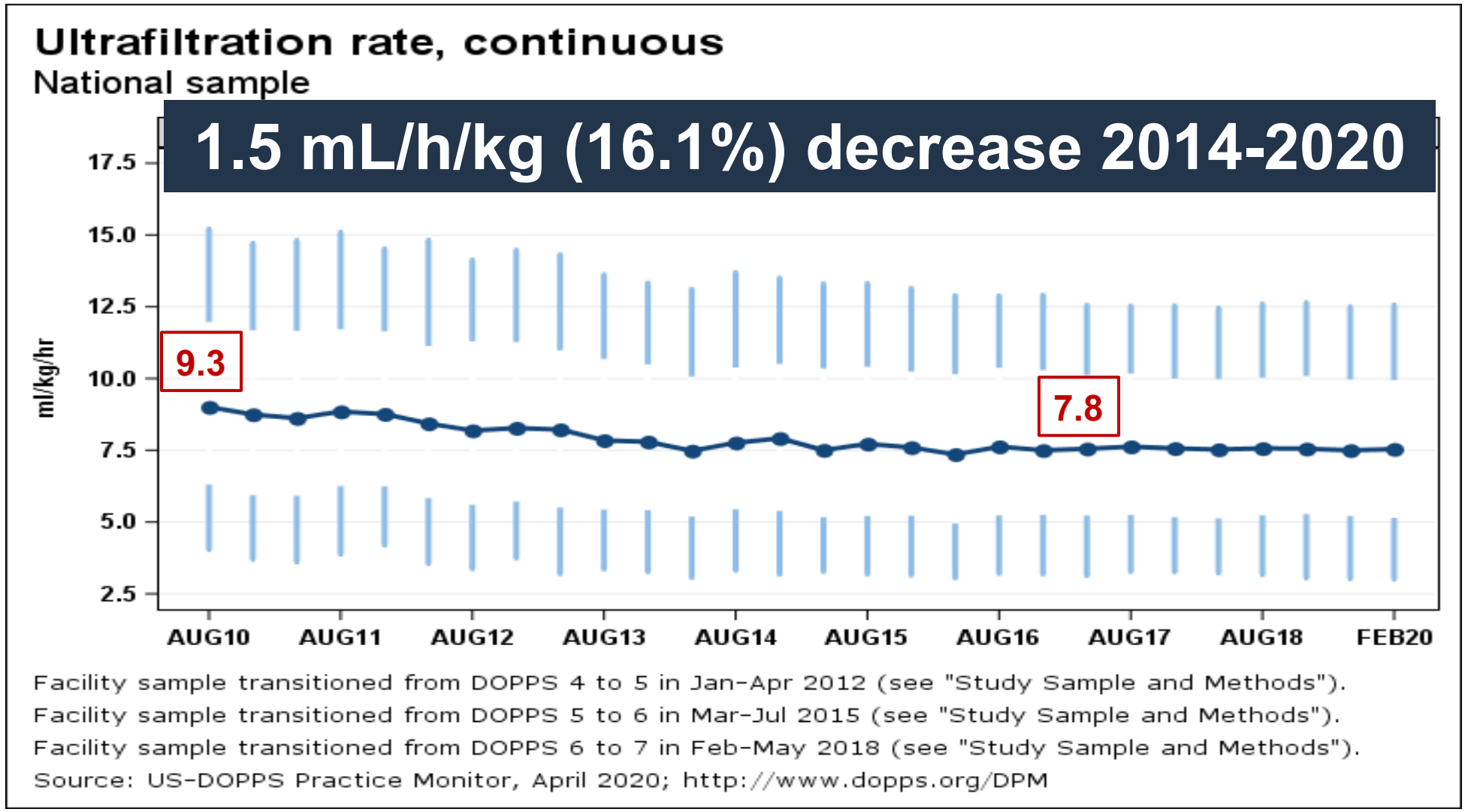
% of patients in the clinic with average **post-HD weight ≥1 kg above or below the prescribed target weight**

Fluid Removal Rate Measure

% of patients in the clinic with average **UF rate ≥13 mL/h/kg**

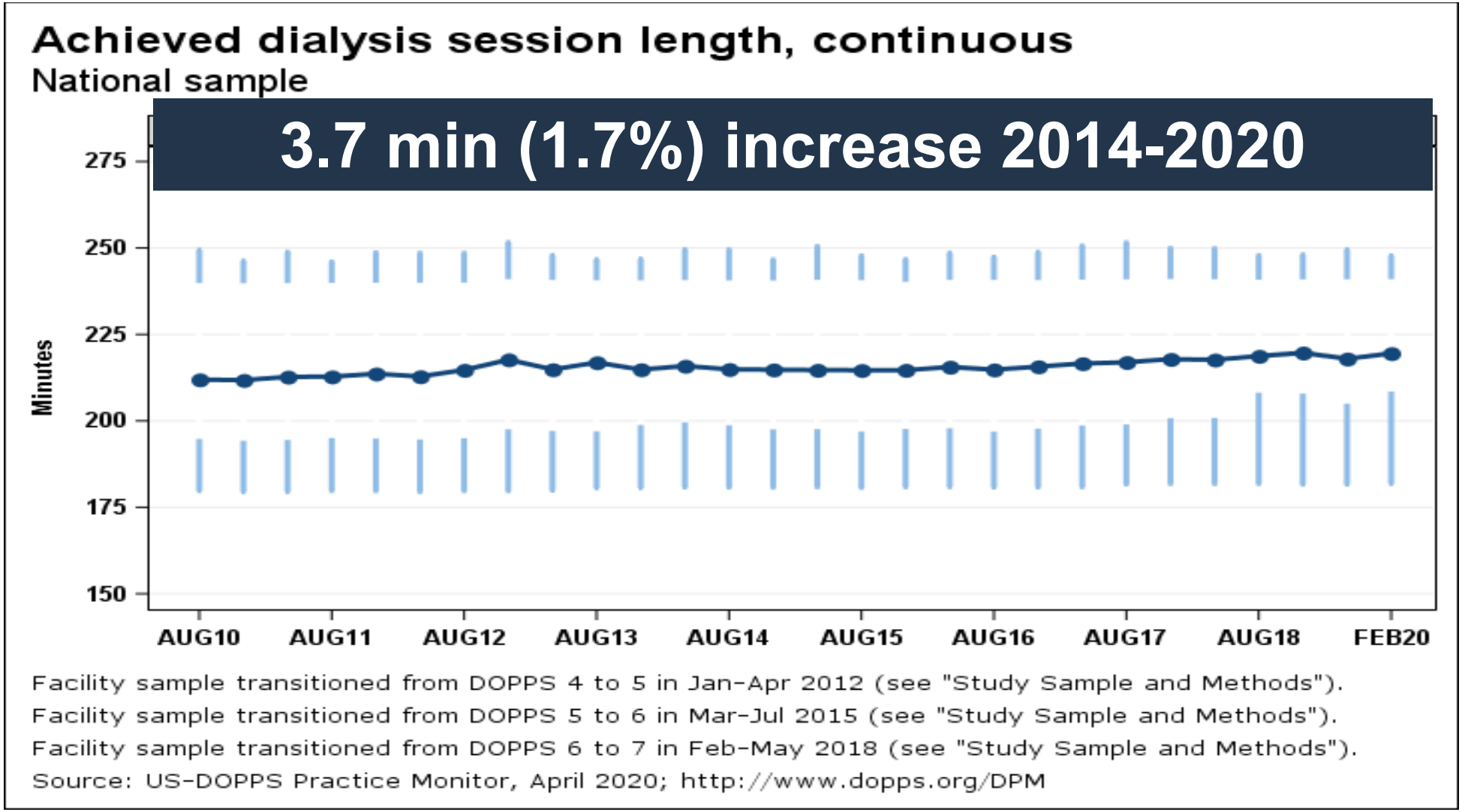


U.S. ultrafiltration rate trends



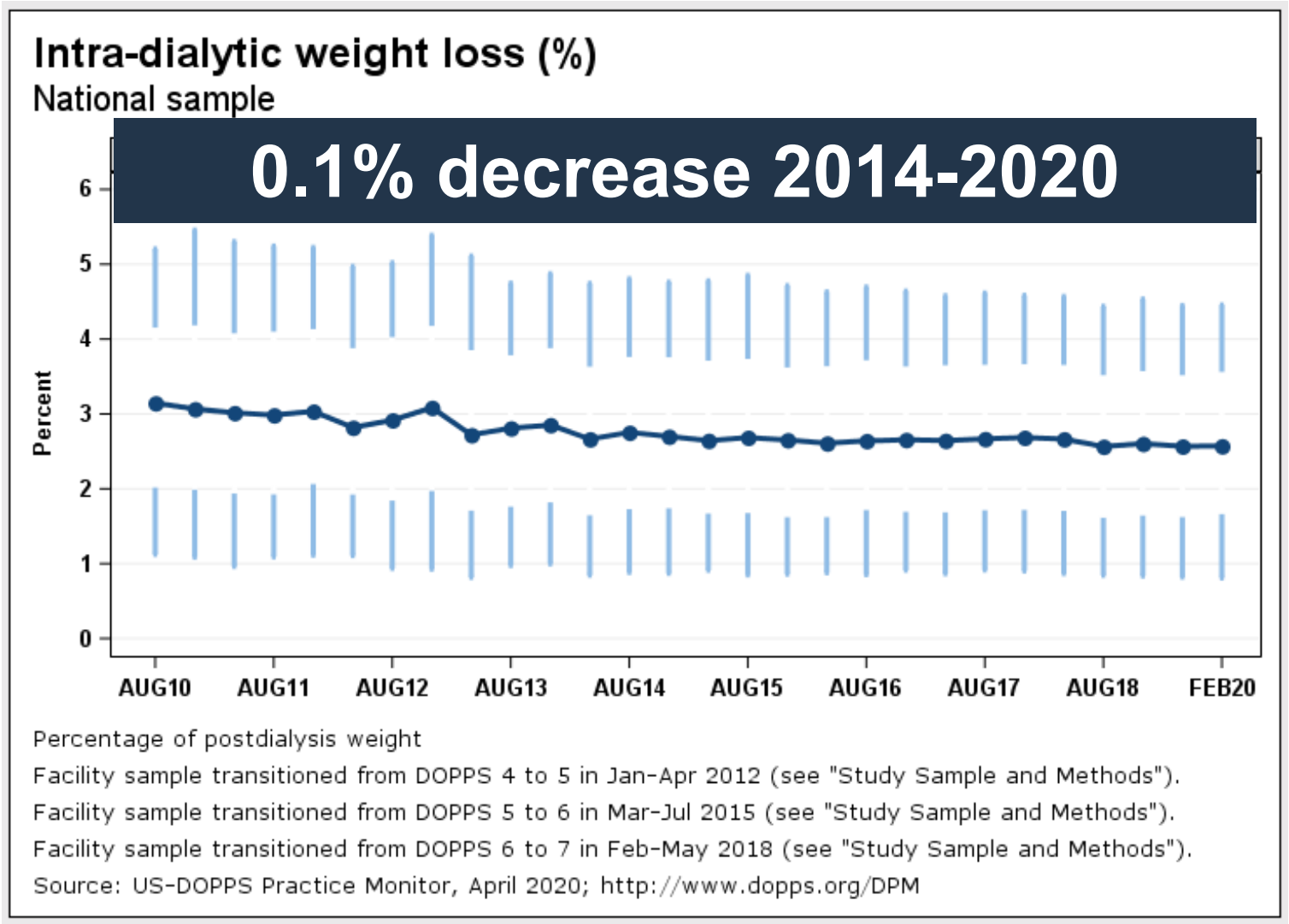
DOPPS Practice Monitor, 2020.

U.S. treatment time trends



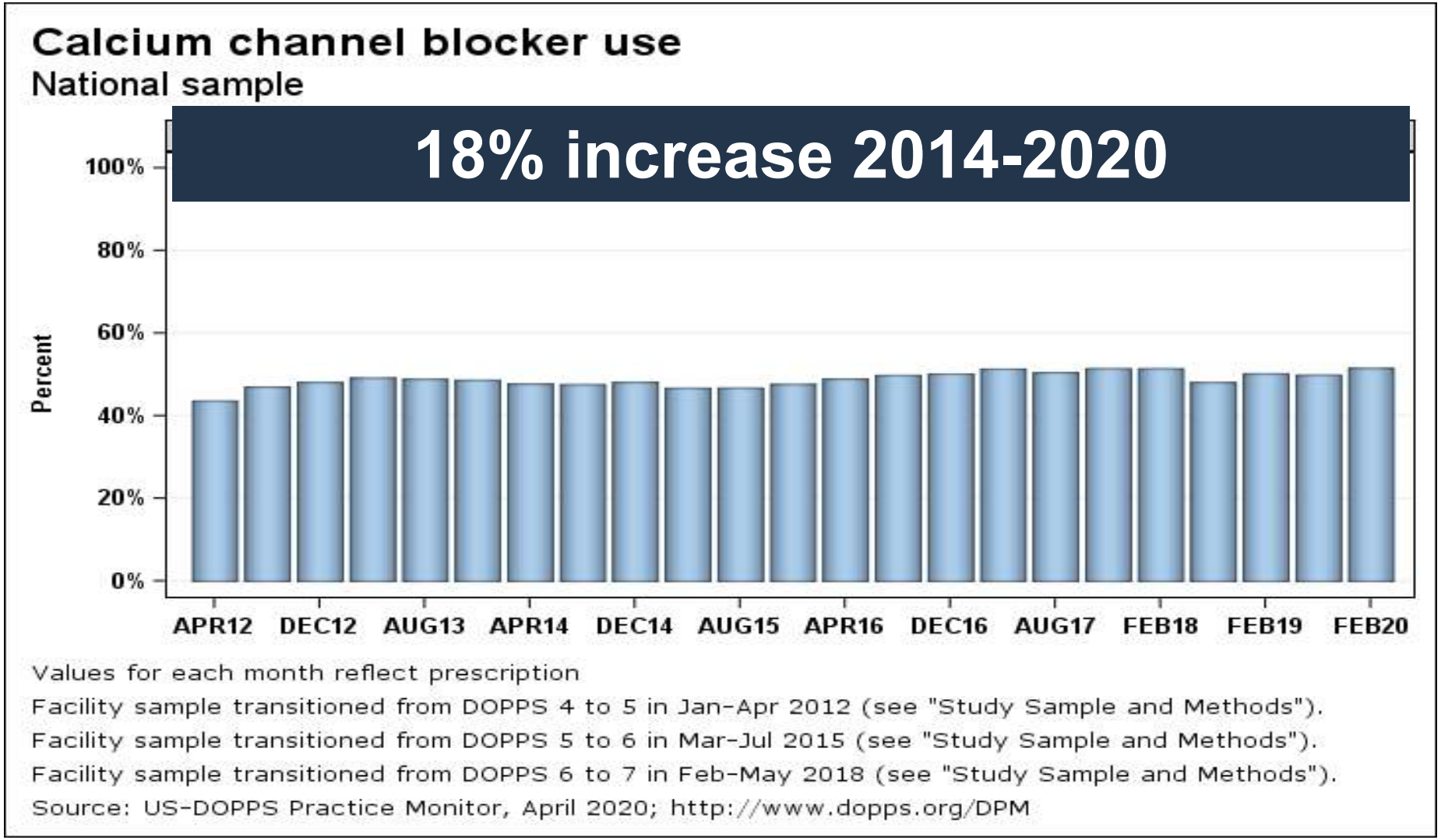
DOPPS Practice Monitor, 2020.

U.S. ultrafiltration volume trends



DOPPS Practice Monitor, 2020.

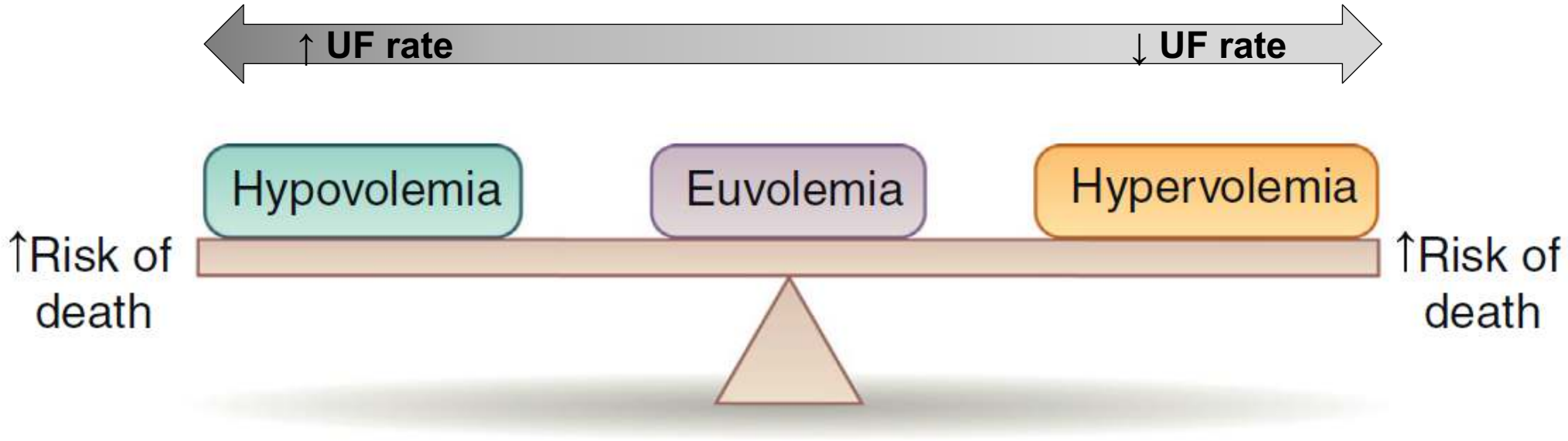
U.S. calcium channel blocker use trends



DOPPS Practice Monitor, 2020.

Ultrafiltration rate minimization *without* volume expansion

Volume management must be individualized



"Managing blood pressure and volume in dialysis requires an *individualized approach* with integration of numerous clinical, dialysis treatment, and patient factors."

Flythe. Kid Int, 2020.

Existing opportunities for improvement

Individualized volume management

Strategies

- Home therapies
- Cooled dialysate
- Longer treatment time
- Extra treatments
- Sodium balance alteration
  - ✓ Dialysate sodium
  - ✓ Exogenous sodium
- UF profiling
- Adjunct diuretics
- Patient priorities

Tools

- Longitudinal data
  - ✓ BP (HD tolerance)
  - ✓ Weights
  - ✓ UF volume/ rate
- Symptoms
- Volume measurement
  - ✓ Blood volume monitors
  - ✓ Physical exam
  - ✓ Ultrasound (?)
  - ✓ Bioimpedance (?)

Individualized volume management

Strategies

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- Cooled dialysate
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  - ✓ Ultrasound (?)
  - ✓ Bioimpedance (?)

Case 1: adjunct diuretics

- Hemodialysis
  - IDWG = 5-6 kg
  - TT = 4 h
  - Target weight = 98 kg
  - No furosemide
  - ~250 mL urine output/ day

- Hemodialysis
  - IDWG = 4-5 kg
  - TT = 4 h
  - Target weight = 98 kg
  - Furosemide 160 mg BID
  - ~750 mL urine output/ day

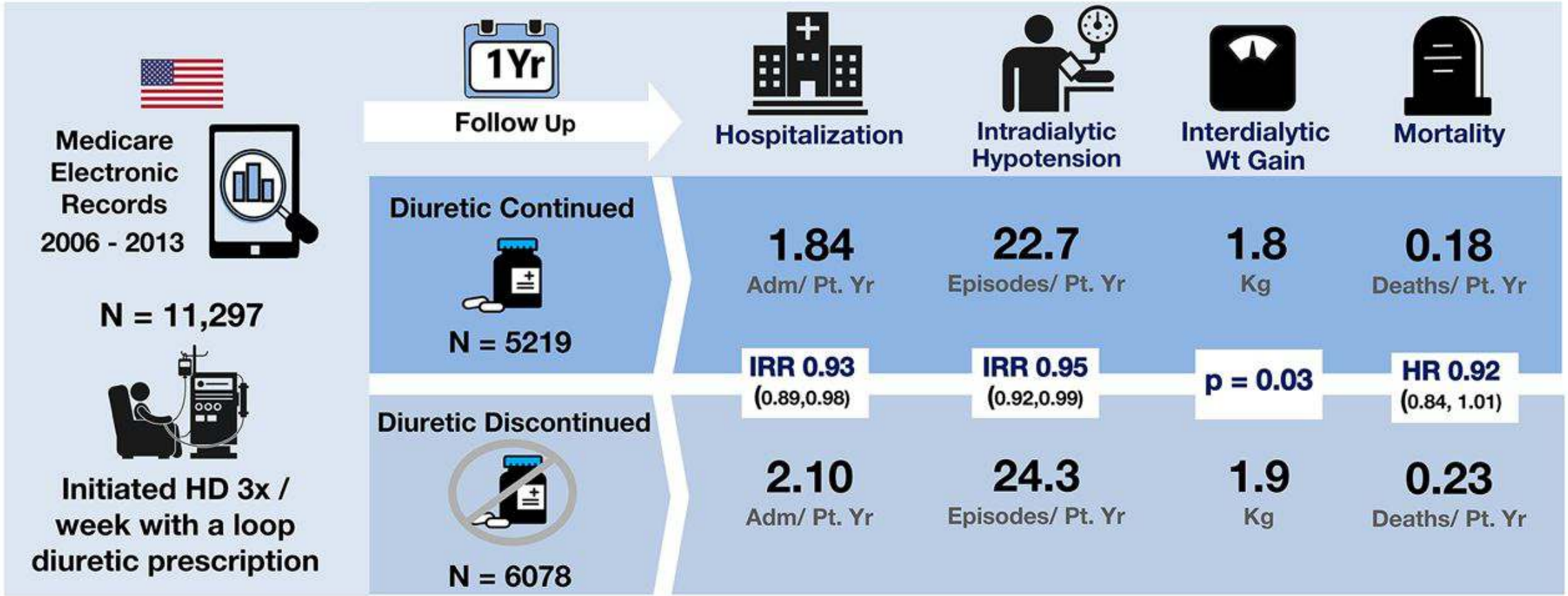
UF rate = 12.8 - 15.3 mL/h/kg → UF rate = 10.2 - 12.8 mL/h/kg

Adjunct diuretics in dialysis patients

Study (year)	Population (N; location)	Study design/ diuretic	Outcome with diuretic
Bragg-Gresham (2007)	Incident & prevalent **HD** (16,420; multinational)	Observational cohort: diuretic vs. not	•↓ IDWG •↓ IDH •↓ hyperkalemia •↓ CV mortality
van Olden (1992)	Prevalent **HD** & 100 mL UO/day (13; Netherlands)	Prospective cohort: furosemide	•↑ 24-h urine vol. & Na^+
Flinn (2006)	Prevalent **PD** (61; Canada)	Prospective cohort: furosemide vs. control	•↓ anuria (non-sig trend)
Medcalf (2001)	Incident **PD** (61; U.K.)	RCT: furosemide vs. control	•↑ 24-h urine vol. & Na^+ •↓ weight gain

Can continuing loop diuretics improve clinical outcomes in HD?

CJASN
Clinical Journal of American Society of Nephrology



Conclusions Continuation of loop diuretics is associated with lower rates of hospitalization, intradialytic hypotension and lower interdialytic weight gain, but no difference in mortality over first year of HD initiation.

Scott Sibbel, Adam Walker, Carey Colson, Francesca Tentori, Steven Brunelli, Jennifer Flythe.
Association of Continuation of Loop Diuretics at Hemodialysis Initiation with Clinical Outcomes. CJASN doi: 10.2215/CJN.05080418.
Visual Abstract by Divya Bajpai, MD

Case 2: target weight vigilance

- 66y man with heart failure (EF 25%) with frequent hospitalizations

- Hemodialysis
  - Typical IDWG = 3 – 3.5 kg
  - TT = 4h M-W-F
  - Target weight = 70 kg
  - Post-HD weights (last 4 treatments)
    - Mon: 73 kg
    - Wed: 72 kg
    - Fri: 71.5 kg
    - Mon: 72 kg

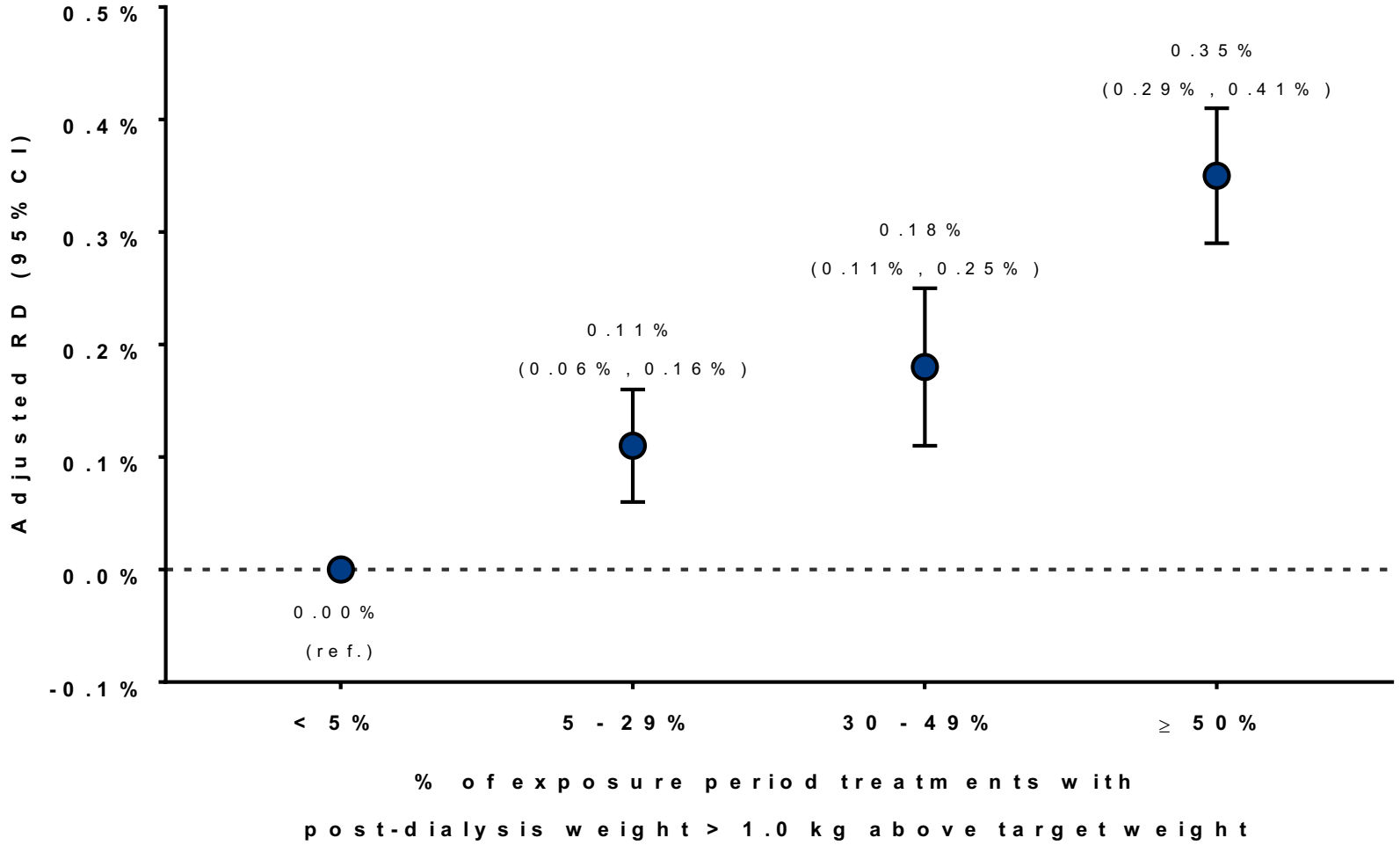
UF rate = 10.7 - 12.5 mL/h/kg

Failure to achieve target wt

Post-dialysis weight > target weight → 30-day death

- U.S. cohort (N=113,561)

The more frequent the target weight "misses" → the higher the 30-day death risk

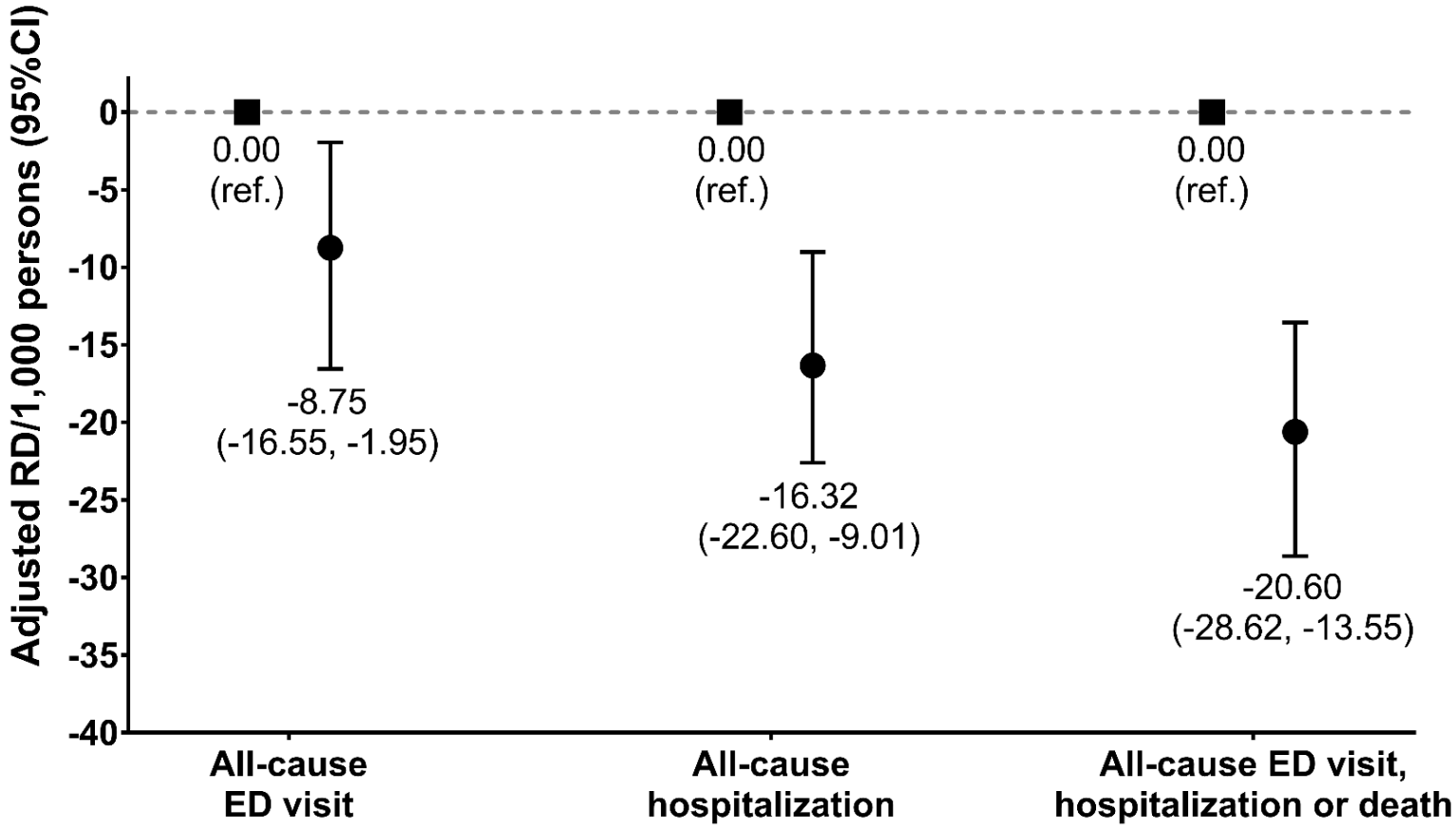


Assimon/ Flythe. J Am Soc Nephrol, 2018.

Target weight prescription and readmissions

- N= 44,460 patients with hospitalizations
- Exposure: target weight adjustment (vs. not) within 7 days of hospital discharge

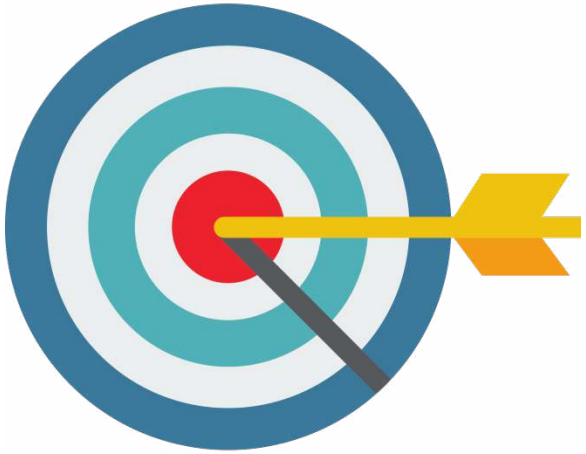
Target weight adjustment (any direction) after hospitalizations → ↓ adverse events



Assimon/ Flythe. J Am Soc Nephrol, 2018.

Target weight achievement vigilance

- Identify target weight achievement problem
  - Assess reasons (hemodynamics, symptoms, other)
  - Target weight adjustment? (exam, history, treatment tolerance and history)
  - Additional treatment?
  - Treatment time adjustment?
  - Other



- Take action
  - Root cause: single episode of large IDWG 10 days ago
  - Solution: **add single extra treatment (3h) to return to target weight**
  - Achieved target weight after extra treatment

Case 3: patient priorities

- 48y woman with vascular disease s/p L BKA, heart failure (EF 40%)

- Hemodialysis
  - Typical IDWG = 2.5 – 3 kg
  - TT = 3.5h T-R-Sat
  - Target weight = 82.0 kg

UF rate = 8.7 - 10.4 mL/h/kg

Hypotension

Cramping

Inadequate HD

  - Pre-HD SBP: 90s (nadir ~80 mmHg)
  - Leg cramping ¾ way through treatment
  - Kt/V = 1.1

Patient priorities and clinical performance metrics do not align

Patient priorities

- Quality of life
- Symptoms
- Dialysis-free time
  - ✓ Travel
  - ✓ Work/ go to school
- Caring relationships

Clinical metrics

- Hospitalizations
- KT/V (adequacy)
- Calcium, phosphorus
- Hemoglobin
- UF rate
- Vascular access type

Identify and align priorities

Medical Priorities

- Minimize cardiovascular risk
- Avoid hypotension
- Prevent cramping

Patient Priorities

- Spend time with family
- Pain-free dialysis

Cramping
Post-dialysis fatigue

Priority-directed Dialysis

- ↑ TT to 4 hours for 4 weeks
- Follow symptoms weekly (cramping, recovery time)
- (+) Patient-perceived improvement: *maintain TT ↑*
- (-) Patient-perceived improvement: *return to prior TT*

Case 4: patient priorities

- 55y man
  - Diabetes, heart failure (EF 45%, history of hospitalizations)
  - Myasthenia gravis on bimonthly plasmapheresis

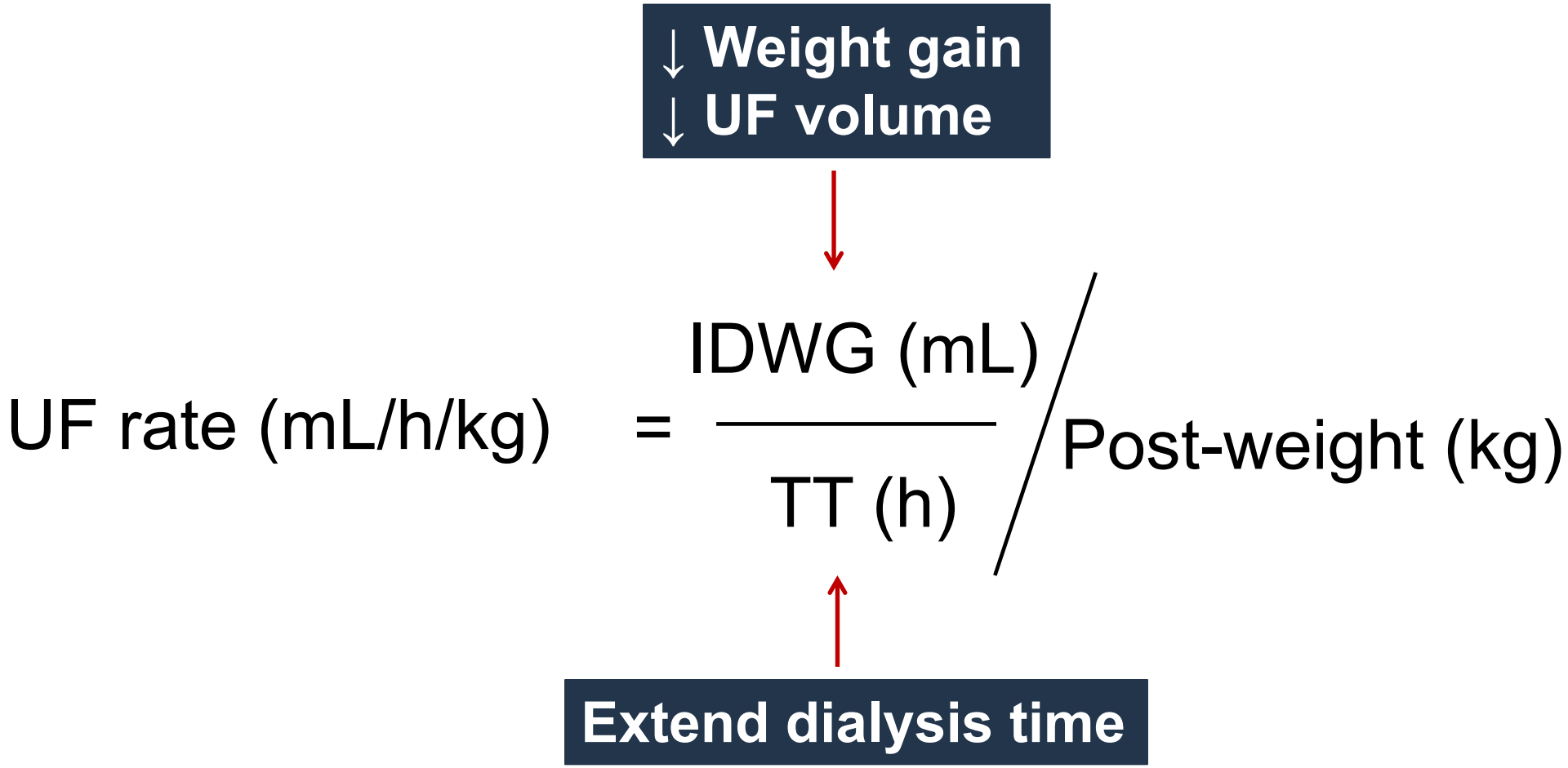
- Hemodialysis (3x/week)
  - IDWG = 3 - 4.5 kg
  - TT = 3.5 hours
  - Target weight = 73 kg
  - Post-weights = ~73 kg
  - eKt/V = 1.6
  - No urine output

UF rate = 11.7 – 17.6 mL/h/kg

Weekly mean
UF rate = 14.6 mL/h/kg

Asymptomatic hypotension

UF rate mitigation



$$\text{13 (mL/h/kg)} = \frac{\text{IDWG (kg)}}{\text{TT (h)}} \Big/ \text{73 (kg)}$$

UF rate

Post-weight

Patient priority: Minimize time at clinic

Tuesday

4h treatment

weekend IDWG goal = <3.8 kg

1.3 L/day w 72 h break

~13 mL/h/kg

Thursday and Saturday

3.25 h treatment

IDWG goal = <3 kg

1.5 L/day w 48 h break

~12.6 mL/h/kg

10.5 h/week treatment

Actual mean UF rate = 12 mL/h/kg

"The new schedule works great for me. It is a good balance between what is good for me- more time at dialysis- and my quality of life- which is more time at home."

MY DIALYSIS PLAN™

YOUR CARE PLAN MEETING IS COMING UP!

During this meeting, you and your care team will work together to make decisions about your health, well-being, and dialysis care. This brochure explains what to expect and how to prepare.

Your dialysis care plan should be made just for you!

- What matters to you?
- What does a good day look like for you?
- What changes do you want to see in your life?
- What would you like to be able to do that you can't do now?
- What questions or concerns do you have about dialysis or your care?

https://unckidneycenter.org/kidneyhealthlibrary/my-dialysis-plan/

Dorough/Forfang/Flythe. Neph Dial Trans, 2020.

Future opportunities for improvement

Volume management: policy drivers

Executive Order on Advancing American Kidney Health

HEALTHCARE | Issued on: July 10, 2019

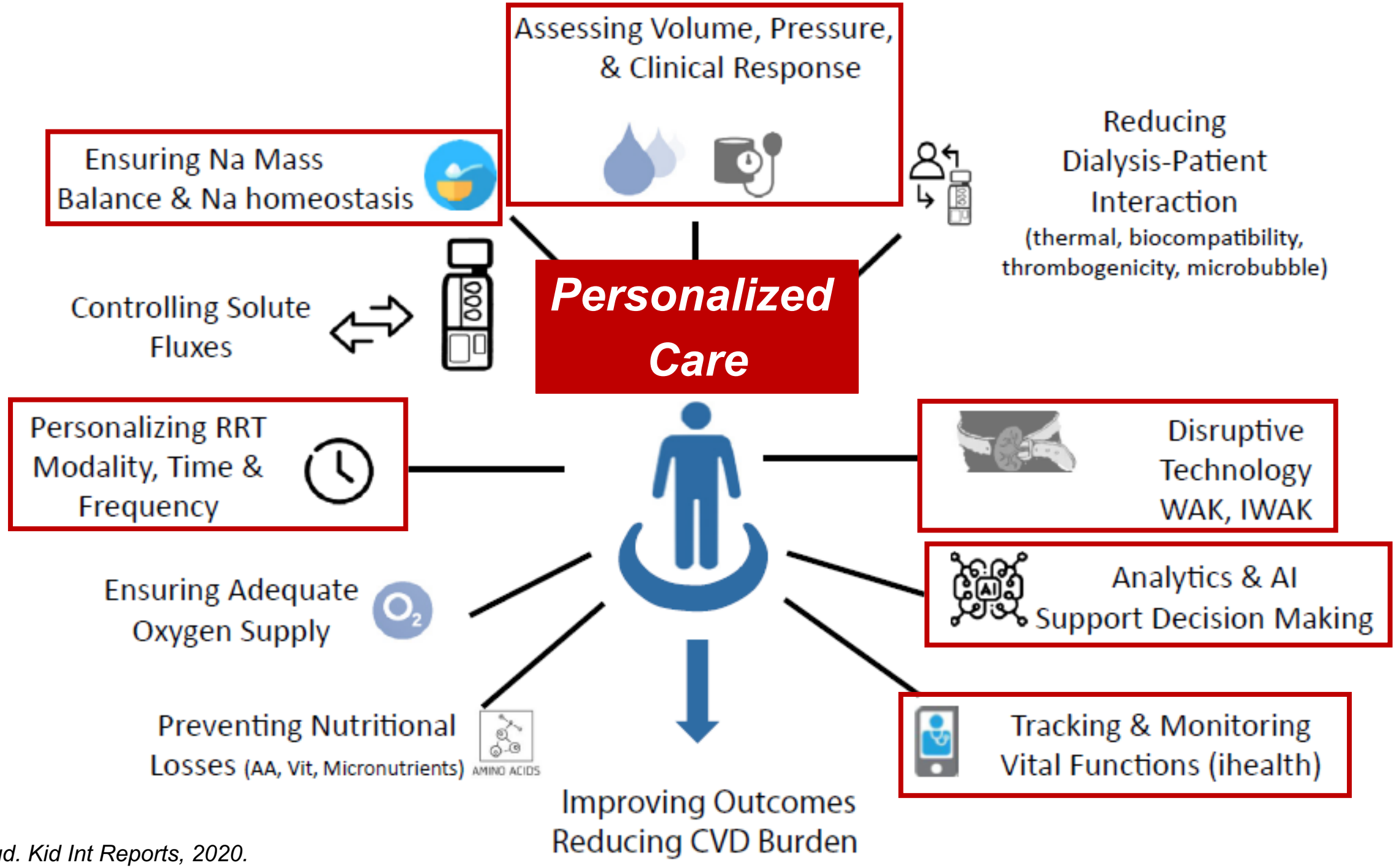
★ ★ ★

KIDNEY X
INNOVATION ACCELERATOR

Public-private partnership between HHS and ASN to accelerate innovation in the prevention, diagnosis, and treatment of kidney disease

Redesign Dialysis

https://www.hhs.gov/cto/initiatives/kidneyx/index.html and https://www.kidneyx.org/prizecompetitions/RedesignDialysisPhaseII



Canaud. Kid Int Reports, 2020.

Summary and Key Take-Aways

- Higher UF rates and extracellular volume expansion are associated with adverse outcomes.
- UF rate minimization and euvolemia are both important. Their relative importance is unknown.
- Fluid management plans should be individualized based on patient risk profiles, preferences and, possibly, symptoms.
- Coming advances will make individualization of volume management easier, but individualization in the current care setting ***is ACHIEVABLE.***

Questions?