The 21th Budapest Nephrology School

August, 29,2014

Dialysis 2014

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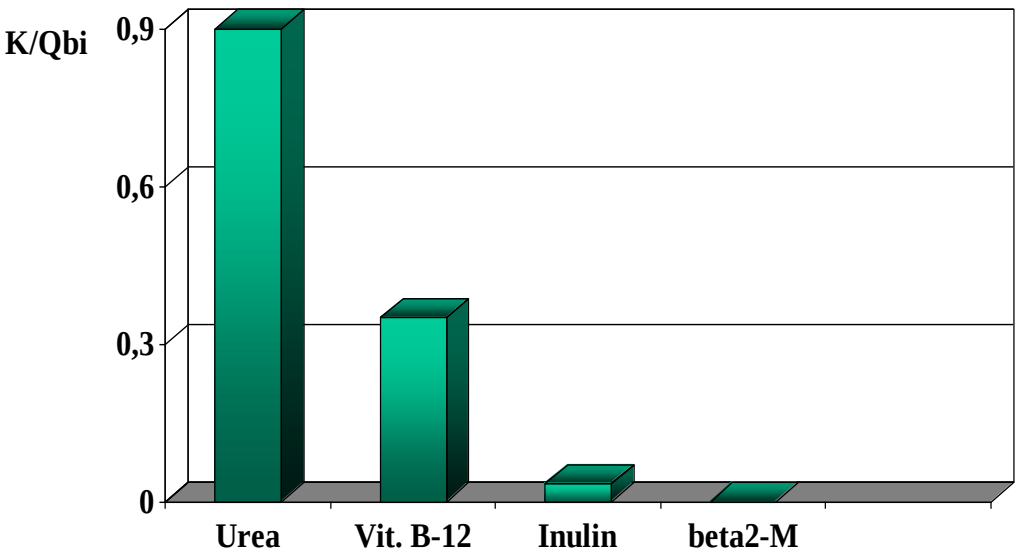
Standard Haemodialysis

3 times weekly, 4 h per session

low flux membranes

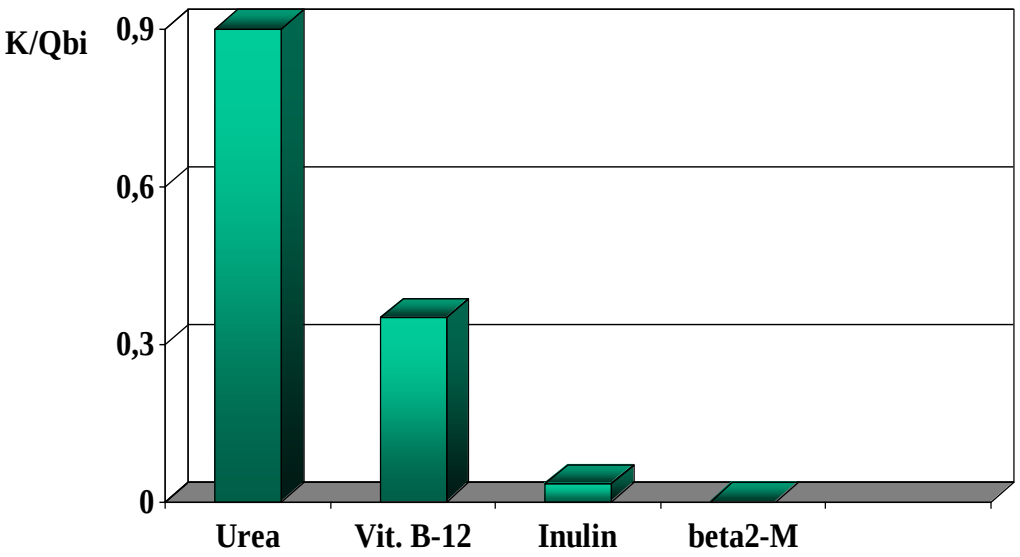
.... it is far from ideal in that it supports life but it fails to restore the patient to full functional normality and longevity

Standard Haemodialysis “in vitro clearances”



The low effectiveness of conventional HD is mainly referred to the hypothesis that high morbidity and mortality rates are associated with inadequate removal of “middle molecules”

Standard Haemodialysis “in vitro clearances”



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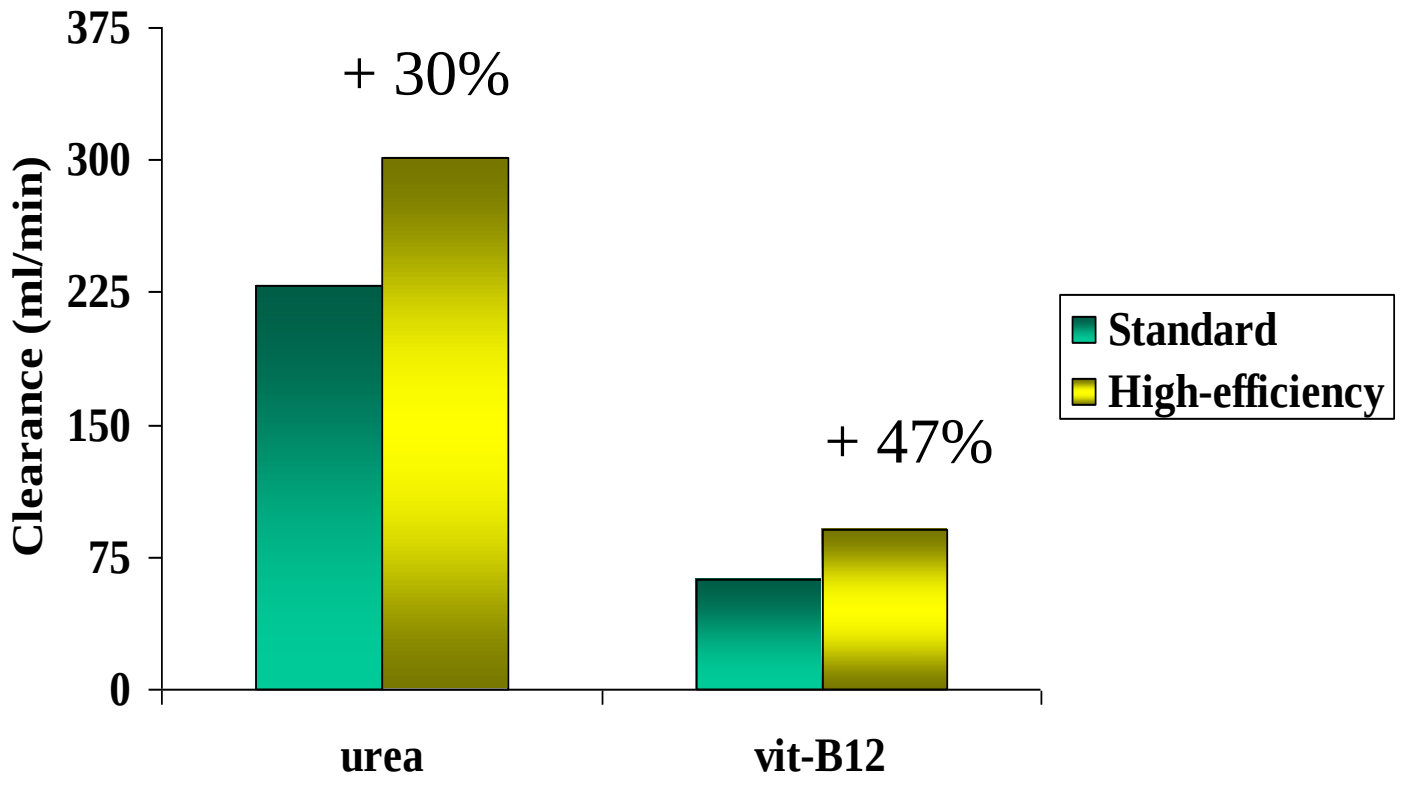
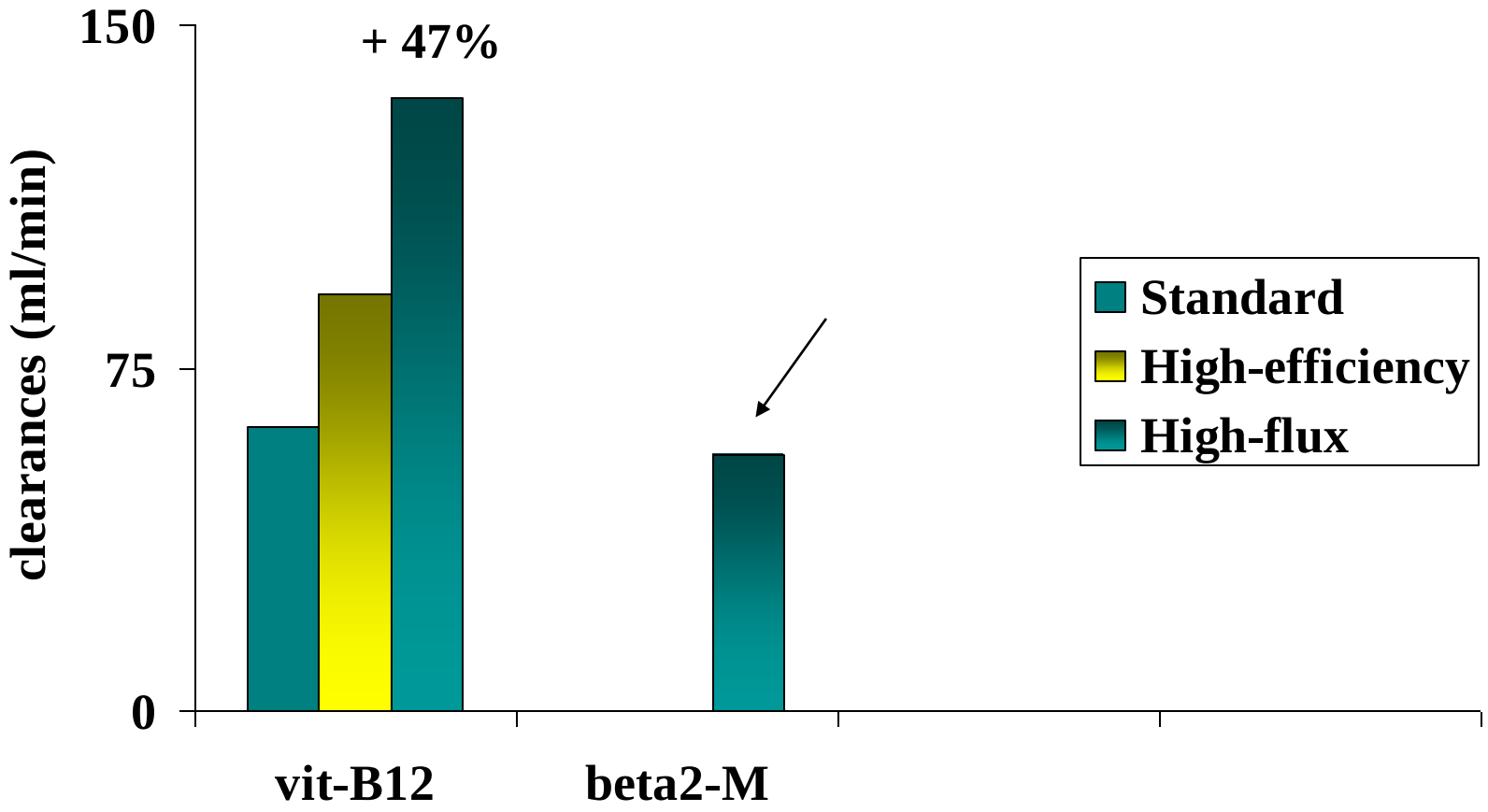
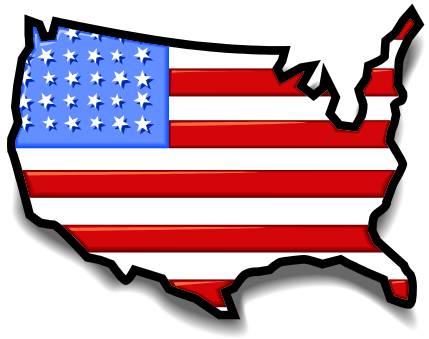
High-efficiency vs Standard Haemodialysis



High-Flux vs High-Efficiency and Standard Haemodialysis



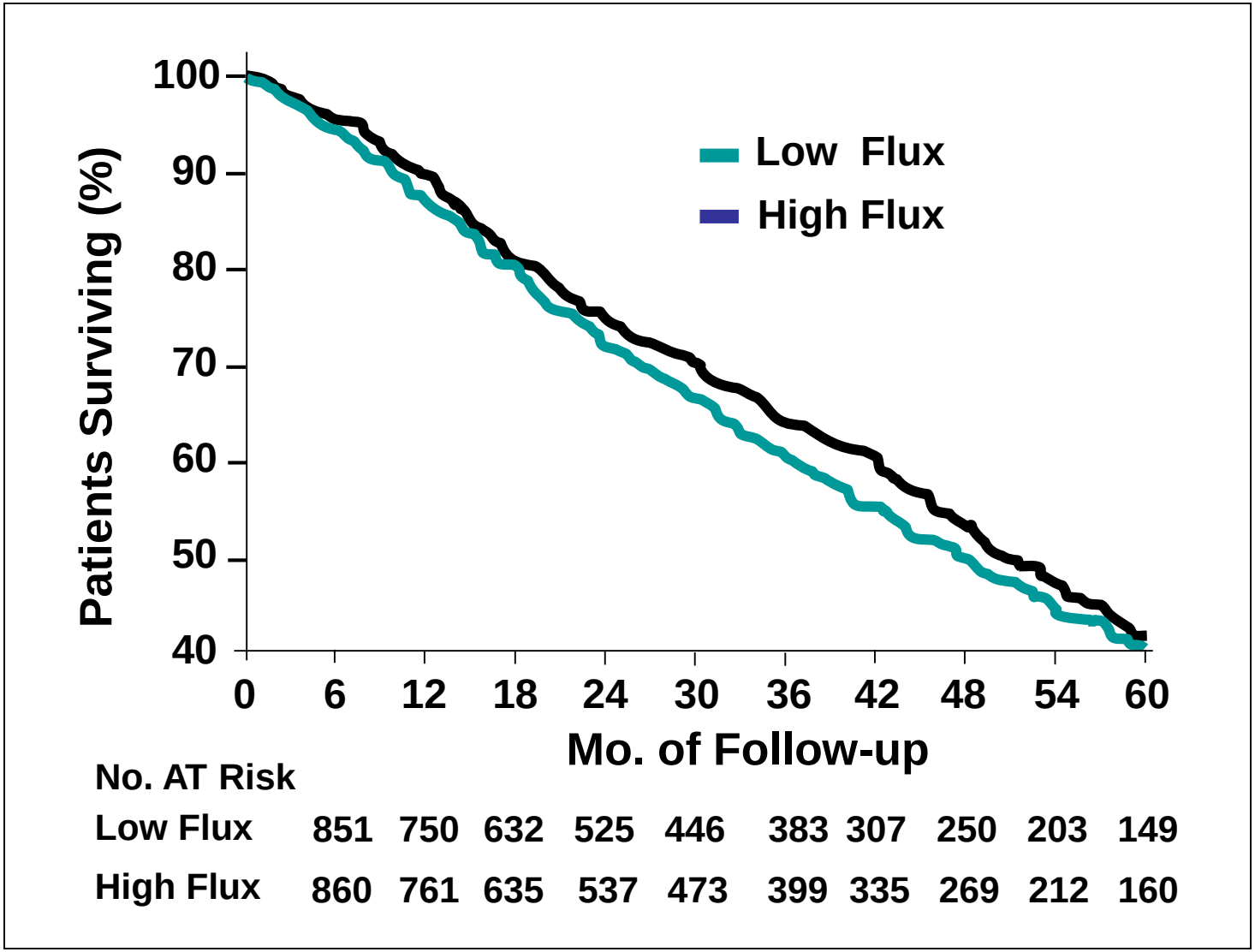


The HEMO Study in the US

The MPO Study in Europe

HEMO Study

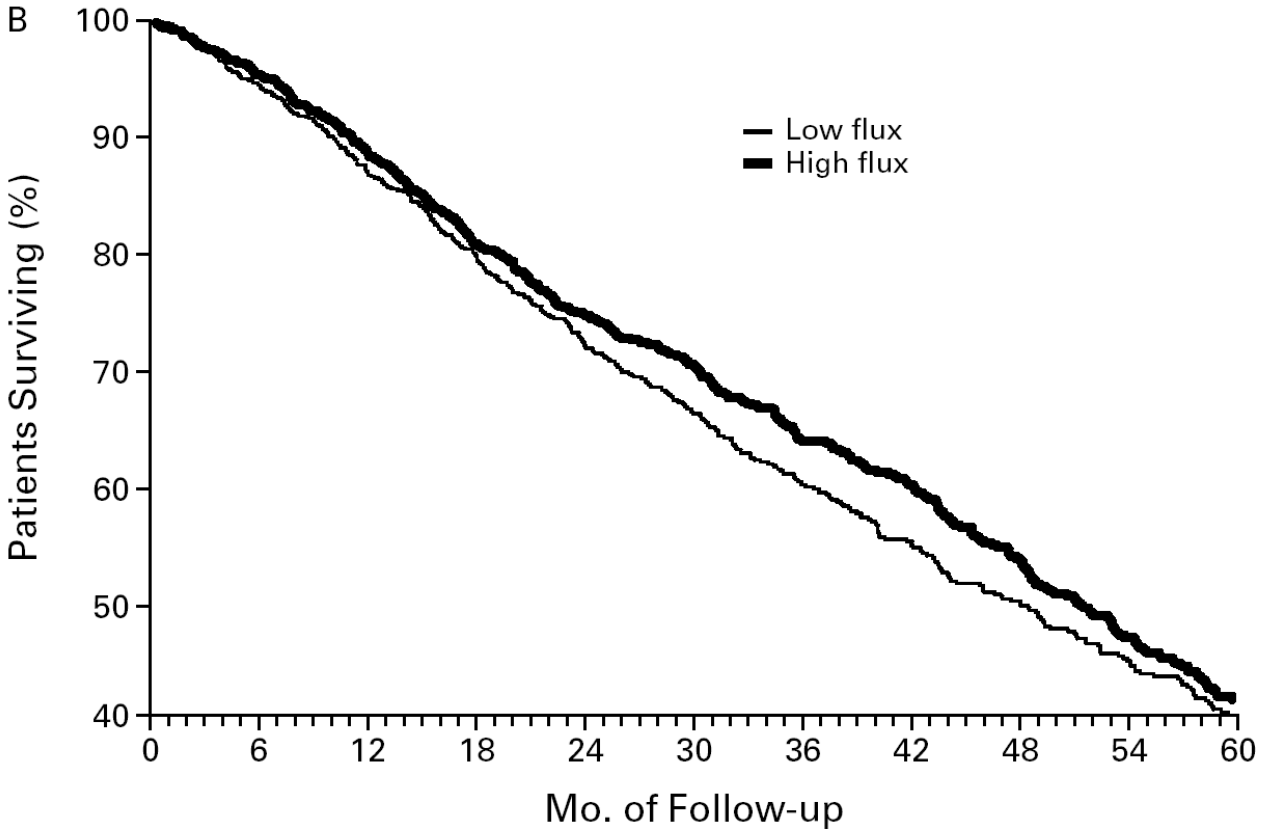
Effect of Membrane Flux on All-cause Mortality



No. AT Risk										
Low Flux	851	750	632	525	446	383	307	250	203	149
High Flux	860	761	635	537	473	399	335	269	212	160

Eknoyan et al. New Eng J Med 347: 2010-2019, 2002

After adjustment for the base-line factors, mortality in the high-flux group was 8 percent lower (P=0.23) than that in the low-flux group



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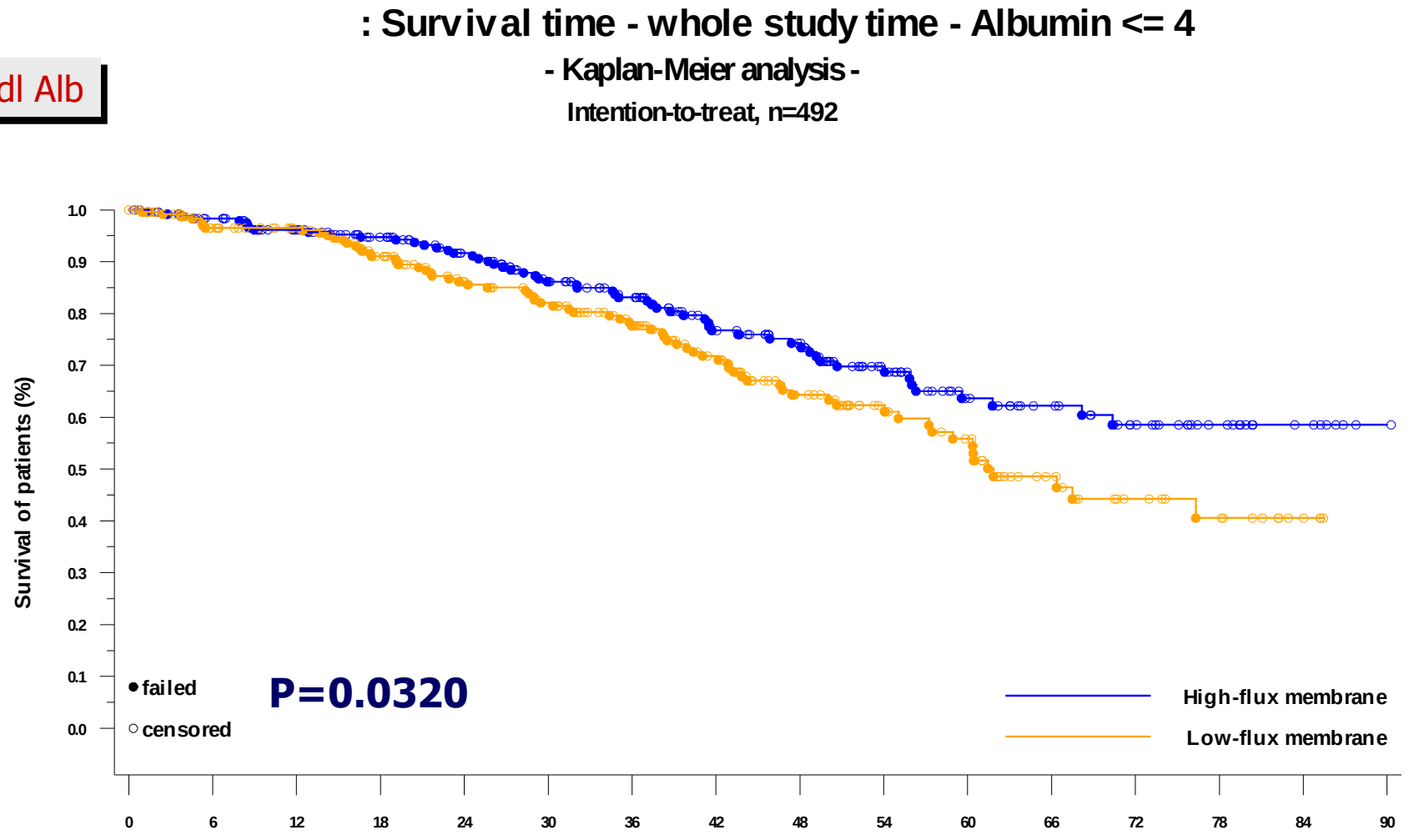
Eknoyan G et al N Engl J Med Vol 347, 2002

MPO : Kaplan-Meier Survival Analysis

≤ 4g/dl Alb

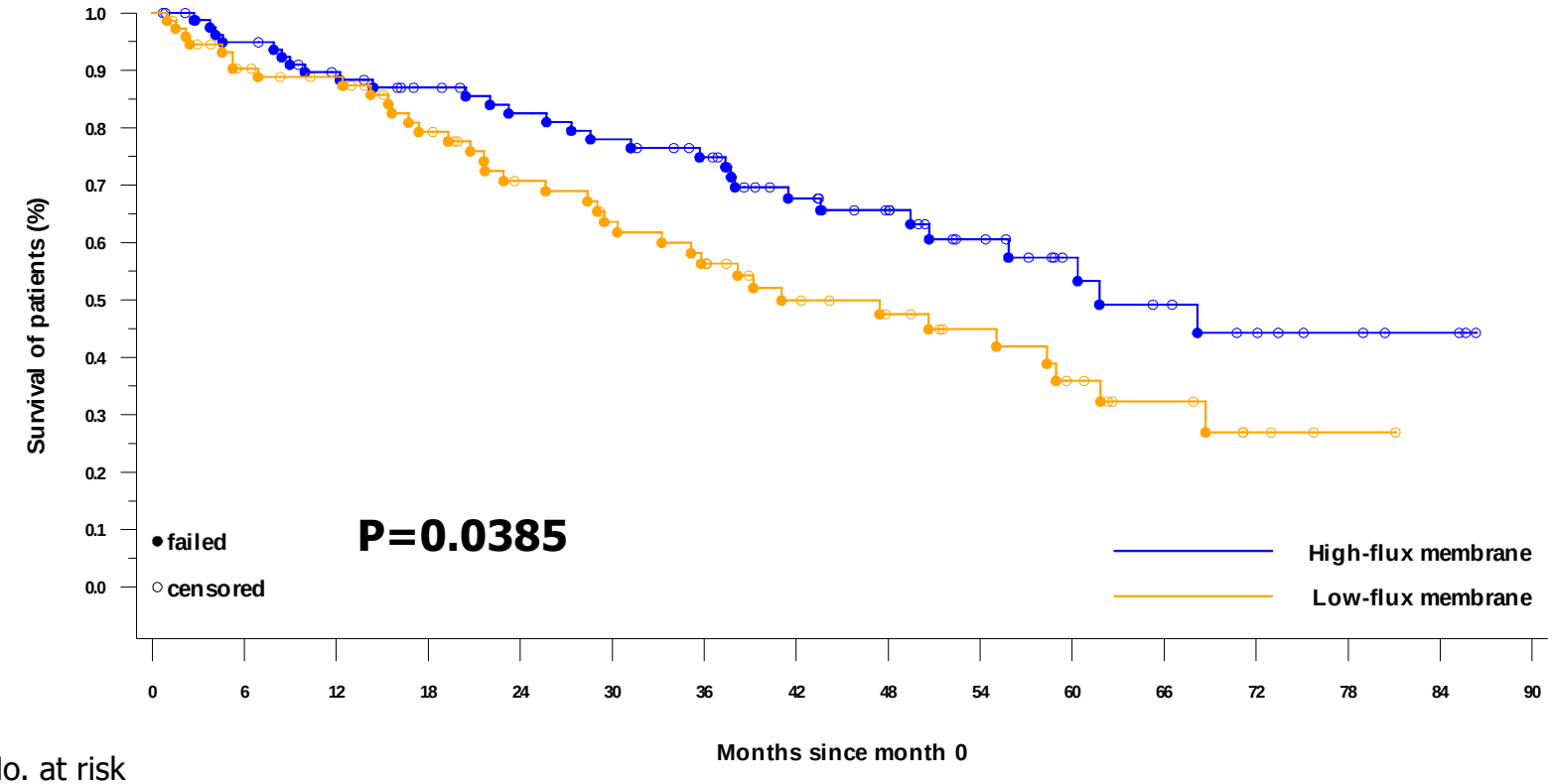


No. at risk								
High-flux	250	212	173	134	85	44	26	7
Low-flux	243	202	152	117	67	41	15	3

Locatelli F et al. J Am Soc Nephrol. 2009 Mar; 20 (3): 645-54

MPO : Kaplan-Meier Survival Analysis
Subgroup Analysis – Diabetics*

*Pts. with both serum albumin ≤ 4 and > 4 g/dl albumin



No. at risk								
High-flux	83	67	55	46	27	14	7	3
Low-flux	74	59	40	29	19	11	3	0

Locatelli F et al. J Am Soc Nephrol. 2009 Mar; 20 (3): 645-54

Randomised studies on the effect of High-Flux Haemodialysis on mortality risk

	Design	Treatment (patients)	Sample size	% relative risk reduction	P value
Locatelli et al. 1996	**Randomised, prospective**	Cuprophan-HD (132) LF-HD (147) HF-HD (51) HDF (50)	**380**		**NS**
Eknoyan et al. 2002	**Randomised, prospective**	HF-HD (921) LF-HD (925)	**1,846**	**8**	**NS**
Locatelli et al. 2009	**Randomised, prospective**	**Albumin ≤ 4 g/dl** HF-HD (279) LF-HD (283)	**562**	**37**	**0.032**
	Randomised, prospective	**Albumin > 4 g/dl** HF-HD (84) LF-HD (92)	**176**		**NS**
	Randomised, prospective, post-hoc analysis	**Diabetics** HF-HD (83) LF-HD (74)	**157**	**38**	**0.039**

LF-HD: low-flux haemodialysis; HF-HD: high-flux haemodialysis; HDF:haemodialfiltration

Locatelli F et al. Contrib Nephrol 2011; 168: 5-18

ERBP

European Renal Best Practice

High-flux or low-flux dialysis: a position statement following publication of the MPO study

- **MPO study provides sufficient evidence to upgrade the strength of guideline 2.1 to a level 1A (strong recommendation, based on high-quality evidence): high-flux HD should be used to delay long-term complications of hemodialysis in the case of high-risk patients (comparable to the low-albumin group of the MPO study)**

- **Because the substantial reduction of an intermediate marker (beta2-microglobulin) in the high-flux group of the MPO study, synthetic high-flux membranes should be recommended even in low-risk patients (level 2b: weak recommendation, low quality evidence)**

Tattersal J et al. Nephrol Dial Transplant 2010; 25(4):1230-1232

Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

Time of treatment initiation and dialysis modality

- Studies of patients on HD (Kazmi, Wilson), reported a higher mortality with early treatment
- Studies of patients on PD indicated better survival with early initiation in one case (Tang) and “contradictory” results in the other (Shiao)
- Mixed HD/PD studies in one case (Beddhu) indicated a 1.4-fold rise in the risk of death for every increase of 5 mL/min in eGFR at initiation of treatment, and in the other (Korevaar) a small beneficial effect of early initiation

Cantero-Munoz P et al. Nephrol Dial Transplant 2010; 25: 2214-2221

Influence of early dialysis among patients with advanced chronic renal disease: results of a systematic review

- The main limitation of these studies is the presence of lead-time bias: an erroneous survival benefit is

The main limitation is the presence of lead-time bias

that is, earlier initiation of dialysis prolongs time on dialysis but does not change patient survival

- **No conclusions can be drawn as to the optimal time for initiating RRT as these studies are contradictory and include methodological shortcomings**

from prospective studies

Cantero-Munoz P et al. Nephrol Dial Transplant 2010; 25: 2214-2221

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 12, 2010 VOL. 363 NO. 7

A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

Bruce A. Cooper, M.B., B.S., Ph.D., Pauline Branley, B.Med., Ph.D., Liliana Bulfone, B.Pharm., M.B.A., John F. Collins, M.B., Ch.B., Jonathan C. Craig, M.B., Ch.B., Ph.D., Margaret B. Fraenkel, B.M., B.S., Ph.D., Anthony Harris, M.A., M.Sc., David W. Johnson, M.B., B.S., Ph.D., Joan Kesselhut, Jing Jing Li, B.Pharm., B.Com., Grant Luxton, M.B., B.S., Andrew Pilmore, B.Sc., David J. Tiller, M.B., B.S., David C. Harris, M.B., B.S., M.D., and Carol A. Pollock, M.B., B.S., Ph.D., for the IDEAL Study*

Multicenter, randomized, controlled trial

- **To examine whether the timing of the initiation of maintenance dialysis influenced survival among patients with chronic kidney disease.**
- **Primary outcome: death from any cause.**

Study Course

July 2000 – Nov. 2008

GFR 10-15 ml/min

2928 pts were screened

32 Centers in Australia and New Zealand

mean 60.4 years
542 M, 286 F

828 underwent randomization

(355 diabetes)

Early-Start Group

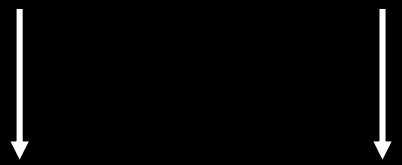
Late-Start Group

GFR 10-14 ml/min/1.73 m²	Cockroft-Gault	GFR 5-7 ml/min/1.73 m²
n.		n.
404	randomized	424
10	deaths before dialysis start	22
383	started dialysis	386
1.8 months	median time to dialysis initiation	7.4 months
(95% CI, 1.60 to 2.23)		(95% CI, 6.23 to 8.27)

Cooper BA et al. N Engl J Med 2010;363:609-19

Results

	Early-Start	Late-Start	
eGFR (ml/min/1.73 m^2) (Cockroft-Gault)	12.0 (18.6%<10)	9.8 (75.9%>7)	P< 0.001
MDRD (post-hoc)	9.0	7.2	P < 0.001
started HD/PD	n. 383	n. 386	
completed follow-up	134	166	
years of f-up (median, CI)	3.64 (0.03-9.15)	3.57 (0.02-8.78)	

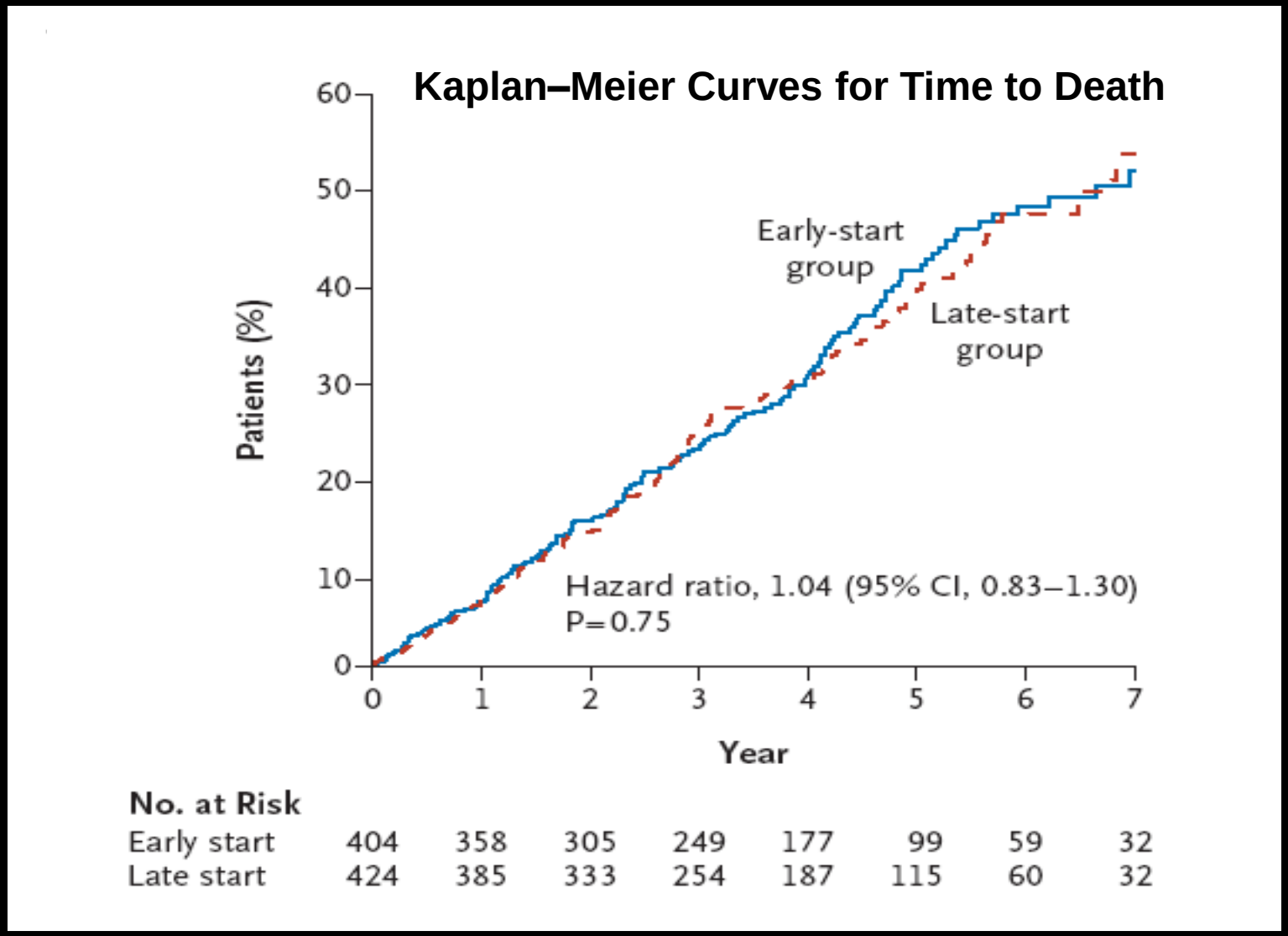


DEATHS	152 (37.6%)	155 (36.6%)

P < 0.75

Cooper BA et al. N Engl J Med 2010;363:609-19

Primary Outcome



Cooper BA et al. N Engl J Med 2010;363:609-19

A randomized, controlled trial of early versus late initiation of dialysis

Conclusions of the Authors

- Early initiation of dialysis, which has enormous implications in terms of cost and organization, had no s… h f… r complications of dialysis)

Early initiation of dialysis had no significant effect on clinical outcomes

- Dialysis should not be started on the basis of an … al … e … e traditional clinical indicators for HD initiation are present

Dialysis should not be started on the basis of GFR alone

Cooper BA et al. N Engl J Med 2010;363:609-19

A randomized, controlled trial of early versus late initiation of dialysis

Acknowledged Study Limitations

- **Use of eGFR based on the Cockcroft–Gault equation.**

  MDRD equations were not widely used when the trial was designed and had not been validated in patients with low levels of renal function.

- **Lack of the use of a uniform method of creatinine assessment. Pitfalls related to creatinine level variability with sex, race, mass, etc.** Likely to have been mitigated by patients stratification according to the study center.

- **Mean eGFR difference of only 2.2 ml/min between the two groups.**

  … its effect was an important difference of 6 months between groups in the start time for HD, reflecting the importance of close clinical follow-up in these patients.

Cooper BA et al. N Engl J Med 2010;363:609-19

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

The initiation of Renal-Replacement Therapy — Just-in-time delivery

Lameire N and Van Biesen W

- Do the results of the IDEAL trial imply that the initiation of dialysis can be delayed until an estimated GFR of 5 to 7 ml/min x 1.73 m^2 is r[illegible] **Clinical symptoms and patient follow up are of greater importance than eGFR** [illegible] patient follow-up are of greater importance in decision making than eGFR.
- A mean difference between the groups of 2.2 ml/min x 1.73 m^2 in [illegible] **Starting RRT on the basis of predefined eGFR does not improve the outcome** [illegible] and that starting RRT on the basis of a predefined eGFR does not improve the outcome.

New Eng J Med 2010; 363 (7): 678-680

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

The initiation of Renal-Replacement Therapy — Just-in-time delivery

Lameire N and Van Biesen W

- T… …or a… …6 m…

For asymptomatic patients, RRT can be delayed by an average of 6 months

- An important prerequisite for a “wait and see” policy is careful c… …ly a… …g p… …at permits the immediate initiation of dialysis if the patient becomes symptomatic

An important prerequisite for a “wait and see” policy is careful clinical follow up

- … …on… …he cornerstones of such a strategy

Early referral, patient-education program and planning before dialysis are the cornerstones

New Eng J Med 2010; 363 (7): 678-680

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

The patients were relatively healthy

No clear criteria for diagnosis of “uremia”

The Authors have not provided data on urinary output

The IDEAL study is not representative of CKD patients in US and UK

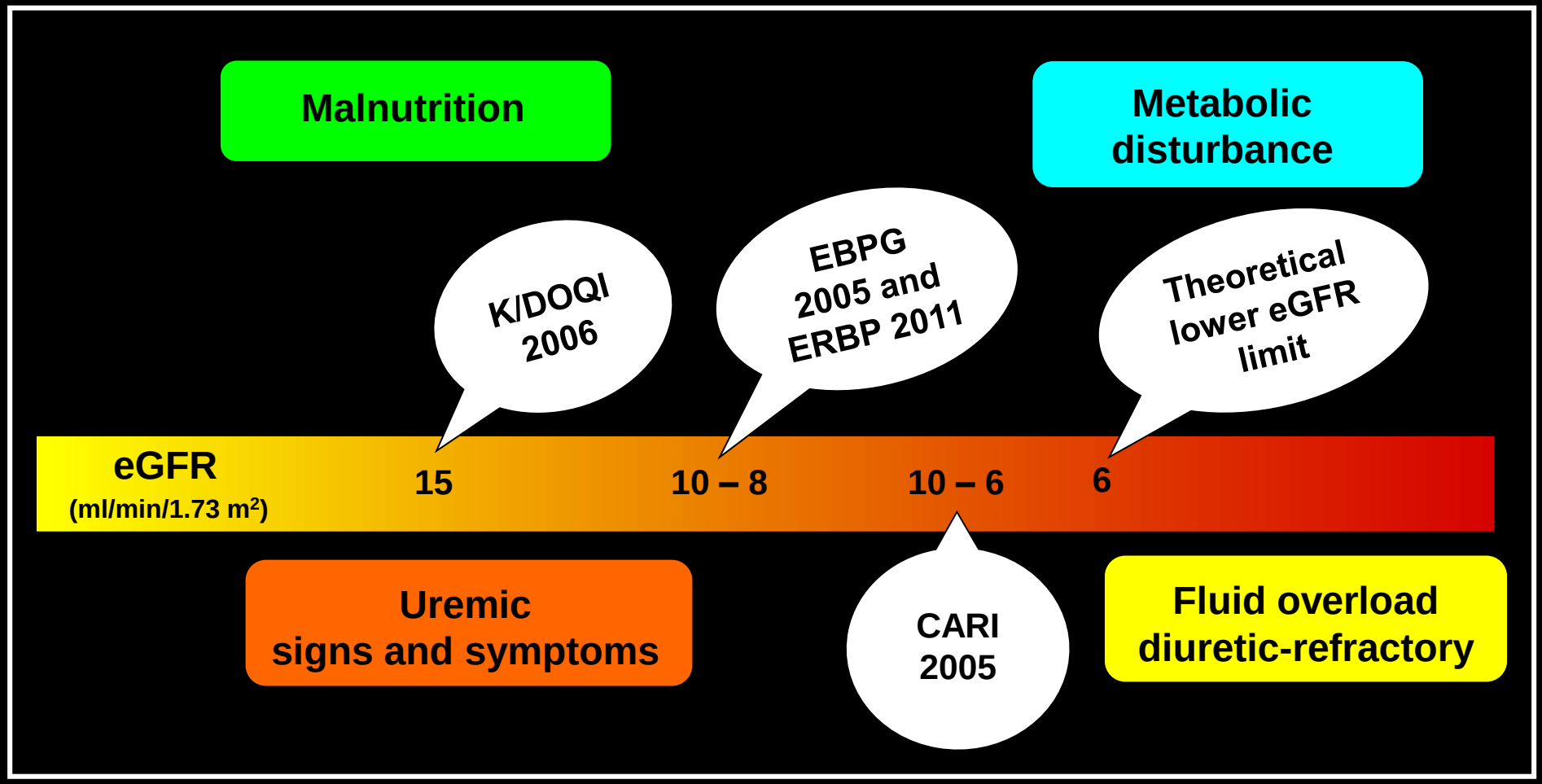
N Engl J Med 2010; 363 (24):2368-2370

Lessons learnt from the IDEAL study

- No benefit from “early-dialysis”
- Conservative therapy is possible also till GFR <10 ml/min (corresponding to 6 months dialysis delay)
- Importance of close clinical follow up in non-dialysis CKD stage 5 patients
- Pay more attention to patient symptoms than to eGFR
- Importance of nutritional status assessment
- Data from 24 hour urine collection (urea, sodium) are mandatory
- It is possible to safely reduce economic burden due to earlier dialysis

Locatelli F et al. Contrib Nephrol 2011

Dialysis beginning according to international guidelines and clinical data



Locatelli F et al. Contrib Nephrol 2011

Lessons from recent trials in hemodialysis

The IDEAL study: what can we learn?

- Even if with some limitations, the IDEAL study represents a very important trial. Its main message is the lack of a fixed GFR value at which to start dialysis in asymptomatic patients, suggesting to give more relevance to close patient monitoring (uremic signs and symptoms, fluid overload, malnutrition, etc.)
- This approach has been proven to be safe for the patients and effective in temporary delaying the need for dialysis

Locatelli F et al. Contrib Nephrol 2011

ERBP

European Renal Best Practice

When to start dialysis: Updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

James Tattersall, Friedo Dekker, Olof Heimbürger, Kitty Jager, Norbert Lameire, Elizabeth Lindley, Wim Van Biesen, Raymond Vanholder, Carmine Zoccali on behalf of the ERBP Advisory board.

Updated guidance

The 2002 guidance is not significantly changed. The evidence levels are increased by the studies published since 2002. The caution against using creatinine and CC to guide dialysis start is strengthened. A caution that eGFR calculated by the MDRD method is not useful in determining need for dialysis has been added. The emphasis on using GFR of 6 ml/min/1.73m^2 as an absolute lower limit to starting dialysis is made more vague. Support for establishing advanced CKD clinics has been added.

Nephrol Dial Transplant 2011,

KDIGO Controversies Conference

Novel techniques and innovation in blood purification:
How can we improve clinical outcomes in hemodialysis?

14-15 October, 2011
Paris, France

CONFERENCE LEADERS

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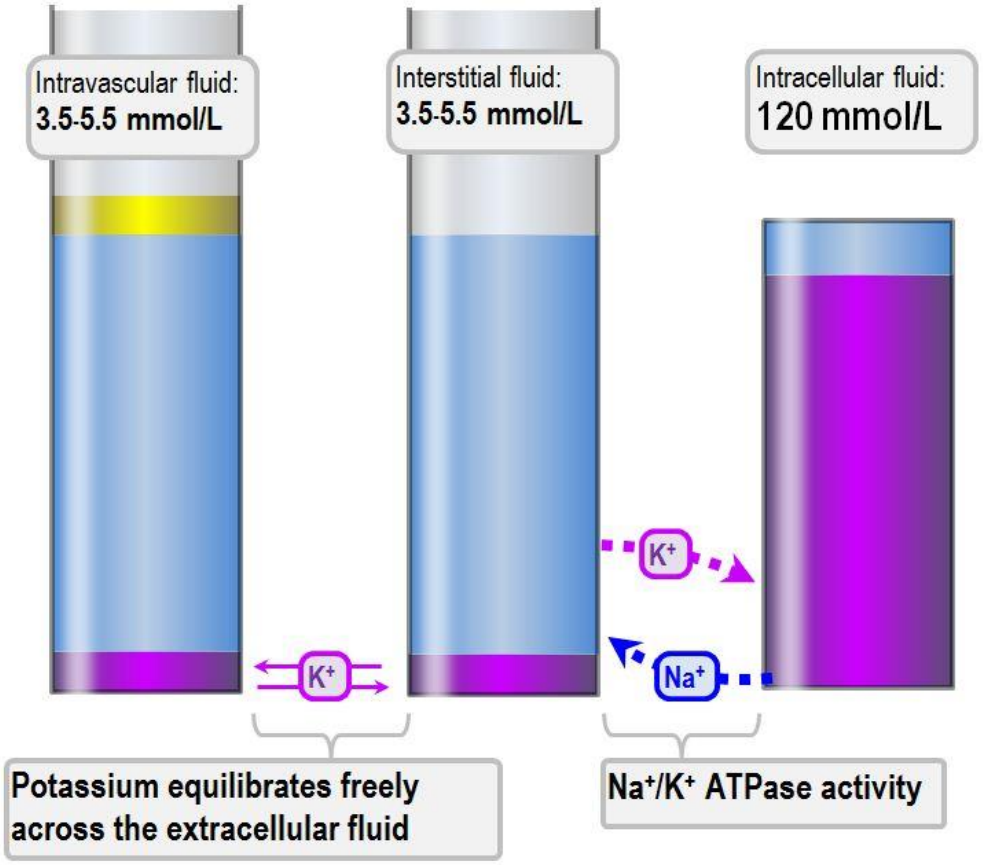
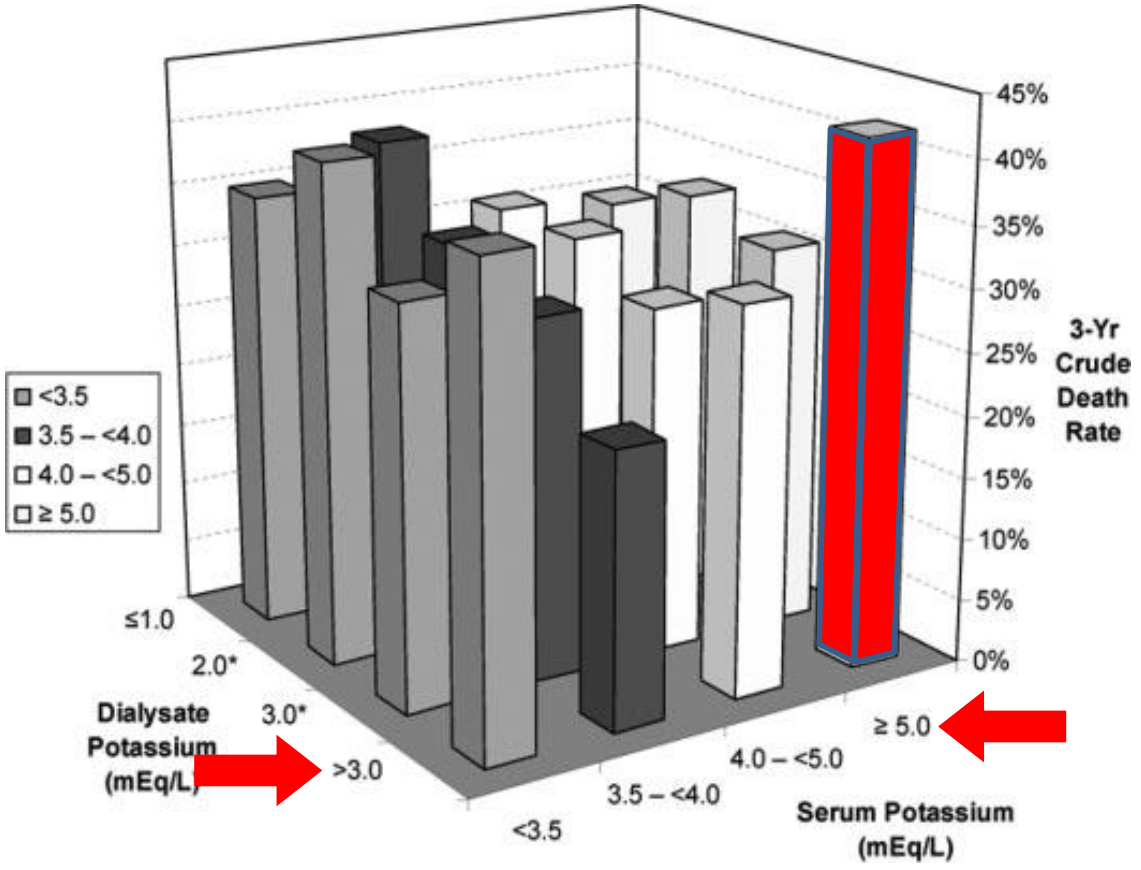
Potassium distribution



Potassium equilibrates freely and rapidly across the extracellular fluid.

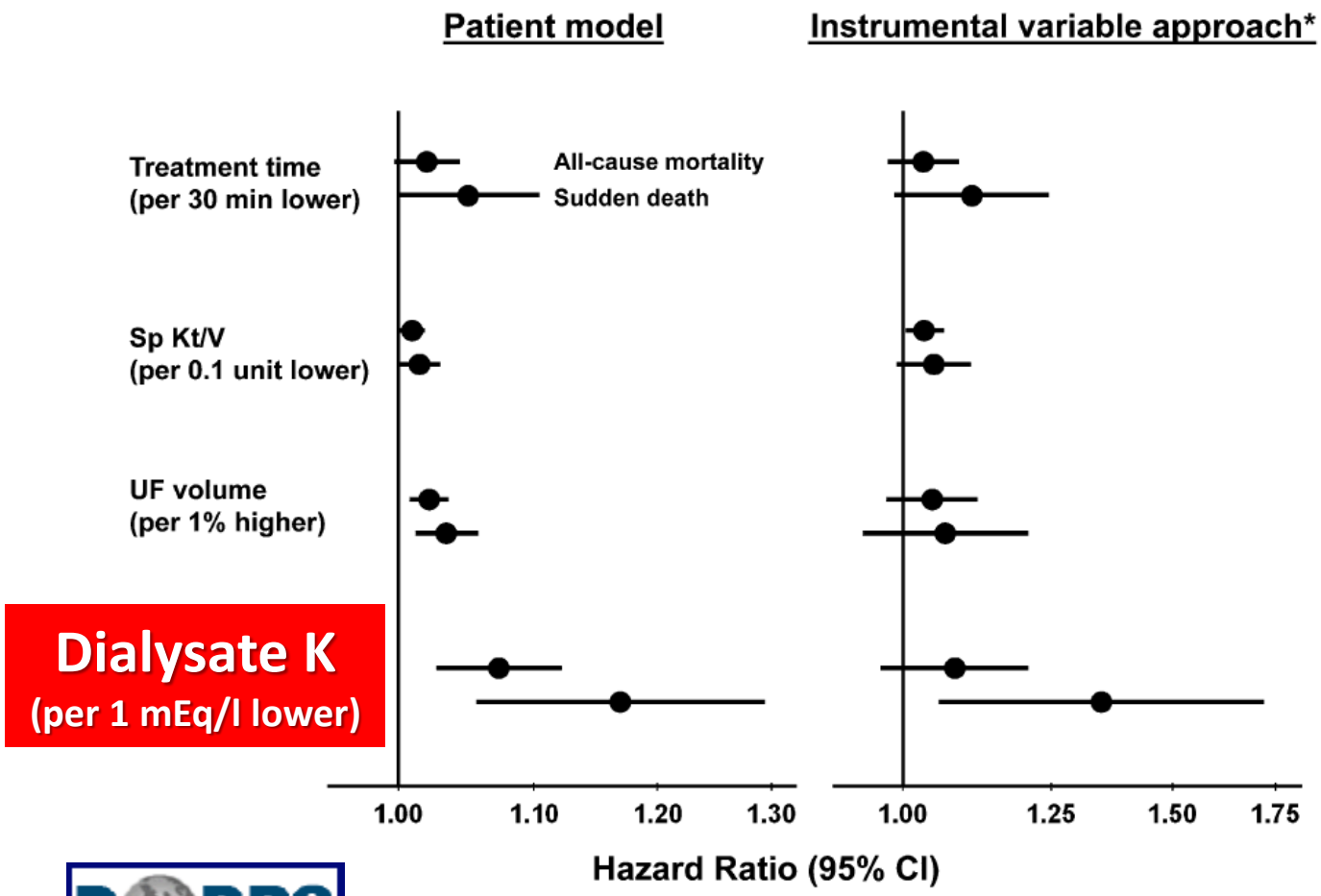
Serum and Dialysate Potassium Concentrations and Survival in Hemodialysis Patients



The highest 3-yr death rate was observed in patients with a predialysis serum K ≥ of 5.0 mEq/L, who were dialyzed against a high dialysate K bath of 3.0 mEq/L (*e.g.*, 3.5 or 4.0 mEq/L K bath).

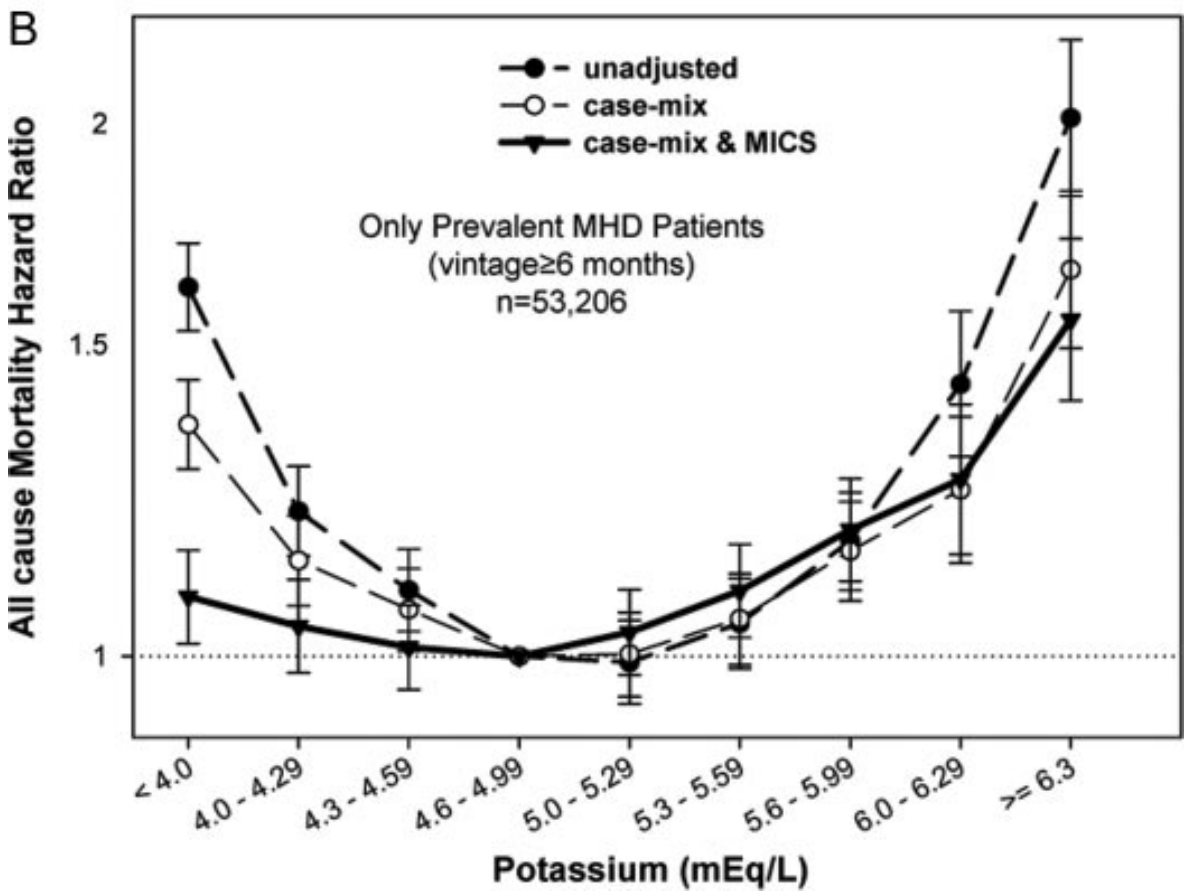
Kovesdy CP et al. Clin J Am Soc Nephrol 2: 999-1007, 2007.

Association of Dialysate K With Mortality, Stratified by Serum K



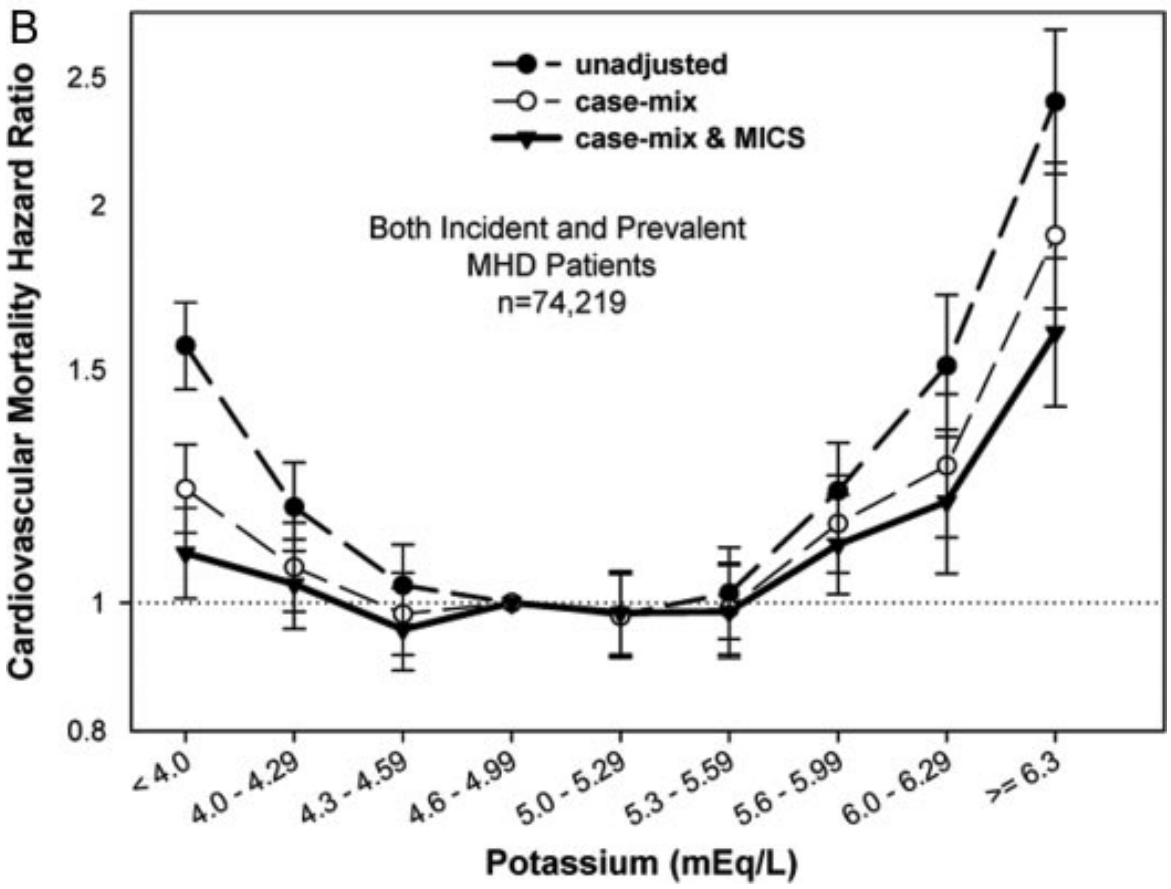
Jadoul M et al. Clin J Am Soc Nephrol 7: 765- 774, 2012

Serum and Dialysate Potassium Concentrations and all Cause Mortality in Hemodialysis Patients



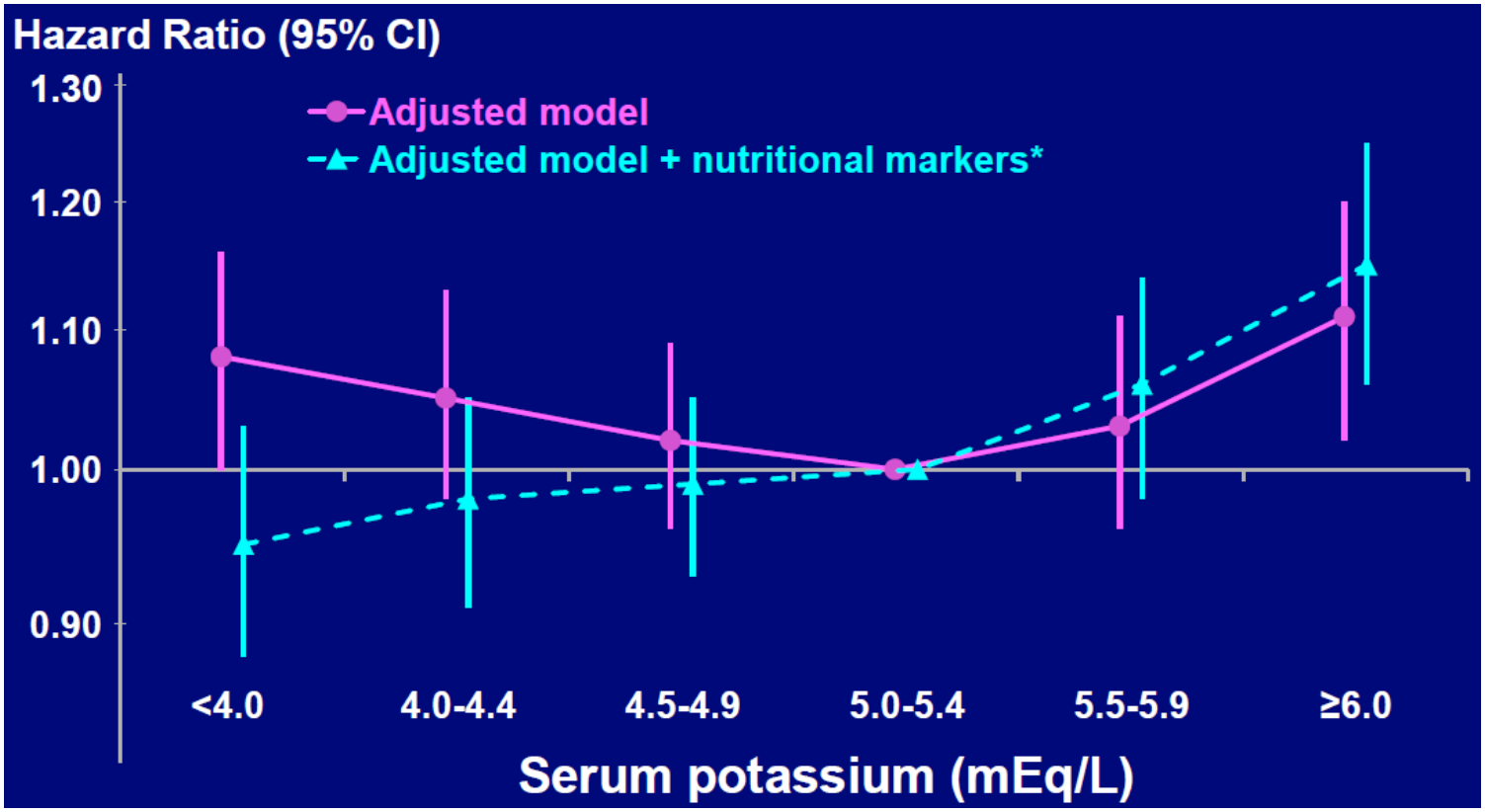
Kovesdy CP et al. Clin J Am Soc Nephrol 2: 999-1007, 2007.

Serum and Dialysate Potassium Concentrations and Cardiovascular Mortality in Hemodialysis Patients



Kovesdy CP et al. Clin J Am Soc Nephrol 2: 999-1007, 2007.

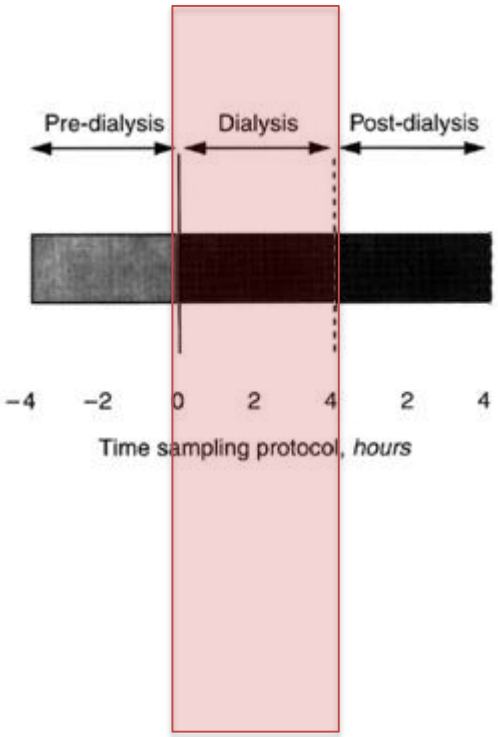
Mortality Risk is Higher at Low and High Serum Potassium Levels (low K explained by poor nutrition)

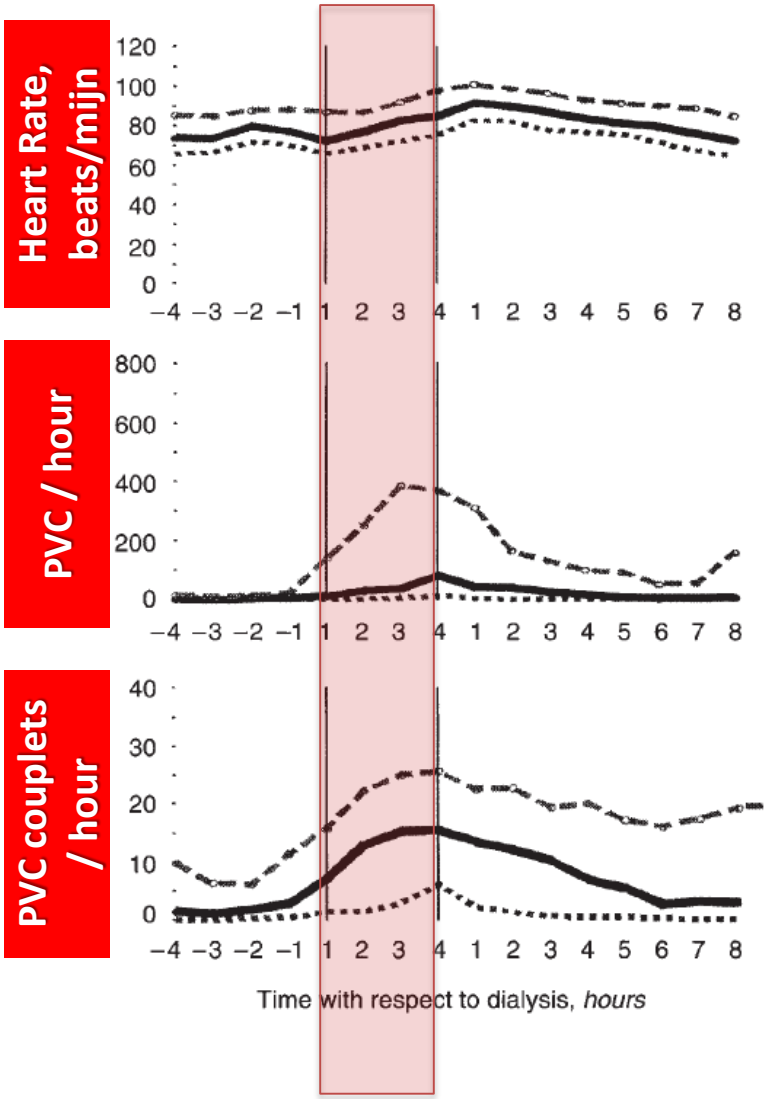


*Model also adjusted for BMI, albumin, creatinine and normalized PCR at study enrollment
N=37,967 patients; model stratified by country and study phase, accounted for facility level clustering, and adjusted for age, sex, race, vintage, 13 comorbidities, smoking, prior TX, catheter use, employment status, education level, living status and marriage status, skipped ≥1 hemodialysis session in past 30 days, shortened ≥1 hemodialysis session by ≥10 minutes in past 30 days, IDWG >5.7% of dry weight, PO4 >7.5 mg/dL, spKt/V, and hemoglobin at study enrollment

Adapted from Saran et al. ASN abstract (2011)

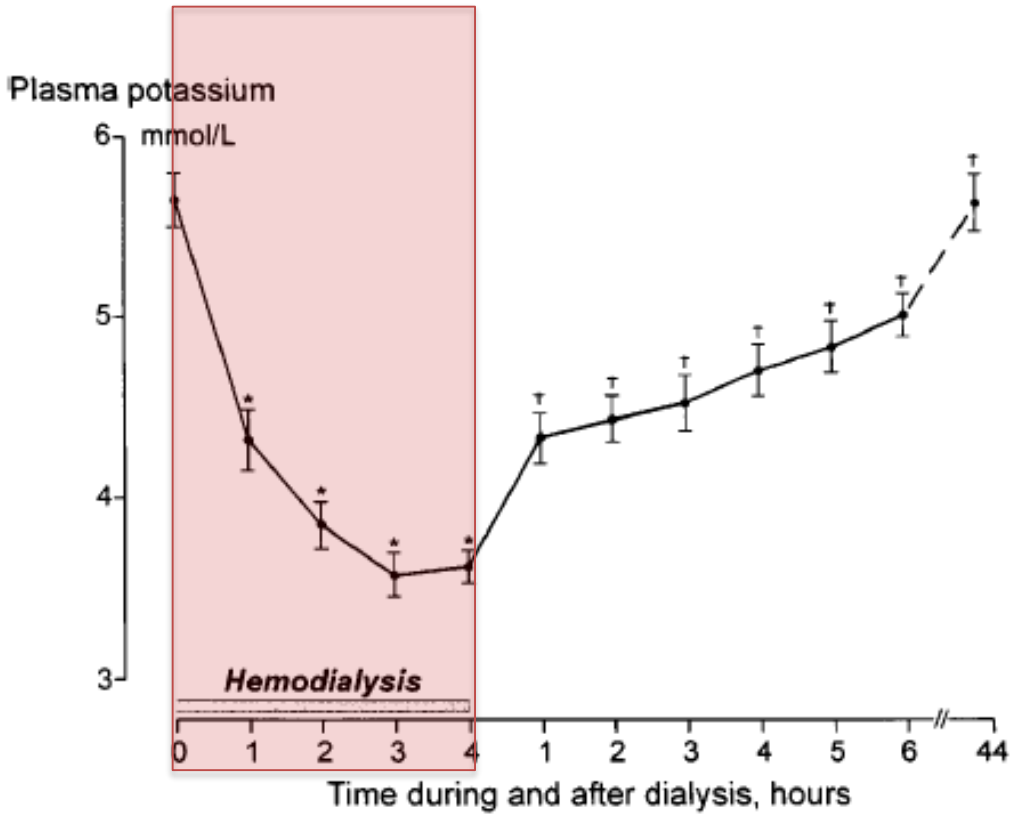
Descriptive trend analysis of cardiac rhythm parameters during, before and after HD





Redaelli B, Locatelli F et al. Kidney Int. 1996 Aug;50(2):609-17.

Plasma K+ during and after HD; relationship with dialytic potassium removal and total body potassium.

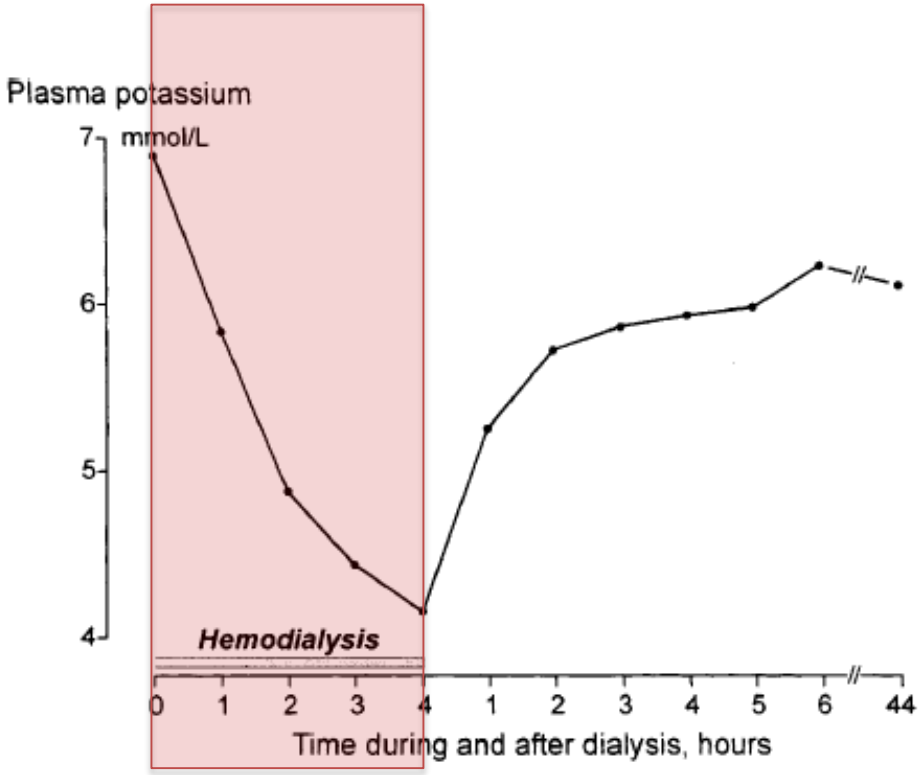


"Mean predialysis plasma K was 5.65±0.14 mmol/l. During haemodialysis plasma K declined continuously reaching a nadir of 3.57±0.12 mmol/l after 3 h and remaining stable (3.62±0.09 mmol/l) at 4 h. "

"Total removal of potassium by the dialysis procedure was highest during the 1st hour (34.2±1.7 mmol) and significantly lower during the 4th hour (21.0±1.8 mmol). "

Blumberg A et al. Nephrol Dial Transplant. 1997 Aug;12(8):1629-34.

Plasma K+ during and after HD; relationship with dialytic potassium removal and total body potassium.

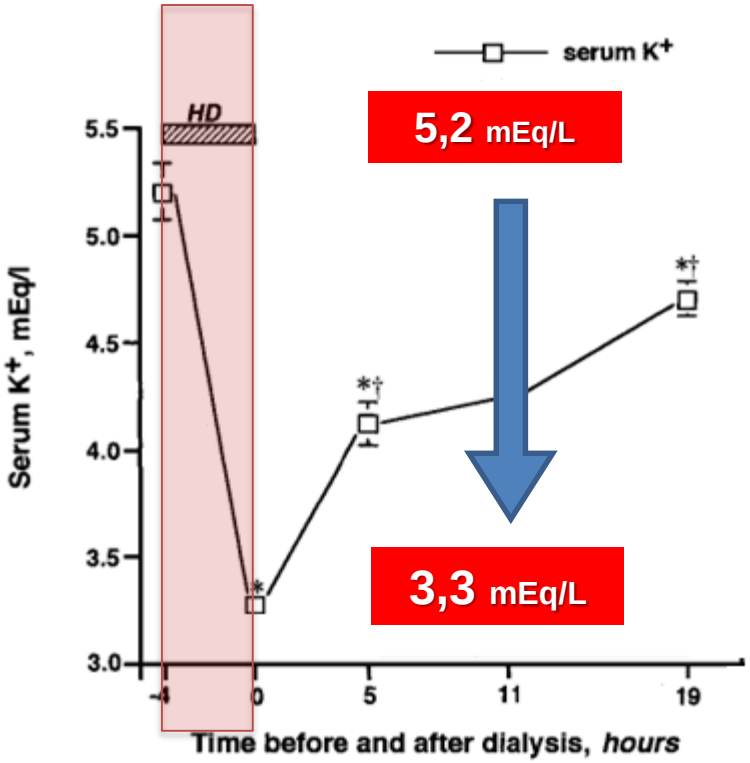


"There was a close correlation between the predialysis and the 6-h post-HD plasma K concentrations. Accordingly, this postdialysis rebound of plasma K was particularly impressive in the patient with the highest predialysis potassium of 6.91 mmol/l."

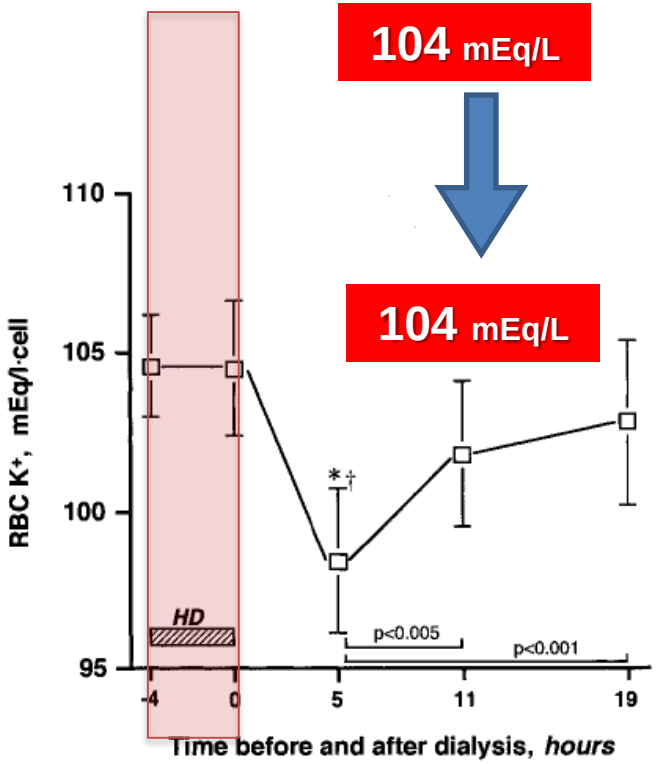
Blumberg A et al. Nephrol Dial Transplant. 1997 Aug;12(8):1629-34.

Serum potassium handling at pre- and post- HD in patients with ESRD

EXTRACELLULAR K+



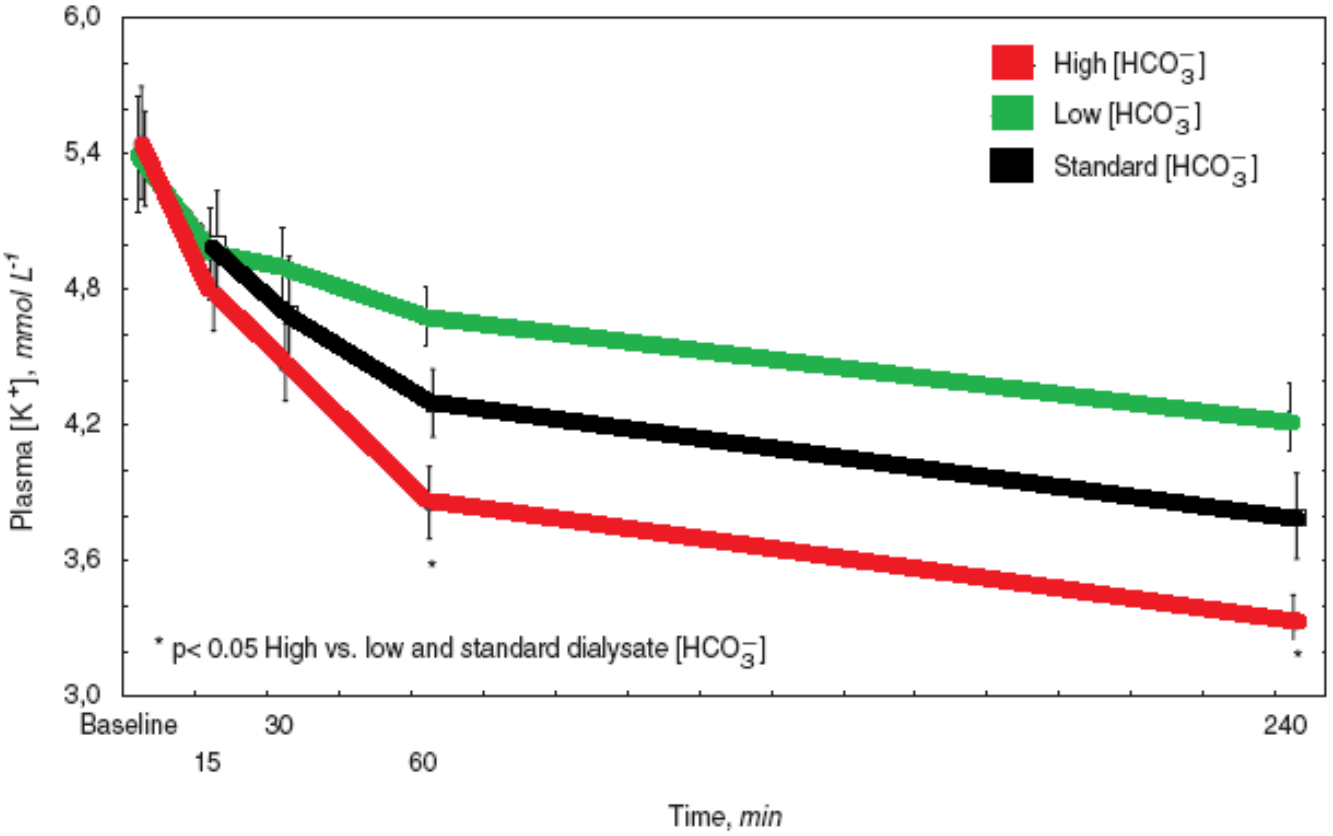
INTRACELLULAR K+



At end-dialysis, serum K levels decreased, but RBC K levels were not changed. At this time point, the decrease in serum K levels was exclusively caused by removal of extracellular K by dialysis.

Muto S et al. ASAIO J. 2003 Nov-Dec;49(6):660-6.

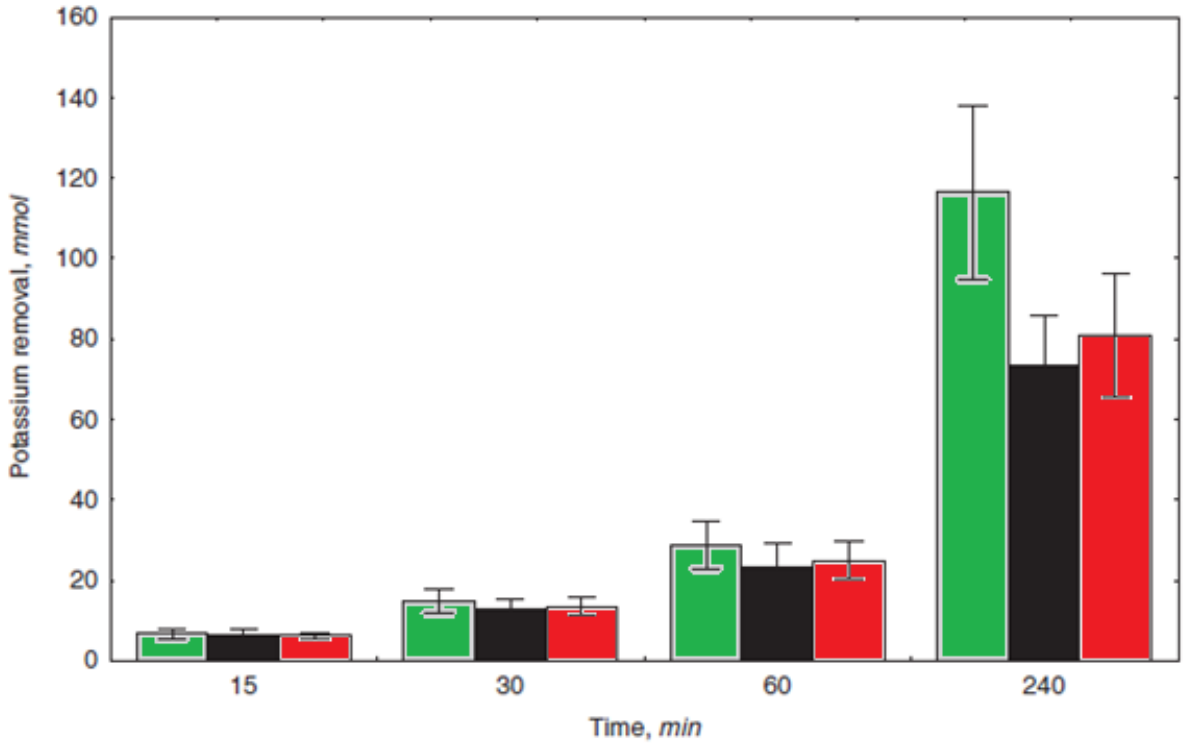
Potassium removal and dialysate bicarbonate concentration



"High dialysate [HCO3] was associated with a faster decrease in serum K+."

Heguilén RM et al. Nephrol Dial Transplant. 2005 Mar;20(3):591-7

Potassium removal and dialysate bicarbonate concentration



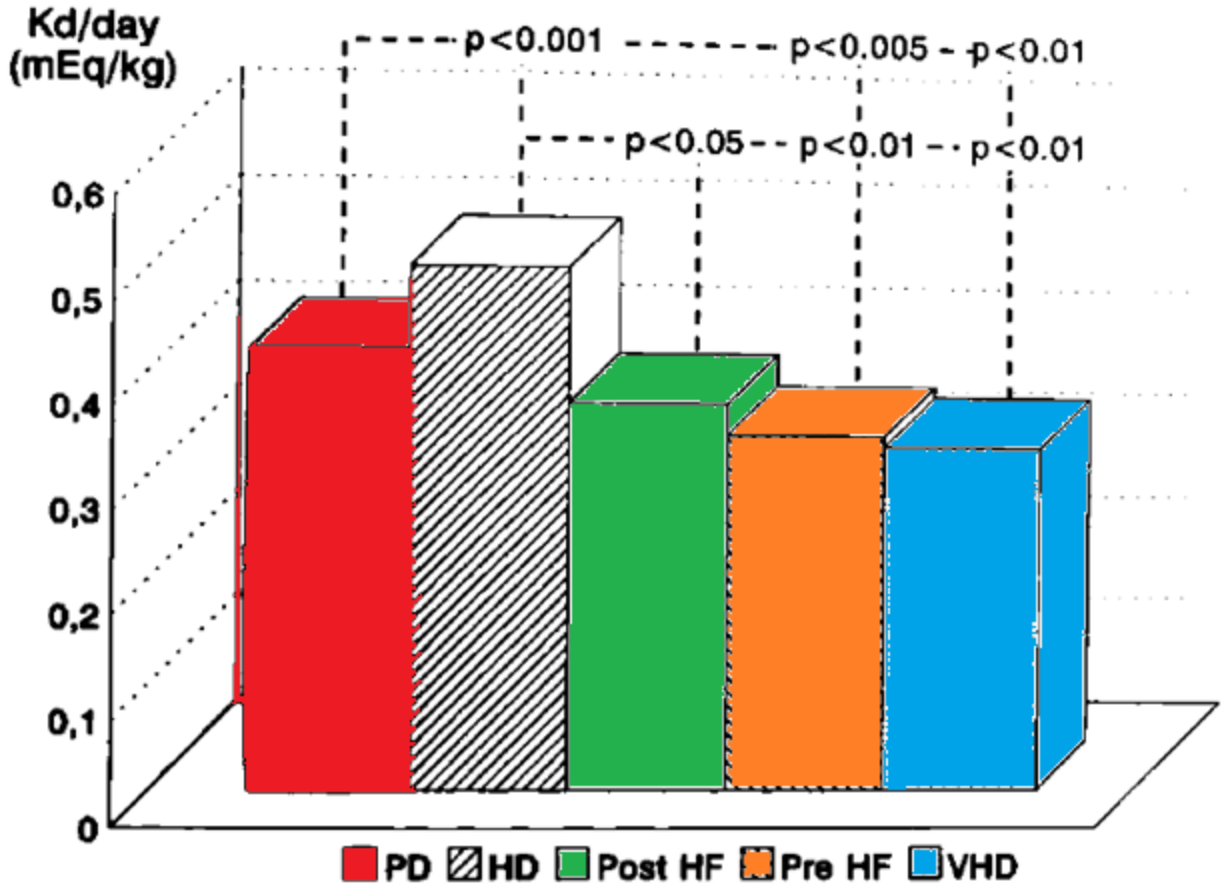
HCO3 dialysate concentration:

- 27 mmol/L
- 35 mmol/L
- 39 mmol/L

"… this reduction was due to the enhanced shifting of K from the extracellular to the intracellular fluid compartment rather than its removal by dialysis."

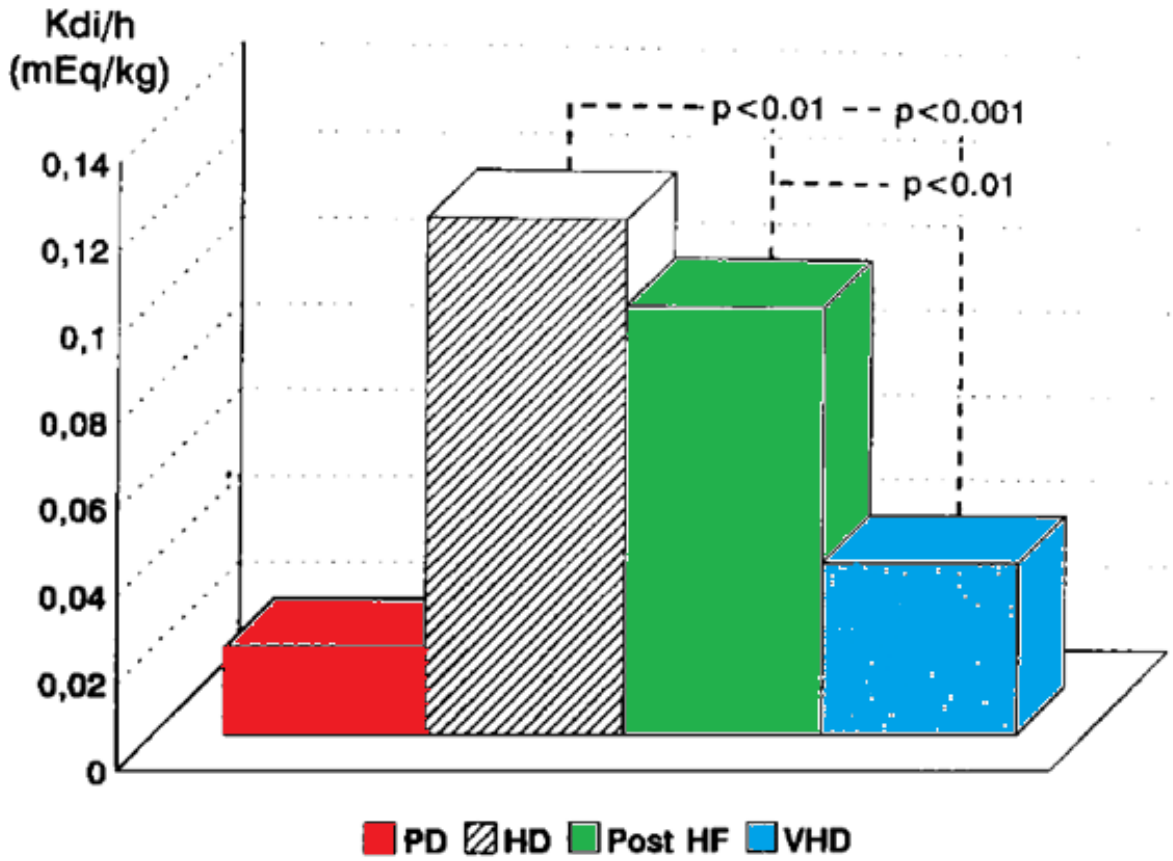
Heguilén RM et al. Nephrol Dial Transplant. 2005 Mar;20(3):591-7

Behaviour of daily K removal in different dialytic schedules.



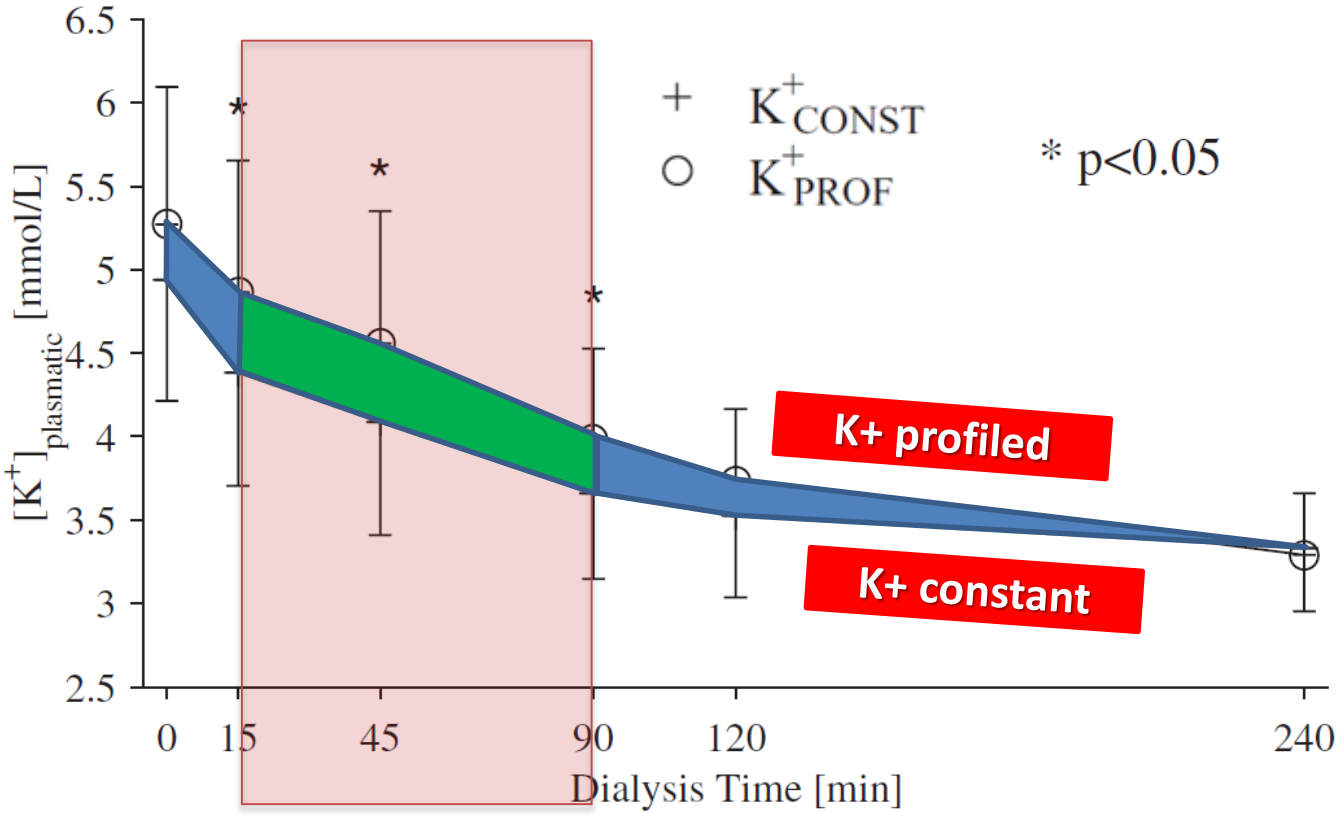
Redaelli B et al. Nephrol Dial Transplant. 1998;13 Suppl 6:35-8.

Behaviour of intracellular K removal in different dialytic schedules.



Redaelli B et al. Nephrol Dial Transplant. 1998;13 Suppl 6:35-8.

Model-Based Analysis of Potassium Removal During Hemodialysis



A significant gap, higher than 0.3 mmol/L, was observed between 15–90 min but at the end of dialysis, K+ plasma concentrations were similar

Ciandrini A. Artif Organs. 2009 Oct;33(10):835-43

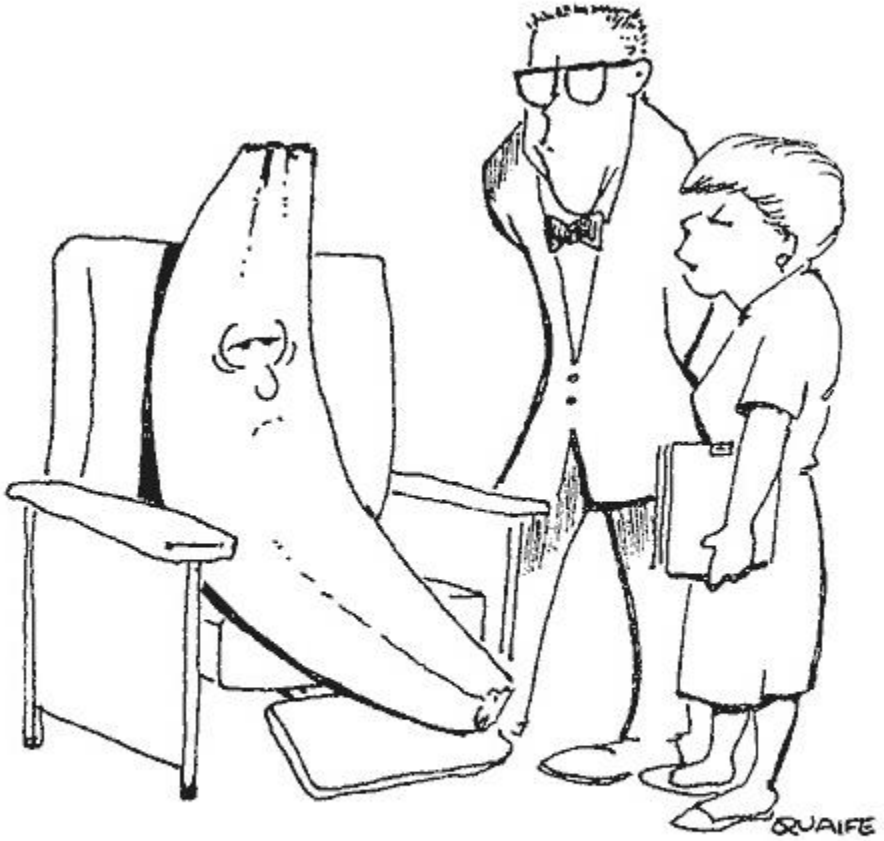
CONCLUSIONS

Use of dialysate K<3 mEq/L is very common and leads to low post-HD K levels

Risk of sudden death is higher for patients in HD units where more patients have dialysate K below 3 mEq/L

Higher risk with low dialysate K is especially clear for patients with pre-HD serum K<5 mEq/L

Use of profiled potassium dialysate concentration reduces arrhythmogenic risk



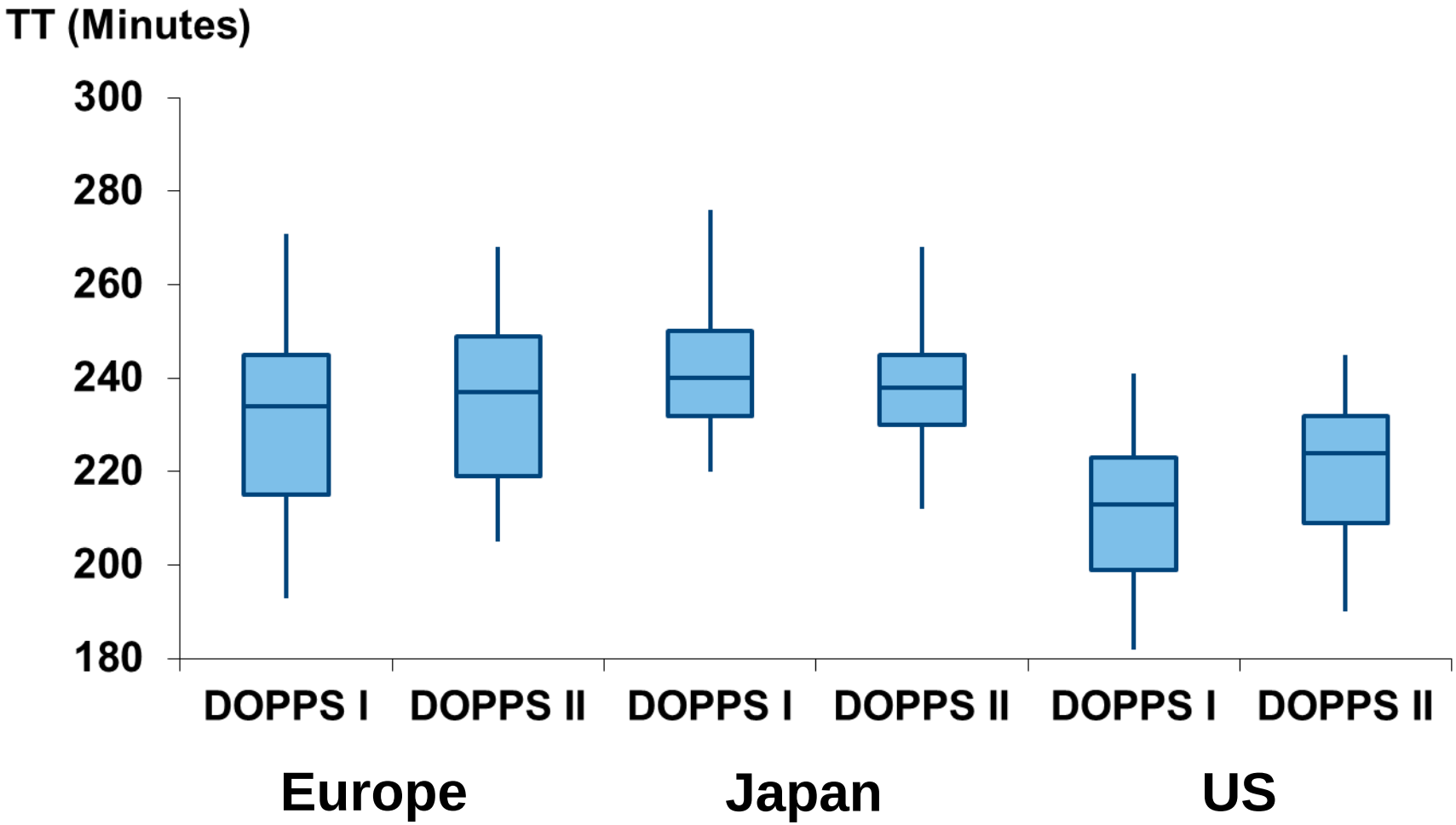
We're a little concerned
about your potassium levels.

Introduction

- **Hemodialysis (HD) patients continue to experience high mortality rates**
- **Several studies have suggested that longer duration of HD sessions is associated with a survival advantage**
- **Potentially, long, slow dialysis sessions may result in improved middle molecular clearance and better blood pressure and volume control, particularly if high-flux dialysis membranes are used**

Saran et al. *KI 69*:1222-1228, 2006

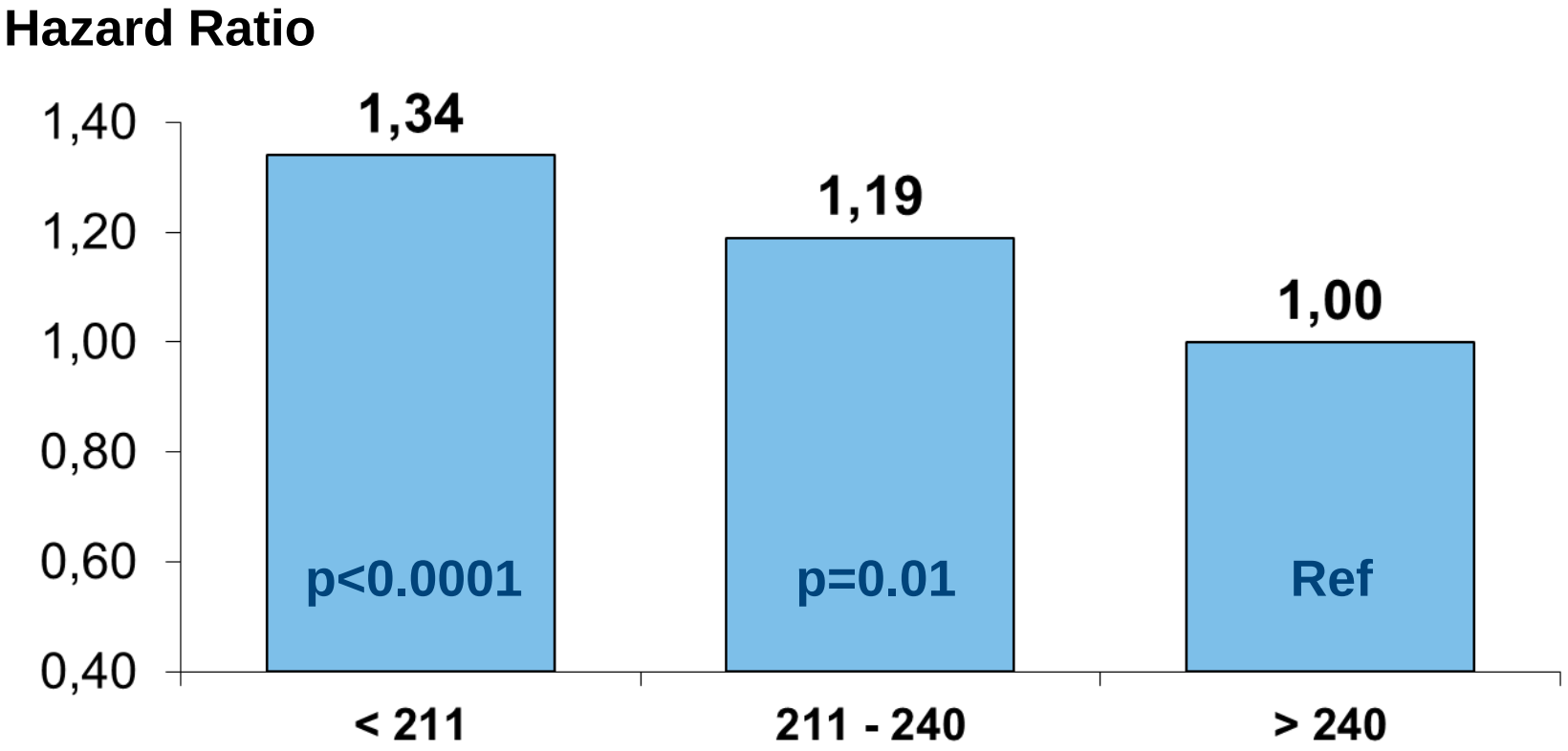
Distribution of Facility Mean TT, by Region and Phase



n = 536 facilities

Saran et al. *KI 69*:1222-1228, 2006

Hazard Ratio of All-Cause Mortality by Treatment Time Category*

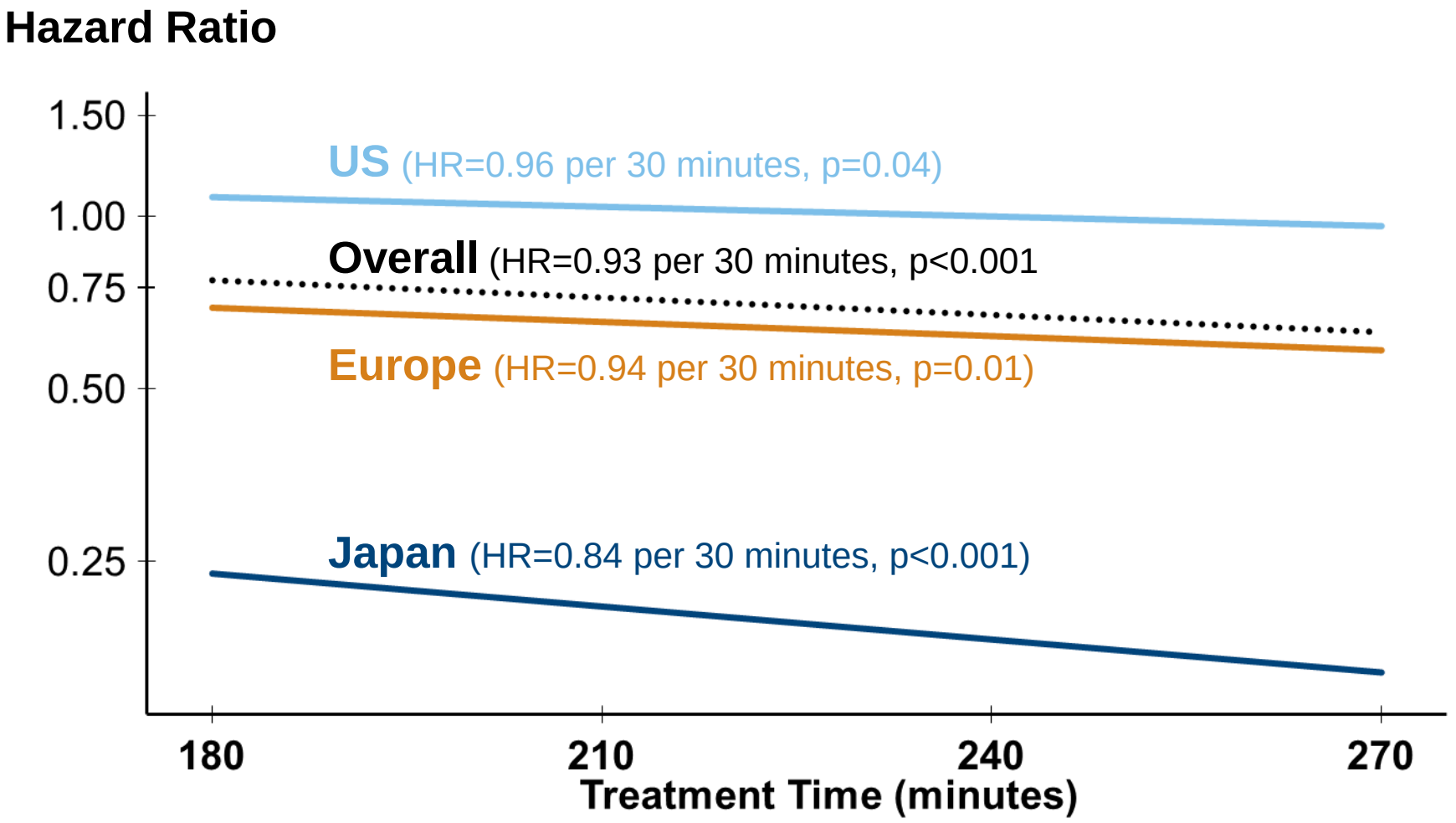


*Adjusted for: age, sex, race, ethnicity, time on dialysis, 14 summary comorbidities, living status, height, weight, Kt/V, blood flow, residual renal function, and catheter use as access. Stratified by geographical region and phase of study. Accounts for facility clustering.

DOPPS

Saran et al. *KI 69*:1222-1228, 2006

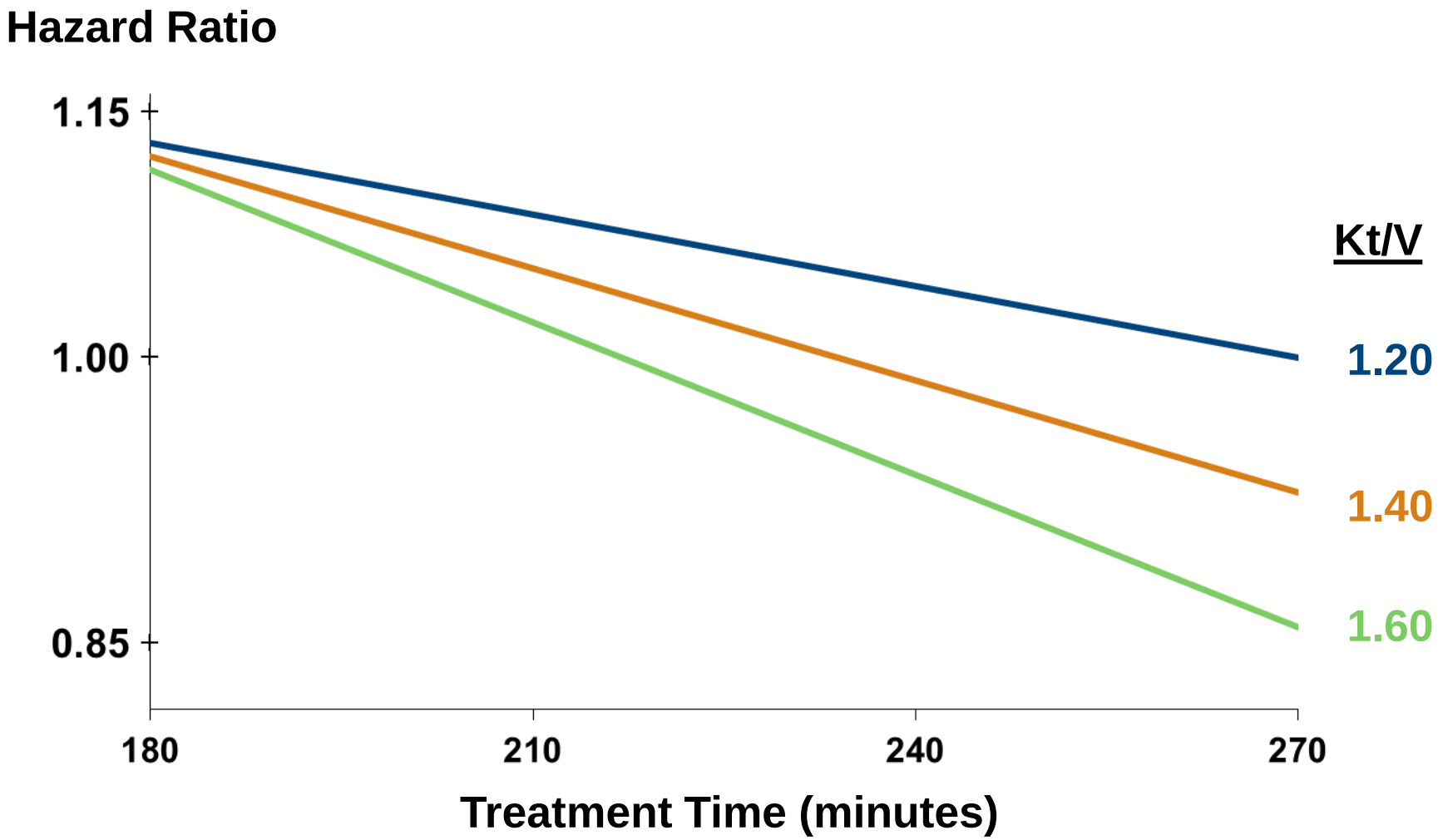
Treatment Time and Mortality, by Region



DOPPS

Saran et al. *KI 69*:1222-1228, 2006

Incremental HR of Mortality by TT in Kt/V Categories*



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*Interaction between Kt/V and TT p=0.007

Saran et al. *KI 69*:1222-1228, 2006

Summary

- **Longer TT and higher Kt/V were independently predictive of lower mortality, with additional evidence of a synergistic interaction between these two variables**
- **Rapid UFR during HD was also independently associated with higher mortality risk**
- **These results warrant a randomized clinical trial of longer dialysis sessions in the setting of thrice-weekly HD**

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Saran et al. *KI 69*:1222-1228, 2006

Introduction

- **Abnormalities in serum calcium, phosphorus and parathyroid hormone (PTH) concentrations are common among patients with chronic kidney disease and have been associated with increased cardiovascular calcification, arterial dysfunction, morbidity, and mortality**

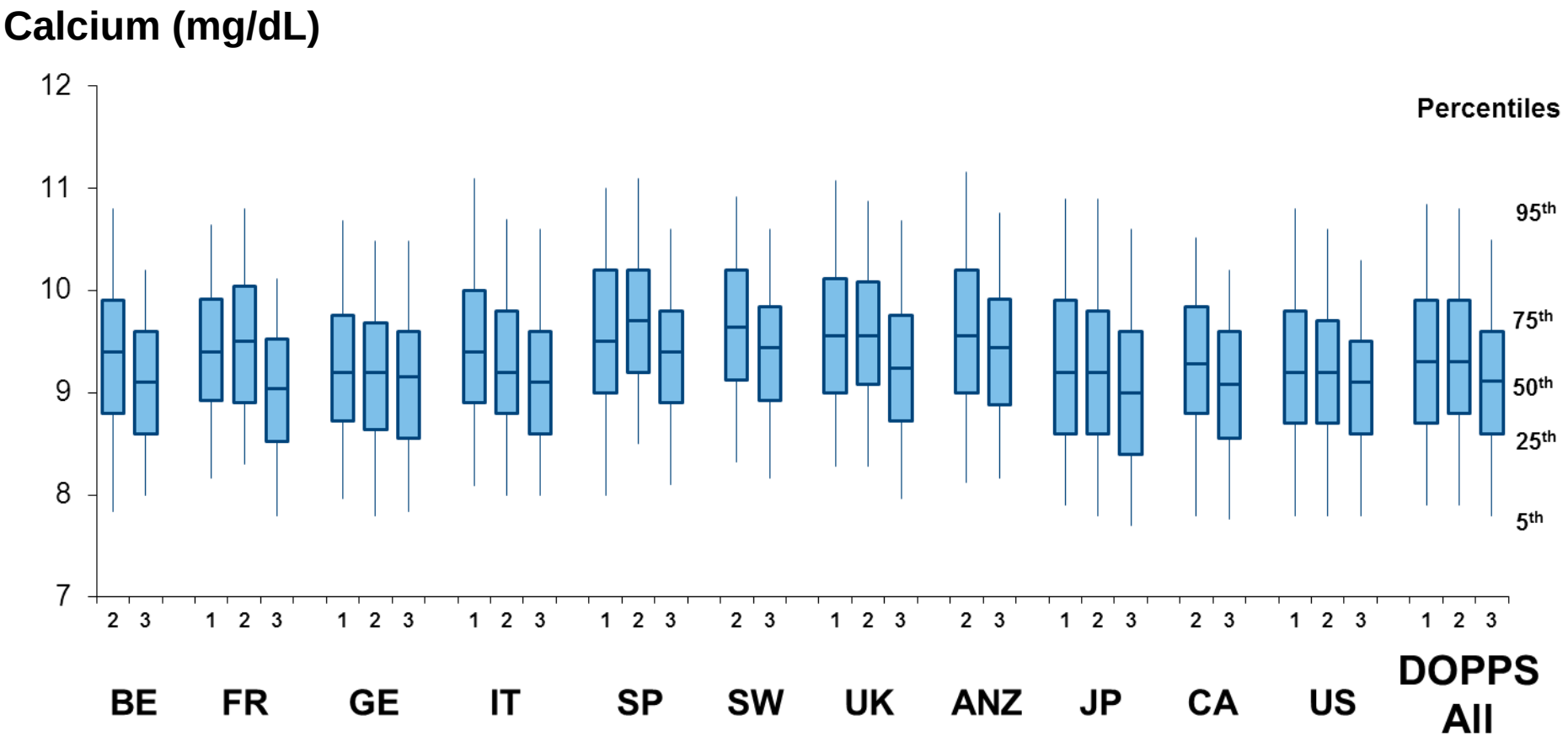
- **These biochemical changes, together with abnormalities in vitamin D metabolism and bone turnover, constitute a systemic syndrome known as chronic kidney disease-mineral and bone disorder (CKD-MBD)**

- **No conclusive clinical trials on this topic have been conducted**

Tentori et al. *AJKD* 52 (3): 519-30, 2008

Serum Calcium Distributions

Among Patients on HD > 180 days



Percentiles for the overall study sample (n=25,375):

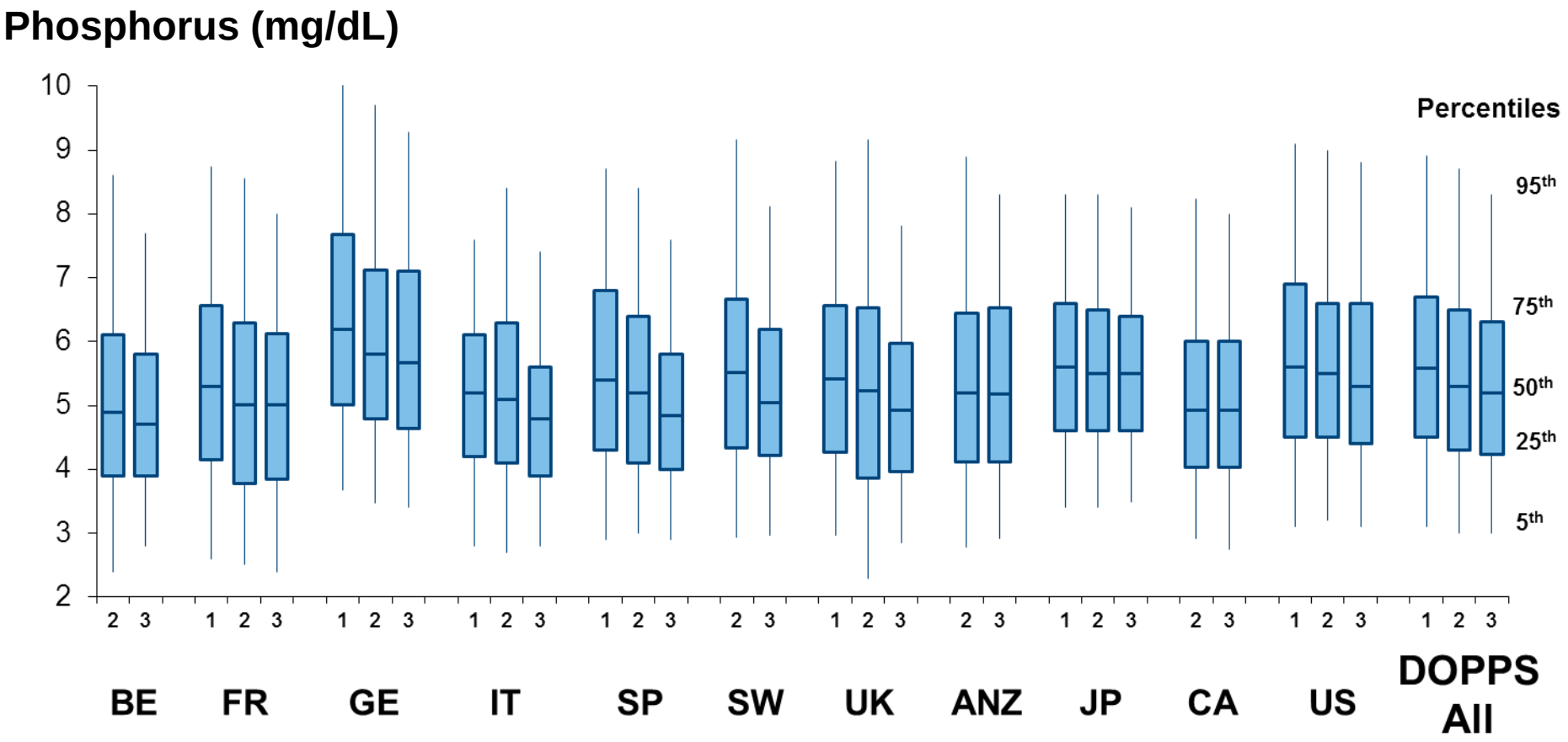
5th=7.9 mg/dL; 25th=8.7 mg/dL; 50th=9.2 mg/dL; 75th=9.8 mg/dL; 95th=10.7 mg/dL

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

Serum Phosphorus Distributions

Among Patients on HD > 180 days



Percentiles for the overall study sample (n=25,375):

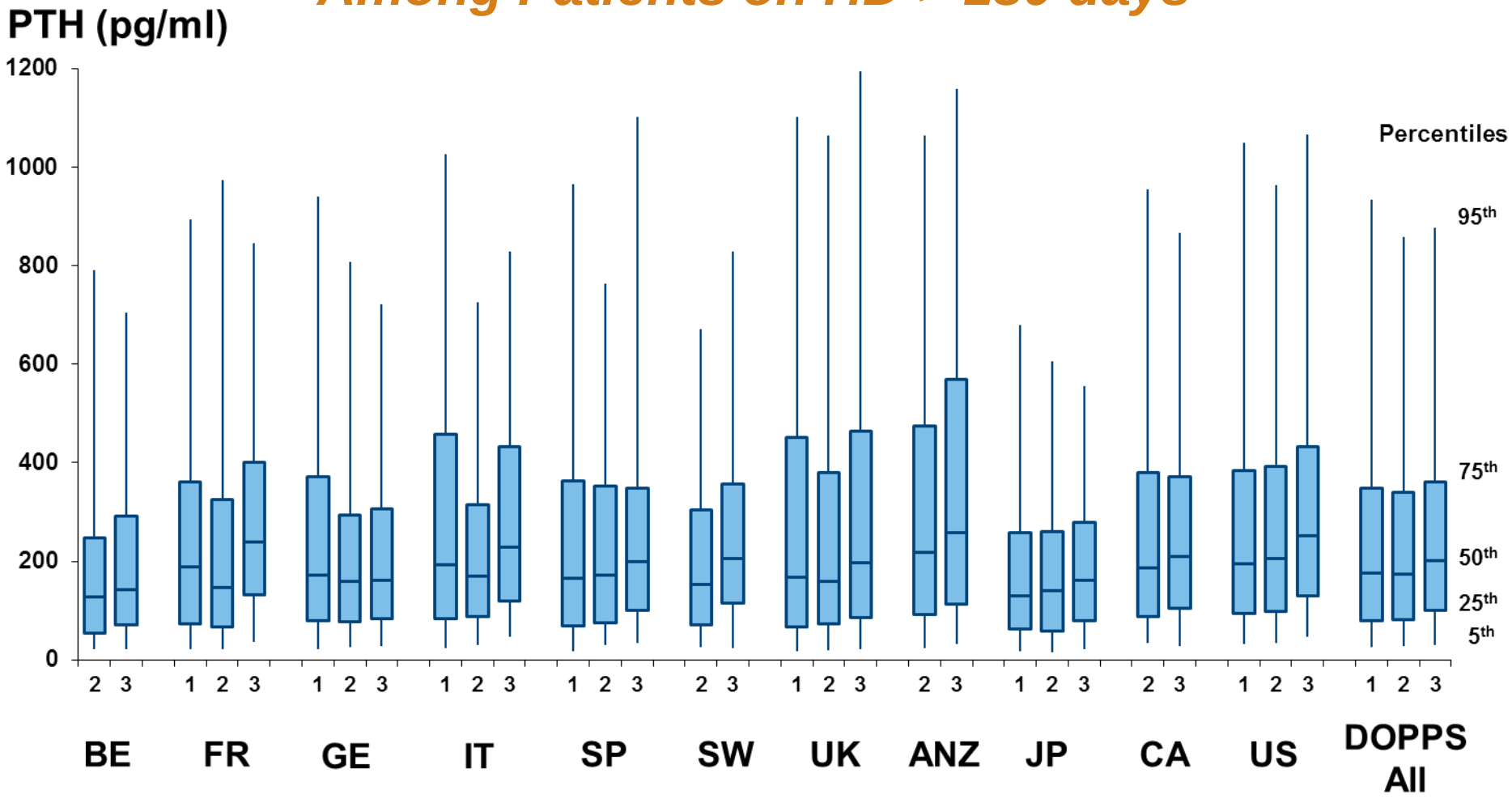
5th=3.0 mg/dL; 25th=4.3 mg/dL; 50th=5.4 mg/dL; 75th=6.5 mg/dL; 95th=8.7 mg/dL

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

PTH Distributions

Among Patients on HD > 180 days



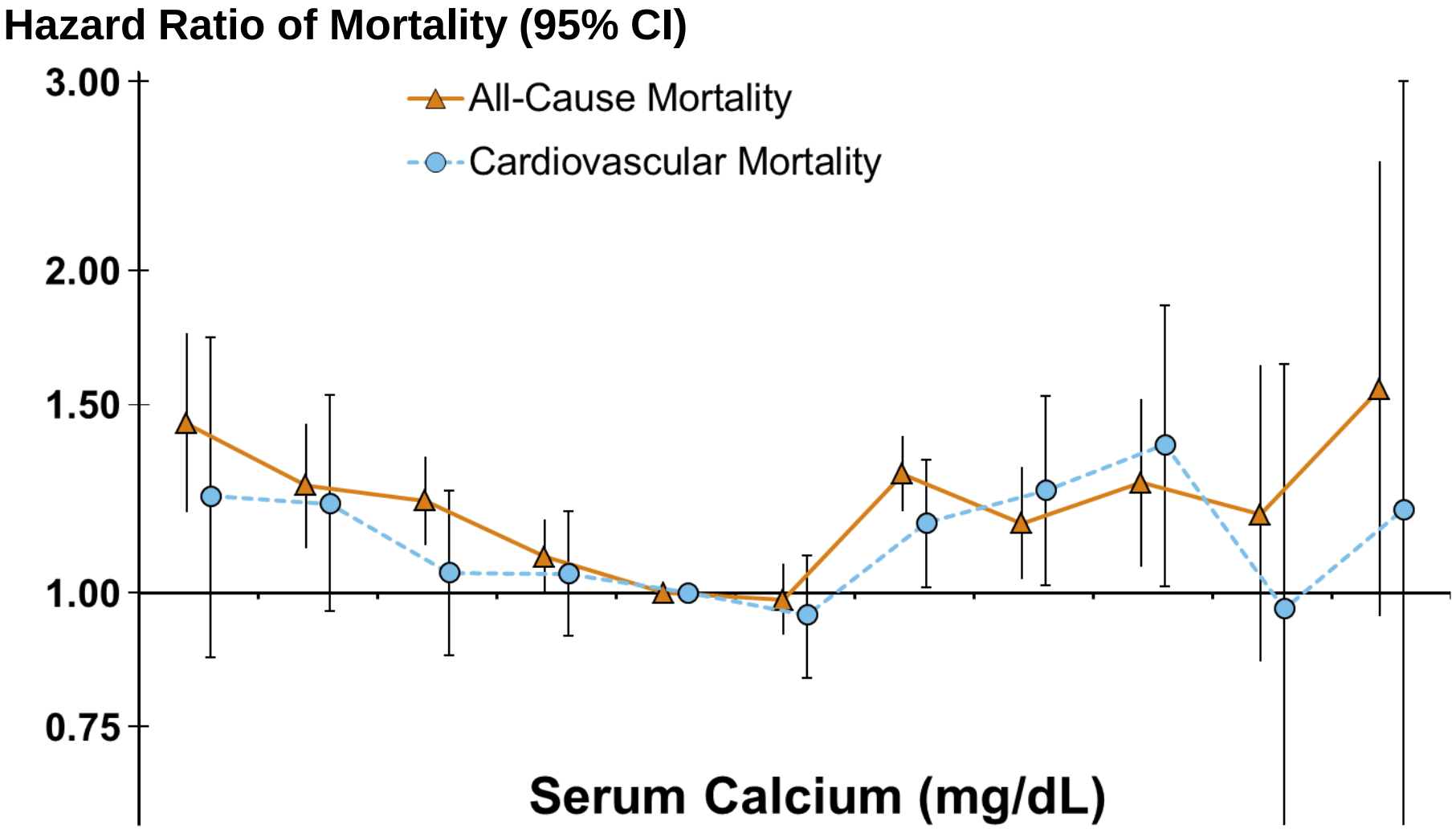
Percentiles for the overall study sample (n=25,375):

5th=28 pg/mL; 25th=83 pg/mL; 50th=177 pg/mL; 75th=342 pg/mL; 95th=831 pg/mL

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

All-cause and cardiovascular mortality risk associated with baseline serum calcium



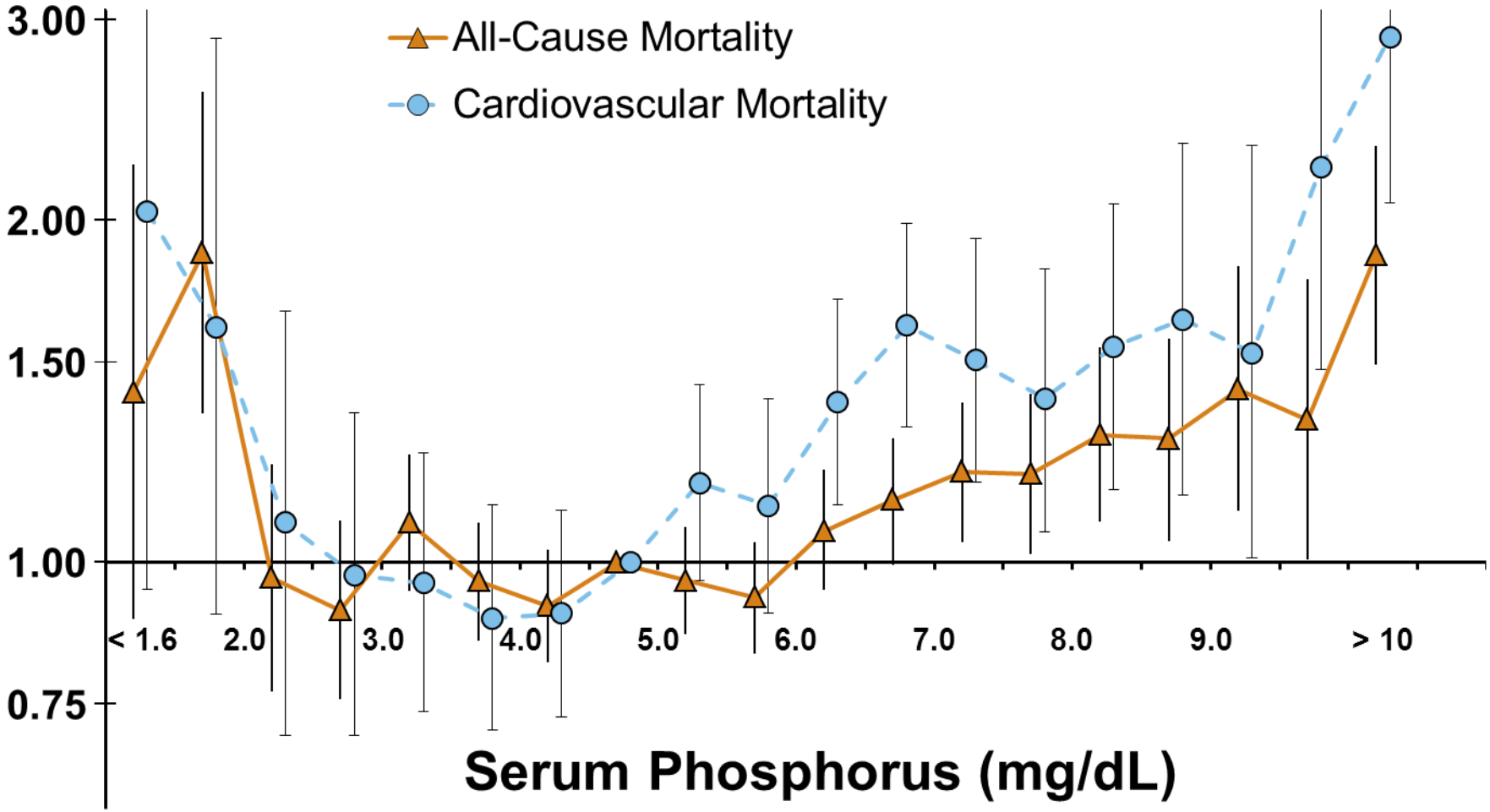
Among patients on dialysis > 180 days (n=25,529). Hazard ratios (HR) and 95% confidence intervals (whiskers) for all-cause (events n=5,857) and cardiovascular mortality (n events=1,930).

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

All-cause and cardiovascular mortality risk associated with baseline serum phosphorus

Hazard Ratio of Mortality (95% CI)

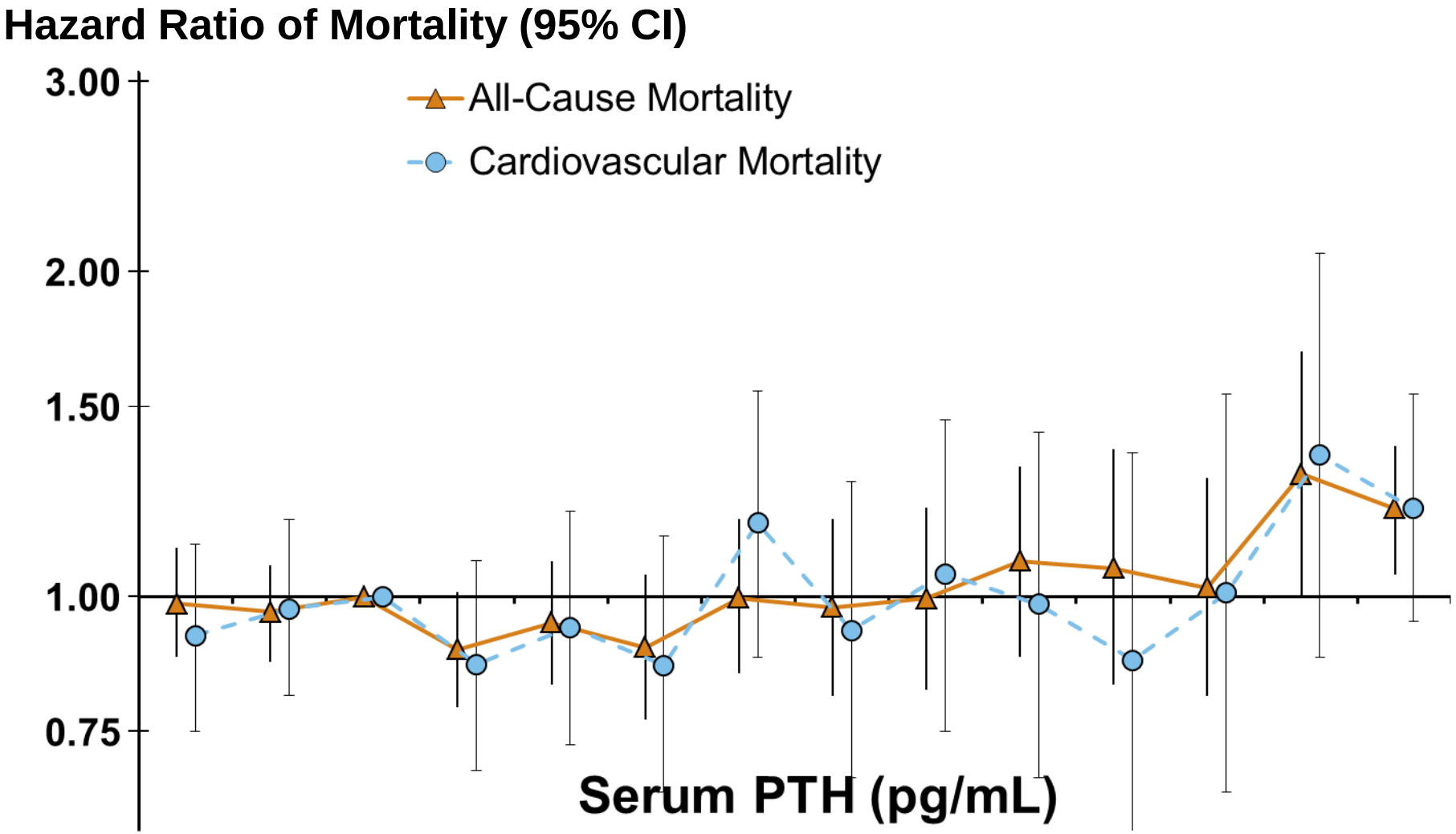


Among patients on dialysis > 180 days (n=25,529). Hazard ratios (HR) and 95% confidence intervals (whiskers) for all-cause (events n=5,857) and cardiovascular mortality (n events=1,930). Grey bars indicate the percent of patients in each category at baseline.

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

All-cause and cardiovascular mortality risk associated with baseline PTH



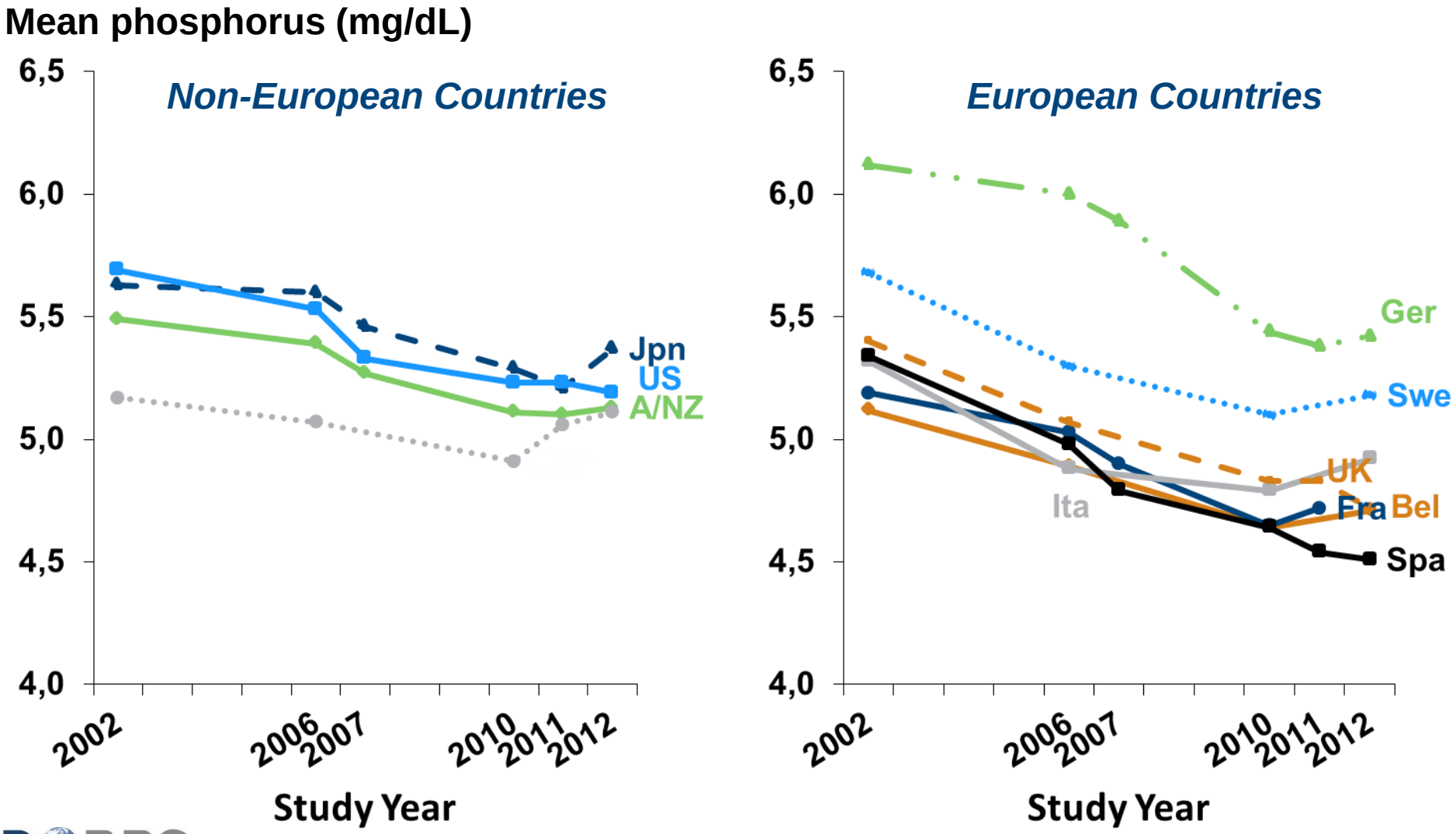
Among patients on dialysis > 180 days (n=25,529). Hazard ratios (HR) and 95% confidence intervals (whiskers) for all-cause (events n=5,857) and cardiovascular mortality (n events=1,930).

DOPPS

Tentori et al. *AJKD* 52 (3): 519-30, 2008

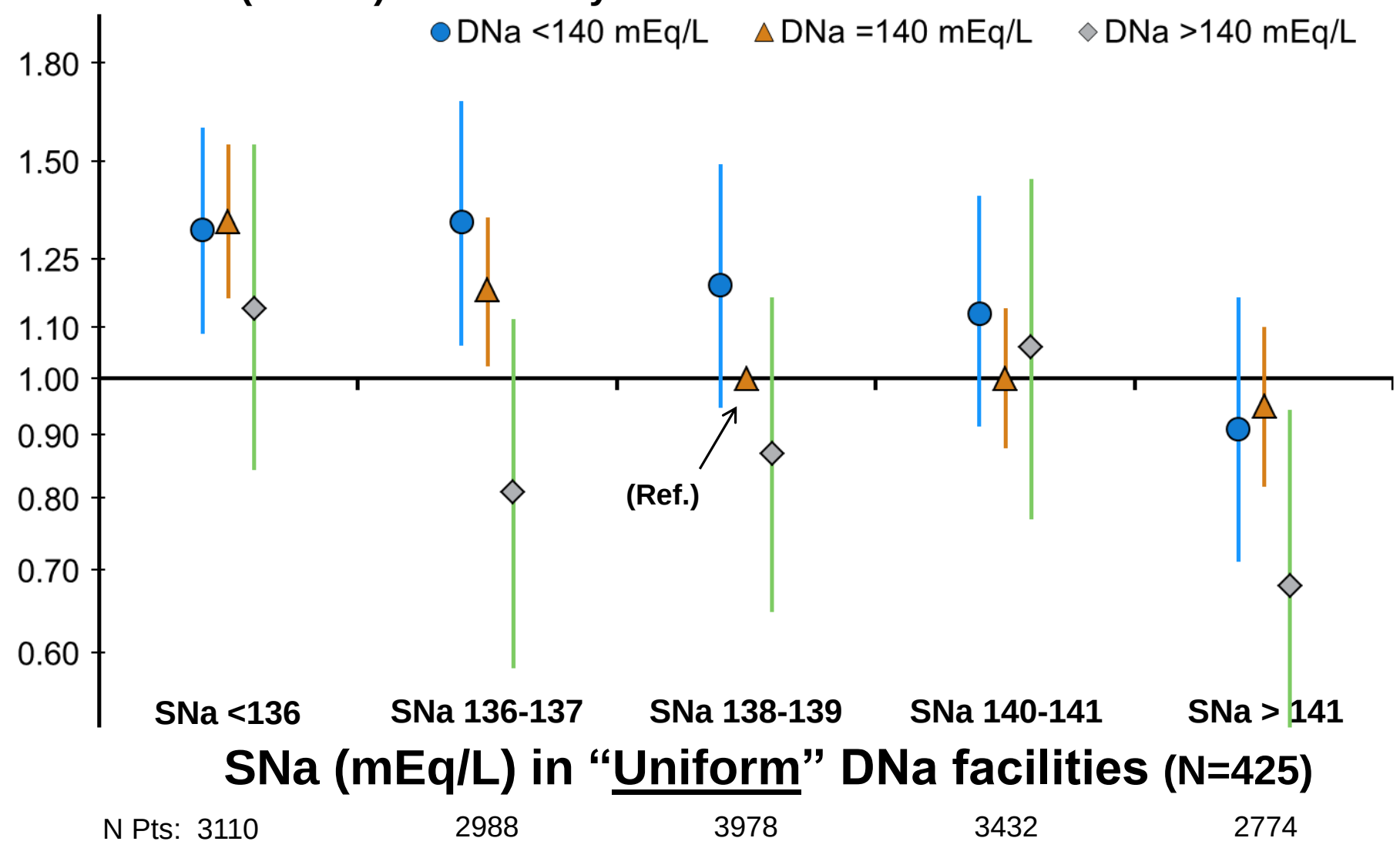
Mean Phosphorus Trends by Country

– DOPPS 2-5 (2002-2012) –



DOPPS

Mortality Risk by Dialysate Na and Serum Na (not selected)



DOPPS

Conclusion for Dialysate Na

- **No survival benefit from lower Dialysate Na**
- **No survival benefit from matching low serum Na with low Dialysate Na**
- **Not shown: I.D. weight gain increased by 0.12 kg per 2 mEq higher DNa**
- **Randomized trials are needed**