CKD and Arrhythmias: Electrolyte Abnormalities and Potential Treatments

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Disclosure of Interests

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Electrolytes for Discussion

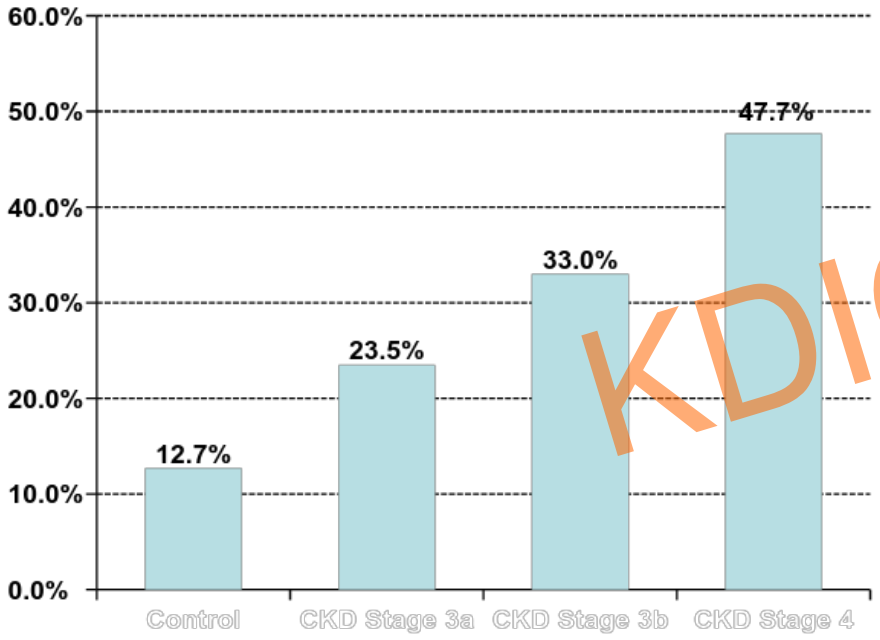
Potassium

Magnesium

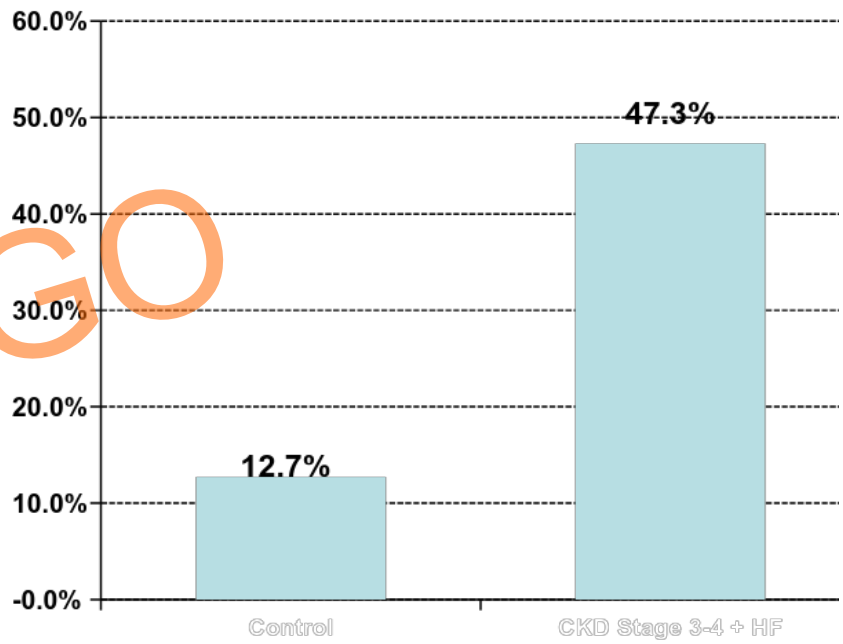
Mineral Metabolism

Hyperkalemia Is Prevalent Among Older Populations With Advanced Kidney Disease and/or Heart Failure

5-Year Database Prevalence of Hyperkalemia Control Population vs CKD Stages 3a, 3b, 4 in Patients ≥65 Years[1]



5-Year Database Prevalence of Hyperkalemia Control Population vs CKD Stages 3-4 + Heart Failure in Patients ≥65 Years[1]



CKD stages are based on estimated glomerular filtration rates (eGFR measured in mL/min/1.73m^2)
Stage 3a (eGFR of 45-59), Stage 3b (eGFR of 30-44), Stage 4 (eGFR of 15-29)[2]

Based on analysis of 1.63 million persons aged 5+ years with potassium values on 2 dates (2008-2012), with >1 K^+ value between 2.5 and 10 mEq/L during 2008-2012.

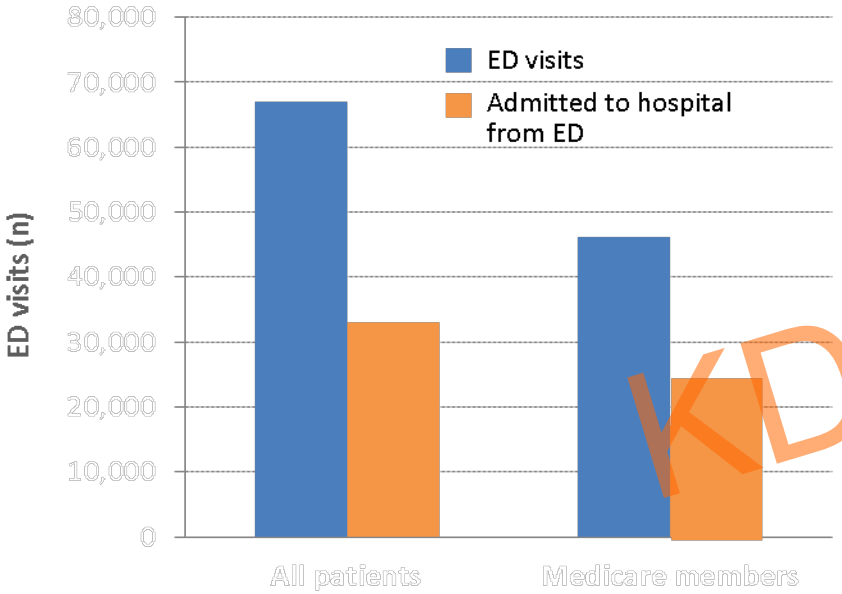
Control population composed of patients ≥65 years without CKD stages 2-5, heart failure, diabetes, or end-stage renal disease (ESRD).

Hyperkalemia defined as highest reported potassium value ≥5.1 mEq/L in 2008-2012.

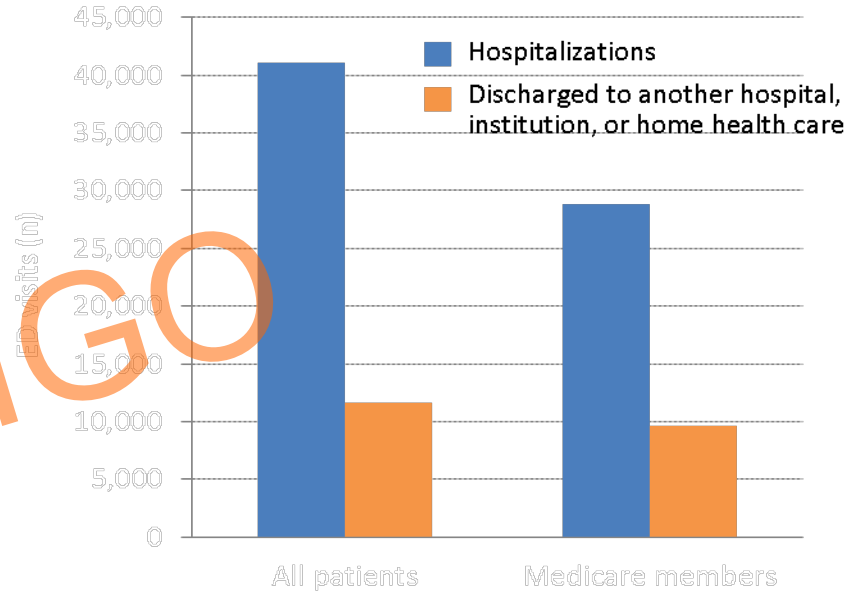
1. Data on file. Relypsa, Inc., Redwood City, CA. Data source: Humedica, Cambridge MA. 2. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1).

Hyperkalemia Contributes to ED Visits, Hospitalizations, and Health Care Costs

2011 ED Visits
Primary Diagnosis of Hyperkalemia



2011 Hospitalizations
Primary Diagnosis of Hyperkalemia

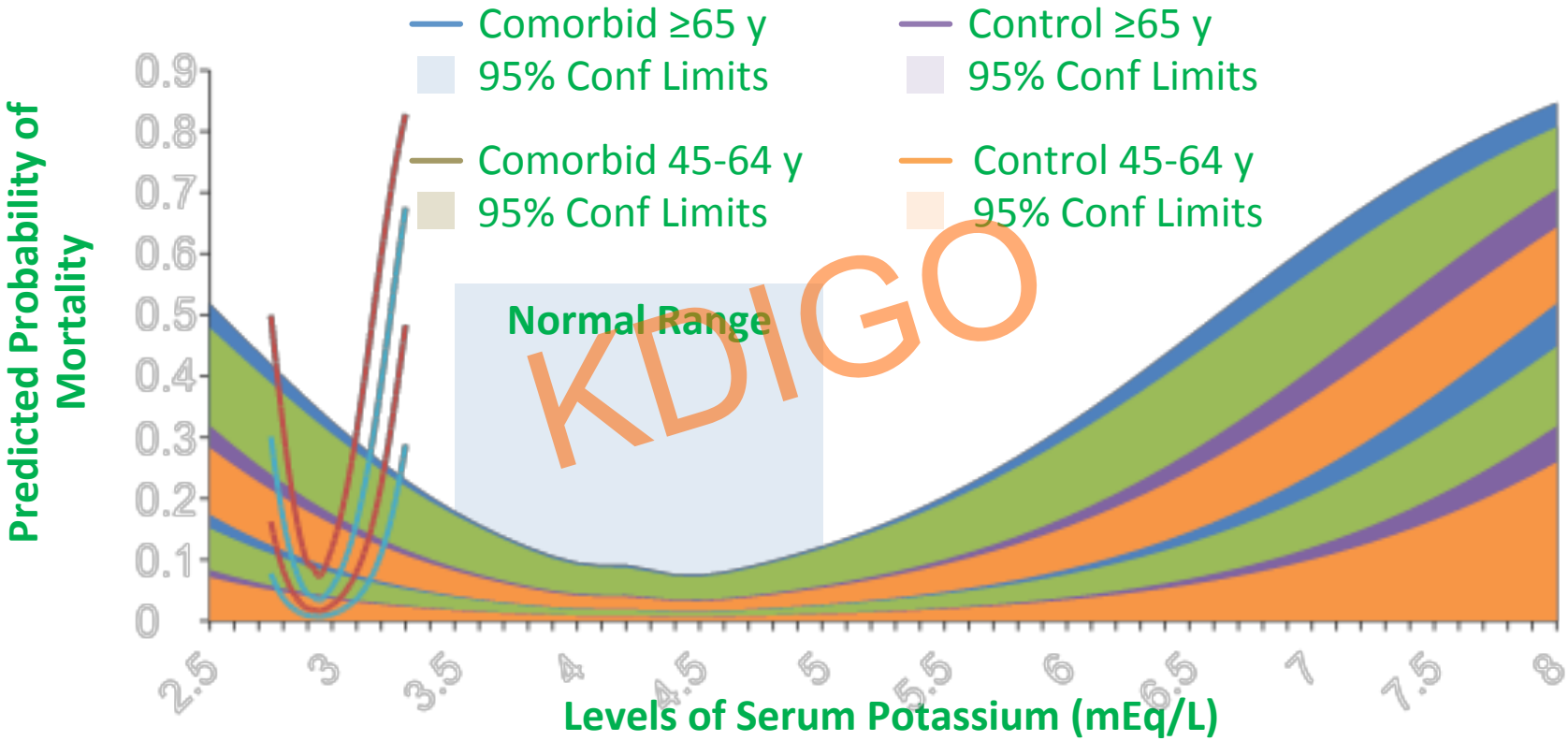


- In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$697 million
- Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay
- One-third were discharged to another short-term hospital, institution, or home health care

ED: emergency department, LOS: length of stay.

Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed October 21, 2014.

Adjusted Mortality* by Serum K+ Level in Patients 45 to 64 Years and ≥65 Years With and Without Comorbid Illness

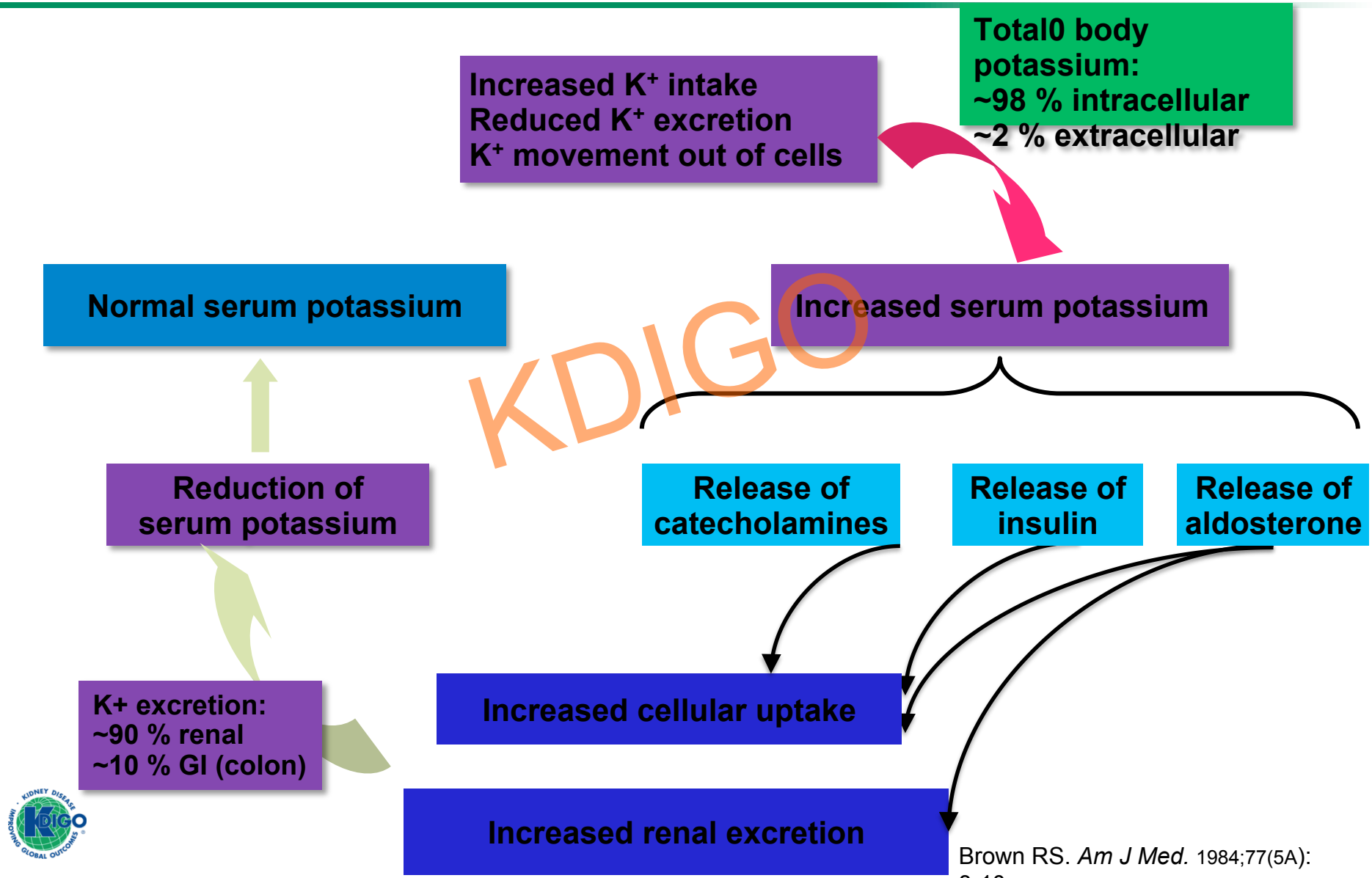


Increases in mortality remained after adjustments for demographic characteristics and comorbidities

*Evaluated with de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K^+ readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K^+ after adjusting for covariates and interactions. Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension.

Pitt B, et al. 2014 AHA Scientific Sessions; November 15-19, 2014; Chicago, IL; Poster 2443.

Serum Potassium Homeostasis and Regulation



Brown RS. *Am J Med.* 1984;77(5A):

Potassium Absorption and Secretion

- Potassium absorption and secretion occurs in distinct areas of the nephron and gastrointestinal tract

- Nephron
  - K^+ reabsorption in the proximal tubule and loop of Henle
  - K^+ secretion in the distal and collecting tubules

- Gastrointestinal tract
  - K^+ absorption in the jejunum and ileum (passive)
  - K^+ secretion in the colon (passive and active)

Diabetic Patient with CKD: Many Reasons for Hyperkalemia

Redistribution

- **Acidosis**
- **Hypertonicity**

Drugs

- **Beta blocker**
- **RAAS blockers**

Reduction of

- **Insulin**
- **Glucocorticoid**
- **Decreased GFR**

Patient with Systolic Heart Failure:

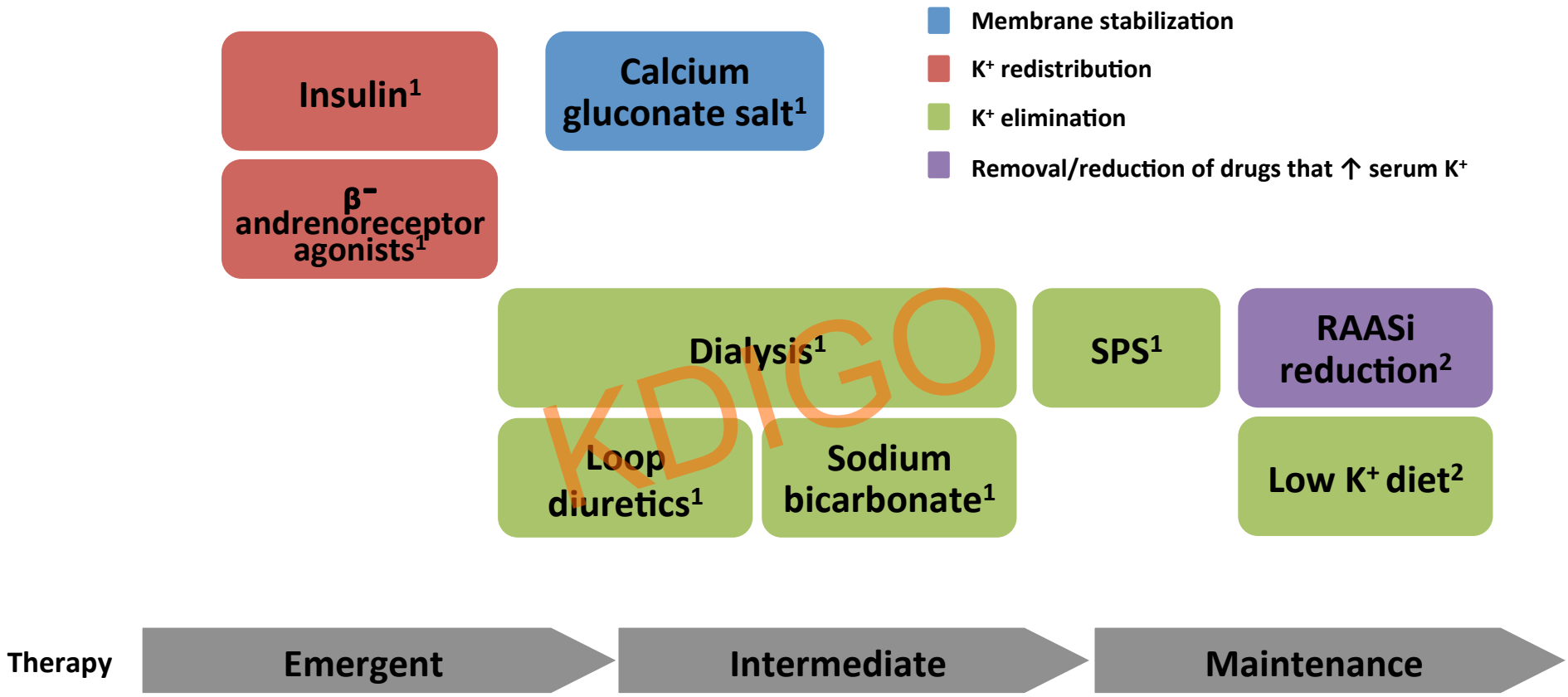
Many reasons for hyperkalemia

Redistribution
- Acidosis

Drugs
- Beta Blockers
- RAAS Blockers
- Potassium Sparing Diuretics

Reduced
- Decreased GFR
- Pre-renal Azotemia

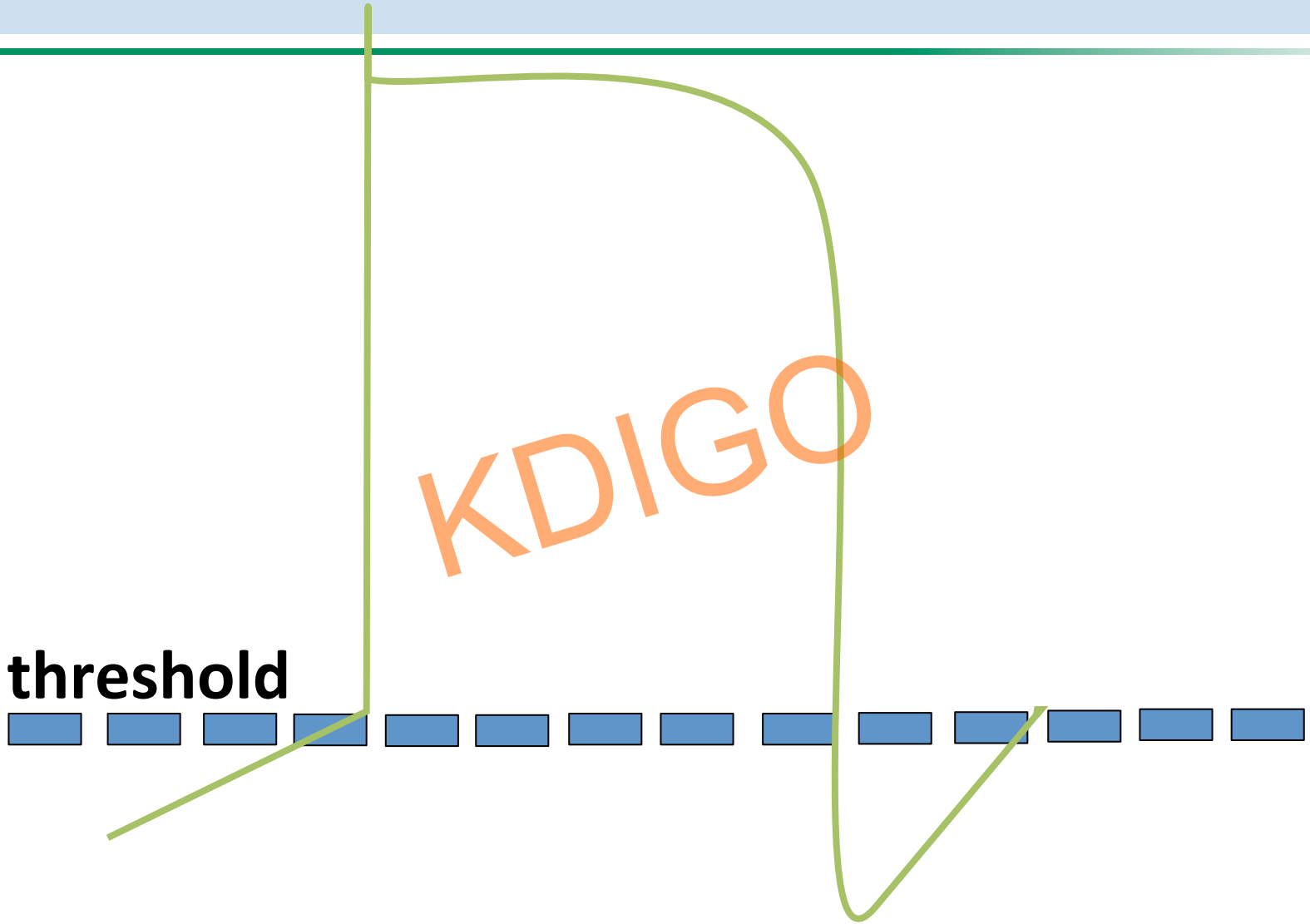
Treatment Options for Hyperkalemia



SPS: sodium polystyrene sulfonate.

1. Weisberg L. *Crit Care Med*. 2008;36(12):3246-3251. 2. Palmer BF, et al. *N Engl J Med.* 2004;351(6):585-592.

Cardiac Action Potential

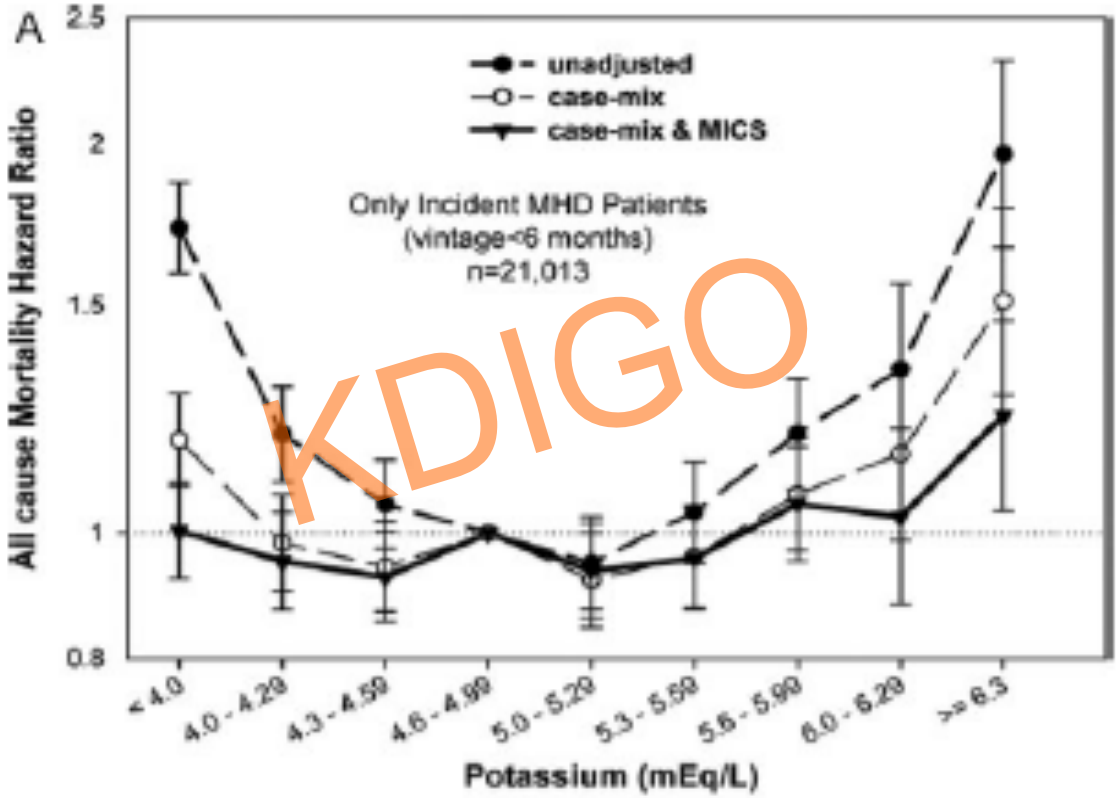


Potassium and Hemodialysis

- n= 81,013 hemodialysis patients followed for 3 years
- Nine quarterly – averaged pre-dialysis serum K groups (<4.0, ≥ 6.3 mEq/L and seven increments in between) and four dialysate K+ concentration groups created in each of 12 calendar quarters
- Death risk associated with pre-dialysis K level and dialysate K

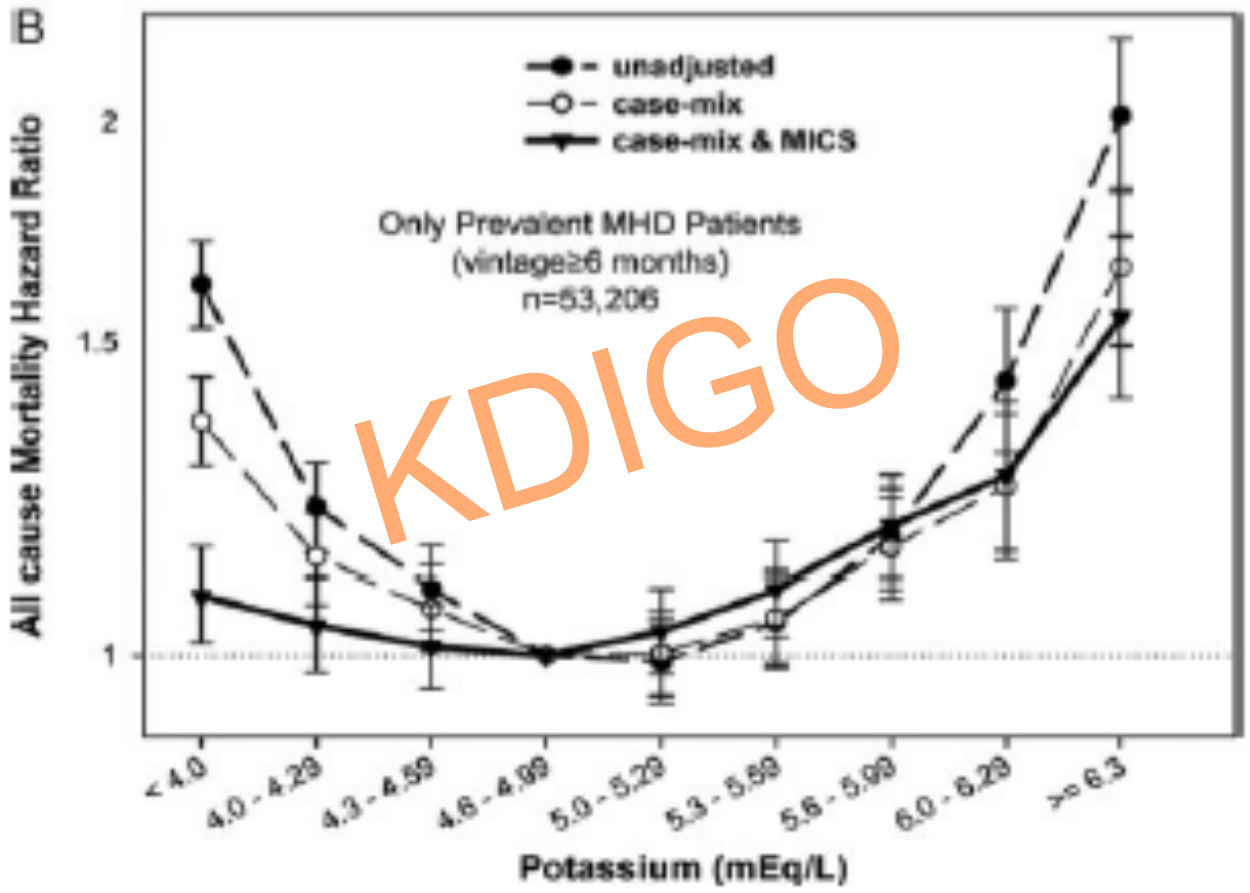
Kovesdy CP, et al. CJASN 2007; 2: 999-1007.

Hazard ratios of all-cause mortality for predialysis serum K categories in 21,013 incident MHD patients observed for up to 3 yr.

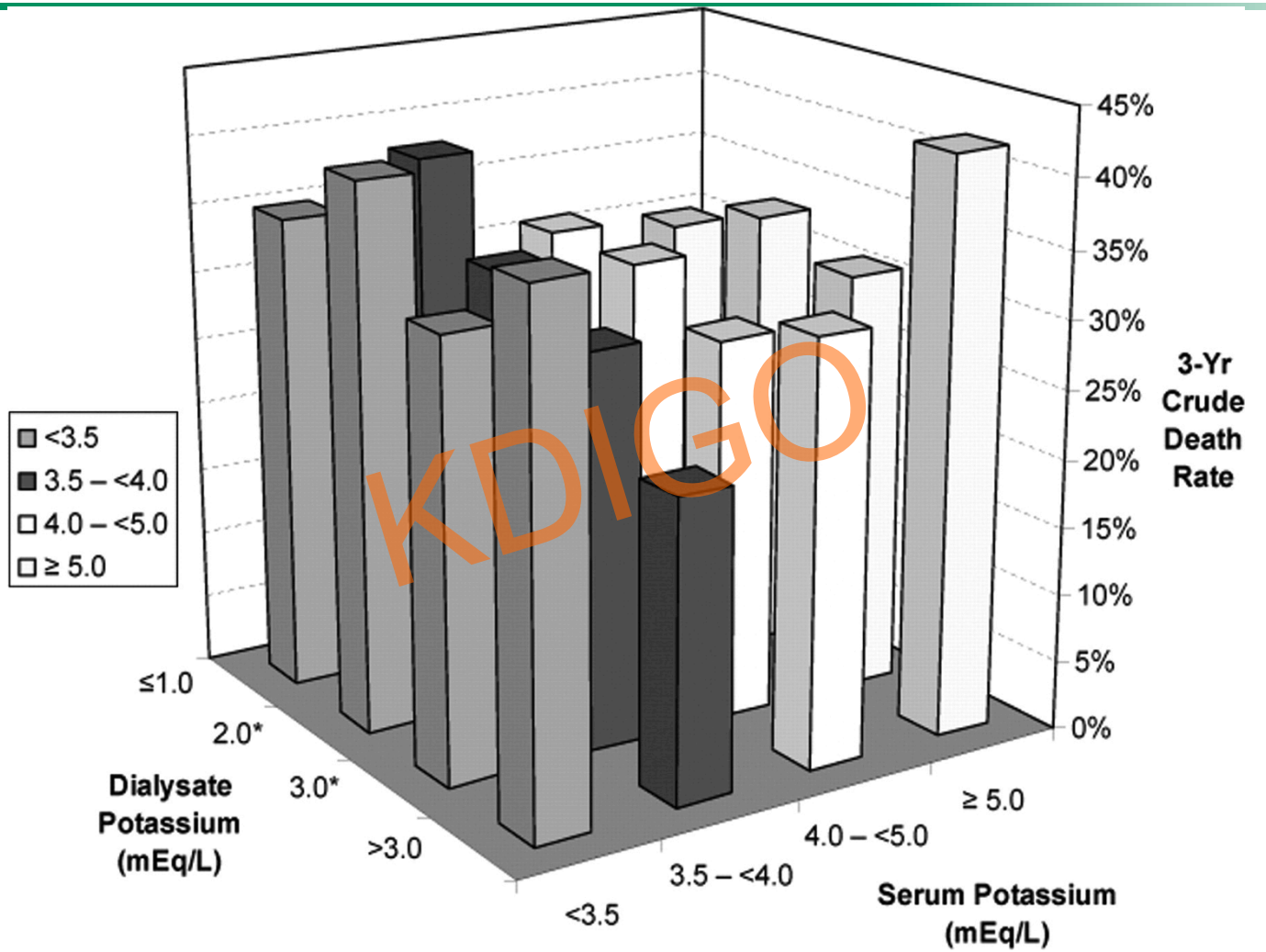


Kovesdy, CP, et al. Clin J Am Soc Nephrol 2: 999-1007, 2007.

Hazard ratios of all-cause mortality for predialysis serum K categories in 53,206 prevalent MHD patients observed for up to 3 yr.



Three-year crude mortality rates in 16 groups of serum and dialysate K concentrations



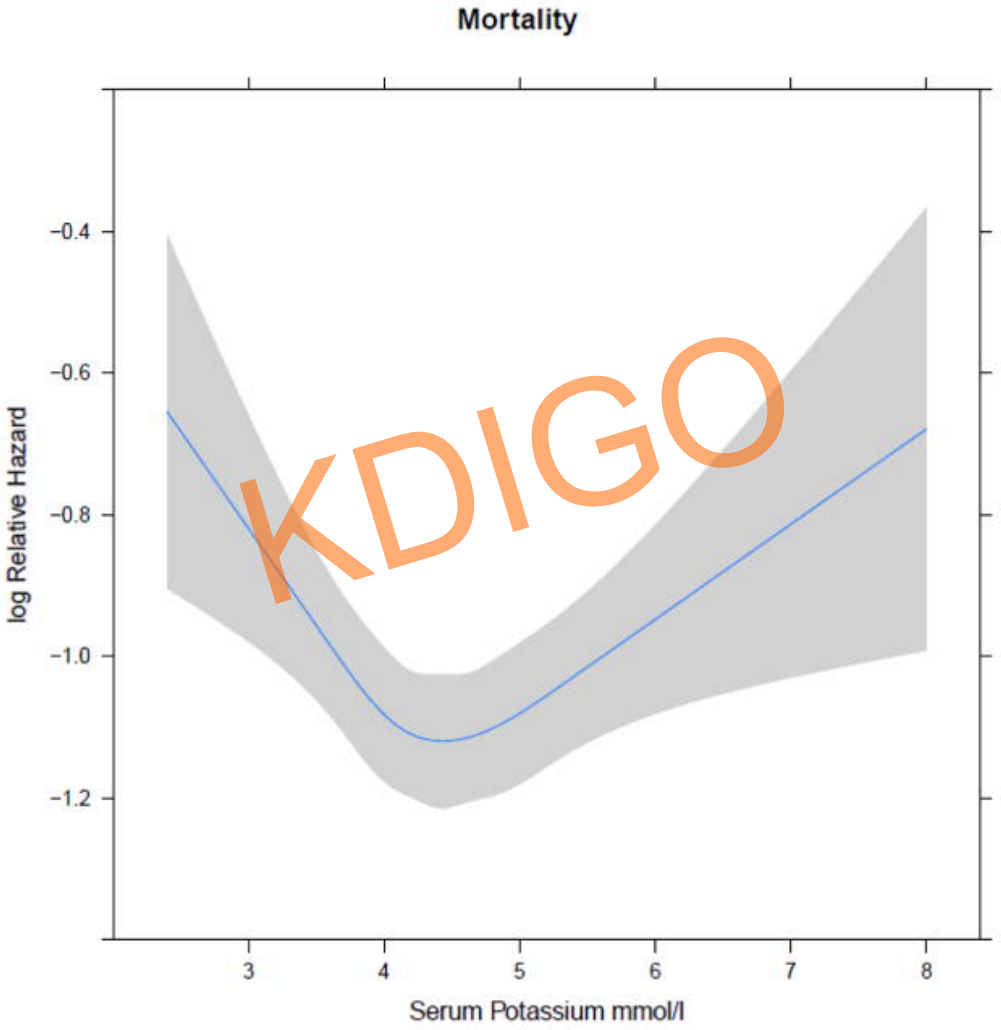
Csaba P. Kovesdy et al. CJASN 2007;2:999-1007

Potassium and CKD

- n= 36,359 patients with eGFR < 60 ml/min
- Cleveland Clinic data base
- Age: 71 years
- eGFR= 47.5 ml/min
- DM%: 18%

Nakhaul GN, et al. Am J Nephrol 2015;41:456-463

Relationship between serum potassium (as a continuous measure) and all-cause mortality

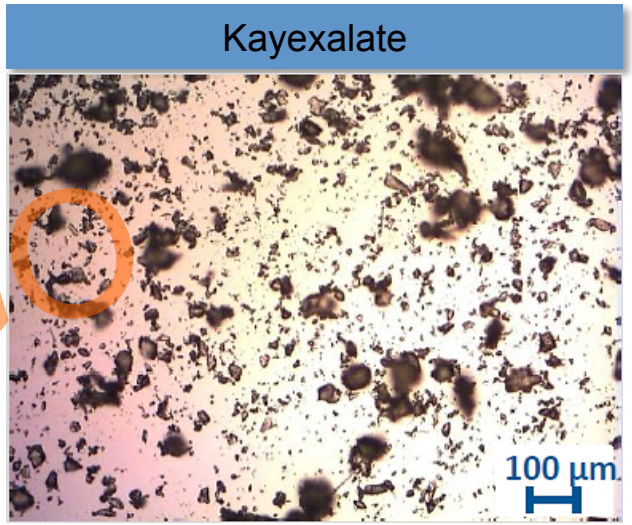


Nakhoul, GN et al.
Am J Nephrol 2015; 41:456-463

KAYEXALATE (Sodium Polystyrene Sulfonate) Is Indicated for the Treatment of Hyperkalemia

PROPERTY	Kayexalate
Mechanism of Action	Potassium binder that is ingested and exchanges sodium for potassium in the GI tract to reduce serum potassium levels[1]
Safety and Tolerability	Intestinal necrosis warning, GI side effects[1]
Design/Active Pharmaceutical Ingredient	Bulk gel material, nonuniform size, and fine, brown, clay-like consistency[1,2]
Counterion	Na^+-loaded, about 1/3 is delivered to the body[1]
Efficacy Data	Efficacy and safety not studied in large, systematic, long-term Trials[2]
Dosing	Average daily adult dose is 15g-60g/day[1]

Microscopic image of SPS showing irregular, nonuniform structure[2]



1. Kayexalate [package insert]. Bridgewater, NJ: Sanofi-Aventis;2010. 2. Sterns RH, et al. *J Am Soc Nephrol.* 2010;21(5): 733-735. Kayexalate is a registered trademark of Sanofi-Aventis.

2. Cope J, et al. Presented at: American Society of Nephrology Renal Week; Denver, CO; Nov 16-21, 2010. Poster F-PO1616.

Kayexalate Precaution: Patients Sensitive to Sodium Increase

- Caution is advised when Kayexalate is administered to patients who cannot tolerate even a small increase in sodium loads (ie, severe congestive heart failure, severe hypertension, or marked edema)
- In such instances compensatory restriction of sodium intake from other sources may be indicated

Kayaxelate [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2010.

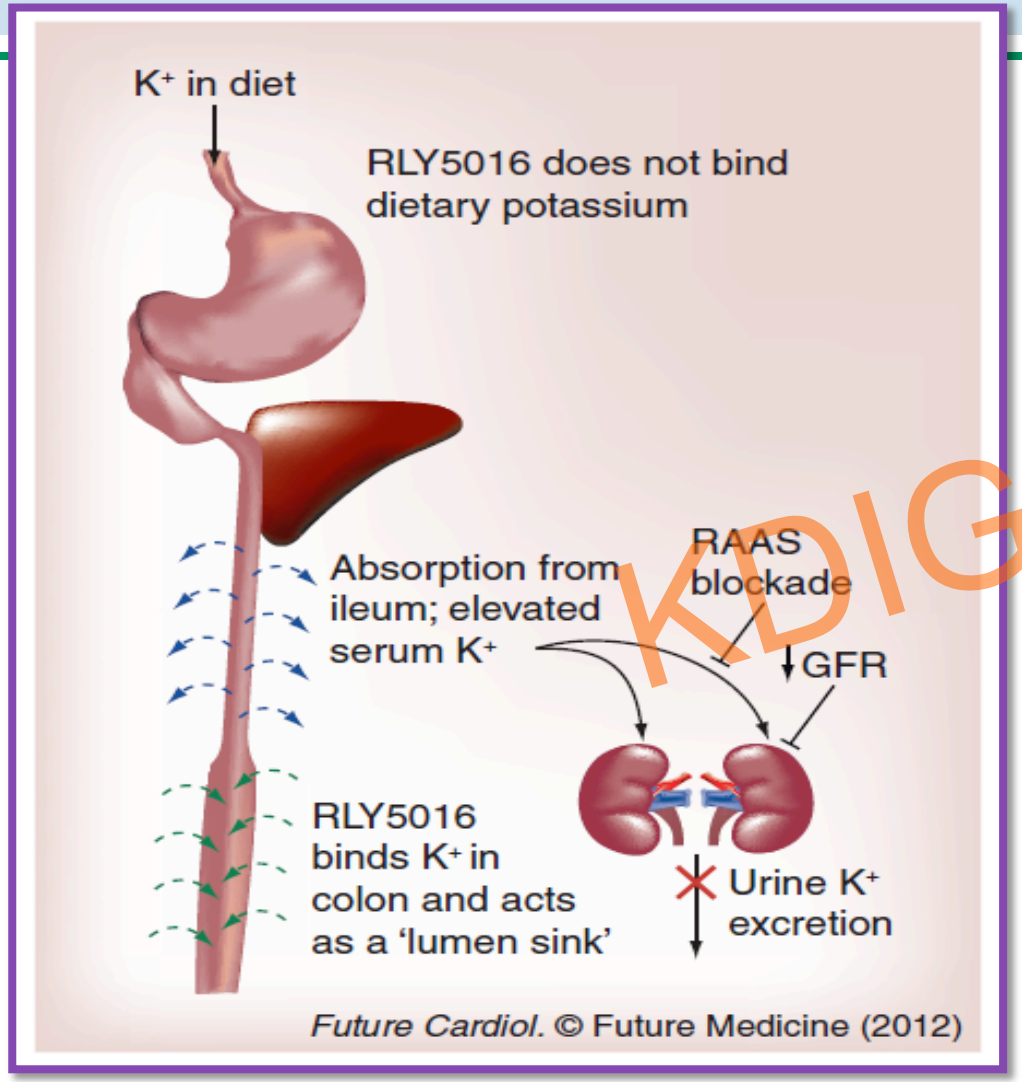
Limitations of Long-Term Hyperkalemia Management Strategies

Treatment focuses on diet changes, removal of therapies that increase serum K^+, and Kayexalate

RAASi reduction	• Limiting the dose or discontinuing treatment of drugs known to be effective in these populations[1]
Kayexalate	• Warnings related to serious gastrointestinal adverse events[2] • Precaution related to sodium[2]
Dietary K^+ restriction of 50-75 mEq/day[1]	• Potassium is common ingredient in many foods[3] • Restricts consumption of healthy foods (such as the DASH diet)[3] • Low K^+ diet often expensive[3]

1. National Kidney Foundation. Guideline 11. http://www2.kidney.org/professionals/KDOQI/guidelines_bp/guide_11.htm. Accessed February 17, 2015. 2. Kayexelate [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2010. 3.National Kidney Foundation. The DASH Diet. https://www.kidney.org/atoz/content/Dash_Diet. Accessed February 17, 2015.

Patiromer (RLY5016) is a Polymer That Binds Potassium in the Colon



Hyperkalemia

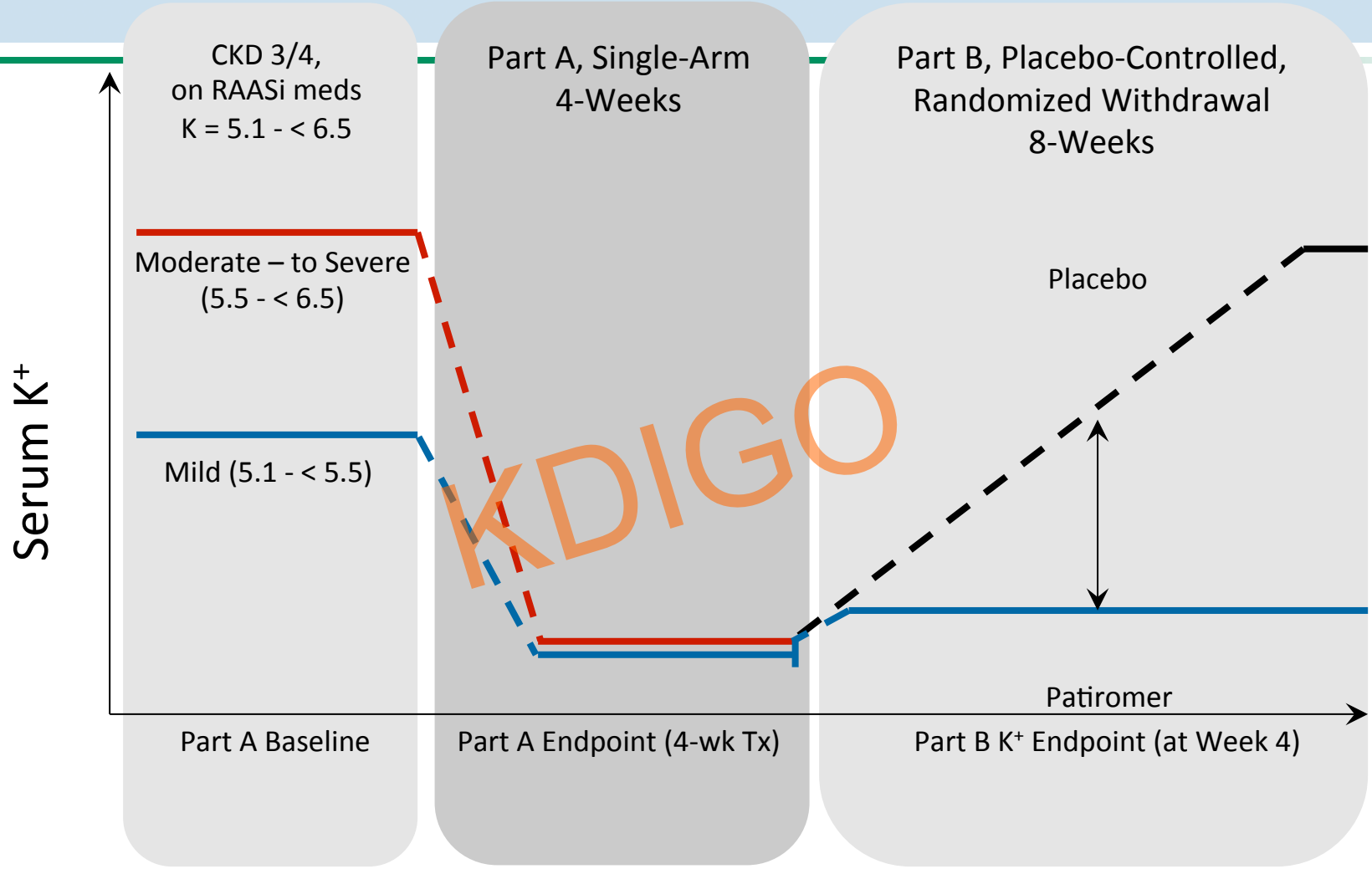
Hyperkalemia is most commonly caused by chronic kidney disease (CKD), or the use of RAAS blockade drugs that limit urinary K^+ excretion and increase serum K^+ level

Patiromer (RLY5016)

- Patiromer is a non-absorbed K^+ binding polymer
- Patiromer binds K^+ in colon (not dietary K^+)
- Patiromer acts as a "sink" to increase colonic K^+ excretion

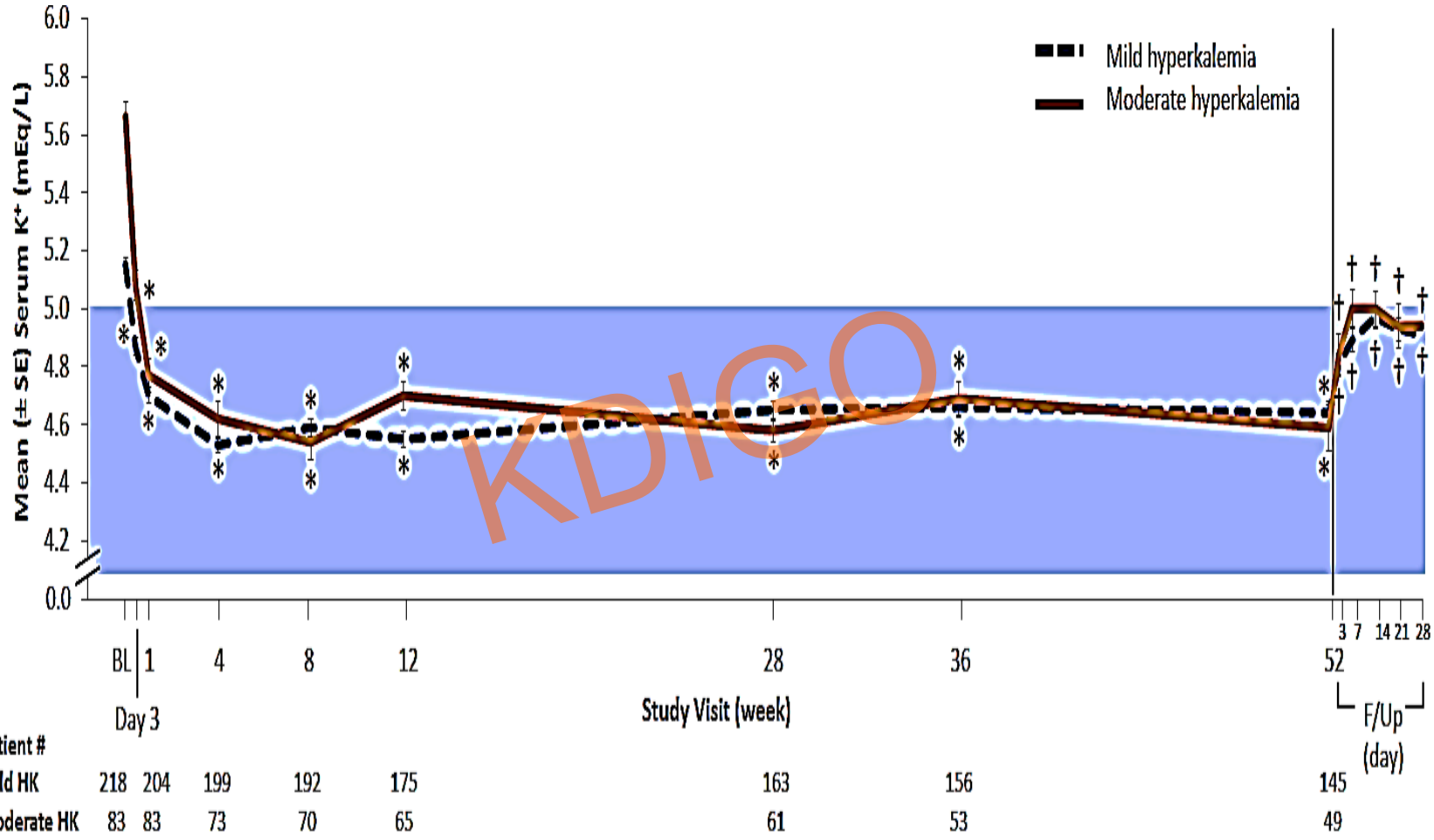
Buysse JM, et al. 2012 Future Cardiol. 8:17-28

Phase 3, 2-Part CKD Pivotal Study in Hyperkalemia Subjects on RAASi: Under Special Protocol Assessment with FDA



Weir M, et al. NEJM. 2015;372:211-221

Change from Baseline in Mean (±SE) Serum K^+ to Week 52



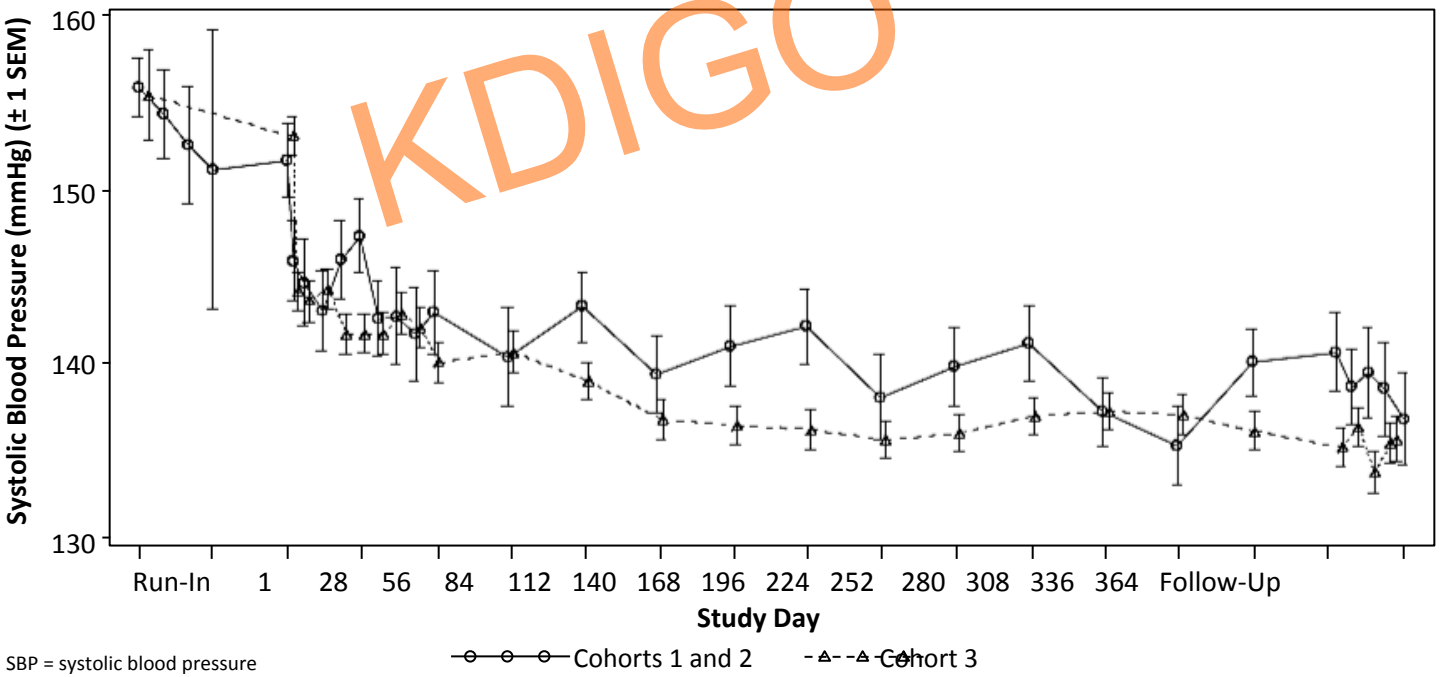
Bakris G, et al. *JAMA 2015;314:151-161.*

All serum K^+ analyses are based on central lab values; 3 patients (2 in the mild HK group and 1 in the moderate HK group) did not have a central lab serum K^+ value at baseline and therefore are not included in the analysis at this timepoint. *$p<0.001$ by t-test for change from baseline. $^{\dagger}p<0.001$ by t-test for change from Week 52 (or from the last dose of patiromer received during the study). BL, baseline; F/Up, follow-up; HK, hyperkalemia.

Study 205

Secondary Endpoint: Change in Systolic Blood Pressure Over 52 Weeks (Intention to Treat Population)

- Clinically relevant reductions in systolic blood pressure were observed in all starting dose groups in both strata
- The 52 week change in SBP – Stratum 1: -15.7 mmHg, Stratum 2: -17.1 mmHg



SBP = systolic blood pressure
Data on File, Relypsa – 205 CSR

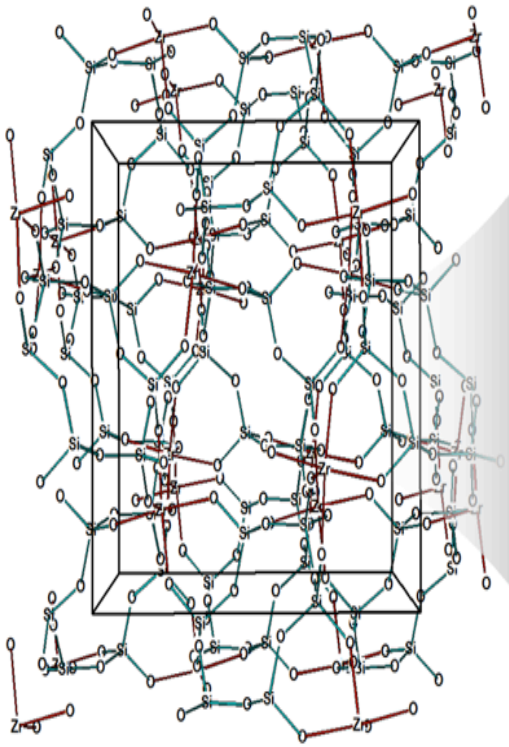
Most Common Adverse Events Over 52 Weeks*

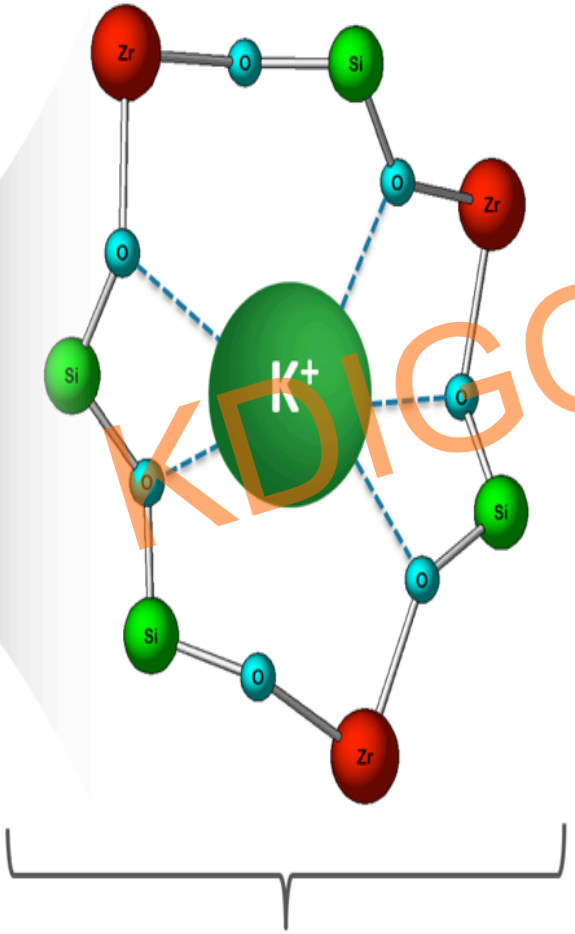
Adverse Event	Mild HK (n=220)	Moderate HK (n=84)	Overall (n=304)
Hypomagnesemia†	15 (7%)	11 (13%)	26 (9%)
Worsening of HTN	14 (6%)	10 (12%)	24 (8%)
Worsening of CKD	14 (6%)	14 (17%)	28 (9%)
Diarrhea	12 (6%)	5 (6%)	17 (6%)
Constipation	11 (5%)	8 (10%)	19 (6%)
Hypoglycemia†	4 (2%)	6 (7%)	10 (3%)

Bakris G, et al. *JAMA 2015;314:151-161.*

Figure 1. ZS-9: A Novel Selective Potassium Trap

ZS-9 Crystal Structure



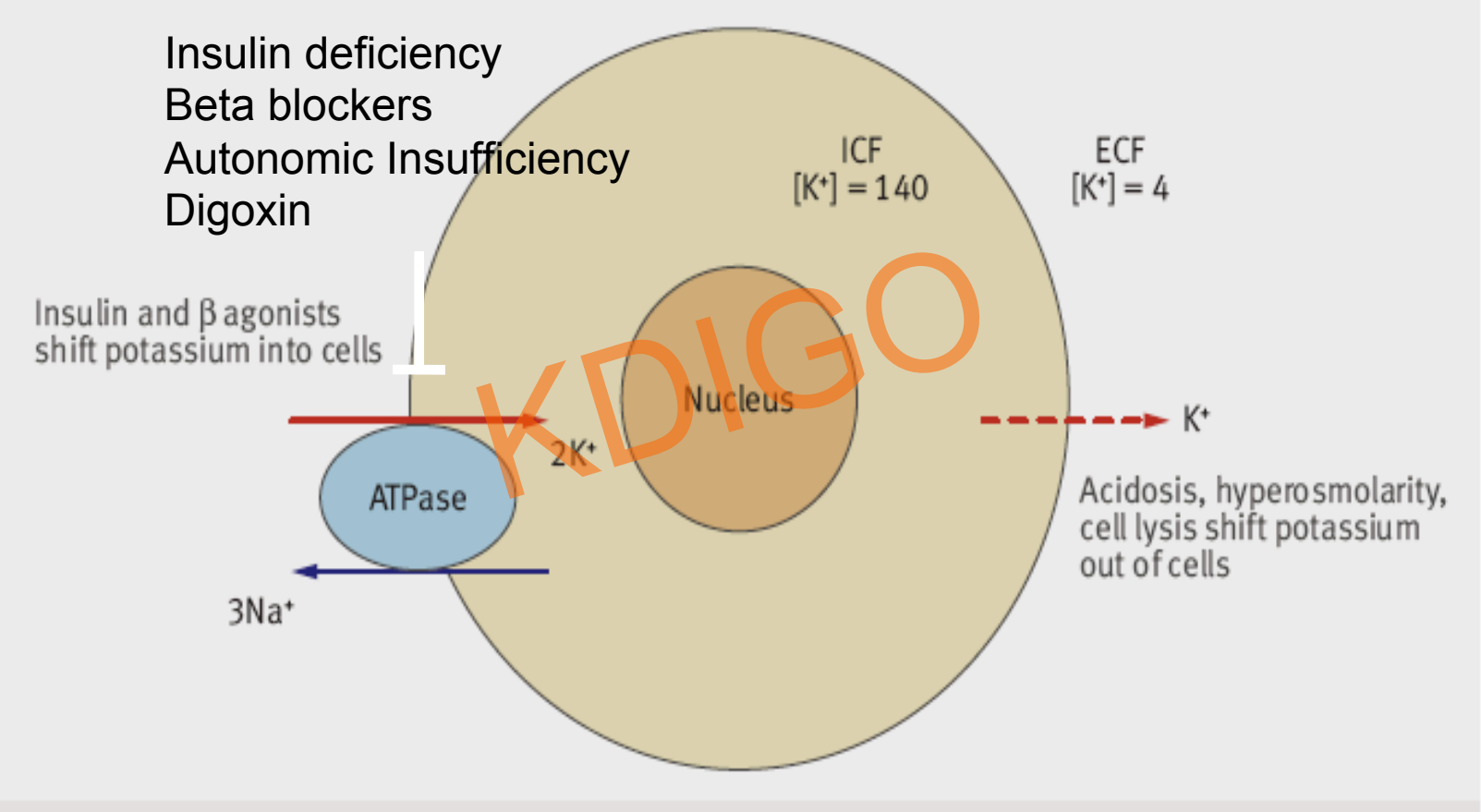


Average Width of Micropore Opening 3Å

ZS-9 PROPERTIES

- Unique microporous zirconium silicate compound
- Designed to be selective for K^+
- Builds on long history of Zr use in dialysis and other biomedical applications
- Insoluble and highly stable
- Non-systemically absorbed
- ZS-9 has 9.3 times more K^+ binding capacity than Kayexalate® (SPS)
- ZS-9 is >125 times more selective for K^+ than Kayexalate
- Kayexalate is more selective for Ca^{2+} than K^+

Predisposition to Hyperkalemia: Impaired Extrarenal Buffering



Magnesium

- Complex effect on myocardial ion flux
- Obligate CO-factor in all reactions that require ATP
- Essential for activity of Na-K-ATPase
- Low serum magnesium impairs Na-K-ATPase, and limits inward potassium current
- More common in older patients on diuretics or with interstitial kidney disease!

Magnesium Depletion

- Widening of QRS, peak T waves
- Prolongation of PR interval
- APC, PVC, atrial fibrillation, ventricular arrhythmias
- Facilitates digoxin cardiotoxicity (additive effect on intracellular potassium depletion)

Magnesium Depletion

- Increases the risk of torsades des pointes, particularly in people taking class IA or III antiarrhythmic drugs
- Low serum magnesium most concerning with acute myocardial ischemia or infarction
- Mild elevation of serum magnesium protects myocardium from ischemia-reperfusion injury by promoting restoration of high energy phosphates.

Treatment?

- Does magnesium supplementation help?
- Where is the data?
- Under what clinical circumstances is it indicated?
- What about hemodialysis patients? No magnesium in dialysate.

Mineral Metabolism and Mortality

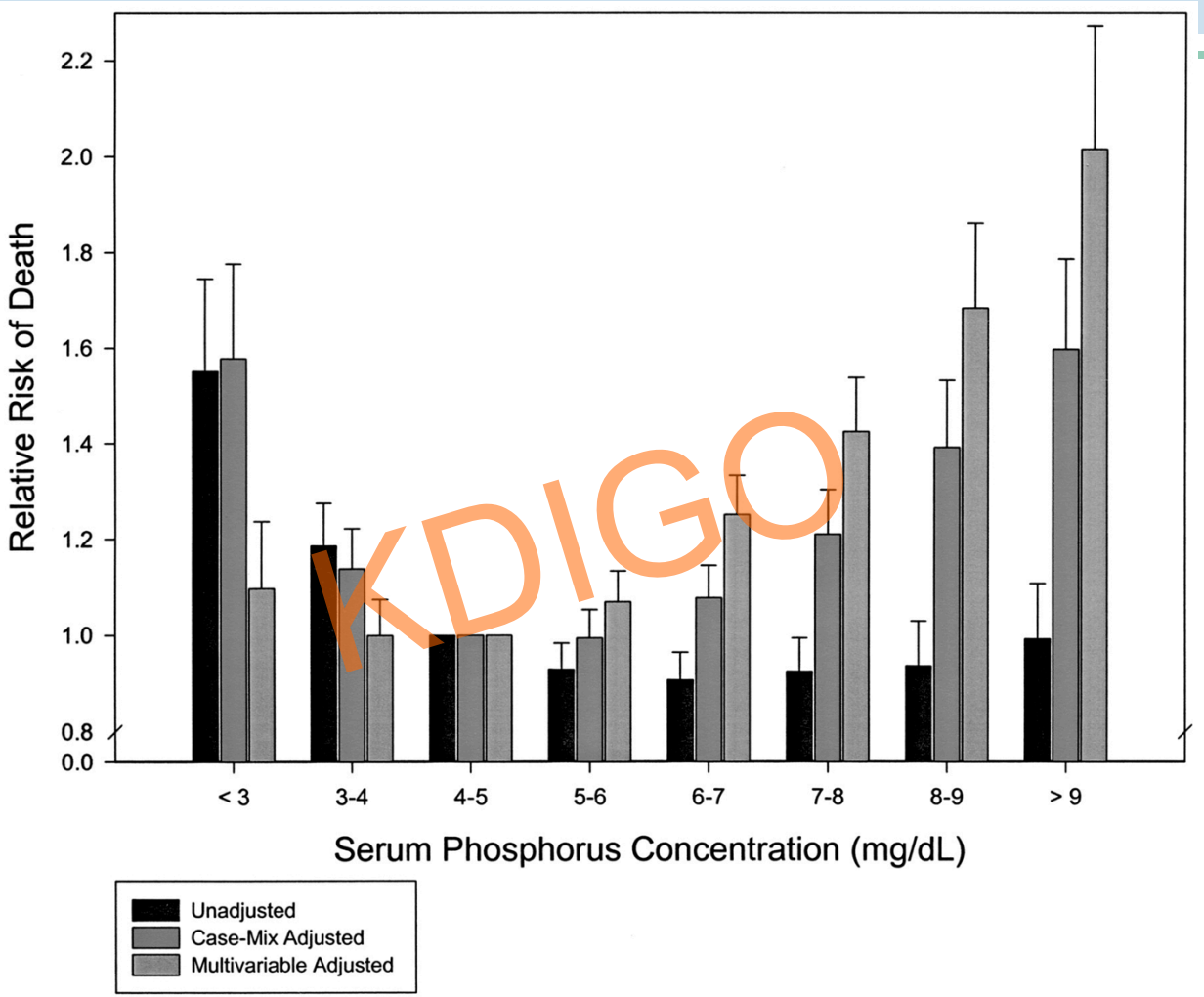
- Decreased survival in dialysis patients with increased serum phosphate, calcium, calcium-phosphate product, and PTH.
- All studies not consistent
- Theory: these mineral bone disease alterations can lead to arterial calcification, accelerated atherosclerosis and increased cardiovascular events and death.

Mineral Metabolism and Mortality

- n= 40,538 hemodialysis patients with at least one measure of phosphorus and calcium in 1997
- Unadjusted, case-mix adjusted and multi-variable adjusted relative risks of death were calculated using proportional hazards regression
- Population attributable risk for disorders of mineral metabolism: 17.5 % (mostly due to hyperphosphatemia)
- Serum phosphate over 5.0 mg/dL and associated with increased risk of death
- PTH concentrations over 600 pg/ml

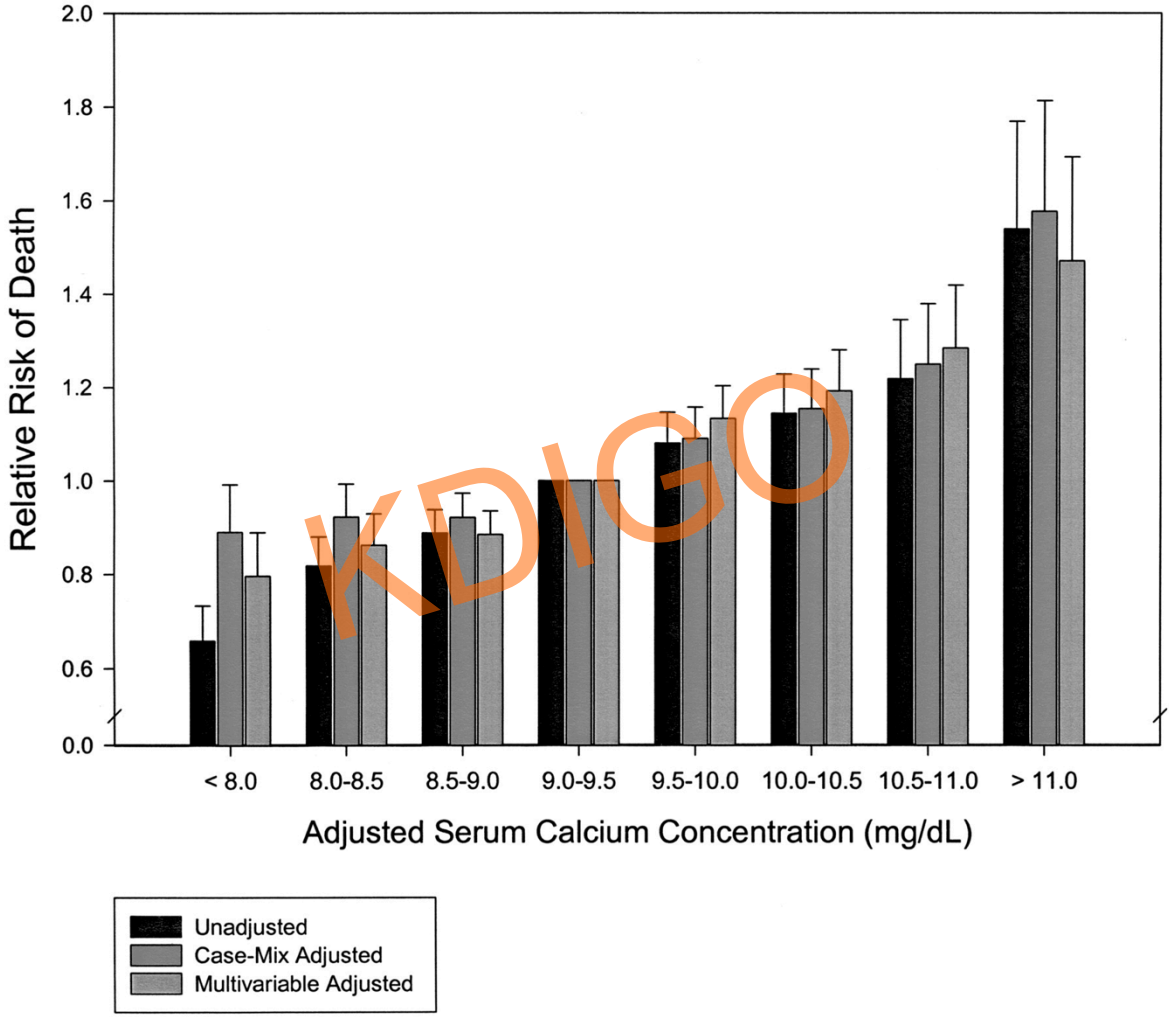
Block GA, et al. JASN 2004; 15: 2208-2218.

Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks (RR; of death) and 95% confidence intervals (CI) for eight categories of serum phosphorus (referent range, 4.0 to 5.0 mg/dl).



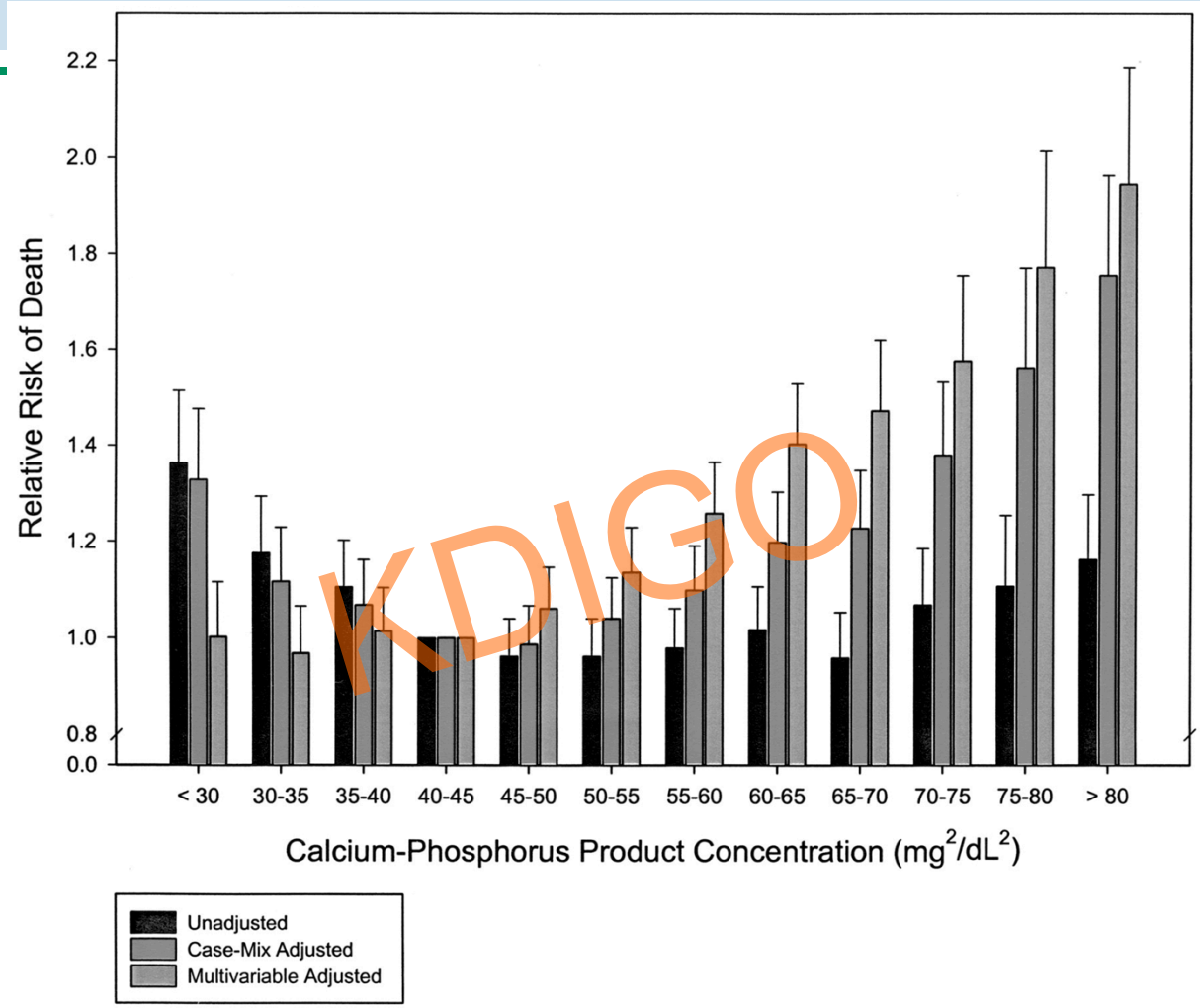
Geoffrey A. Block et al. JASN 2004;15:2208-2218

Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of adjusted serum calcium (measured calcium adjusted for serum albumin, referent range, 9.0 to 9.5 mg/dl).



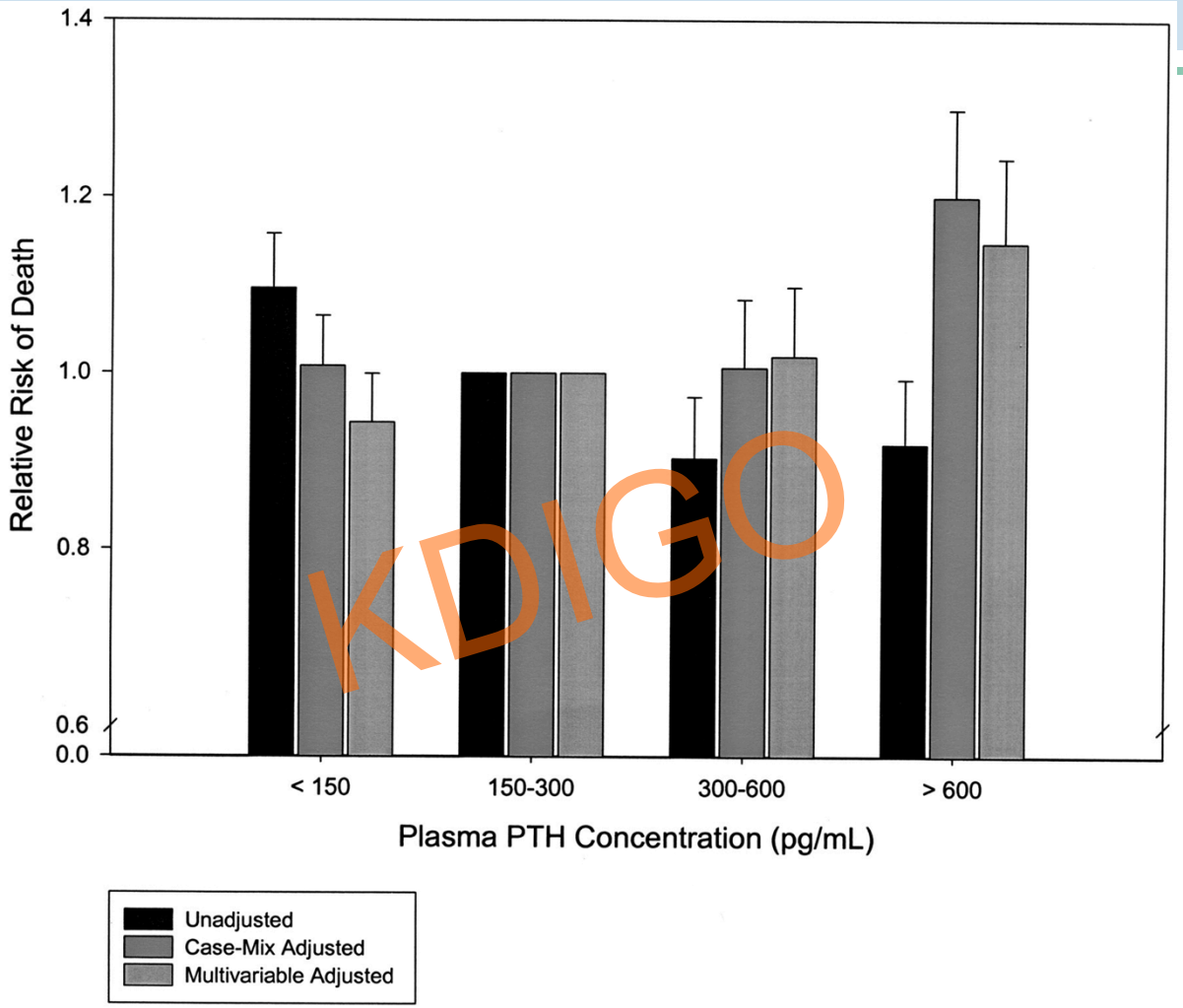
Geoffrey A. Block et al. JASN 2004;15:2208-2218

Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for 12 categories of calcium × phosphorus product (referent range, 40 to 45 mg2/dl2).



Geoffrey A. Block et al. JASN 2004;15:2208-2218

Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for four categories of intact parathyroid hormone (referent range, 150 to 300 pg/ml).



Geoffrey A. Block et al. JASN 2004;15:2208-2218

Mineral Metabolism and Mortality

- n= 25,588 hemodialysis patients in Dialysis Outcomes and Practice Patterns Study (DOPPS)
- Highest mortality noted for patients with calcium over 10.0 mg/dL, phosphorous over 7.0, and PTH level above 600 pg/ml

Tentori F, et al. AJKD 2008; 52 (3): 519-530.

Risk of all-cause and cardiovascular mortality associated with categories of baseline serum calcium, phosphorus, and parathyroid hormone (PTH) levels.

Tentori F, et al. AJKD 2008; 52 (3): 519-530.

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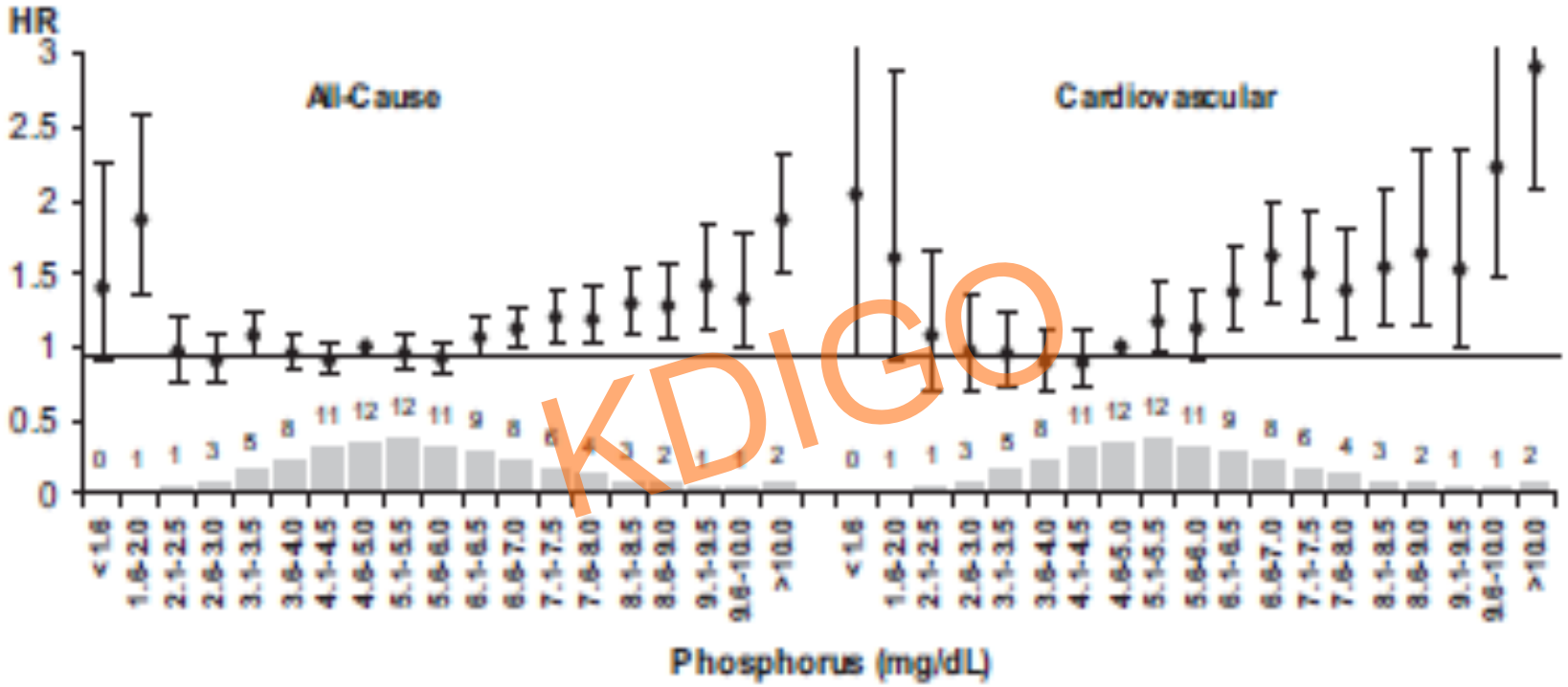


Tentori F, et al. AJKD 2008; 52 (3): 519-530.

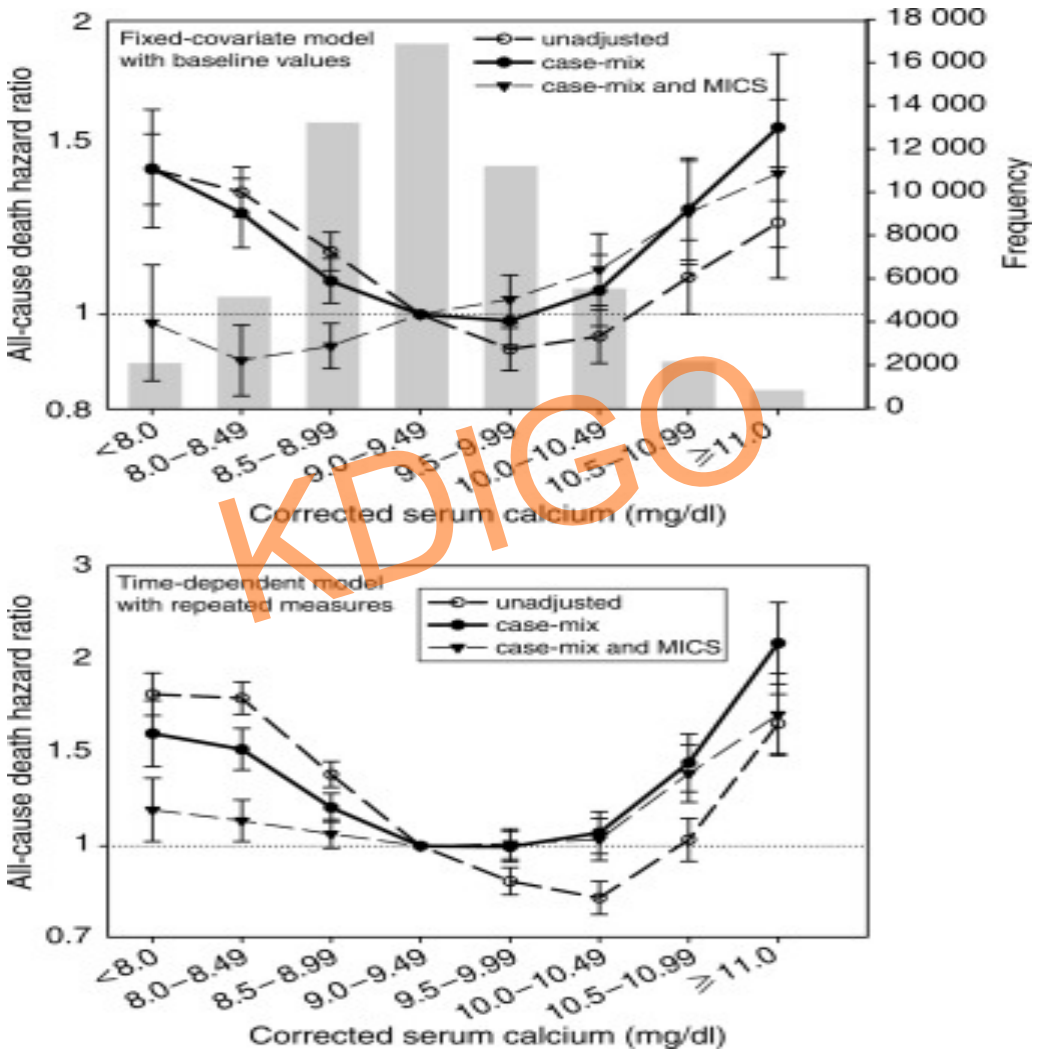
Survival Predictability

Survival Predictability of time-varying indicators of mineral metabolism in hemodialysis patients

- n = 58,058 dialysis patients (2001-2003)
- Time dependent Cox Models with repeated measures and fixed-covariate Cox Models with only baseline values
- Hypercalcemia and hyperphosphatemia were robust predictors in all models
- Association between serum calcium mortality was different in time-varying models
- Changes in baseline serum calcium and phosphorous levels beyond the K/DOQI recommended targets were associated with increased mortality

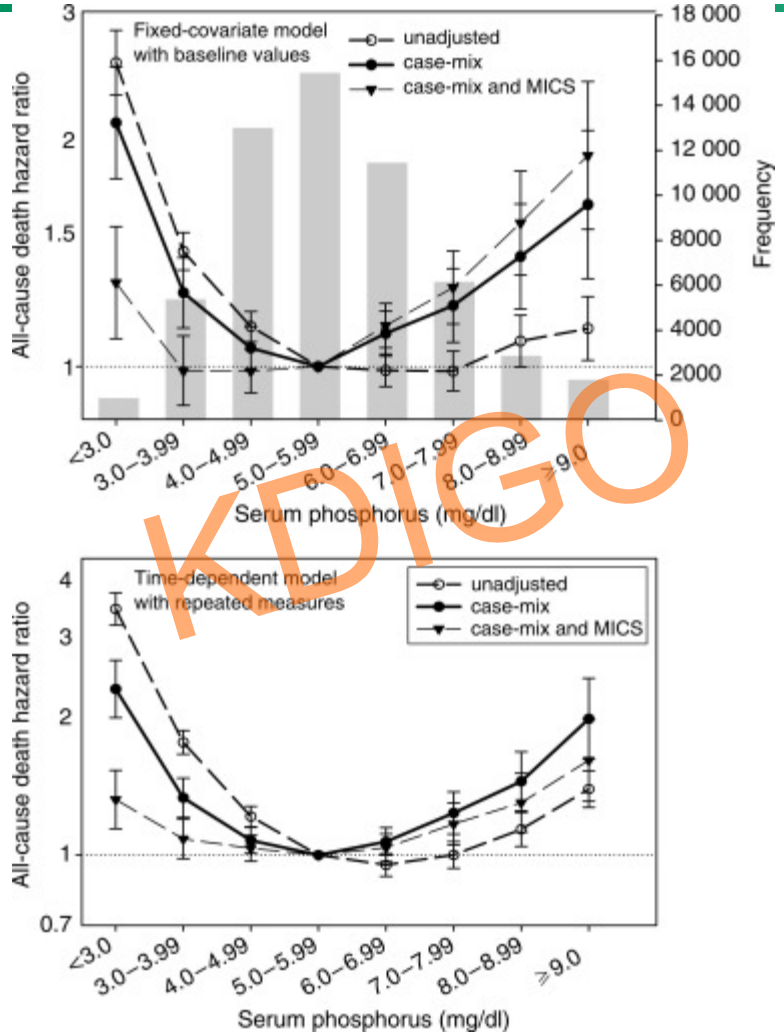
Kalantar –Zadeh, et al. Kidney Int 2006; 70:771-780.

Association between albumin-adjusted serum calcium values and the relative risk of death in 58 058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel).



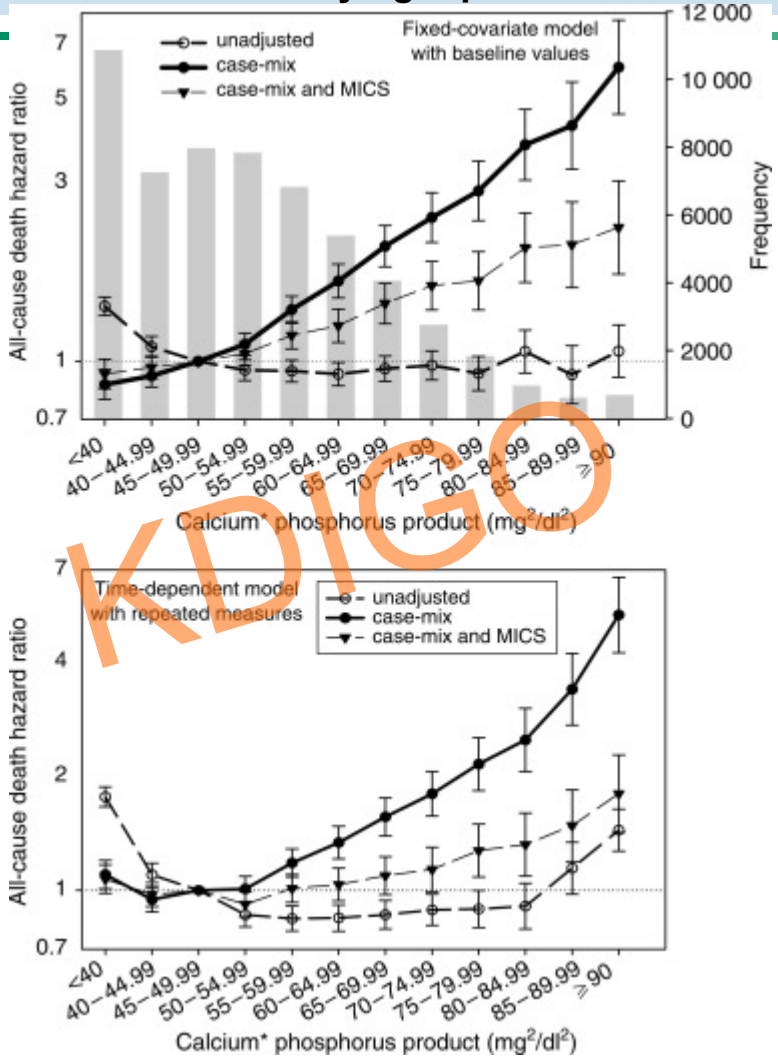
Kalantar-Zadeh, et al. Kidney Int. 2006. 70; 771-780.

Association between the time-varying serum phosphorus values and the relative risk of death in 58 058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel)



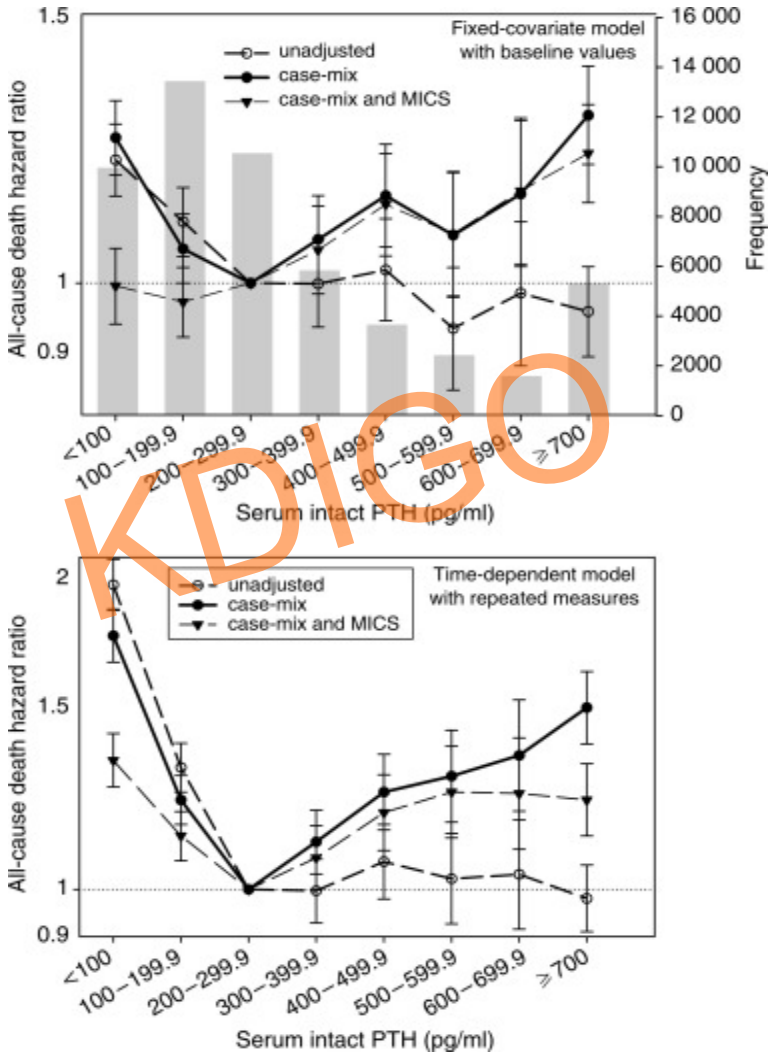
Kalantar-Zadeh, et al. Kidney Int. 2006. 70; 771-780.

Association between the time-varying product of serum calcium and phosphorus values and the relative risk of death in 58 058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel)



Kalantar-Zadeh, et al. Kidney Int. 2006. 70; 771-780.

Association between the time-varying serum intact PTH values and the relative risk of death in 58 058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel)



Kalantar-Zadeh, et al. Kidney Int. 2006; 70: 771-780.

Mineral Metabolism and Mortality

- Other studies indicate that low PTH and calcium levels associated with either no effect or increased mortality
- Why the difference?

  Explanations: variations in study design, differences in populations, use of only single measures of serum samples.

Foley RN et al. AJN 1996: 16: 386.
Avram MM, et al. AJKD 2001; 38:1351-1357.
Teng M, et al. JASN 2005; 16-1115.
Covica A. et al. NDT 2009; 24: 1506.

Mineral Metabolism and Mortality

- No successful interventional trials
- Directionality
- How early should you start treatment?
- What is the target?
- Is there a preferred treatment?

Conclusions

- Treatment of disorders (high and low) of potassium, magnesium, and mineral metabolism may prove to be important in CKD and in ESRD
- We lack evidence from interventional trials
- We lack mechanistic explanations of benefit
- How early should we treat (pre-emptive)?
- What is the target?
- Is there a preferred therapy?