K

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EBAC

K^+ restriction: The patient's dilemma

Dr Deborah Clegg

10:05–10:20

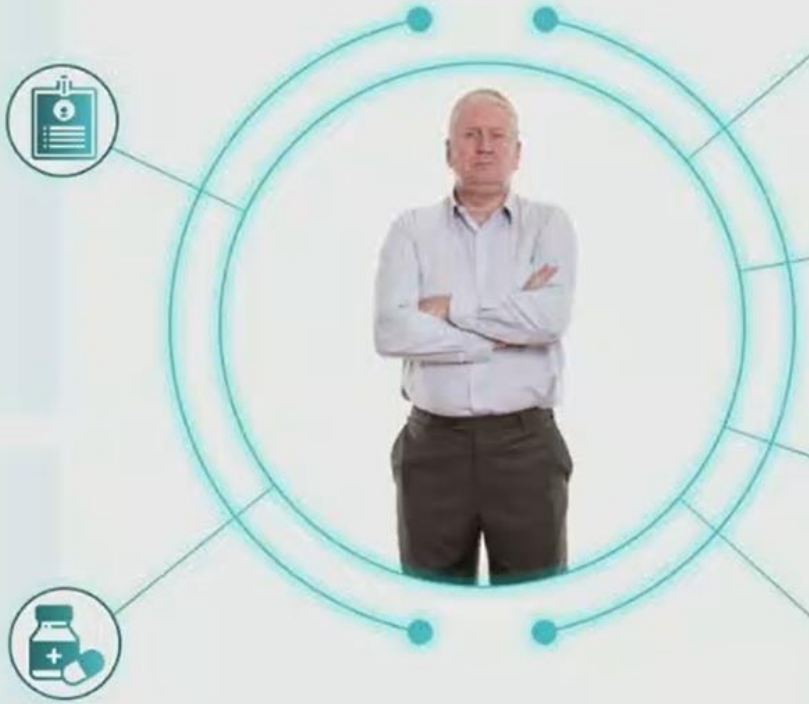
Let's revisit our patient…

Patient information

- 69-year-old male
- CKD stage 4 with albuminuria (diagnosed 2 years ago)
- Hypertension diagnosed and treated with variable success for 20 years
- Type 2 diabetes for 18 years
- Retinopathy controlled with laser therapy
- Mild neuropathy
- NSTEMI 4 years ago; EF 35%

Current treatment:

- Candesartan/hydrochlorothiazide (32/25 mg/day)
  Amlodipine 5 mg/day
- Lantus insulin 24 units nocte and short-acting insulin 3×/day
- Linagliptin 5 mg/day
- Bisoprolol 5 mg/day



Examination:

- Serum K^+: 5.9 mmol/L
- Serum Na^+: 138 mmol/L
- HCO_3^-: 24 mmol/L
- Ca^{2+}, PO_4^{3-}, Mg^{2+}: Normal

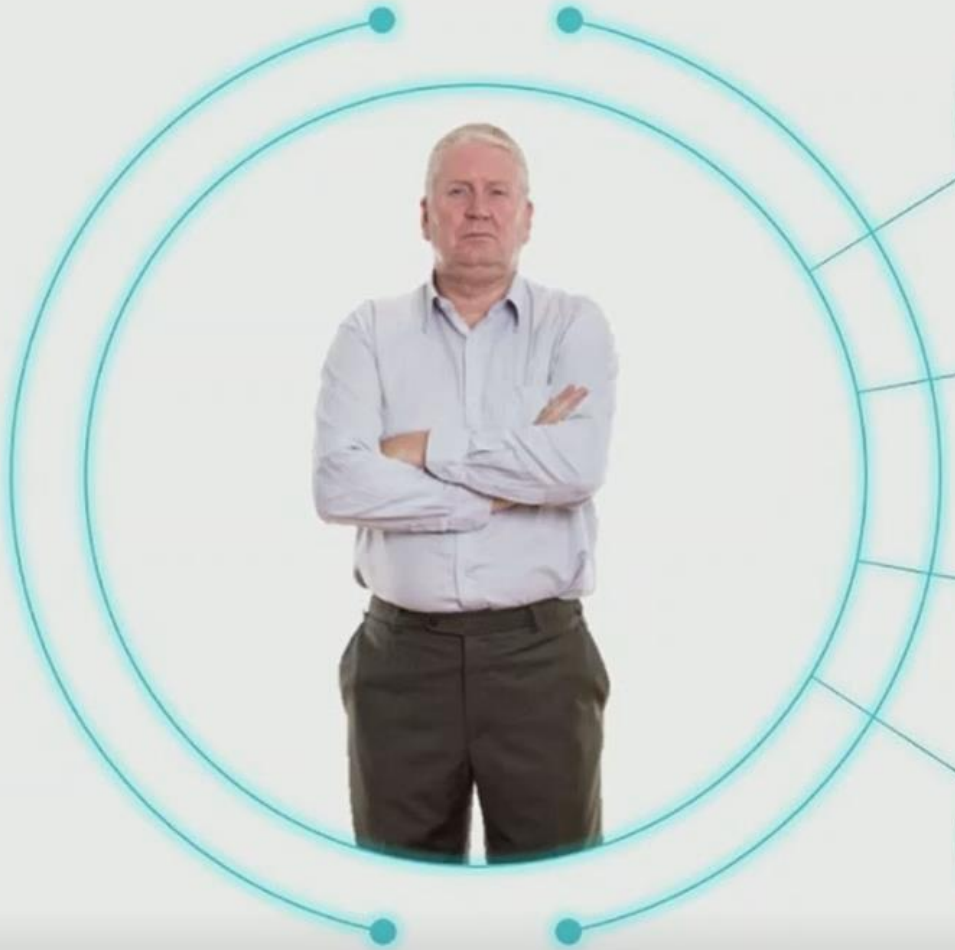
- eGFR: 28 mL/min/1.73 m^2
- Urea: 15 mmol/L
- Creatinine: 208 µmol/L
- UACR: 136 mg/mmoL Cr

- Pulse: 80 bpm
- Sinus rhythm: JVP 3 cm
- Clear chest
- Mild peripheral oedema

- BP: 145/90 mm Hg
- BMI: 35 kg/m^2
- HbA_{1c}: 7.2%

BMI, body mass index; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; JVP, jugular venous pressure; NSTEMI, non-ST-elevation myocardial infarction; UACR, urine albumin:creatinine ratio

What was the best way forward for this patient?



Addition of spironolactone 12.5 mg BID
2 weeks later, K^+ increased to 6.4 mmol/L

Dietary advice provided by renal dietitian

K^+ improved to 6.1 mmol/L after a month

Spironolactone ceased

BID, twice daily

Outline

1. Dietary K^+ intake, nutrition, and cardiorenal benefits
2. Measures of dietary K^+ intake and their association with the development of HK
3. Evidence linking high dietary K^+ intake to HK in CKD

CKD, chronic kidney disease; HK, hyperkalemia

Question

Epidemiologic studies in patients with CKD have shown that high K^+ intake is associated with cardiorenal benefits?

a) True

b) False

CKD, chronic kidney disease

Current dietary intake of K^+

Mismatch between the modern diet introduced over the last 10,000 years and the nutritional requirements encoded into the human genome, which developed over the several million years from the Stone Age[1]

K^+ intake of prehistoric man was estimated to be 15,000 mg/day[2]

Diet has shifted from:

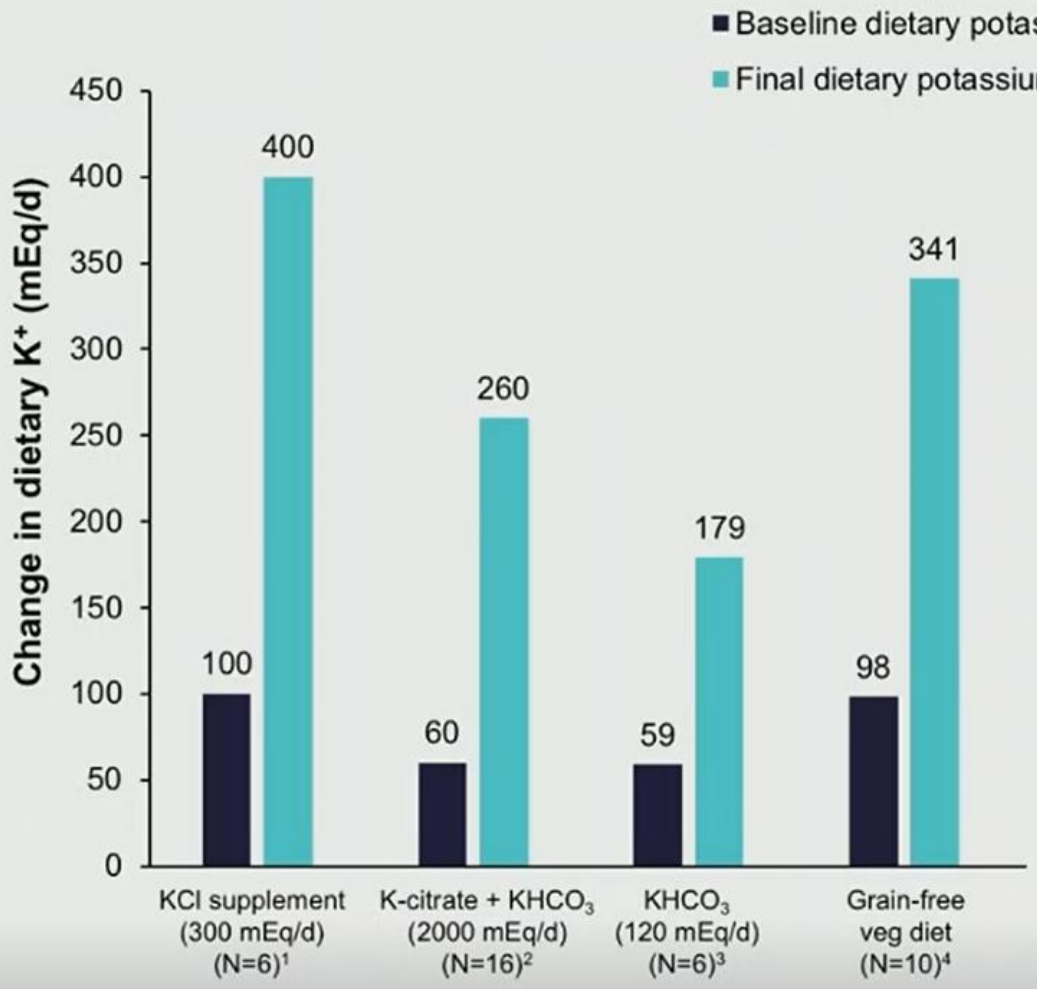
HIGH K^+ and LOW Na^+

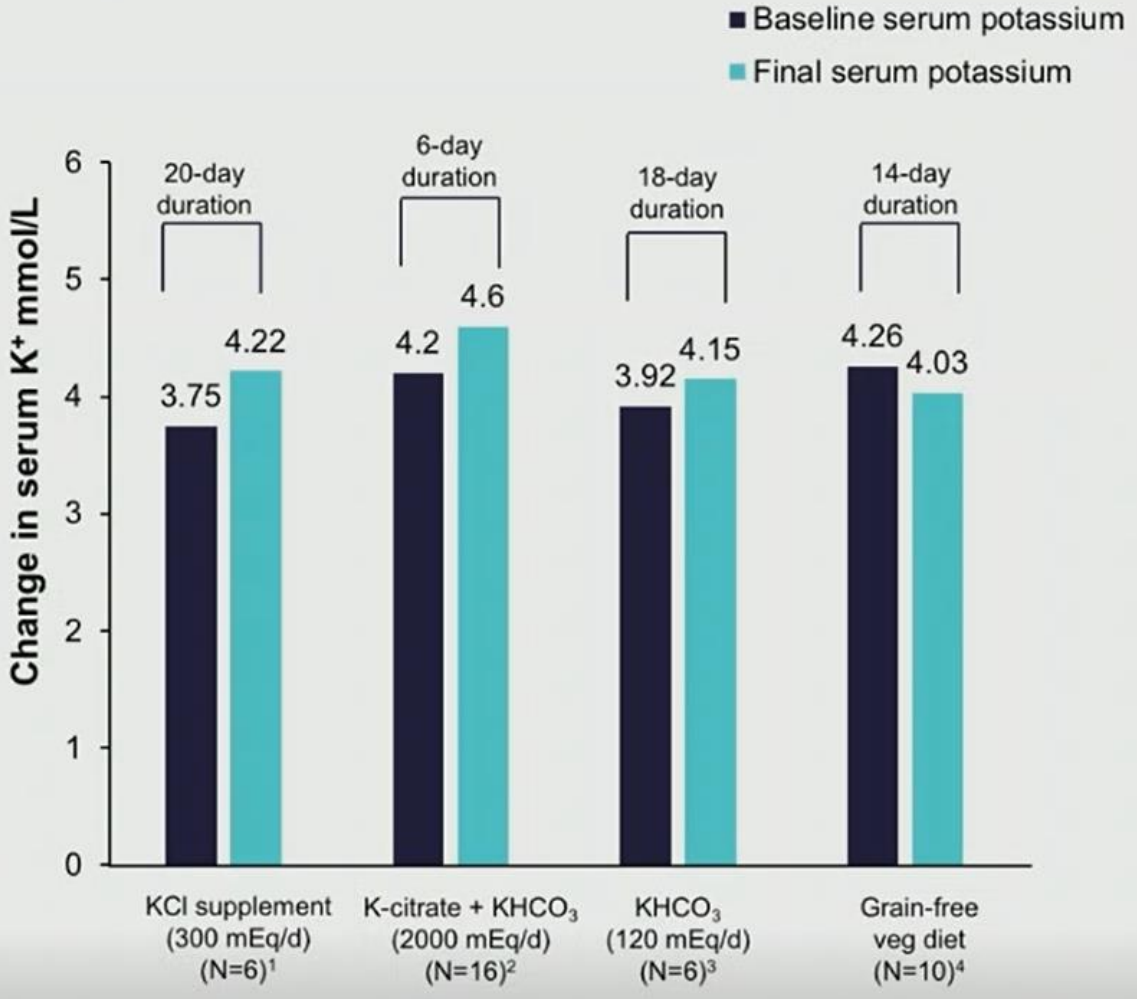
to

LOW K^+ and HIGH Na^+

1. Milne G. *Arch Int* 2015;18:84–96; 2. Palmer BF, Clegg DJ. *Mayo Clin Proc* 2016;91:496–508

Effect of prolonged K^+ intake in healthy humans





KCl, potassium chloride; $KHCO_3$, potassium bicarbonate

1. Rabelink TJ, et al. *Kidney Int* 1990;38:942–947; 2. Witzgall H, et al. *J Hypertens* 1986;4:201–205; 3. Sebastian A, et al. *N Engl J Med* 1994;330:1776–1781; 4. Jenkins DJ, et al. *Metabolism* 2001;50:494–503

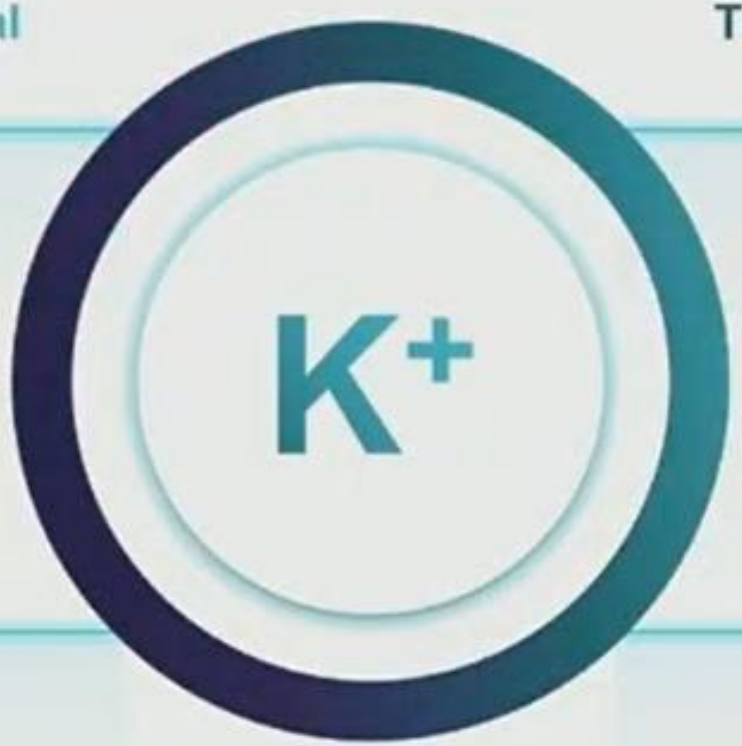
K^+ listed as a 'nutrient of concern'

Inadequate dietary K^+ is implicated in the pathophysiology of several chronic diseases including:[1,2]

- Hypertension
- CVD
- Osteoporosis
- Nephrolithiasis

The 2015–2020 Dietary Guidelines for Americans:[3]

List K^+ as a nutrient of public health concern



NHANES estimated the mean K^+ intake in the USA as:[4]

- 2.290 g/day for women
- 3.026 g/day for men

The Food and Nutrition Board of the Institute of Medicine:[2]

Recommended K^+ intake levels of 4700 mg/day

CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey

1. Linus Pauling institute, Oregon State University. Potassium. Available at: https://lpi.oregonstate.edu/mic/minerals/potassium (Accessed March 2020); 2. Institute of Medicine. *Dietary reference intakes for water, potassium, sodium, chloride, and sulfate*. Washington, DC, USA: The National Academies Press; 2005; 3. US Department of Health and Human Services and US Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*. 8th Edition. December 2015. Available at: https://health.gov/our-work/food-and-nutrition/2015-2020-dietary-guidelines/ (Accessed March 2020); 4. US Department of Agriculture, Agriculture Research Service 2010. What we eat in America, NHANES 2007–2008. Available at: http://www.ars.usda.gov/ba/bhnrc/fsrg (Accessed March 2020)

Dietary K^+ intake recommendations in CKD

	Guidance	g/day	mmol/day
DRI-AI >19 years	Males	3.4	88
	Females	2.6	68
KDOQI	CKD G1–G2	<4.0	>104
KDOQI	CKD G3a–G4	2.0–4.0	52–104
KDOQI	CKD/hemodialysis	2.0–4.0	52–104
KDOQI	Hemodialysis	2.7–3.0	70–78
KDOQI	Peritoneal dialysis	3.0–4.0	78–104
Expert Opinion	**HK**	**<3.0**	**<78**

CDK, chronic kidney disease; DRI-AI, Dietary Reference Intake – Adequate Intake; HK, hyperkalemia; KDOQI, Kidney Disease Outcomes Quality Initiative
Adapted from Clase CM, et al. *Kidney Int* 2020;97:42–61

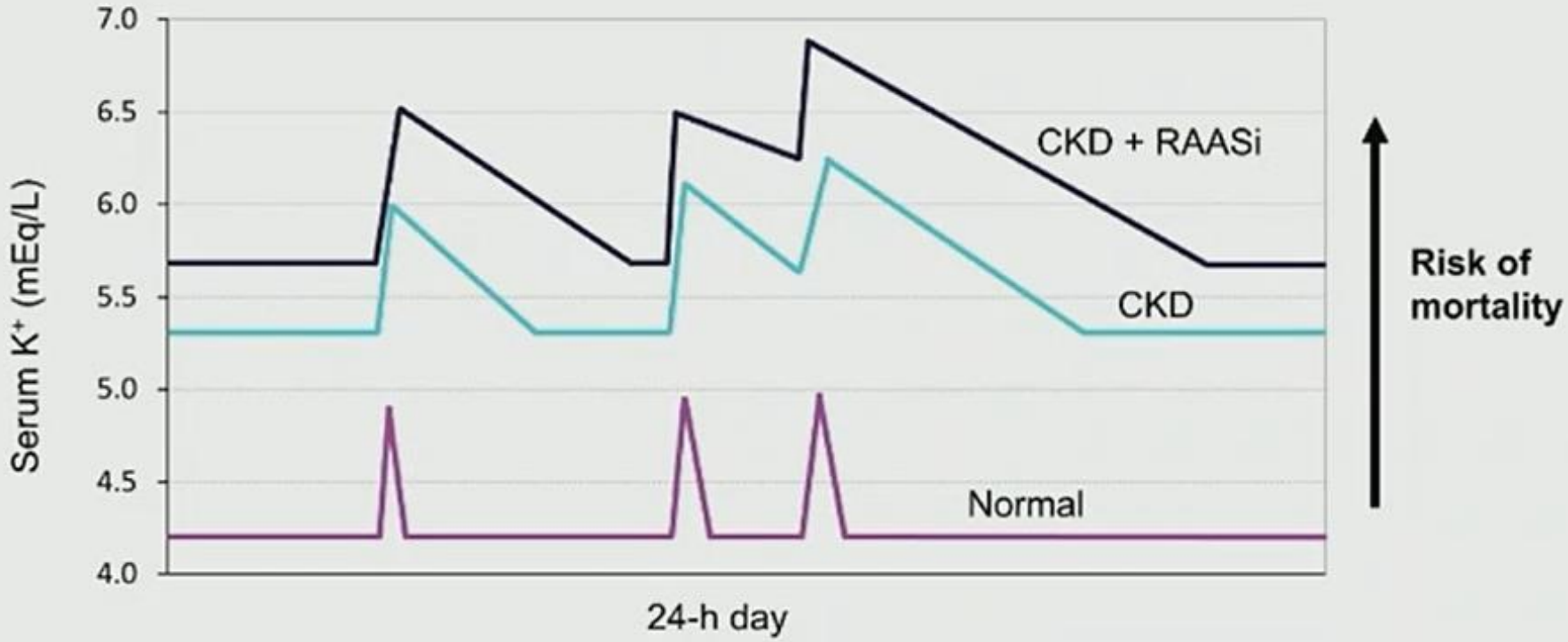
Health benefits of K^+

- Boosts the nervous system
- Maintains optimal fluid balance
- Improves bone health and muscle tissue growth
- Keeps brain functioning normal and prevents strokes

- Prevents muscle cramps
- Maintains electrical conductivity in brain
- Stabilizes blood sugar levels and blood pressure
- Maintains optimal muscle and nerve function

Figure adapted from: https://www.organicfacts.net/health-benefits/minerals/health-benefits-of-potassium.html (Accessed March 2020)

K^+ excursions in patients with CKD are higher and more prolonged than those without CKD, leading to increased mortality



Note: The figure is a conceptual model and is for illustrative purposes
CKD, chronic kidney disease; RAASi, renin–angiotensin–aldosterone system inhibitor

What is there to eat in a K^+-restricted diet?

Fruits

Prune juice (600 mg/cup)
Orange (263 mg/1 medium)
Dried apricots (318 mg/ ¼ cup)
Watermelon (158 mg/cup)
Banana (440 mg/1 medium)

Vegetables

Avocado (680 mg/ ½ cup)
Bamboo shoots, raw (805 mg/cup)
Baked potato with skin (844 mg/medium potato)
Pinto beans, cooked (574 mg/ ½ cup)
Sweet potato (542 mg/medium potato)
Tomato (444 mg /1 medium)

Dairy

Skim milk (400 mg/cup)
Whole milk (370 mg/cup)
Yogurt (531 mg/cup)
Low-fat cottage cheese (110 mg/ ½ cup)
Ricotta cheese (154 mg/ ½ cup)

Potassium-rich foods

Potassium salts in the body work to neutralize bone-depleting metabolic acids. The RDA for potassium is 4700 mg.

Unprocessed meat and fish

Flounder (498 mg/3 oz)
Scallops (475 mg/3.5 oz)
Chicken (350 mg/3 oz)
Pork (335 mg/3 oz)
Salmon (378 mg/3 oz)

Other sources

Chili w/ beans (1090 mg/cup)
Coconut water (600 mg/cup)
Tomato sauce, canned (811 mg/cup)
Bran Buds (1080 mg/cup)
Cooked lentils (366 mg/ ½ cup)

TOP 10 POTASSIUM-RICH FOODS

Top10 Home Remedies
To explore more, visit www.Top10HomeRemedies.com

RDA, recommended daily allowance
Adapted from: https://www.betterbones.com/bone-nutrition/fact-charts-potassium/ (Accessed April 2020)

Question

Which of the following food sources has the most K^+?

a) 1 medium-sized banana

b) 1 avocado

c) 3-oz burger

d) 1 tomato

e) 1 cup of low-fat yogurt

Wildman REC, Medeiros DM. *Advanced Human Nutrition*. Boca Raton, FL, USA: CRC Press; 2014

The recommendation to avoid K^+-rich foods in patients with CKD is based on the assumption that dietary intake correlates to serum K^+ concentration

CKD, chronic kidney disease
Cupisti A, et al. *Nutrients* 2018;10:261

Hidden sources of K^+ can substantially increase total daily intake

Salt substitutes[1]

- Contain K^+ instead of sodium
- Used as a salt replacement in patients needing to reduce sodium intake
- 5–6 g of a salt substitute can increase K^+ load from 1000 to 1800 mg
- Safety of substituting K^+-chloride in patients with CKD requires study – and should be cautioned against

K^+-containing additives[1,2]

- Preservatives
- Antioxidants and acidity regulators
- Stabilizers, emulsifiers, thickeners
- Flavor enhancers
- Most reduced-sodium meats and poultry products have K^+-containing additives

CKD, chronic kidney disease

1. Cupisti A, et al. *Nutrients* 2018;10:261–276; 2. Parpia AS, et al. *J Acad Nutr Diet* 2018;118:878–885

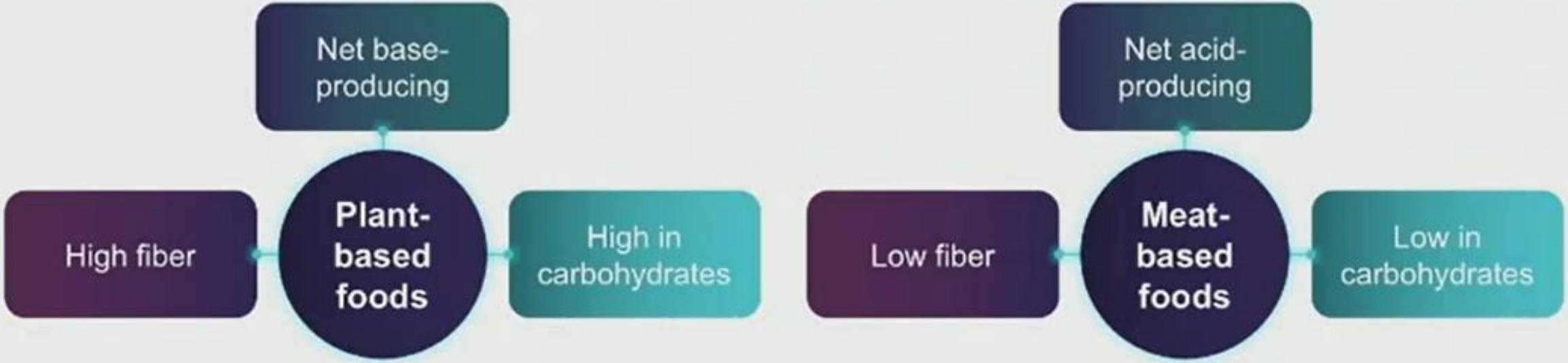
Macronutrients enhance extrarenal disposal of K^+ load

Study by Allon et al. showed that oral K^+ **plus** concomitant oral glucose significantly attenuated the maximal rise in K^+ in hemodialysis patients compared with K^+ alone (0.40 ± 0.09, $P<0.005$)

Allon M, et al. *Am J Med* 1993;94:475–482

Dietary K^+ bioavailability

Although K^+ from different foods is chemically equivalent, other nutrients influence K^+ distribution and excretion

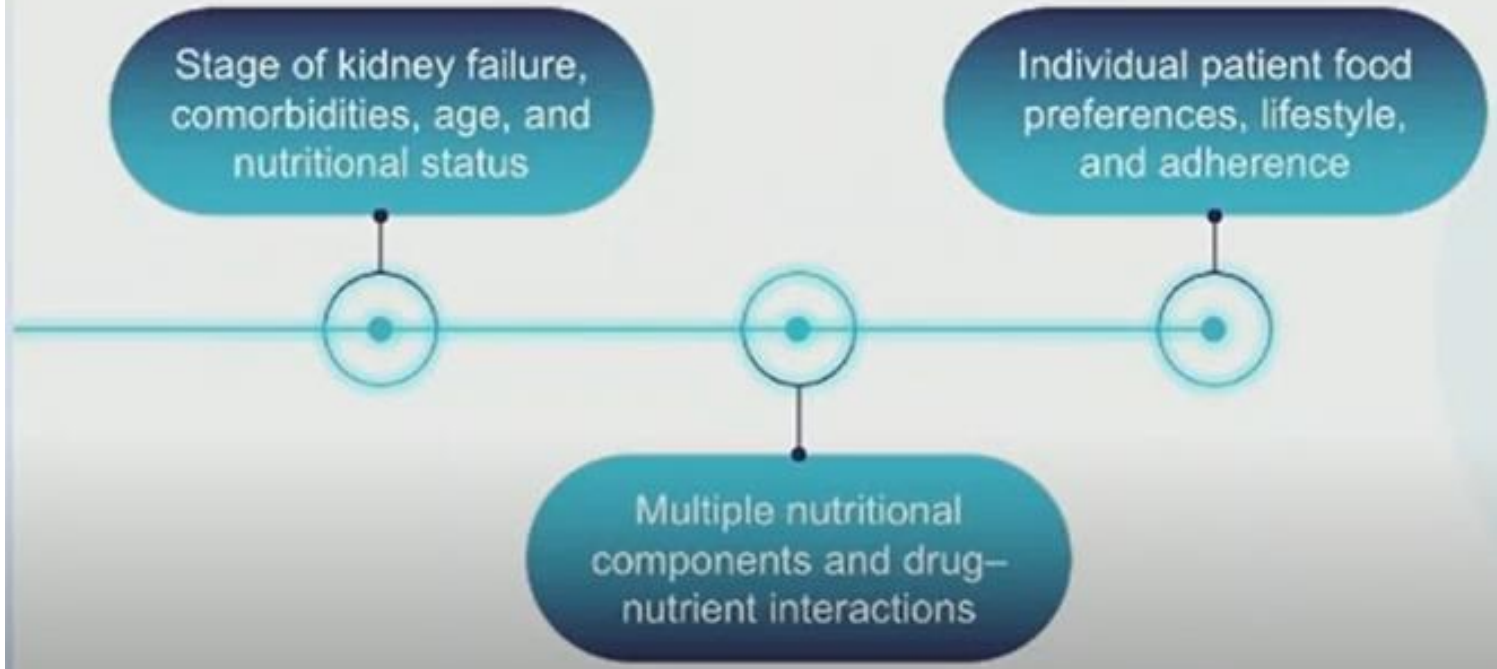


Compared with meat-based foods, plant-based foods high in K^+ *may promote distribution of a greater proportion of dietary K^+ intracellularly* (alkaline and insulin-stimulating) and excretion of K^+ in stool by increasing fecal bulk

St-Jules DE, et al. *J Ren Nutr* 2016;26:252–257

Modifying dietary K^+ intake in patients with kidney failure

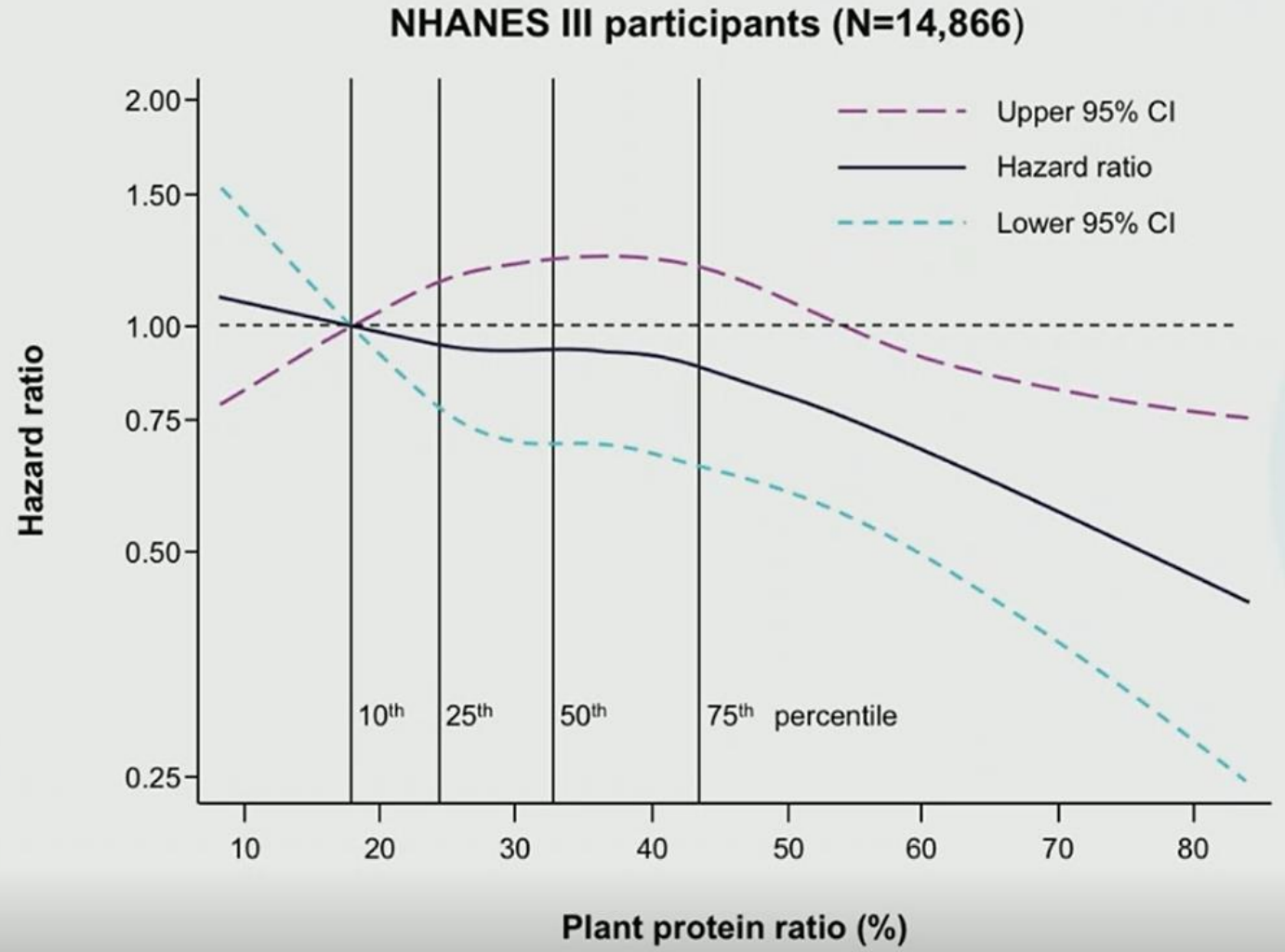
Successful individualized dietary intervention must balance several factors:



Dietary intake of K^+ is a modifiable risk factor for HK; however, strict dietary restrictions in CKD and ESKD may impact nutrition and contribute to worse outcomes

CKD, chronic kidney disease; ESKD, end-stage kidney disease; HK, hyperkalemia
Kalantar-Zadeh K. et al. *Semin Dial* 2015;28:159–168

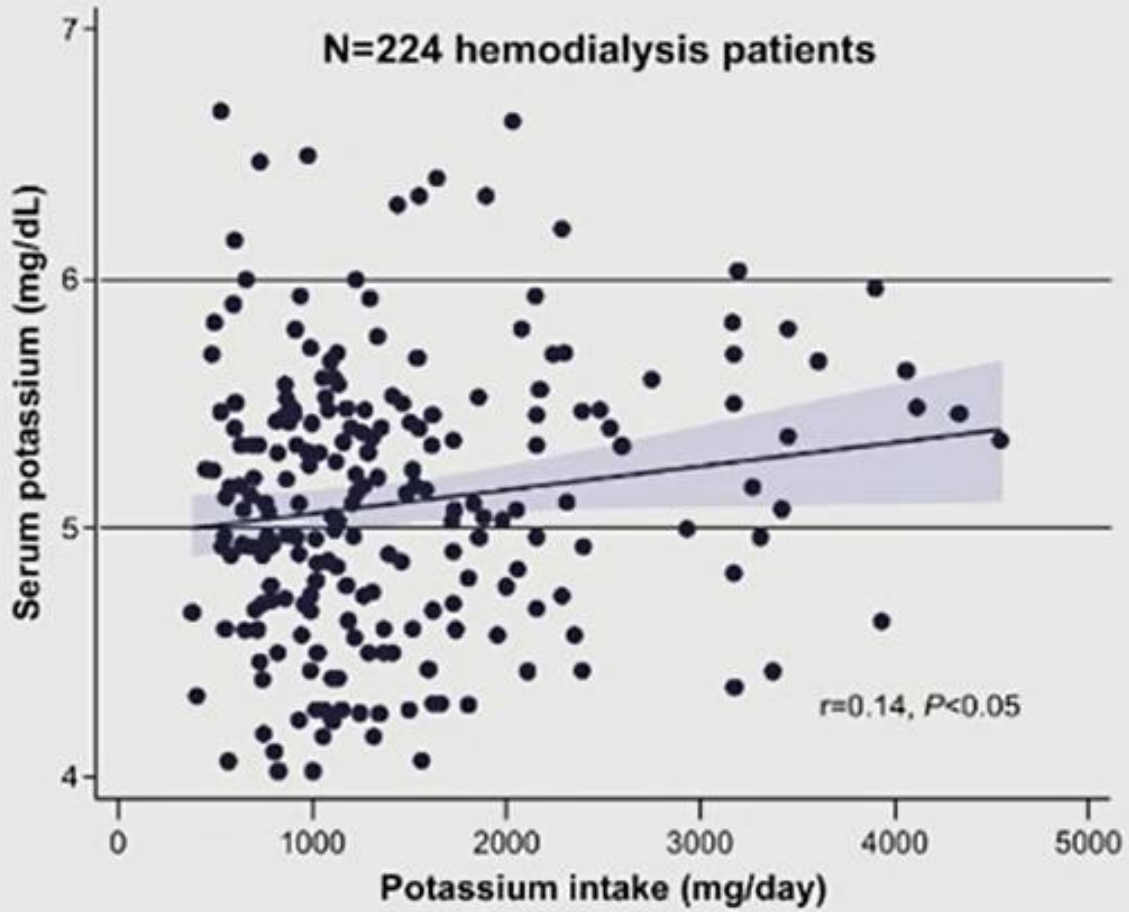
Consumption of a plant-based diet (containing K^+) is associated with *lower mortality in CKD*

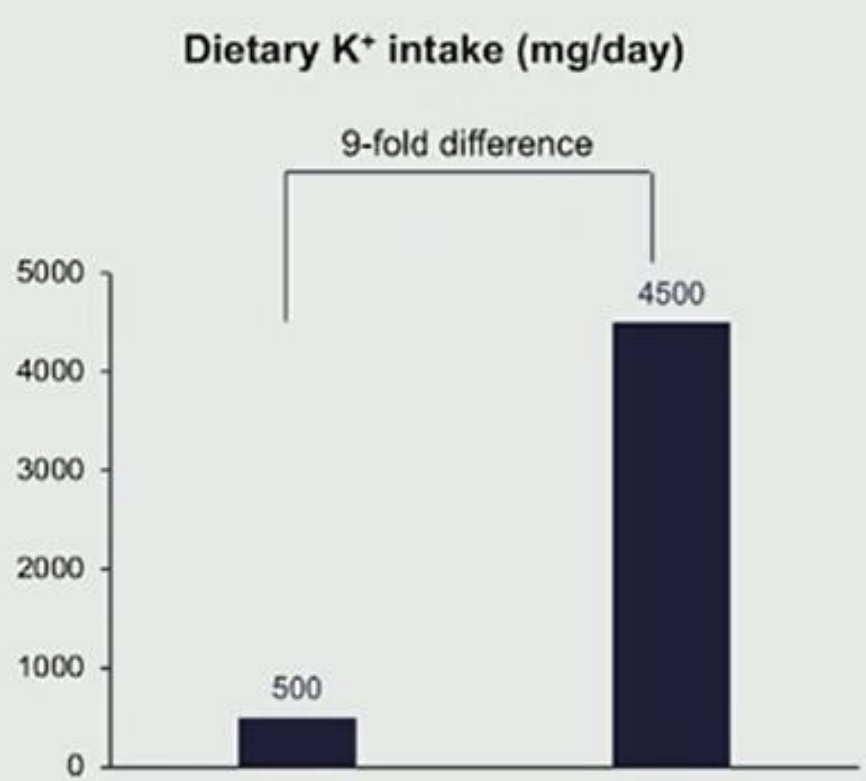


Each 33% increase in the plant protein ratio had a statistically significant lower risk of all-cause mortality among patients with eGFR <60 mL/min/1.73 m²

CI, confidence interval; CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate, NHANES, National Health and Nutrition Examination Survey
Chen X, et al. *Am J Kid Dis* 2016;67:423–430

NIED cohort study: Correlation between K^+ intake with baseline predialysis serum K^+





- Daily K^+ intake estimated using the Block Food Frequency Questionnaire
- ***Serum K^+ was only about 0.4 mEq/L higher***

Regression line (solid line) and 95% confidence interval (shaded area) are shown for the linear regression analysis
NIED, Nutritional and Inflammatory Evaluation in Dialysis patients
Noori N, et al. *Am J Kidney Dis* 2010;56:338–347

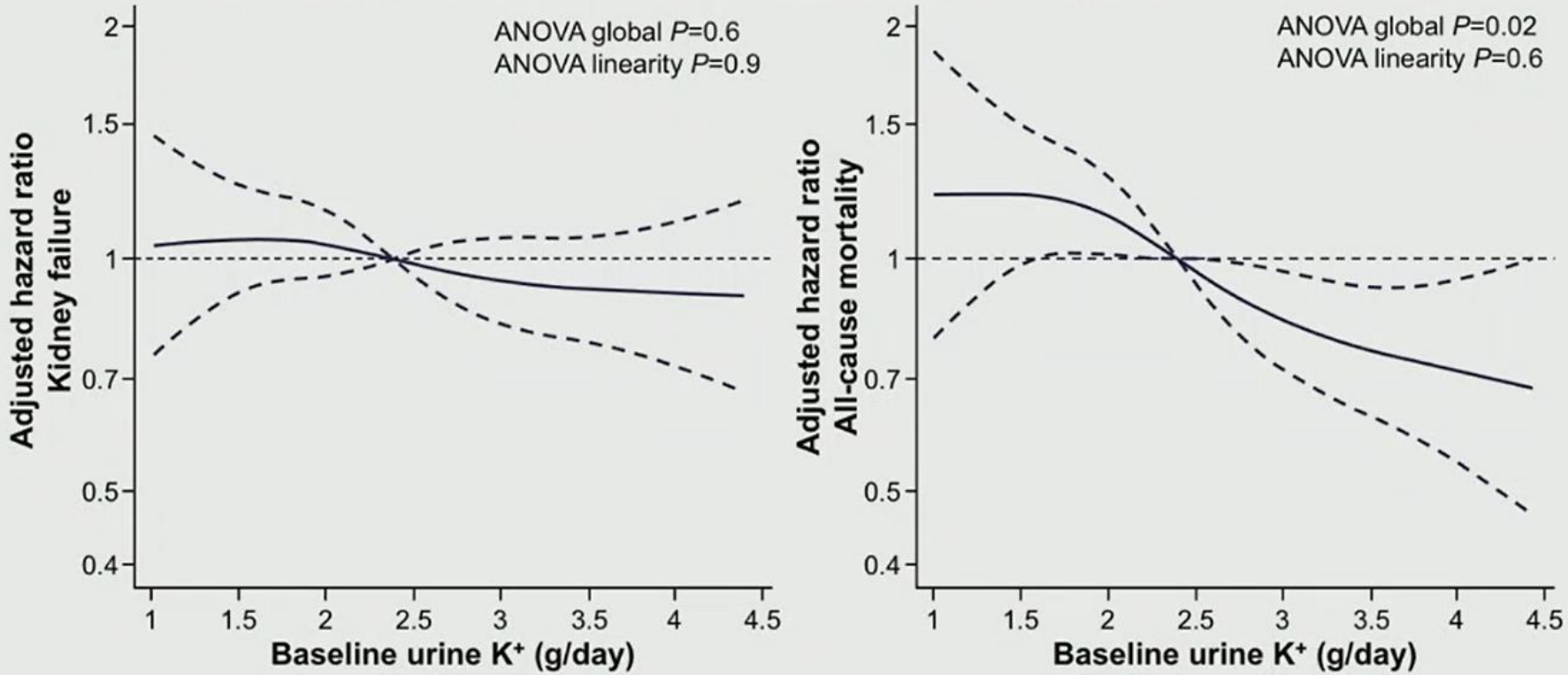
Measures of dietary K^+ intake: Advantages and limitations

Method	Advantages	Limitations
Food frequency questionnaire	• Assessment is simple and cost-effective • Ideal for large cohorts	• Close-ended questions • Low accuracy (recall bias) • Inaccuracies in natural K^+ content in food composition tables • Often does not account for hidden sources of K^+ or cooking methods
Dietary recall	• Provides detailed intake information • Fewer recall bias	• Possible to account for K^+ additives and cooking methods
Spot urine collection	• Assumes that natural nutrient excretion is proportional to recent intake	• Moderate agreement with 24-h urine K^+ excretion, over- or underestimating extreme intakes • Circadian pattern • % of K^+ excreted is influenced by GFR
24-hour urine collection	• More accurate than spot urine	• <80% of K^+ intake is excreted in urine • Varies by race • Requires multiple urine collections • % of K^+ excreted is influenced by GFR

GFR, glomerular filtration rate
Adapted from Clase CM, et al. *Kidney Int* 2020;97:42–61

Urinary K^+ excretion and clinical outcomes in CKD

***Post-hoc* analysis of MDRD study**
(N=812 participants, CKD stages 3–5; median follow-up 6.1 years)



For each 1-SD increase in baseline urinary K^+ excretion, there was a **17%** lower all-cause death rate and a nonsignificant change in the risk of kidney failure

CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; SD, standard deviation
Leonberg-Yoo AL, et al. *Am J Kidney Dis* 2017;69:341–349

Increased K^+ intake and cardiorenal outcomes in the *general population*

Meta-analysis included 22 RCT (N=1606) and 11 cohort studies (N=127,038) adults with hypertension and no CKD:

1. Overall, increased K^+ intake reduced SBP by 3.49 mm Hg (95% CI: 1.82, 5.15) and DBP by 1.96 mm Hg (0.86, 3.06)
2. SBP was reduced by 7.16 mm Hg (1.91, 12.41) with higher K^+ intake (90–120 mmol/day), without any dose response
3. Higher K^+ intake was associated with a 24% lower risk of stroke
4. Associations between K^+ intake and incident CVD or CHD were not statistically significant
5. Increased K^+ intake had no significant adverse effect on renal function

CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; RCT, randomized controlled trial; SBP, systolic blood pressure
Aburto NJ, et al. *BMJ* 2013;346:f1378

Increased K^+ intake and cardiorenal outcomes in patients with CKD and ESKD

1

The effects of dietary K^+ intake on cardiovascular and renal outcomes has primarily been investigated in non-CKD populations[1]

2

Findings from epidemiologic studies provide insight into the relationship between dietary K^+ intake and cardiorenal outcomes in CKD but these associations require prospective evaluation[2]

3

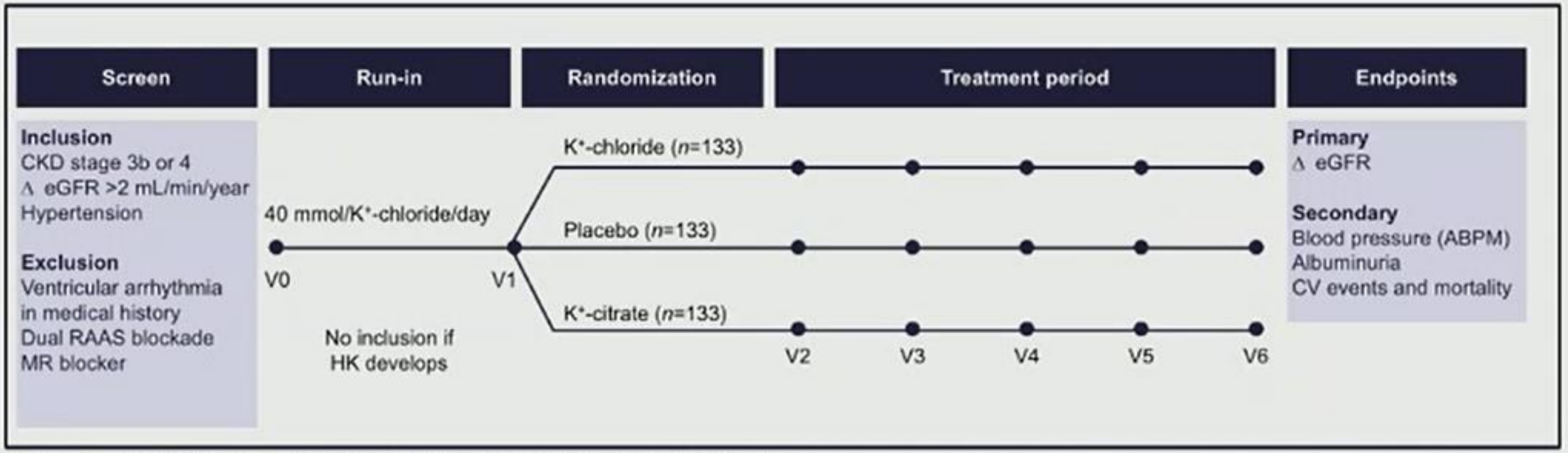
RCTs are urgently needed to evaluate whether a high dietary K^+ intake will contribute to better cardiorenal outcomes in CKD and ESKD[3]

CKD, chronic kidney disease; ESKD, end-stage kidney disease; RCTs, randomized controlled trials

1. Gritter M, *et al. Nephron Clin Pract* 2018;140:48–57; 2. Gritter M et al. *Hypertension* 2019;73:15–23; 3. Kendrick J, Linas S. *Clin J Am Soc Nephrol* 2017;12:1559–1560

Interventional study to evaluate the renoprotective effect of K^+ supplementation in CKD (2017–2023)[1,2]

- Randomized, double-blind, placebo-controlled trial in 399 patients with CKD stage 3b or 4, hypertension, and an average eGFR decline >2 mL/min/1.73 m^2/year
- Primary endpoint is the difference in eGFR after 2 years of treatment
- Secondary endpoints: >30% decrease in eGFR, doubling of serum creatinine, ESKD, albuminuria, ambulatory blood pressure, CV events, all-cause mortality, and incidence of HK



Note: V0, t= −2 weeks; V1, t=0; V2, t=1 month; V3, t=6 months; V4, t=12 months; V5, t=18 months; V6, t=24 months
ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HK, hyperkalemia; MR, mineralocorticoid receptor; RAAS, renin–angiotensin–aldosterone system

1. Gritter M, *et al*. *Nephron* 2018;140:48–57; 2. ClinicalTrials.gov. NCT03253172. Available at: https://clinicaltrials.gov/ct2/show/NCT03253172 (Accessed March 2020)

Summary: Modifying dietary K^+ intake in patients with kidney failure

- Dietary K^+ intake is a modifiable risk factor for HK; however, strict restriction of K^+ in patients with kidney impairment may adversely impact nutrition and contribute to worse outcomes[1]
- Epidemiologic analyses in a majority of studies indicates high K^+ intake was associated with cardiorenal benefits in CKD patients[2]
- In CKD and ESKD patients receiving RAASi/MRA therapy who are at high risk for developing HK, dietary intervention alone may not be sufficient[3]
- Novel K^+ binders may enable consumption of plant-based/heart-healthy diets in high-risk CKD patients, thereby leading to improved cardiorenal outcomes[3]

CKD, chronic kidney disease; ESKD, end-stage kidney disease; HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

1. Kalantar-Zadeh K, et al. *Semin Dial* 2015;28:159–168; 2. Gritter M, et al. *Nephron Clin Pract* 2018;140:48–57; 3. Palmer BF. *Mayo Clin Proc* 2020;95:339–354