Advances in the Management of HYPERKALEMIA

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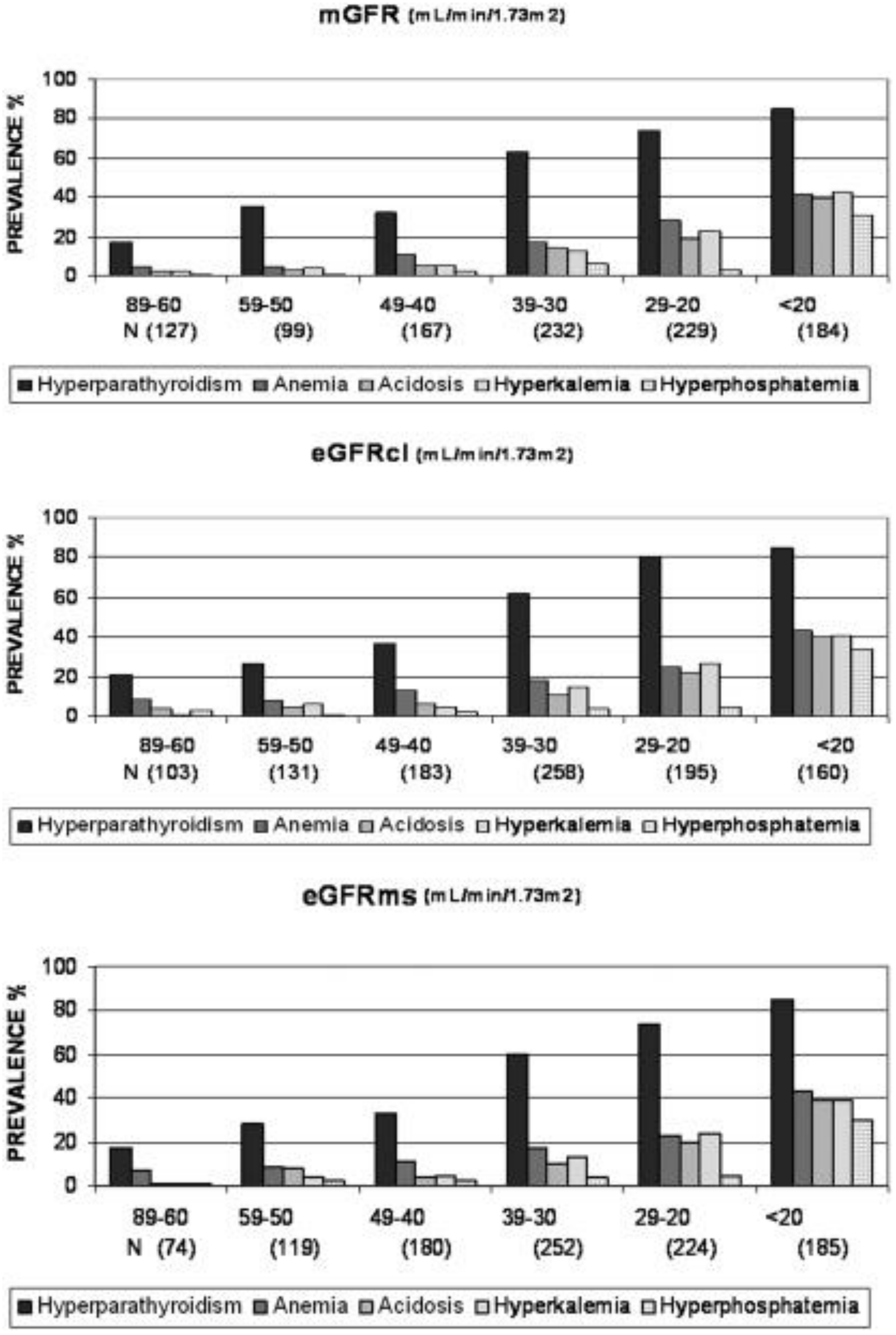
Outline

- **Epidemiology**
- **Morbidity**
- **Potassium Homeostasis**
- **Management strategies for CHRONIC Hyperkalemia.**

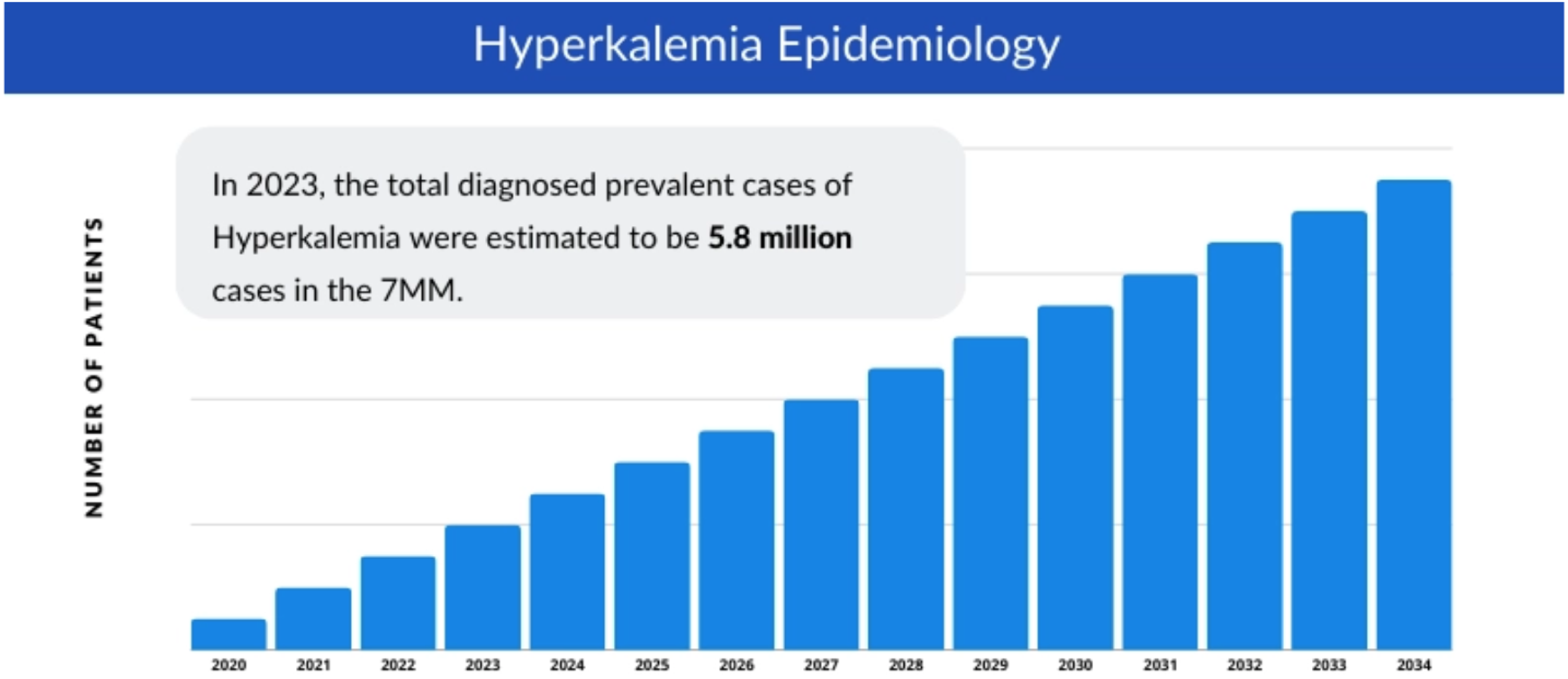
Epidemiology

- Hyperkalemia is the most common electrolyte disturbance among patients with CKD.
- 6-20% , with increasing prevalence associated with declining GFR.
- Risk factors : Age , DM, worsening eGFR , RAASi, CHF



JASN 2009;20(1):164-71.

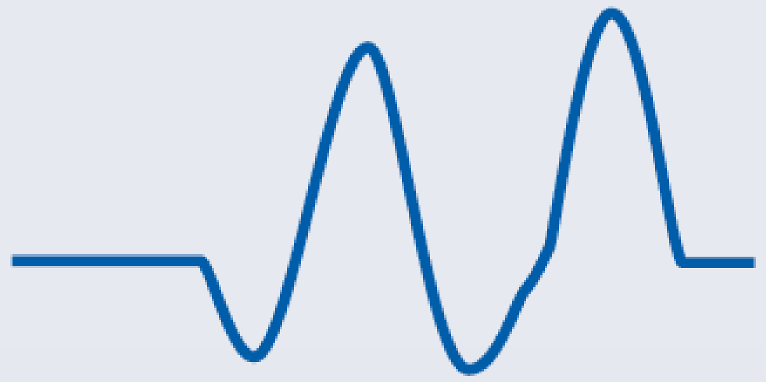
Prevalence of hyperkalemia is in rise



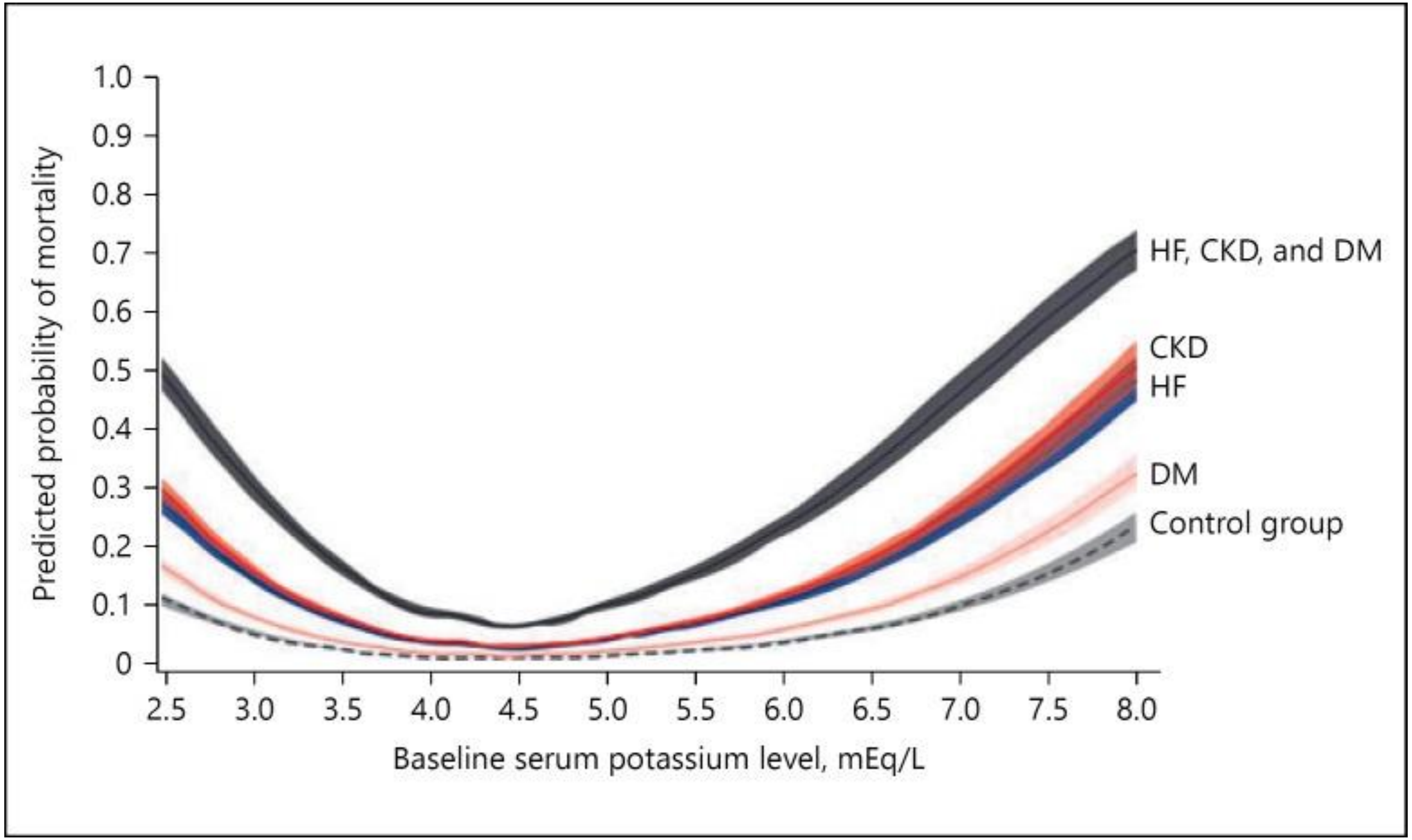
Morbidity

- Cadiac arrhythmias.
- Sudden death.
- Hospitalization burden.

ECG Changes in Hyperkalemia

QRS Complex	Approximate Serum Potassium (mmol/l)	ECG Change
	~4	Normal
	6–7	Peaked T waves
	7–8	Flattened P wave, prolonged PR interval, depressed ST segment, peaked T wave
	8–9	Atrial standstill, prolonged QRS duration, further peaking T waves
	>9	Sine wave pattern

Hyperkalemia is a major risk factor of mortality in patients with AND without comorbidities (CKD, CHF, DM).



Am J Nephro. 2017;46(3):213-221

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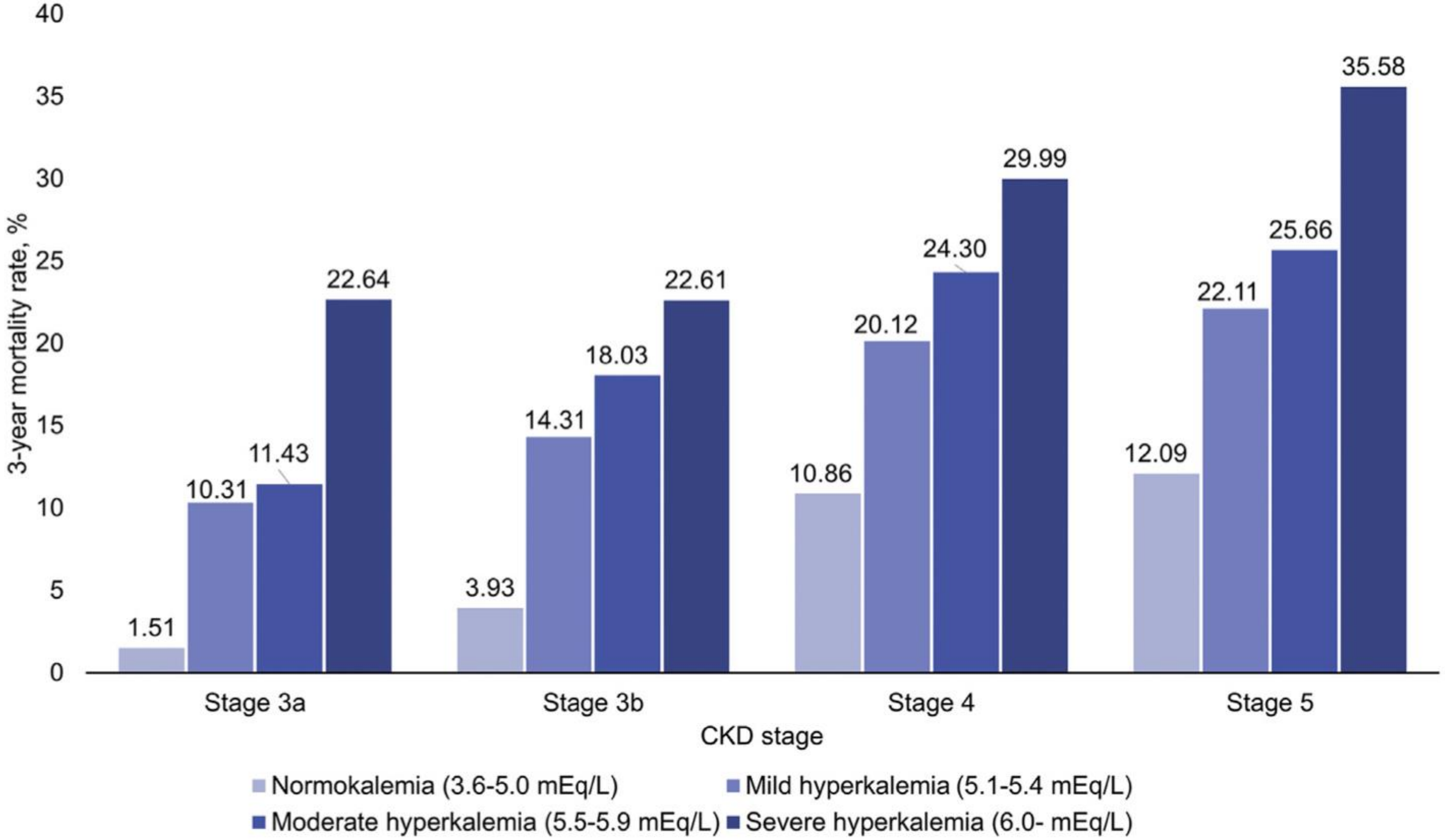
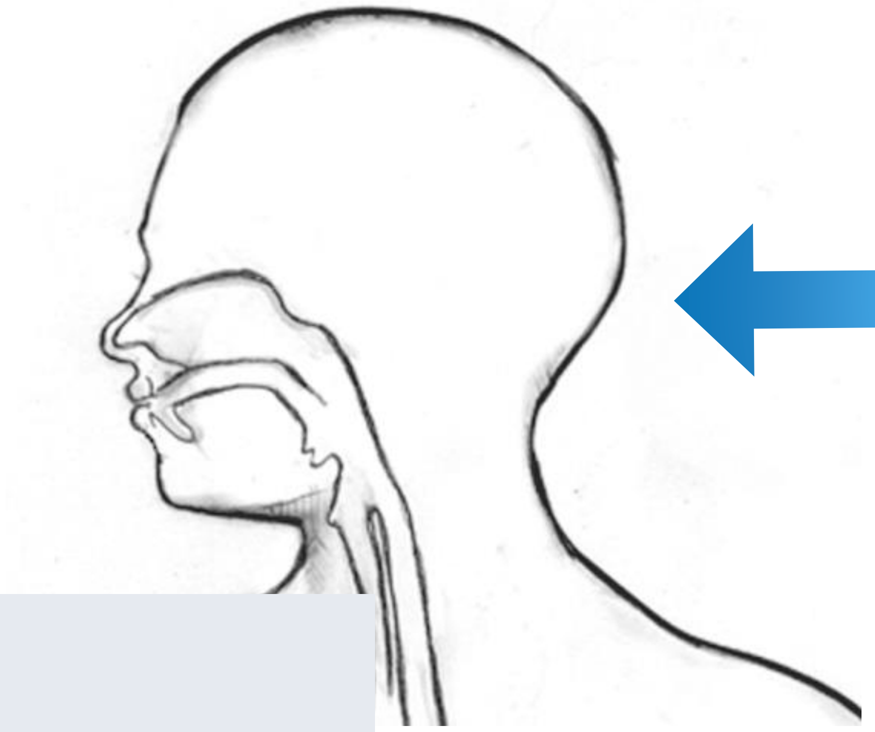
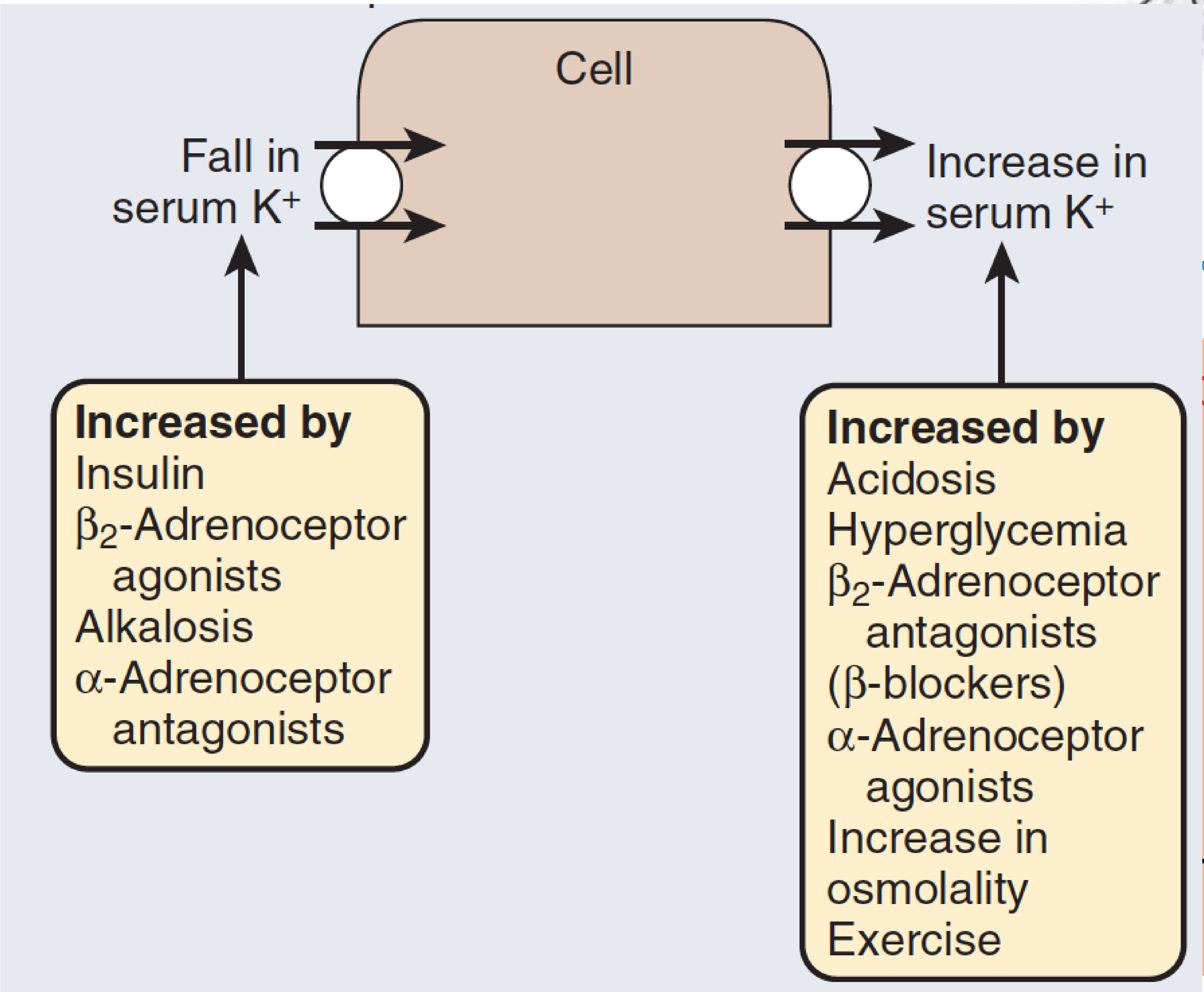


Figure 4. Cumulative incidence of death in hyperkalemic and normokalemic (serum potassium [S-K] 3.6–5.0 mEq/l) patients according to chronic kidney disease (CKD) stages and index S-K levels.

KI reports. 2019 4, 1248–60

Potassium Homeostasis



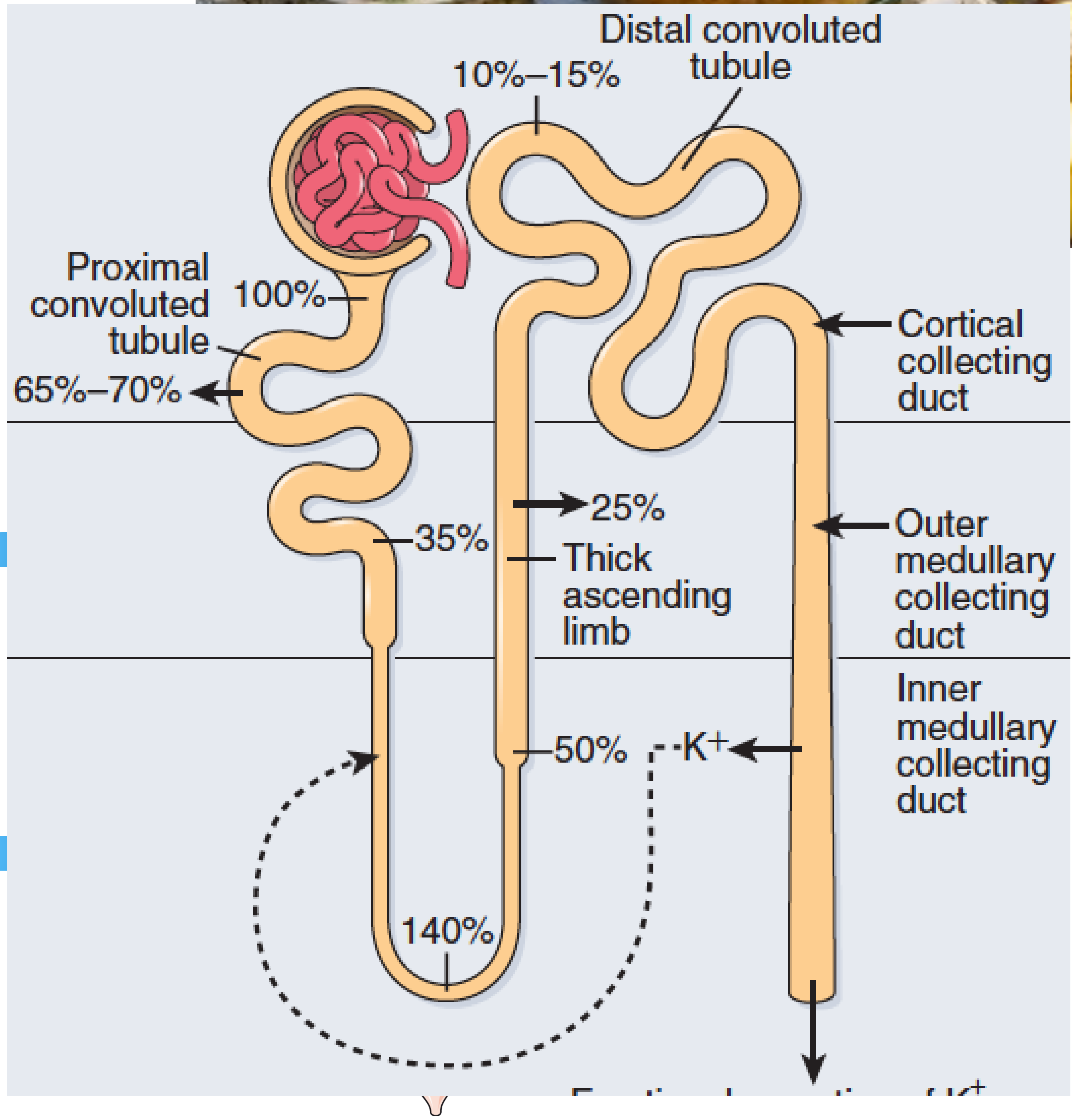


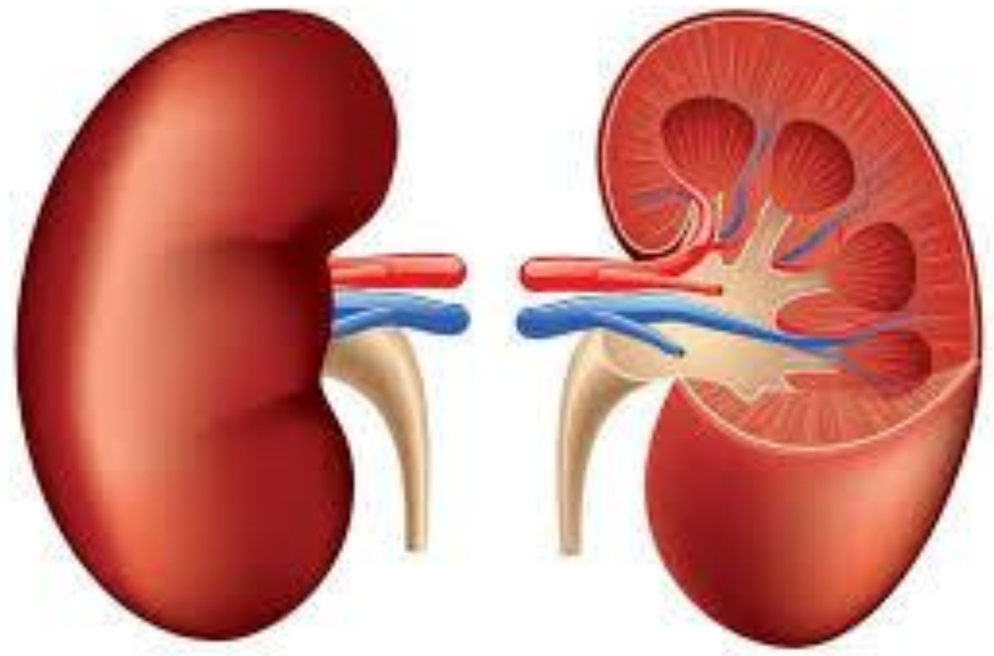
cellular

K+]

mmol/L

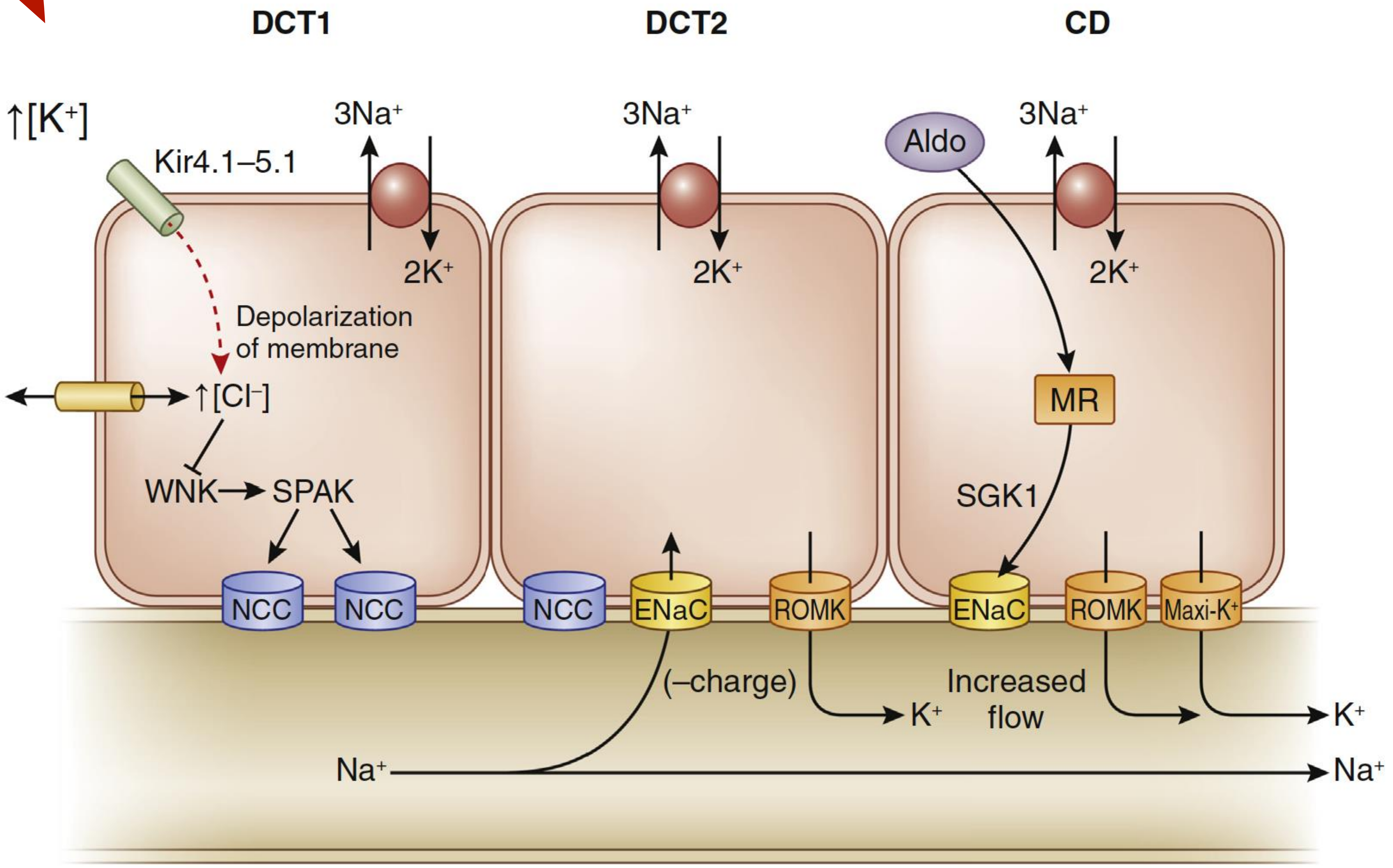
a+





Renal K^+ Excretion stimulated by:
1) increase Plasma K+
2) ALdosteron
3) Increased Na+ delivery into collecting tube

Distal Tubules

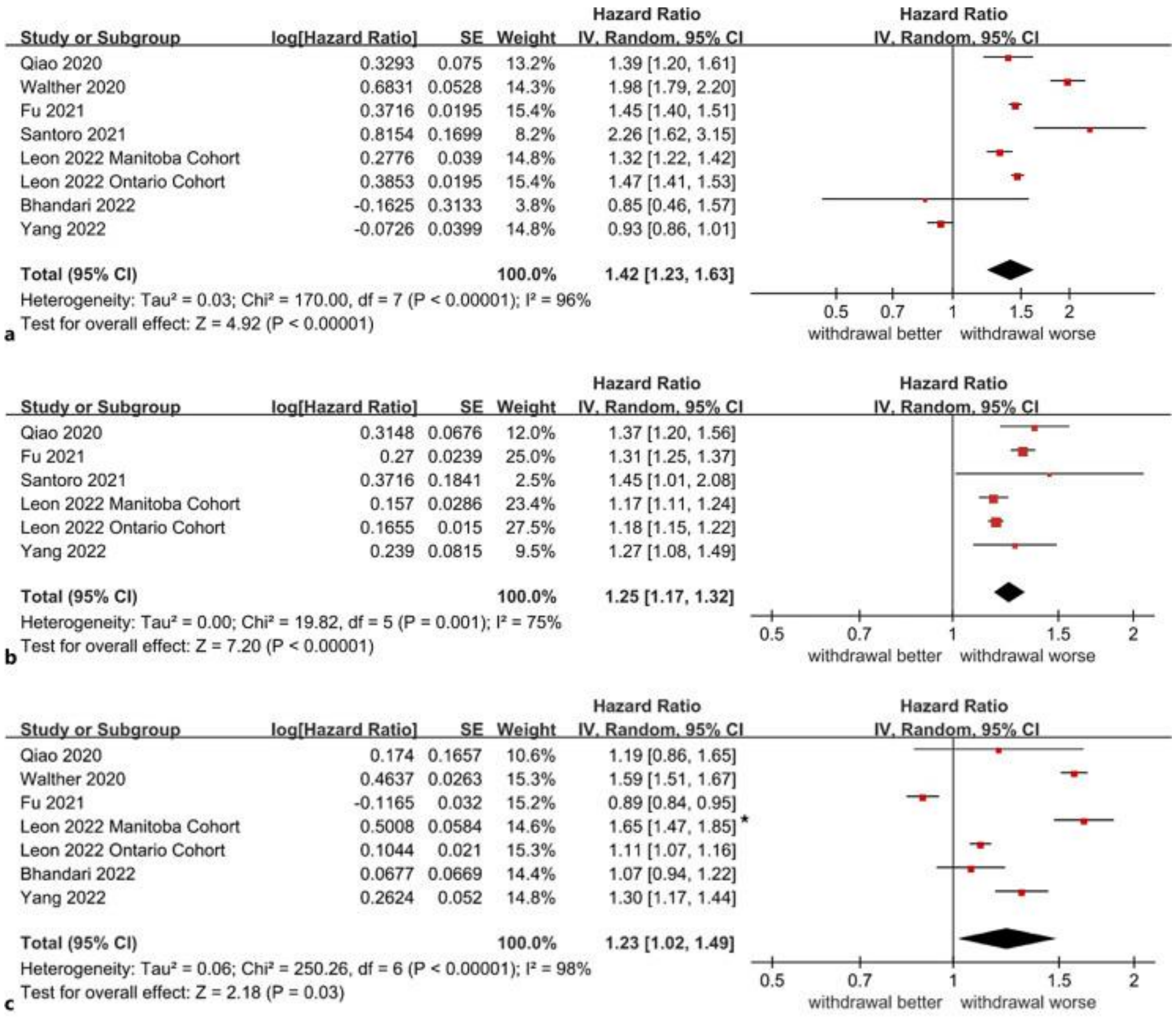


RAASi and HyperKalemia

	Rate of Hyperkalemia
• SOLVD Trial (Ealapril)	7.8%
• CHARM Trial (Candesartan)	5.5%
• RALES Trial (Spironolactone)	19%
• FIDELIO (Finerenone)	11.8% (1.6% Serious)
• FIGARO (Finerenone)	6.5% (0.7% Serious)

Stopping RAASi

↑ mortality & CV events.



Am J Nephro . 2023;54(5-6):234–244

Management strategies for CHRONIC Hyperkalemia.

A 63-year-old male with hypertension, CHF (EF 40%) and presumed diabetic nephropathy with proteinuric CKD (serum creatinine 180 umol/L, estimated glomerular filtration rate [eGFR] 36 ml/min, urine albumin-to-creatinineratio 60 mg/mmol). Average BP at home around 140/80. Kidney function has been slowly worsening over past few years.

Home Medications : Amlodipine 10mg daily, Metformin 500mg daily, Lipitor.

Lisinopril 10mg daily was initiated.
On repeat blood testing 3 weeks later, serum potassium was 5.9 mmol/l and then 5.8 mmol/l on repeat testing few days later with no significant change in eGFR.

Stopping or Reducing dose of RAASi

- Simplest solution, but unlikely the best longterm option.

- Hyperkalemia from RAASi alone is usually mild (< 5.5) and not clinically significant.

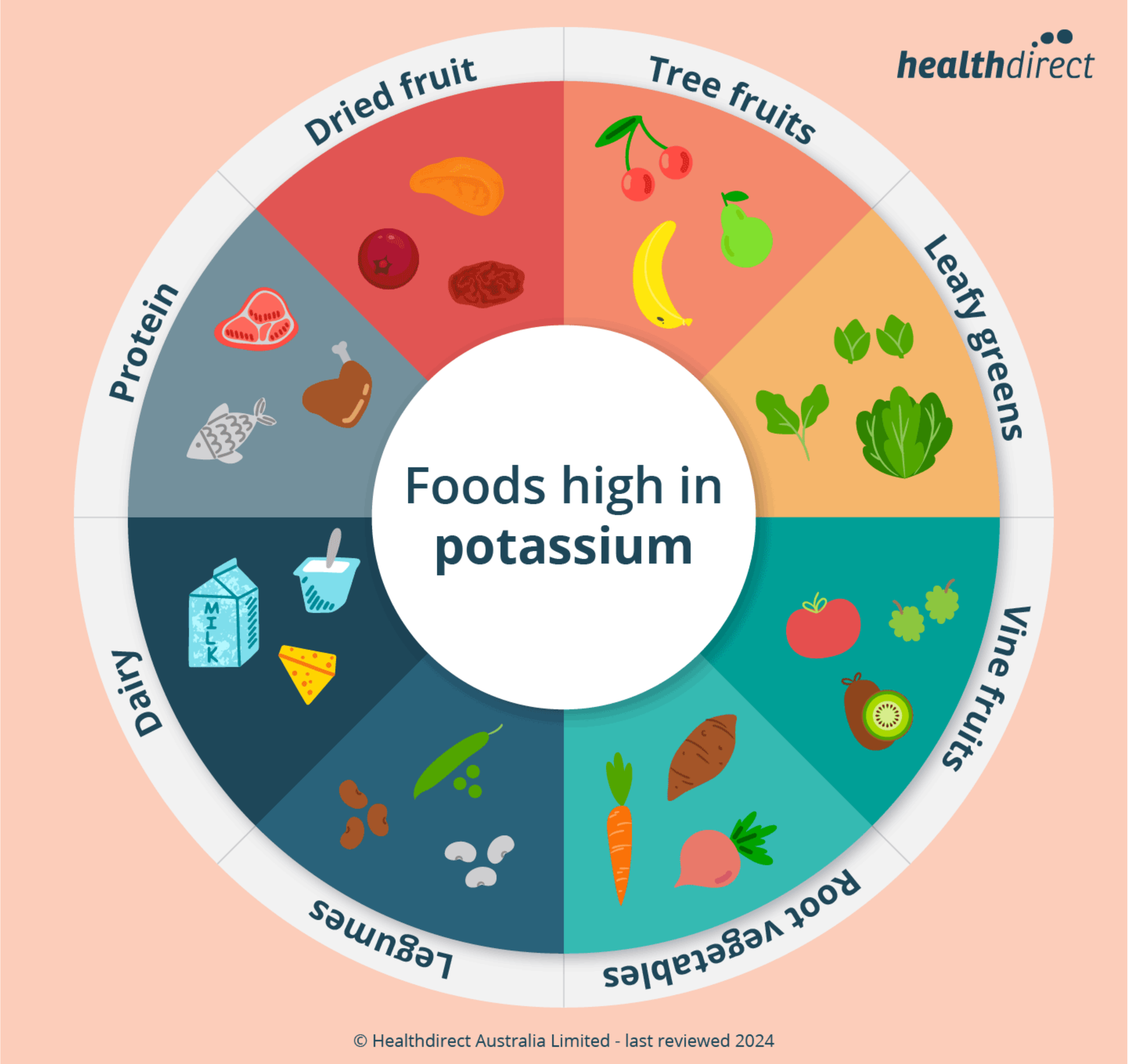
- Might be implemented in severe cases as a temporizing measure until instituting more appropriate anti-hyperkalemic measures.

- **KDIGO CKD guidelines (2024):**
  - Practice Point 3.6.3: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.
  - Practice Point 3.6.5: Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m_2).

Dietary Potassium Restriction.

- Potassium-rich diets are generally consistent with dietary patterns that are considered Healthy. (Mediterranean , DASH)
- Estimated daily intake : 2.1g (China) —> 2.6g (US) —> 4.8g (Spain).

- Plant-based sources of Potassium are also sources for Net base production (Citrate).
- Also sources of vitamines, fibre and antioxidants
- Facilitates intracellular entry of Potassium, and excretion in Stool by increasing fecal volume.
- Meat leads to Net Acid Production.
- Consider also KCL in salt substitution .



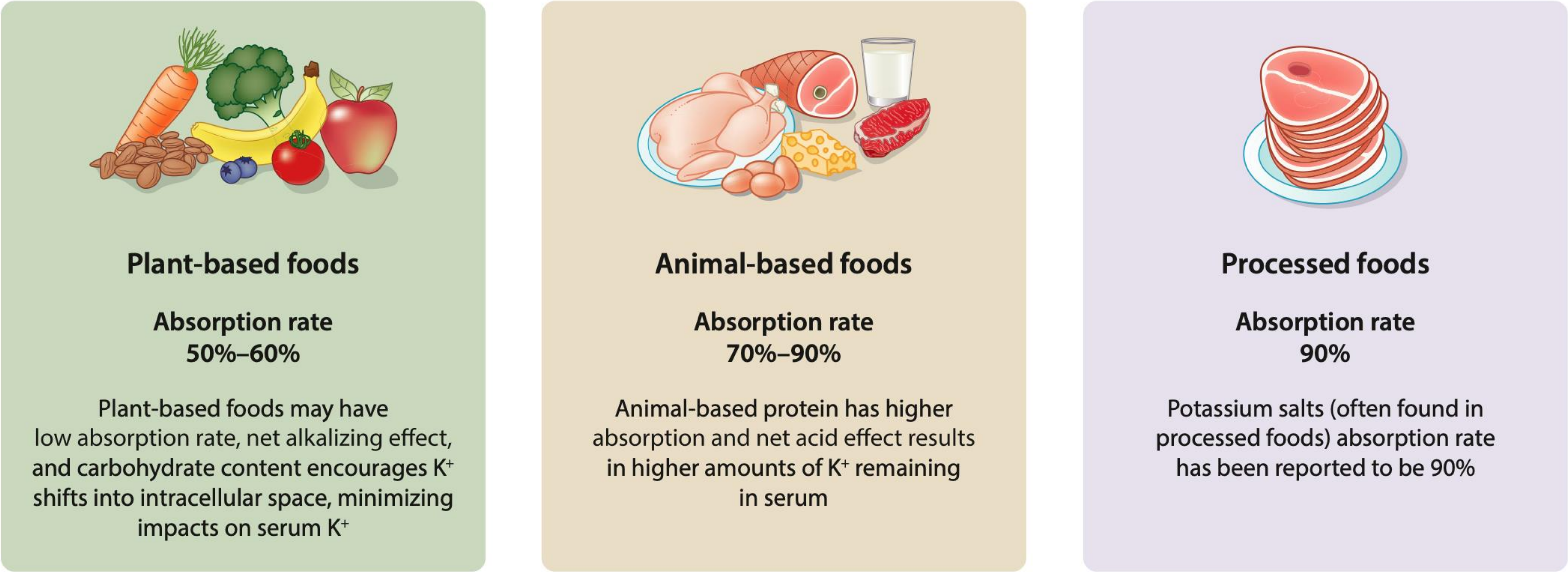


Figure 33 | Potassium absorption rates of plant-based, animal-based, and processed foods. Data from Picard K, Griffiths M, Mager DR, Richard C. Handouts for low-potassium diets disproportionately restrict fruits and vegetables. *J Ren Nutr*. 2021;31:210–214.[592]

Dietary Potassium Restriction.

Table 1 | Studies associating potassium intake, CKD outcomes, and mortality

Study	Population	Dietary K^+ assessment	Outcome definitions	Factors associated with higher K^+ intake
Araki *et al.*, 2015[82]	623 Japanese patients with diabetes and eGFR ≥60 ml/min per 1.73 m^2 enrolled between 1996–2003 and followed up until 2013	Estimated from a single baseline 24-h urine collection	eGFR ↓ ≥50% or progression to CKD G4 or annual rate of eGFR decline	↓ risk of both outcomes Slower rate of annual eGFR decline
Smyth *et al.*, 2014[71]	*Post hoc* analysis of ONTARGET and TRANSCEND studies; >30,000 patients from 18 countries with vascular disease or diabetes with end-organ damage	Estimated 24-h urine K^+ from a single urine sample	eGFR ↓ ≥30% or CD, or eGFR ↓ ≥40% or CD, or rapid progression, or doubling of SCr or CD, or progression of proteinuria	↓ risk of CKD progression
Kieneker *et al.*, 2016[85]	5315 Dutch participants aged 28 to 75 yr in the PREVEND study and followed up for a median of 10.3 yr	Two 24-h urine collections at baseline and midway during follow-up	CKD incidence	↓ risk of incident CKD
Smyth *et al.*, 2016[88]	544,635 participants in the NIH-AARP Diet and Health Study, aged 51–70 yr	FFQ to assess K^+ intake over the preceding year	Death due to renal causes or need for dialysis	↓ risk of both kidney outcomes
Leonberg-Yoo *et al.*, 2017[86]	*Post hoc* analysis of MDRD study; 812 patients aged 15–70 yr with CKD G2–G4	Estimated from 24-h urine collection at baseline and at multiple time points	Initiation of chronic dialysis or kidney transplantation (kidney replacement therapy) Death from all causes	No association with kidney replacement therapy Association with ↓ risk of death
Mirmiran *et al.*, 2018[87]	1780 participants in the Tehran Lipid and Glucose study and followed up for 6.3 yr	Validated 168-item FFQ	CKD incidence	No association
He *et al.*, 2016[84]	3939 participants aged 21–74 yr with CKD (GFR 20–70 ml/min per 1.73 m^2) in the CRIC study	Estimated from 24-h urine collection at baseline and at years 1 and 2	Composite of ESKD or halving of GFR Death from all causes	↑ risk of CKD progression No association with risk of death
Noori *et al.*, 2010[69]	224 chronic HD patients from the NIED Study	Estimated 24-h urine K^+ from FFQ	Death from all causes	↑ risk of death only when comparing extreme intakes
Eisenga *et al.*, 2016[83]	Prospective cohort of 705 stable kidney transplant recipients	A single 24-h urine collection and FFQ	Graft failure Death from all causes	↓ risk of graft failure and death
Kim *et al.*, 2019[89]	1821 participants aged 20–75 yr with CKD G1–G5 (nondialysis) in the KNOW-CKD study	24-hour urine collection at baseline; spot urine	Composite of GFR ↓ ≥ 50% or ESKD	↓ risk of CKD progression

? Potassium intake

? Potassium as a proxy for Plant-based Diet

No Evidence of Safety for Liberalization of Potassium intake in CKD patients

Kidney International (2020) 97, 42–61;

Dietary Potassium Restriction.

- Potassium restriction as a general strategy to ***prevent*** hyperkalemia in persons with CKD may deprive patients of the beneficial effects associated with potassium-rich diet.

- Still advised in cases of ***Acute*** Hyperkalemia.

- Dietary advice to focus on restricting Animal-based , Acid-producing, Sources of potassium, rather than Restricting Plant-based diet.

Diuretics

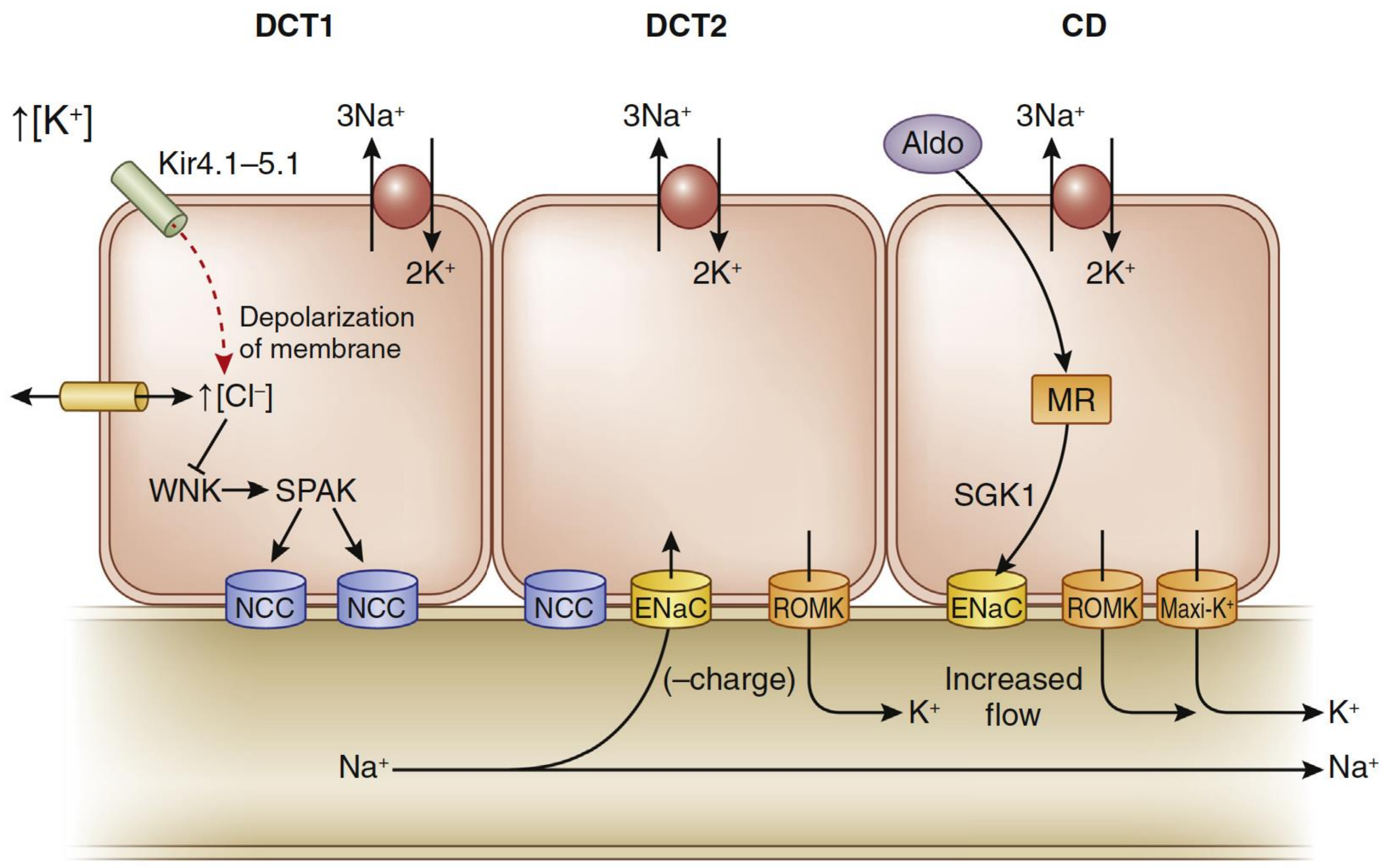
- Diuretics (Thiazide , Thiazide like, or loop) can potentiate urinary potassium excretion by :

  ➡Increasing Na delivery in collecting tubules —> increase Na/K ATPas function

  ➡increasing aldosterone release by hypovolemia-inducing effect.

- Decrease of approx 0.3 - 0.6 mmol/L can be expected.

- Useful if evidence of hypervolemia or uncontrolled HTN.



SGLT2 inhibitors

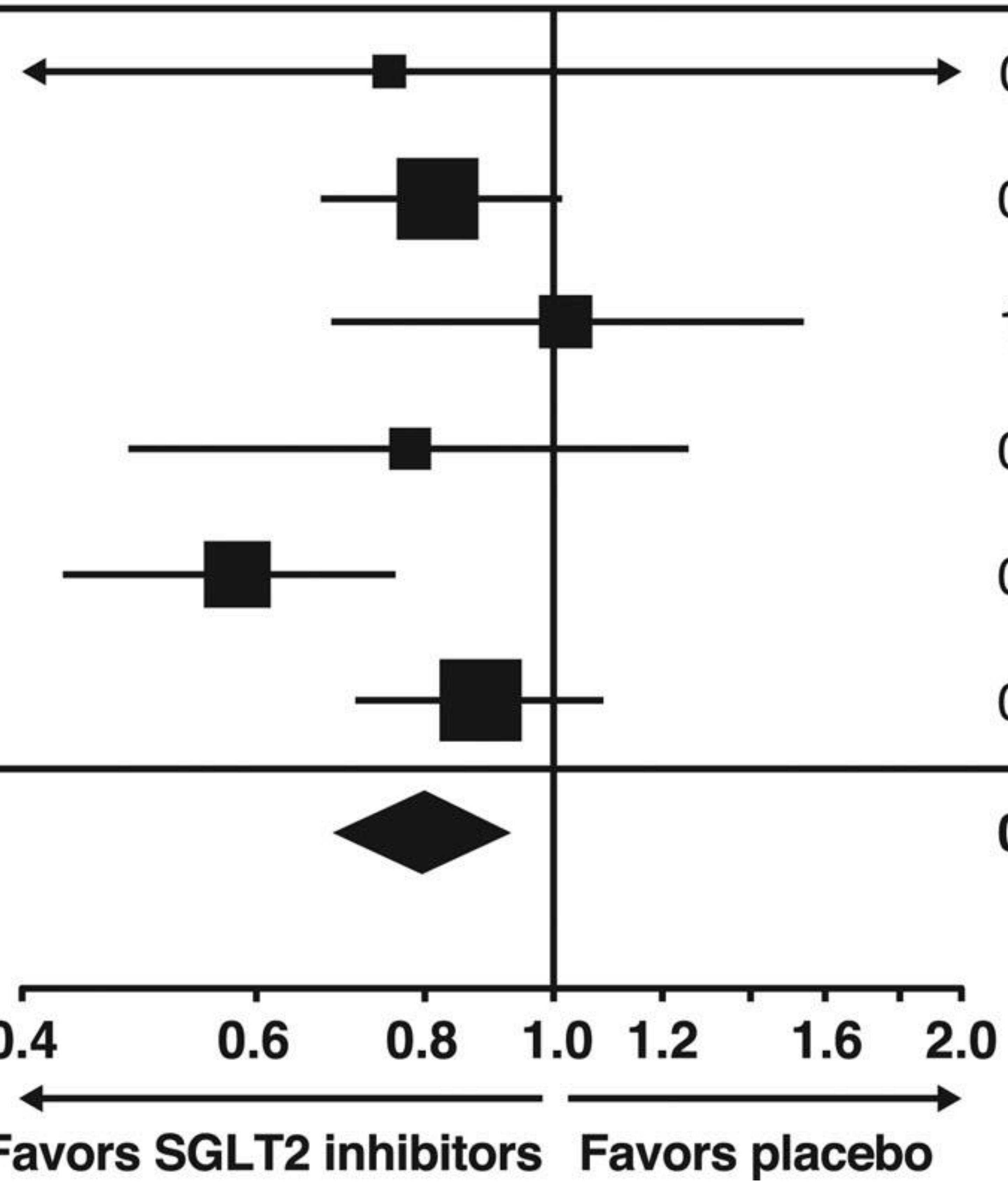
- showed significant reduction in progression of CKD , decrease in albuminuria and reduction in CV events regardless of DM status.

- through effect of natriuresis it and enhancement of aldosterone release , it can potentiate urinary K excretion.

- Lower rates of hyperkalemia compared to placebo (EMPA-REG, EMPA-Kidney)

- an Attractive option to address renal/CV protection and tackle hyperkalemia esp in patients with protienuric CKD.

	SGLT2 inhibitors		Placebo		Hazard Ratio
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	(95% CI)
CANVAS Program	8/5795	0.4	7/4347	0.6	0.75 (0.27, 2.11)
CREDENCE	169/2202	30.7	203/2199	37.4	0.82 (0.67, 1.01)
DAPA-CKD	48/1455	33.0	47/1451	32.0	1.02 (0.68, 1.54)
DECLARE-TIMI 58	30/8582	0.9	38/8578	1.1	0.78 (0.48, 1.26)
EMPA-REG OUTCOME	104/4687	7.7	88/2333	13.4	0.58 (0.43, 0.76)
VERTIS CV	243/5493	15.4	134/2745	17.7	0.88 (0.71, 1.09)
Overall					**0.80 (0.68, 0.93)**
(I^2=29.5%; $P_{heterogeneity}$=0.21)					P=0.004



Neuen BL, Oshima. *Circulation*. 2022;145: 1460–1470

Correcting Acidosis

- Excess H+ ions in acidosis (Metabolic or respiratory) can enhance the release of intracellular K+ into extracellular compartment (H+/K cotransporter) leading to Hyperkalemia.

- Bicarbonate therapy can be a good strategy to correct Hyperkalemia in context of metabolic acidosis ($HCO_3 < 18$) and CKD. (in addition of its benefit in slowing GFR decline)

- Data from studies did not show significant potassium lowering efficacy if there is no Metabolic acidosis present.

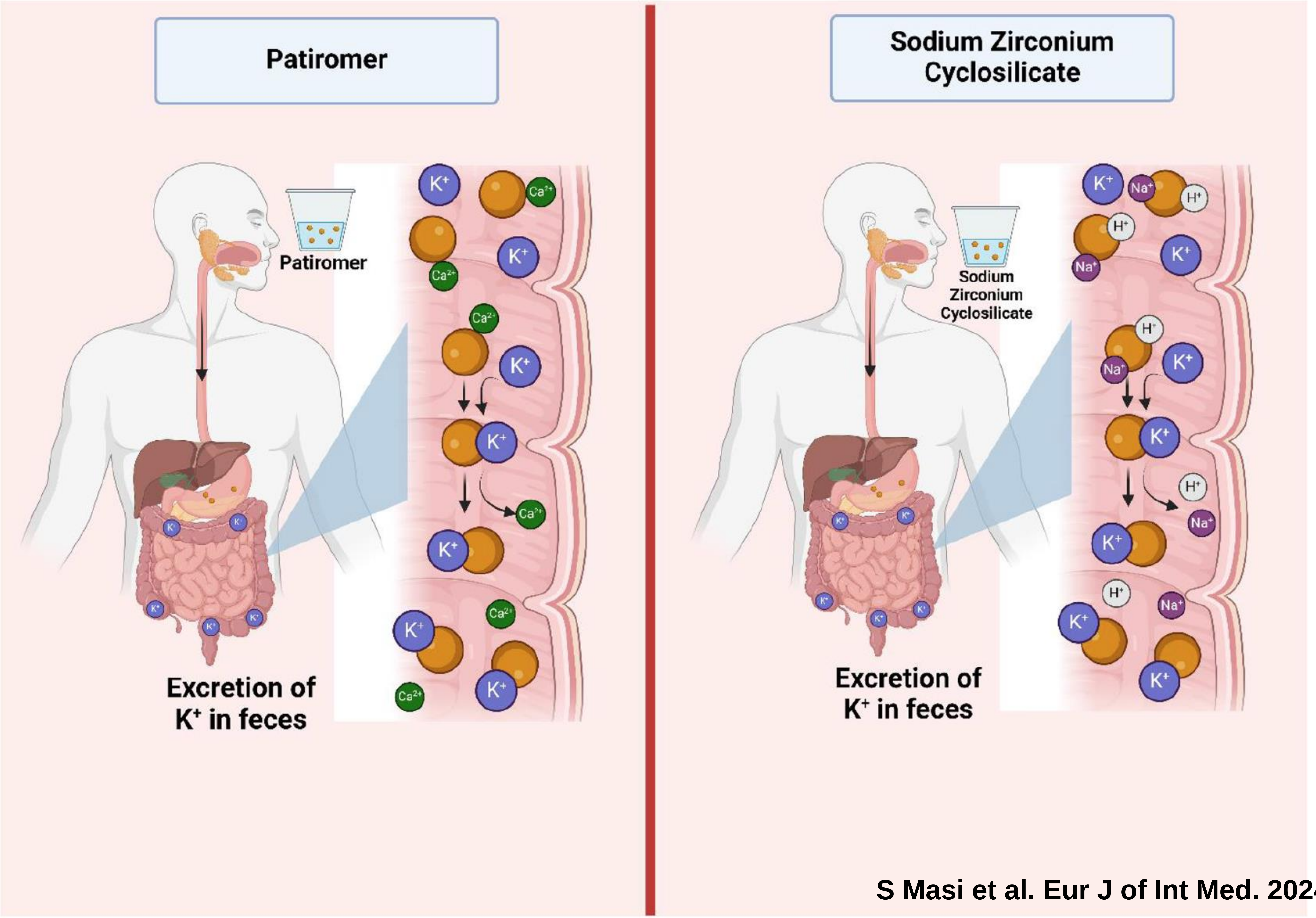
GI cation Exchangers (AKA potassium binders)

- **Calcium resonium .**
- **Sodium polystyrene sulfonate**

- Old
- Sparse data o efficacy and safety
- issue with side effects (bowel necrosis) raise concern of longterm use.

- **Patiromer.**
- **Sodium Zirconium cyclosilicate.**

- New
- More evidence (RCTs)
- can be used chronically.



S Masi et al. Eur J of Int Med. 2024 :

Many studies showed that the new K binders (Patiromer /SZC) were effective in :

- **Lowering Potassium levels in different stages of CKD**
- **Preventing Hyperkalemia and enabling persistent use of RAASi in context of protienuric CKD and CHF**

Patiromer	Sodium Zirconium (SZC)
AMBER Trial (HTN, CKD) PEARL-HF Trial (CHF, CKD) DIAMON Trial (HFrEF, hx of HyperK) AMETHYST-DN Trial (DKD, HyperK) OPAL-HK Trial (CKD , HF)	HARMONIZE Trial (HF) DIALYZE Trial (dialysis , HyperK) REALIZE-K Trial (HF, HyperK)

Feature	Patiromer	Sodium Zirconium Cyclosilicate
Dosage	Initial: 8.4 g once daily Maintenance: 8.4 g to 25.2 g once daily	Initial: 10 g three times a day Maintenance: 5 g to 15 g once daily
Administration	Oral suspension (mixed with water)	Oral suspension (mixed with water)
Onset of Action	~7 h (peak effect in 24 h)	~1 hour (peak effect in 24 h)
Expected Results	Lowers serum potassium levels by ~1.0 mEq/L in 1 week	Lowers serum potassium levels by ~1.0 to 1.5 mEq/L in 48 h
Common Side Effects	- Constipation - Diarrhea - Nausea - Abdominal discomfort	- Edema - Nausea - Vomiting - Constipation
Serious Side Effects	- Hypomagnesemia - Gastrointestinal obstruction	- Edema - Hypokalemia
Contraindications	- Severe constipation - Bowel obstruction	- Bowel obstruction - Known hypersensitivity
Monitoring	Regular monitoring of potassium and magnesium levels	Regular monitoring of potassium levels

S Masi et al. Eur J of Int Med. 2024 :

Summary

- Hyperkalemia is a common finding along CV disease continuum, and is associated with increased morbidity and mortality.

- understanding of the underlying mechanisms in the development of hyperkalemia is crucial for appropriate management.

- Several therapeutic approaches should be implemented to manage hyperkalemia and avoid discontinuation of contributing medications that have CV and renal benefits.

- New K cation exchangers optimized the management of hyperkalemia and aided in the avoidance of discontinuation of RAASi, enhancing CV and renal benefits.

THANK YOU