ROYAL COLLEGE of PHYSICIANS of EDINBURGH

NHS
Hull University Teaching Hospitals
NHS Trust

Managing hyperkalaemia In Chronic Kidney Disease

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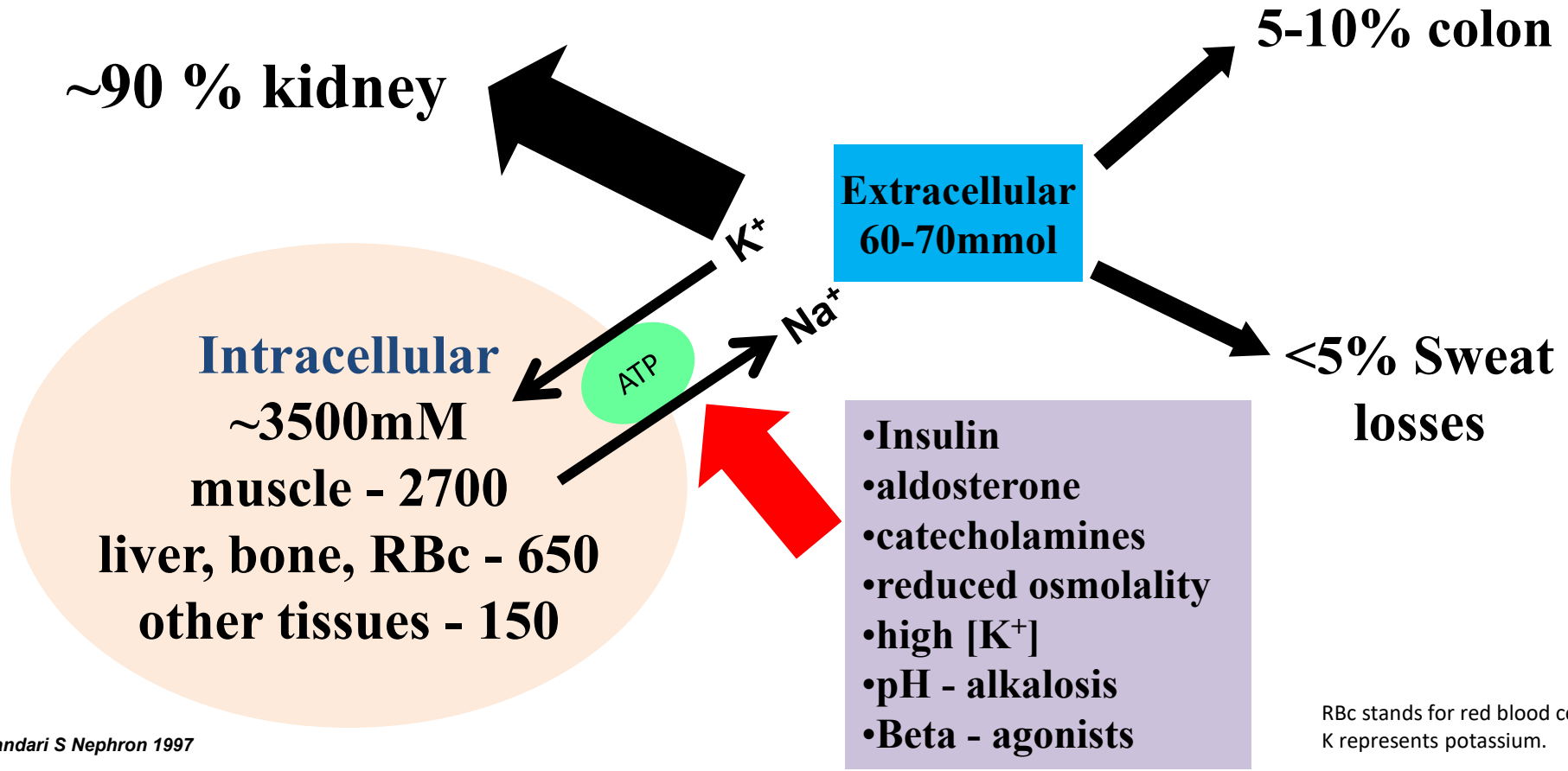
HULL YORK MEDICAL SCHOOL

Importance of Potassium Homeostasis

- Alters membrane excitability
  - resting membrane potential
  - muscle contraction
  - neuromuscular excitability
  - cardiac pacemaker rhythmicity
- maintenance of cell volume
- acid-base balance
- Cell enzyme function/DNA/protein synthesis

Potassium Homeostasis



Bhandari S Nephron 1997

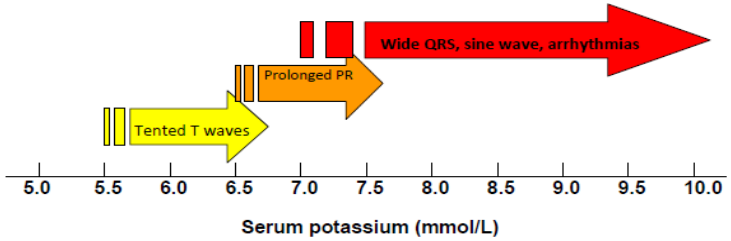
RBc stands for red blood cells.
K represents potassium.

Symptoms of Hyperkalaemia?

- Muscle soreness or lack of strength
- Rapid breathing linked to respiratory muscle weakness
- Tingling sensations
- Feeling nauseated and vomiting
- Heart palpitations - irregular heart rhythms
- Weakness leading to flaccid paralysis
- Malfunction of the pacemaker

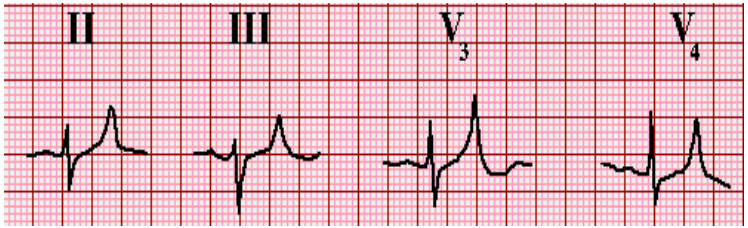
Hyperkalaemia ECG and its Pathophysiology

K^+



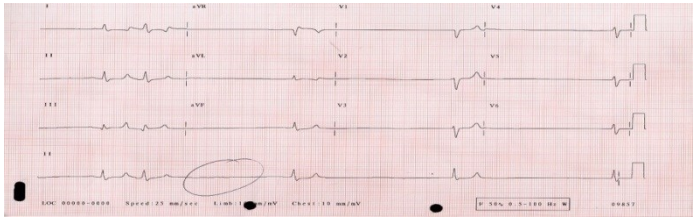
Reduction in RMP
- less electronegative

Increased rate of repolarisation

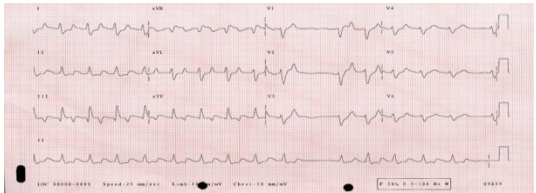


Tenting of T waves
shortened QT interval

Reduced myocardial cell conduction velocity



Sine wave pattern
ventricular standstill



Widening QRS
Increased PR
loss of P wave

RMP = resting membrane potential

Question

?Main factors place patients at risk for hyperkalemia

Co-morbidities

- Ageing
- Diabetes
- CKD
- Cardiac disease/Heart Failure
- Hypertension

Medications

- ACEi/ARB
- ARNI
- MRA (mineralocorticoid)
- NSAIDs
- Beta blockers

Episodes of acute kidney injury
Iatrogenic

RAASi Therapy - The Cornerstone of Guideline-Directed Care

Nephrology

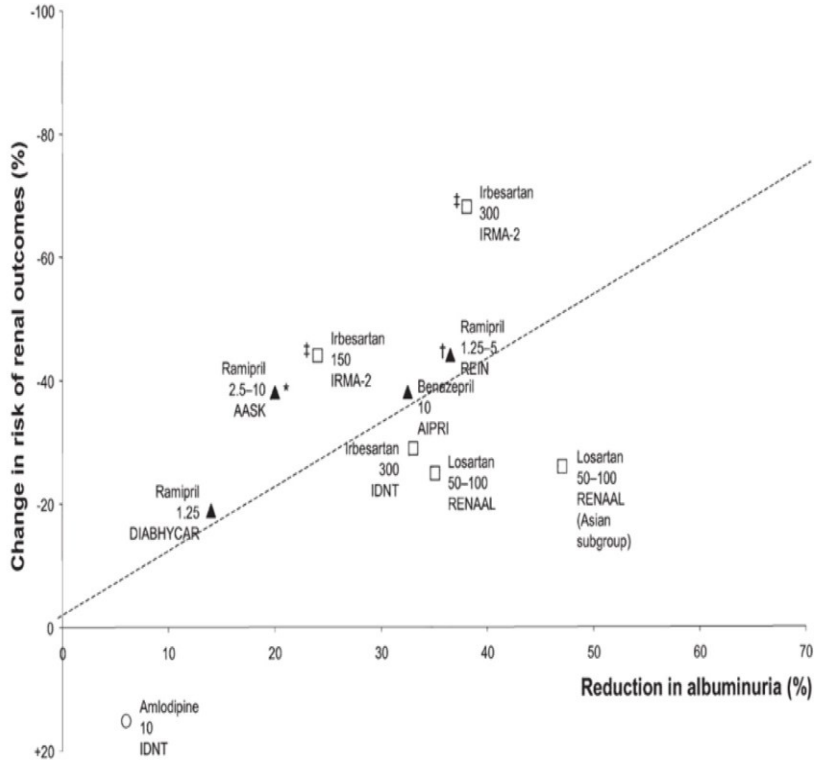
- Kidney Disease Improving Global Outcomes (KDIGO)
- National Institute for Health and Care Excellence (NICE)
- National Kidney Foundation (NKF)

Cardiology

- American College of Cardiology/American Heart Association (ACC/AHA)
- European Society of Cardiology (ESC)
- Heart Failure Society of America (HFSA)

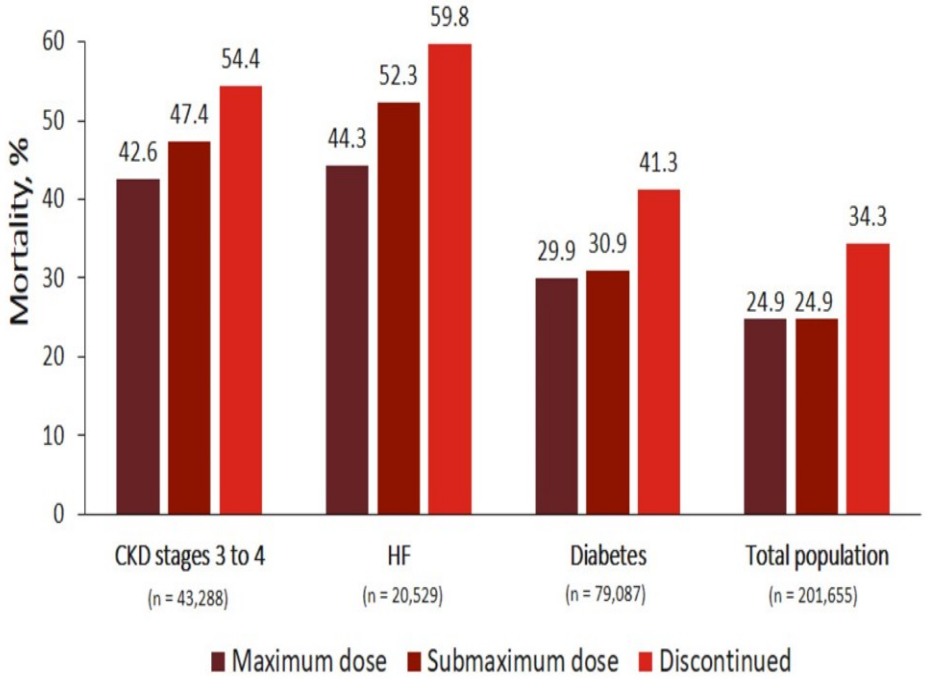
Renin-angiotensin-aldosterone system inhibitor; Yancy CW, et al. *Circulation.* 2013;128(16):1810-1852. Ponikowski P, et al. *Eur J Heart Fail*. 2016;18(8):891- 975.
Heart Failure Society of America, et al. *J Card Fail*. 2010;16(6):e1-194.
KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl (2011)*. 2024;3(1);1-150.
National Institute for Health and Care Excellence. Chronic Kidney Disease in Adults: Assessment and Management. Published July 23, 2014. https://www.nice.org.uk/guidance/cg182.
KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl (2011)*. 2012;2(5);347-356.

Better Renal Outcomes With Higher Doses of ACE Inhibitors/ARBs



Basi S, Lewis JB. *Am J Kidney Dis.* 2006;47:927-946.

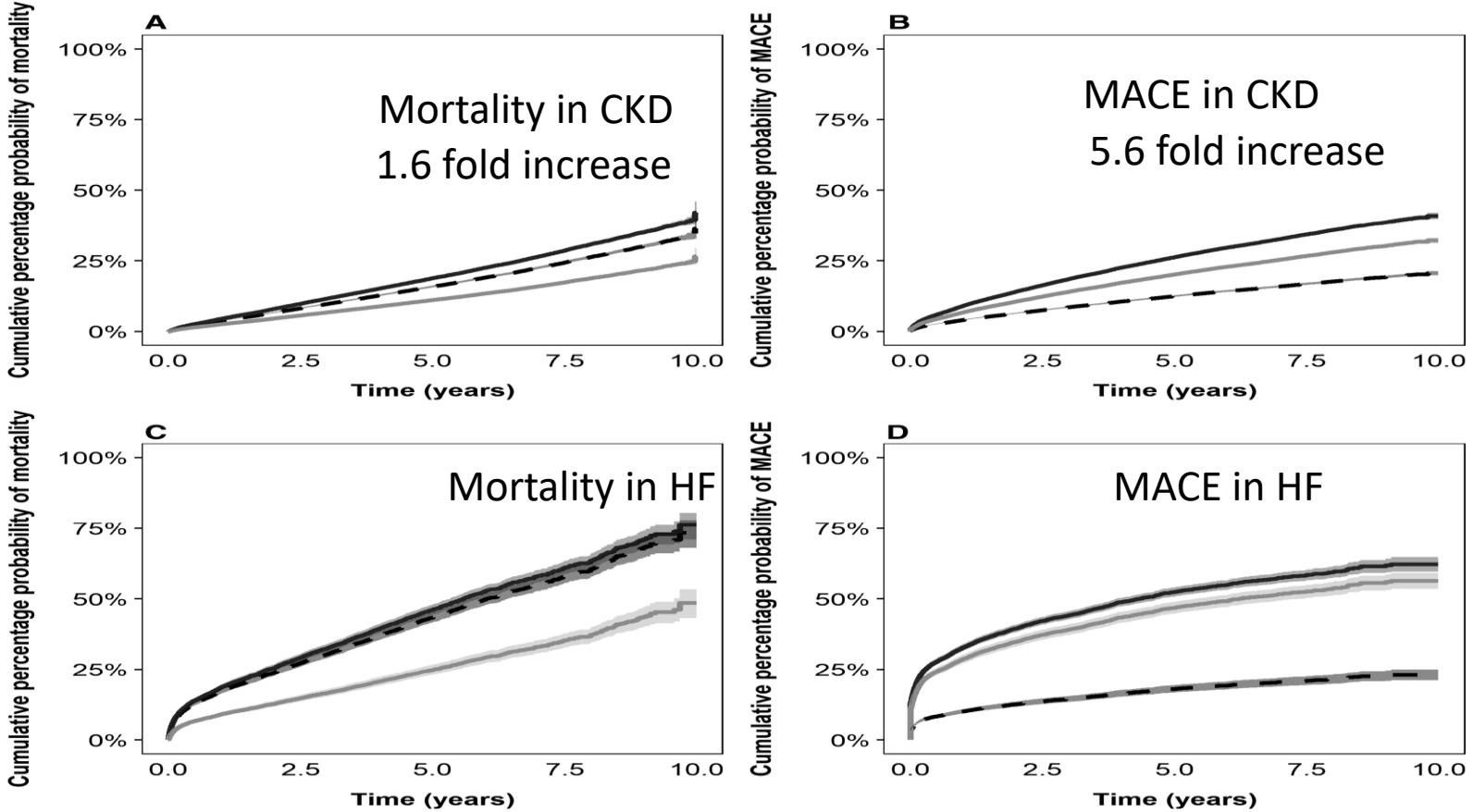
Using Maximum vs Submaximum Doses of RAASi Is Associated With Reductions in Mortality



Epstein M, et al. *Am J Manag Care.* 2015;21(11 Suppl):S212-210.

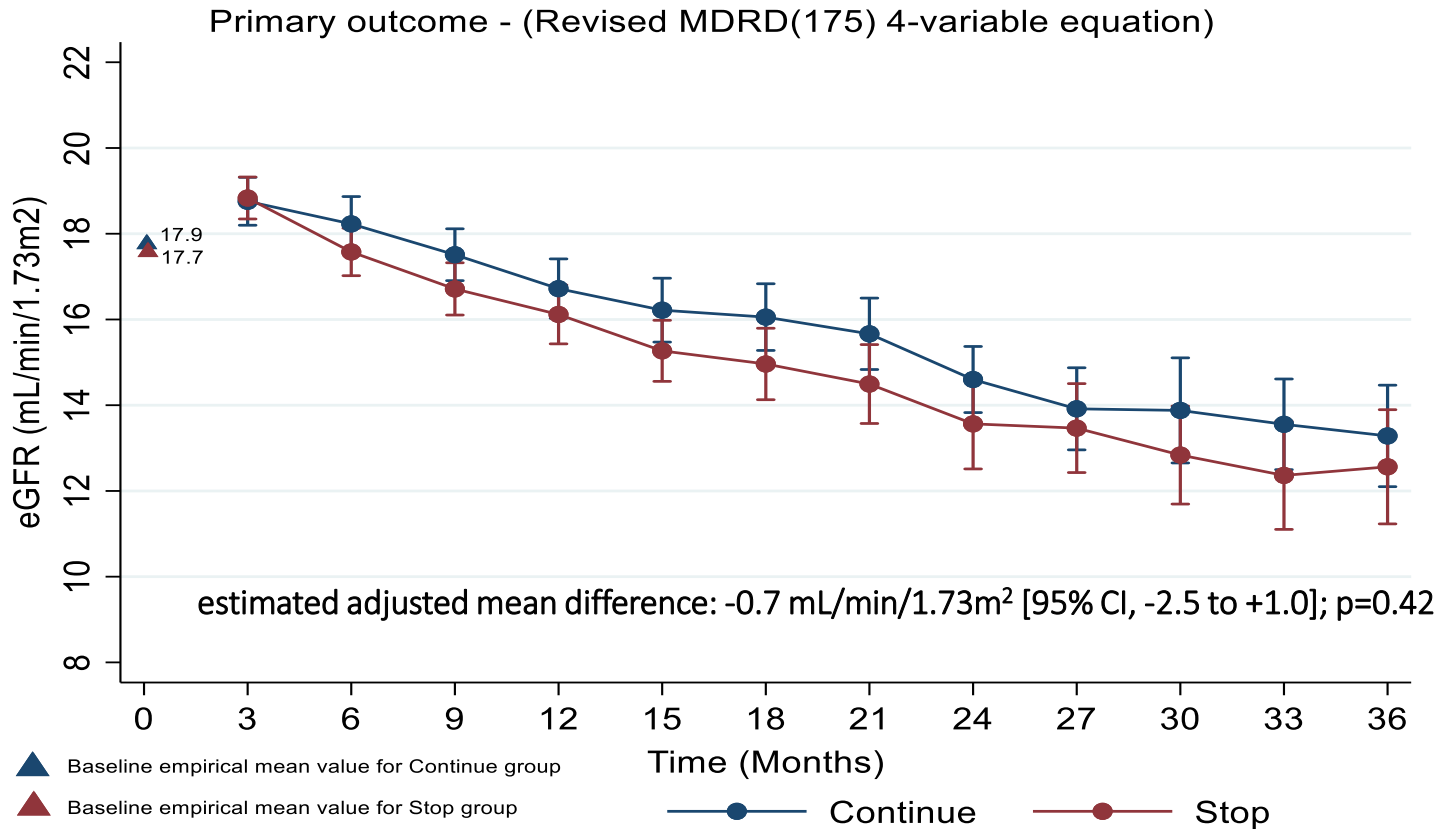
Real-World Evidence: Impact of Suboptimal RAASi Dosing in CKD & HF

<50% vs 50%



Linde C et al. J Am Heart Assoc. 2019;8:e012655

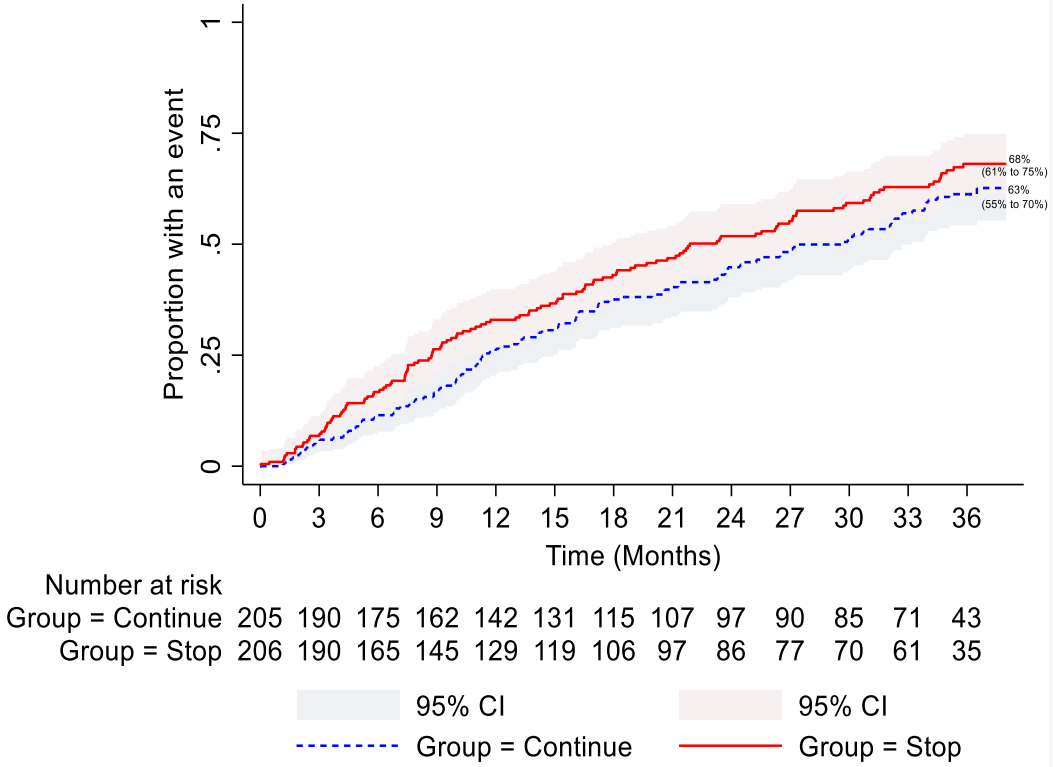
Marginal means (Primary outcome - Primary analysis ($MDRD_{175}$ 4-variable equation)) for patients randomized to stop or continue RAS inhibitor.



Bhandari S et al. *N Engl J Med*. 2022;10.1056/NEJMoa2210639.

Censored for values post dialysis or after transplant

Kaplan-Meier curve by treatment arm (stop or continue RAS inhibitor) for time to kidney replacement therapy or end stage kidney disease



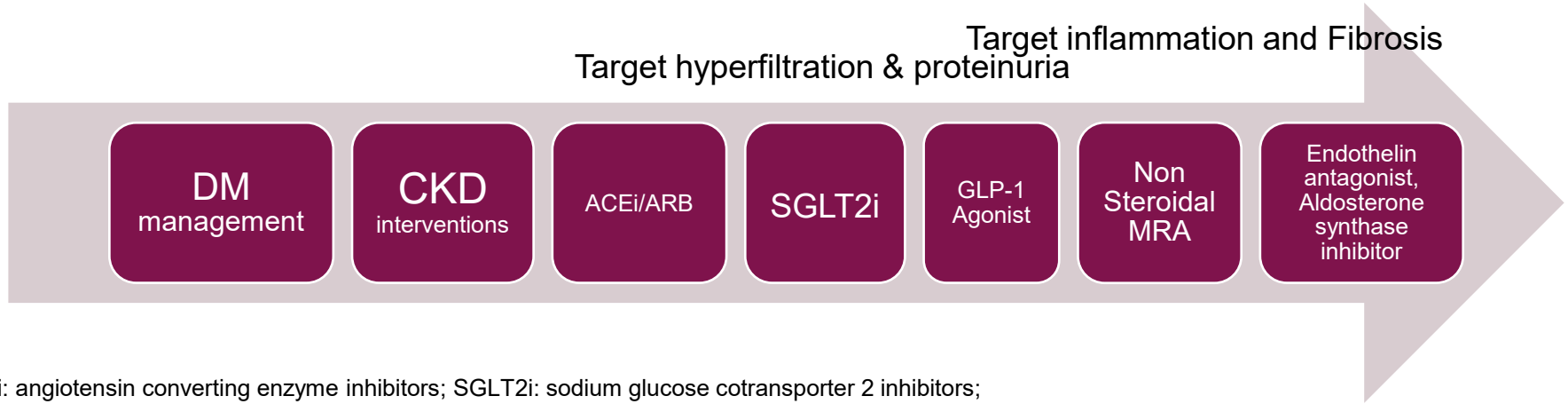
Commenced KRT or reached ESKD	STOP (N=206)	Continue (N=205)	Total (N=411)
No	78 (38%)	90 (44%)	168 (41%)
Yes	128 (62%)	115 (56%)	243 (59%)

Unadjusted HR (95% CI) P-value	Adjusted HR (95% CI)* P-value
1.23 (0.95, 1.58) P=0.11	1.28 (0.99, 1.65) P=0.06

CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; RAS, renin-angiotensin system; KRT, kidney replacement therapy.

Bhandari S et al. *N Engl J Med*. 2022;10.1056/NEJMoa2210639.

Miminising Chronic Kidney Disease Risk

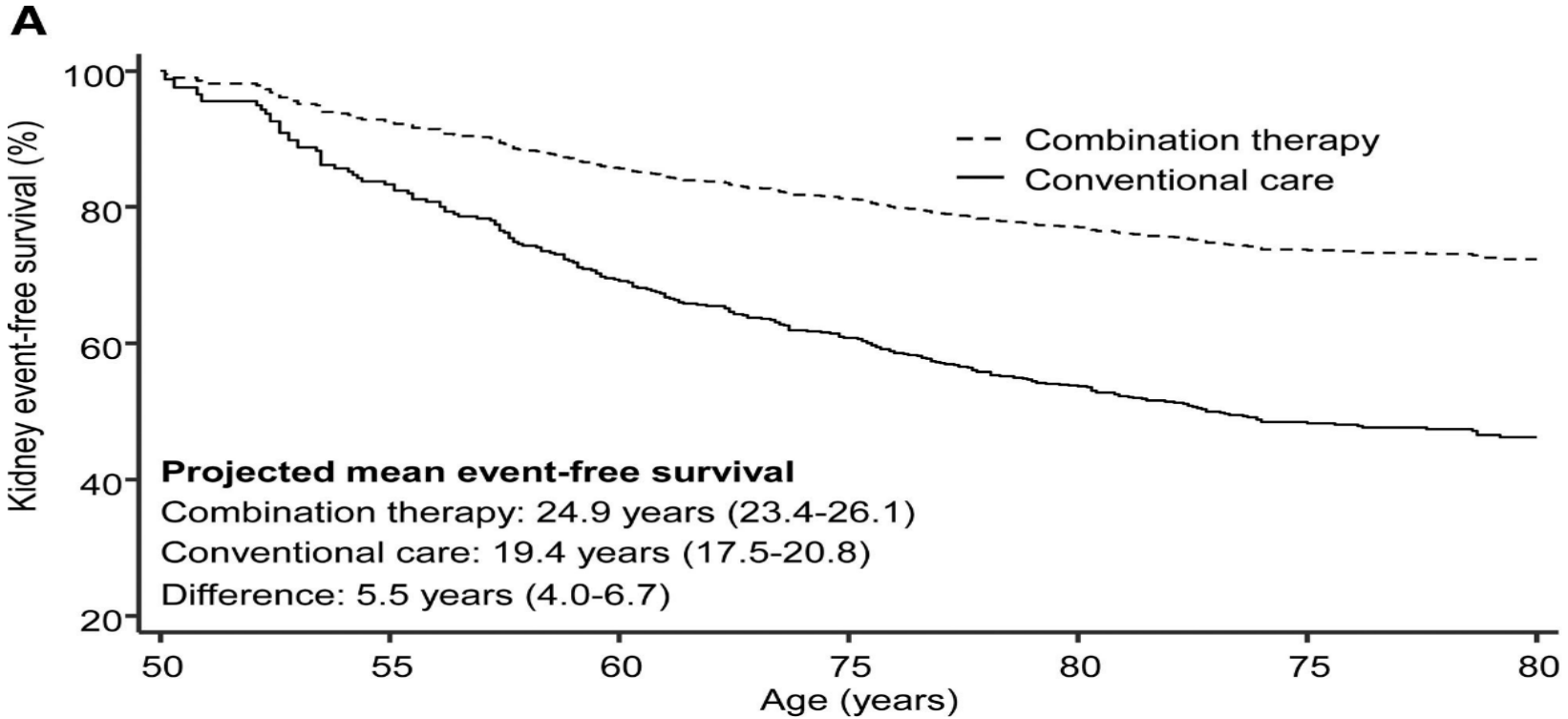


ACEi: angiotensin converting enzyme inhibitors; SGLT2i: sodium glucose cotransporter 2 inhibitors;
MRA: mineralocorticoid receptor antagonists

CKD, chronic kidney disease; DKD, diabetic kidney disease; RAS, renin-angiotensin system; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

KDIGO. 2020. Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease;98. Available from: https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf. Accessed March 2022.

Treatment benefits of combination SGLT2 inhibitor, GLP-1 receptor agonist, and nonsteroidal MRA on survival free from CKD progression when added to RAS blockade in patients with type 2 diabetes and albuminuria (uACR ≥3 mg/mmol)

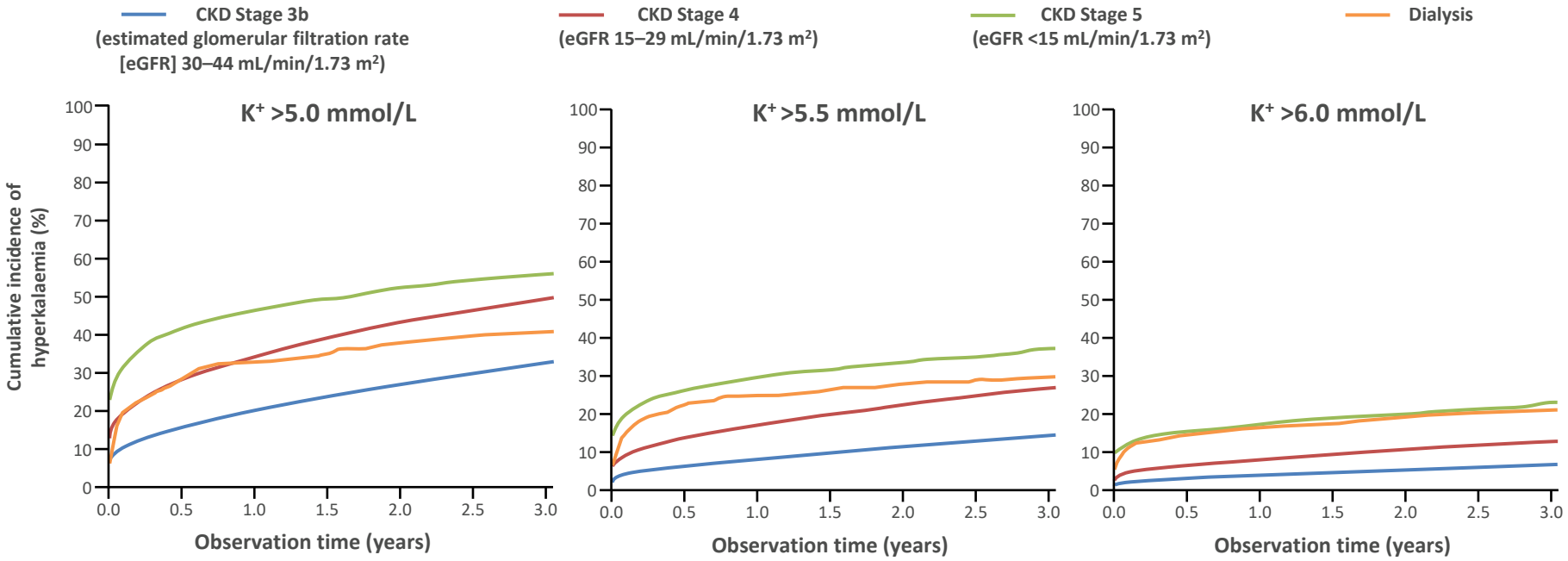


RAS renin-angiotensin system CKD Chronic Kidney Disease
SGLT2 sodium glucose cotransporter-2; GLP1 glucagon-like peptide-1 ; MRA - mineralocorticoid receptor antagonist; uACR urine albumin:creatinine ratio

Neuen BL et al. Circulation. 2024 Feb 6;149(6):450-462. do: 10.1161/CIRCULATIONAHA.123.067584.

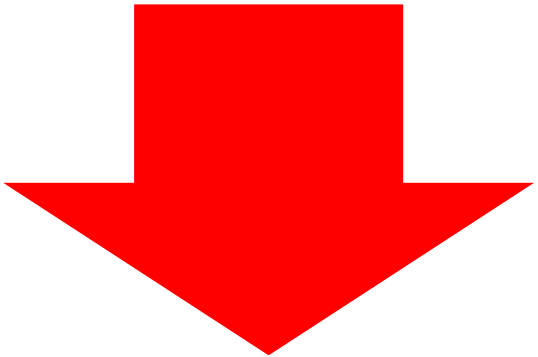
In Patients With Chronic Kidney Disease (CKD), the Incidence of Hyperkalaemia Increases With Deteriorating Kidney Function

Population-based cohort study linking individual data from hospital, prescription and laboratory databases in patients from the Danish National Patient Registry in Northern Denmark (population 1.8 million) during 2000–2012. Patients with a first-time diagnosis of CKD were identified (N = 157,766)



Adapted from Thomsen RW, et al. *Nephrol Dial Transplant* 2018;33:1610–1620.
K⁺=potassium.
Thomsen RW, et al. *Nephrol Dial Transplant* 2018;33:1610–1620.

Dilemma



Optimise therapies to minimize chronic kidney Disease progression and reduce CV events and mortality

Hyperkalaemia

Acute

Chronic

Case Scenario

- 44-year-old male underwent Deceased Donor Kidney Transplant.
- Uneventful surgery with good urine output >3litres/day after day 1

- PMHx
  - Diabetic Nephropathy and Hypertension
  - Single vessel Ischaemic Heart disease <40% stenosis
  - Haemodialysis 2 years – 4hours 5minutes x3/week

- **Medication**
  - Tacrolimus
  - Bisoprolol
  - Ramipril
  - Cotrimoxazole
  - Fragmin
  - Linagliptin
  - Atorvastatin
  - Intravenous Hartmann's solution - 4 hourly

Case Scenario

Examination

- Bp 120/76 mmHg (no postural drop)
- Clinically euvolaemic
- No other findings

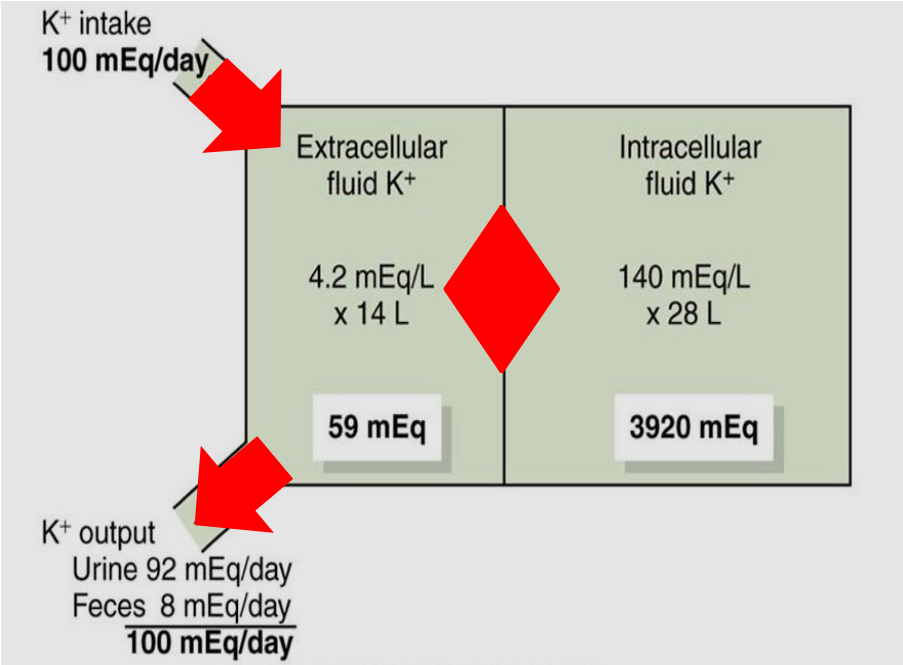
5 days post operatively biochemistry showed the following

Case Scenario

Na^+	132 mmol/L
K^+	6.7 mmol/L
Cl^-	118 mmol/L
HCO_3^-	14 mmol/L
Creatinine	223 µmol/L
Ca^{2+}	2.2 mmol/L
PO_4^{2-}	0.41 mmol/L
Albumin	39 g/L
Urea	18.2 mmol/L
Glucose	11 mmol/L

What is the cause of hyperkalaemia in this case?

- Spurious/pseudo
- Increased intake
- Cellular movement
- Reduced urinary loss
- Other
  - adrenal insufficiency



Spurious/Pseudo Hyperkalaemia

- Pseudo - traumatic venepuncture
- Tight tourniquet
- Delayed centrifuge
- Placing sample in ice
- Acute hyperventilation

- Haemolysis
- Thrombocytosis
- Leucocytosis

- Hereditary spherocytosis

If pseudo-hyperkalaemia suspected, send paired blood samples in a clotted tube (serum) and a lithium heparin tube (plasma). Send FBC to exclude haematological disorder. Pseudo-hyperkalaemia is present if [serum K+] – [plasma K+] > 0.4mmol/L

What is the cause of hyperkalaemia in this case?

- 44-year-old male underwent Deceased Donor Renal Transplant. Uneventful surgery with good urine output >3litres/day after day 1

Medication:

- Tacrolimus
- Bisoprolol
- Ramipril
- Cotrimoxazole
- Fragmin
- Linagliptin
- Atorvastatin
- Intravenous Hartmann's solution - 4 hourly

Na^+	132	mmol/L
K^+	6.7	mmol/L
Cl^-	118	mmol/L
HCO_3^-	14	mmol/L
Creatinine	223	µmol/L
Urea	18.2	mmol/L

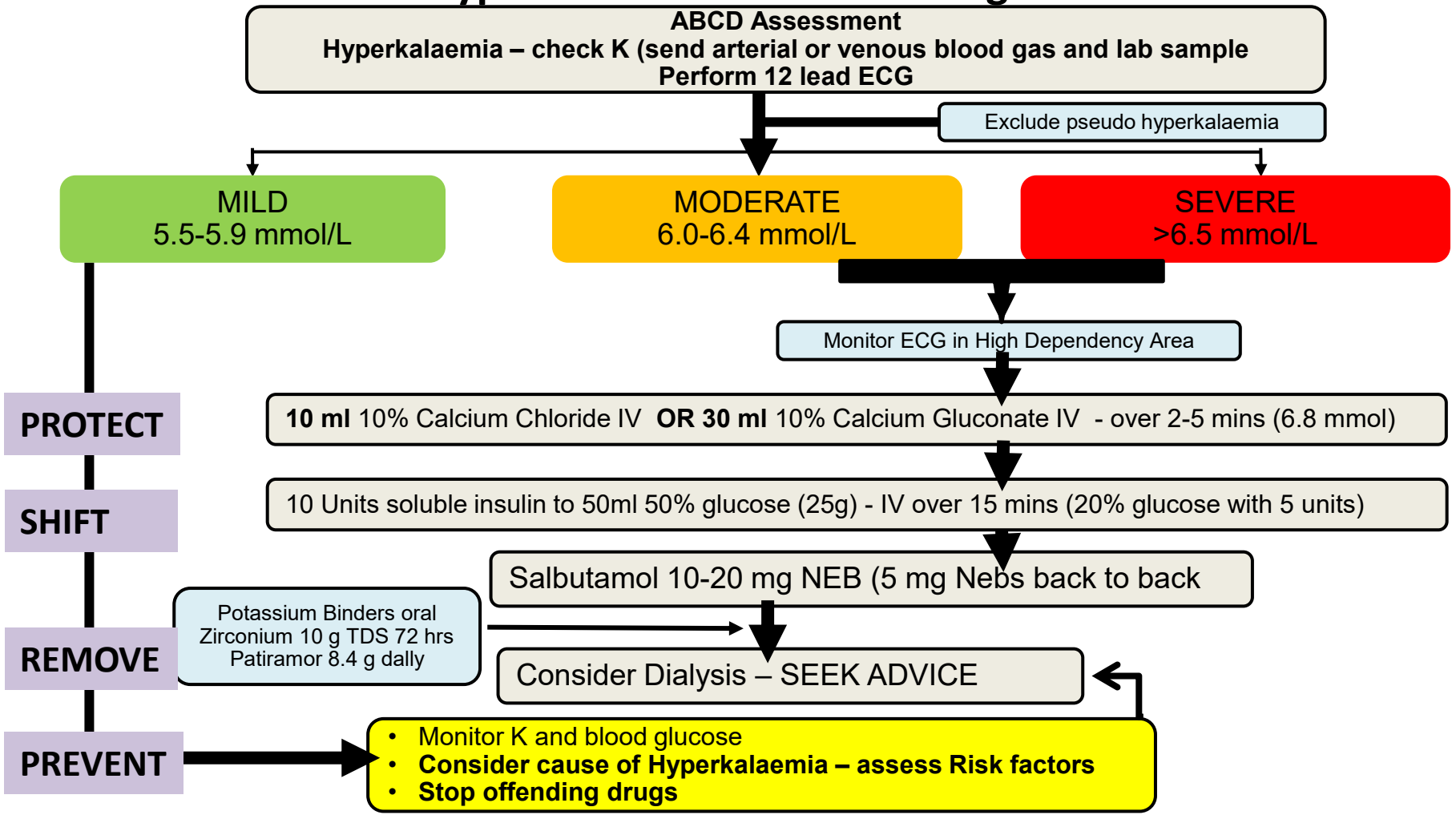
Potassium Intake

mM concentrations Normal plasma values	pH	Na^+ 142	K^+ 4.5	HCO_3^- (As lactate) 24	Cl^- 103	Ca_2^+ 2.4	Glucose g/L	Osmolality Mmol/L
N/saline 0.9%	5.5	154	----	----	154	----	----	308
5% dextrose	5.6	----	----	----	----	----	50	278
Dextrose 4%/Saline 0.18%	5.6	30	----	----	30	----	40	283
Ringers lactate	6.5	130	4	28	109	3.0	----	273
Hartmann's	6.5	131	5	29	111	2.0	----	274
8.4% Sodium Bicarbonate	9.0	1000	----	1000	----	----	----	2000
1.26% sodium bicarbonate		150	----	150	----	----	----	300
0.45% Saline	5.5	77	----	----	77	----	----	154
3% saline		513			513			1026

Potassium Redistribution - Trans-cellular Movement

- tissue catabolism – exercise, surgery
- metabolic acidosis – lactic acid- incomplete dissociation
- hypothermia
- severe exertion
- hyperosmolar non-ketotic coma or mannitol infusion
- cardiac surgery
- tissue necrosis – rhabdomyolysis, burns, tumour lysis
- drugs
  - Beta blockers
  - Ramipril
  - digoxin toxicity
  - Succinylcholine
  - arginine
  - Ocreotide/somatostatin

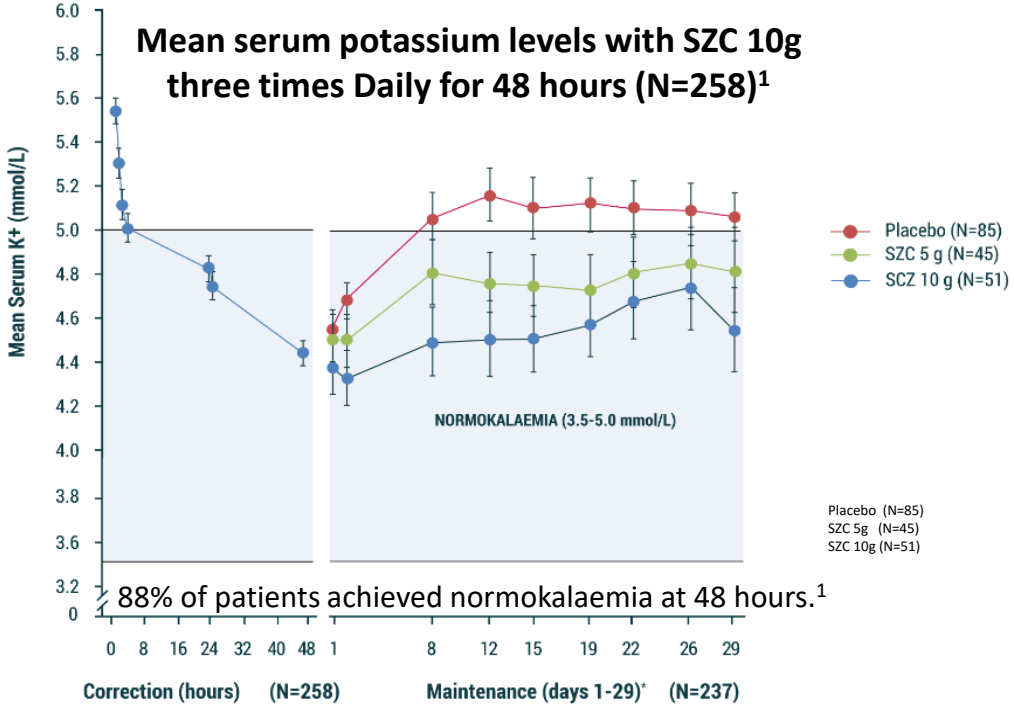
Hyperkalaemia: treatment algorithm



Zirconium – Harmonize Study

In the 48 hour open label phase of the study, one dose (10g) of SZC significantly reduced the mean serum K^+ level after 1 hour.[1,2]

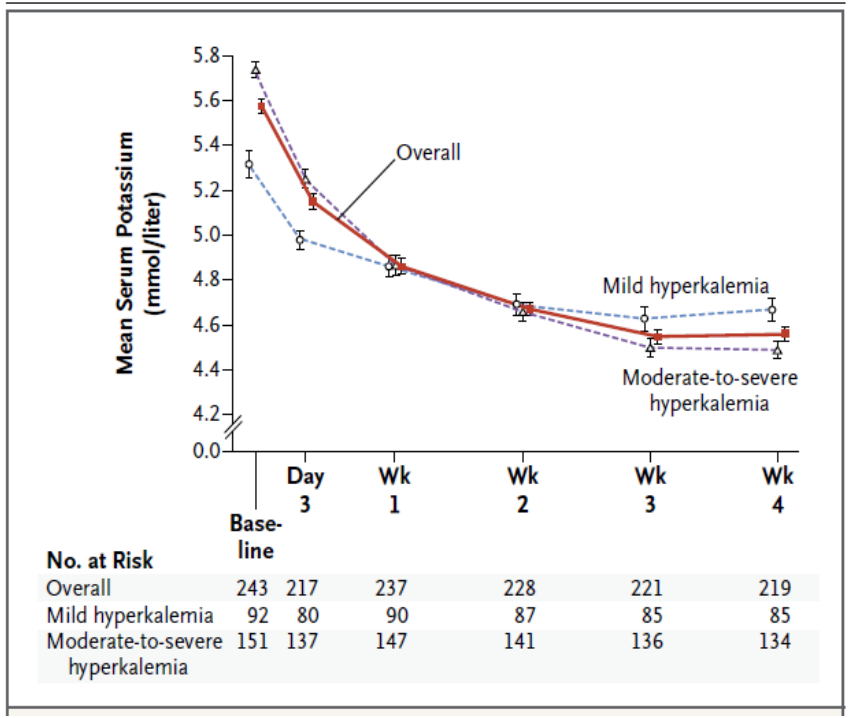
-0.2 mmol/L compared to baseline. 95% CI: -0.3 to -0.2.[2]



88% of patients achieved normokalaemia at 48 hours.[1]

Adapted from Kosiborod et al., 2014[2]

Patiromer –OPAL Study



Weir MR et al. N Engl J Med 2015;372:211-21.

1. AstraZeneca Lokelma (Sodium Zirconium Cyclosilicate [SZC]). Summary of product characteristics. Available from: www.medicines.org.uk/emc Accessed: June 2020.
2. Kosiborod M, et al. Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia. The HARMONIZE Randomized Clinical Trial. *JAMA* 2014;312:2223–2233;

UKKA Clinical Practice Hyperkalaemia Guidelines

UK Kidney Association

Guideline 1.2.1 – We recommend that the **serum K^+ is repeated within 3 days**, or as soon as feasible, if an episode of **mild hyperkalaemia (K^+ 5.5 – 5.9 mmol/l)** is detected unexpectedly in the community. (1C)

Guideline 1.2.2 – We recommend that the **serum K+ is repeated within 1 day** of an episode of **moderate hyperkalaemia (K^+ 6.0 – 6.4 mmol/l)** when detected in the community. (1C)

Guideline 1.2.3 –We recommend that patients with **severe hyperkalaemia ($K^+ \geq 6.5$ mmol/l)** detected in the community are admitted for immediate assessment and treatment. (1B)

Guideline 2.1 –We recommend that urea and electrolytes should be assessed prior to initiation of ACE-I or ARB and these drugs should be used with caution if the serum K^+ is > 5.0 mmol. (1A)

Guideline 2.2 – We suggest that initiation of MRAs should be avoided in patients with a baseline serum K^+ > 5.0 mmol/l or eGFR < 30 ml/min. (1B)

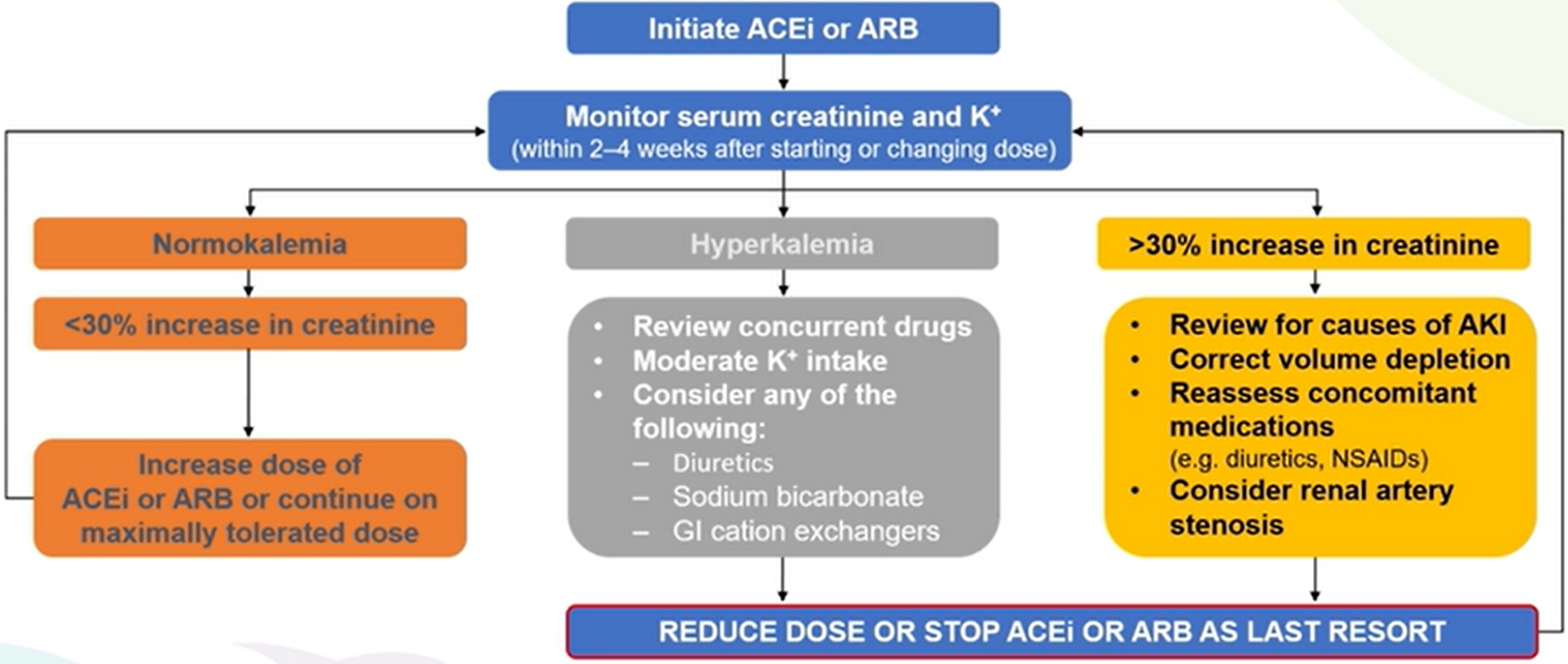
Case Scenario

- 59 year
  - Diabetic Nephropathy — HbA1c 61
  - Ischaemic Heart Disease
  - Progressive kidney deterioration — eGFR 38 ml/min/1.73m^2
  - Hypertension — current BP 148/88 mmHg
  - Increasing Proteinuria — 120 mg/mmol

  - <u>Medication</u>:
    - Bisoprolol — 7.5 mg daily
    - Ramipril — 5 mg daily
    - Dapagliflozin — 10 mg daily
    - Atorvastatin — 20 mg daily
    - Aspirin — 75mg daily
    - Metformin — 1g BD

Serum Potassium 5.9 mmol/L

KDIGO 2020 Guideline for Diabetes Management in CKD: Monitoring of serum creatinine and K^+ during ACEi or ARB treatment



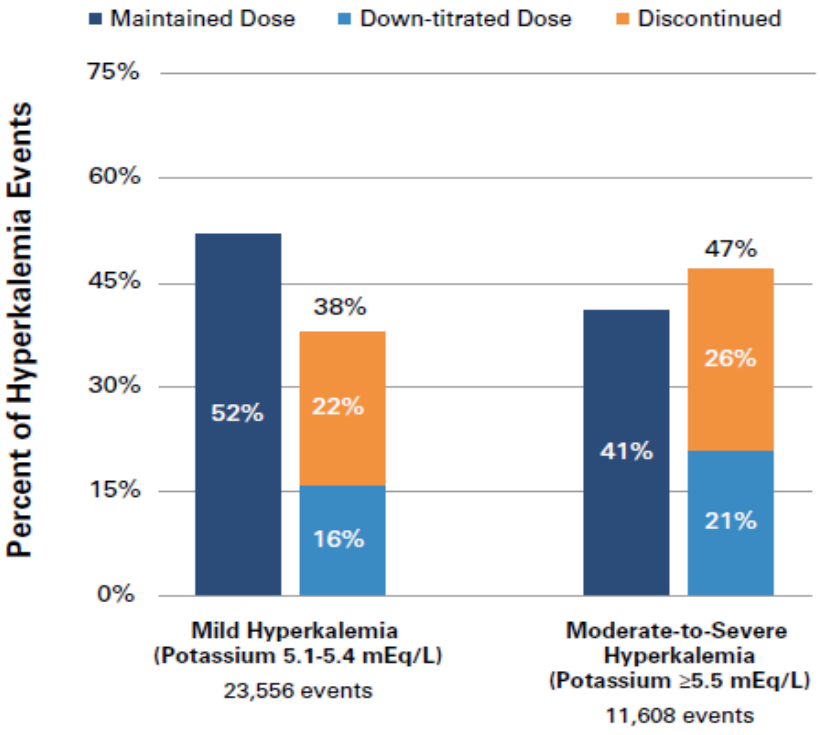
Note: ACEi or ARB should only be reduced or stopped after measures outlined above have failed

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; NSAID, nonsteroidal anti-inflammatory drug

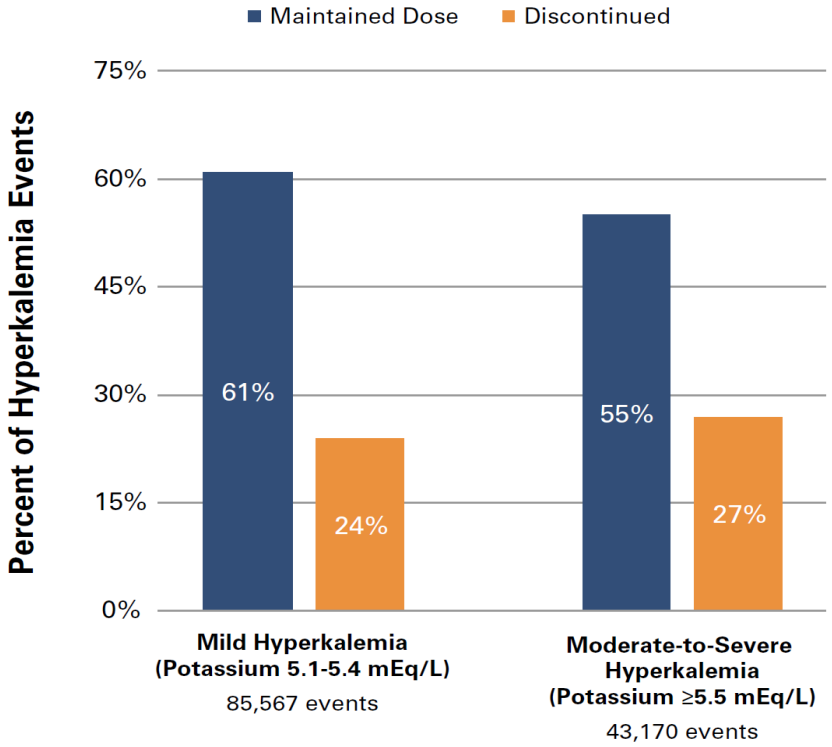
KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020;98:S1–S115

Changes in RAASi Therapy After Hyperkalaemia Event

Among Patients on RAAS Inhibitor at Maximum Dose



Among Patients on RAAS Inhibitor at Submaximum Dose



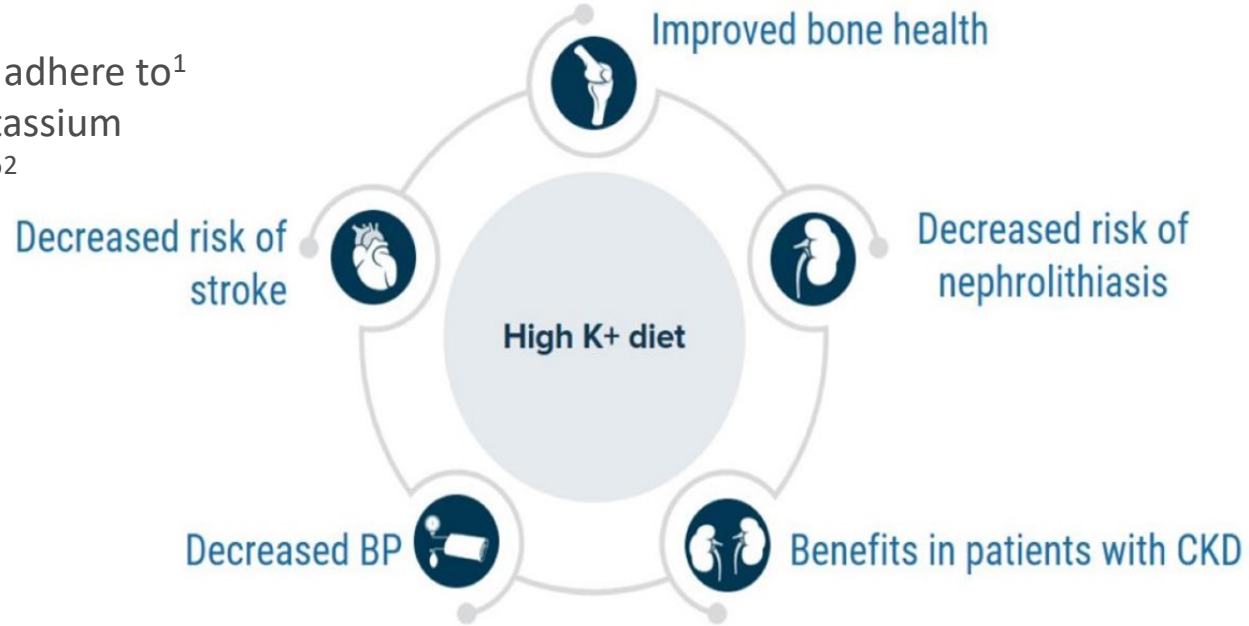
Epstein M et al. The American Journal of Managed Care. 2015, VOL. 21, NO. 11

Patients with chronic kidney disease, heart failure, or diabetes

Low-Potassium Diet- Defined as ≤ 3 g K^+ per day (<77 mmol/day)

Guideline 5.1 – We recommend that dietary strategies to modify potassium intake is instituted for patients with CKD and persistent hyperkalaemia with a serum K+ > 5.5 mmol/l after non-dietary causes of hyperkalaemia (constipation, acidosis and poorly controlled diabetes) have been addressed. (1B)

- Dietary restrictions - difficult to adhere to[1]
- Many healthy foods contain potassium
- A low K^+ intake may increase BP[2]



1. Beto J, et al. *Int J Nephrol Renovasc Dis* 2016;9:21–33
2. Mount D, et al. *Potassium and hypertension.* UptoDate 2020. Available from: https://www.uptodate.com/contents/potassium-and-hypertension/print [Last accessed: January 2025]
3. Palmer BF et al Mayo Clinical Proced 2016, 91, 496-508

Hyperkalaemia in Chronic Kidney Disease

Practice Point 3.11.5.2: Provide advice to limit the intake of foods rich in bioavailable potassium (e.g., processed foods) for people with CKD G3–G5 who have a history of hyperkalaemia or as a prevention strategy during disease periods in which hyperkalaemia risk may be a concern.

Plant-based foods

Absorption rate
50%–60%

Plant-based foods may have low absorption rate, net alkalizing effect, and carbohydrate content encourages K^+ shifts into intracellular space, minimizing impacts on serum K^+

Animal-based foods

Absorption rate
70%–90%

Animal-based protein has higher absorption and net acid effect results in higher amounts of K^+ remaining in serum

Processed foods

Absorption rate
90%

Potassium salts (often found in processed foods) absorption rate has been reported to be 90%

Sodium Bicarbonate for Hyperkalaemia

- Often used to assist in the intracellular shift of potassium.
- Evidence is limited and heterogeneous
  - 2 long-term studies (i.e. > 2 months), alkali therapy shown to be associated with a significant net decrease in serum K^+ by approximately 0.7 mmol/l
  - No significant change was shown in short term studies (≤ 7 days).1, 2
- Its use remains common in clinical practice.

- Guideline 6.1: We recommend that sodium bicarbonate is used in CKD patients with a serum bicarbonate level < 22 mmol/l with or without hyperkalaemia. (1B) (KDIGO indicates a level <18 mmol/L)

- NICE CKD Guideline (2021) suggests that oral sodium bicarbonate should be considered in patients with and eGFR < 30 ml/min (CKD G4 or G5) with a serum bicarbonate < 20 mmol/l

de Brito-Ashurst I et al. JASN, 2009. 20(9), 2075-84
Mathur RP et al.. Ren Fail, 2006. 28(1): 1-5
UKKA 2024 Hyperkalaemia Guidelines

Diuretics for Hyperkalaemia

- Diuretic therapy has a place in the management of chronic hyperkalaemia in patients who are **normovolaemic or hypervolaemic**.

- The ‘sick day rules’ apply, - diuretics should be withheld during acute illness.

- Guideline 7.1: **We suggest that loop diuretics may be a useful adjunct for the treatment of chronic hyperkalaemia in patients who are non-oliguric and volume replete. (2C)**

- Joint guideline from UKKA and British Society of Heart Failure (2019) recommends consideration of combination therapy with a loop and thiazide diuretic in patients with decompensated heart failure (HFrEF) and mild-moderate hyperkalaemia.

Watson KE et al. Kidney Med, 2022. 4(9): 100491.
Clark AL et al. Heart, 2019. 105(12): 904-910.

Use of Potassium Binders

NICE and SmPC criteria for the use of potassium binders (sodium zirconium or patiromer) in the treatment of chronic hyperkalaemia:

- CKD Stage 3b-5 or heart failure
- AND
- Serum K^+ confirmed to be ≥ 6.0 mmol/L
- AND
- Receiving a sub-optimal dose or not taking RAASi due to hyperkalaemia
- AND
- Not on dialysis

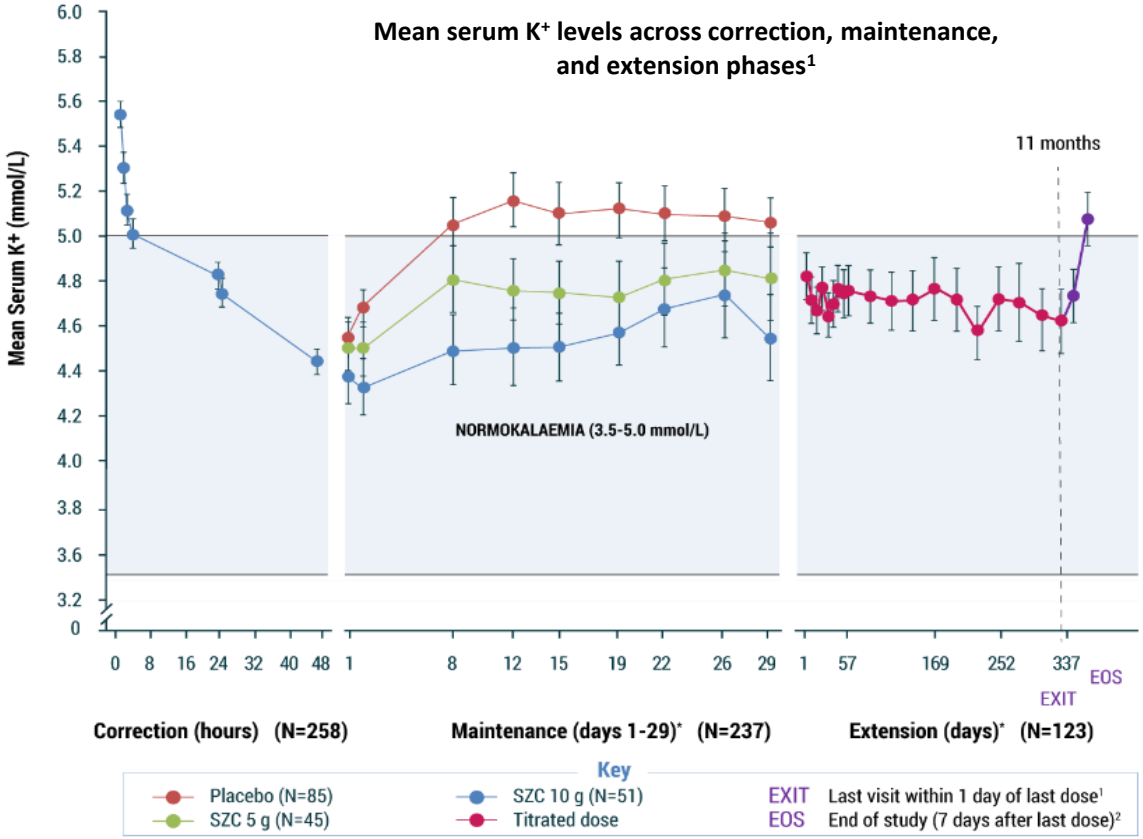
Binder should be initiated by a specialised /secondary care and can be continued in Primary care

- STOP Potassium Binders if RAAS inhibitors are no longer suitable or discontinued

NICE and UKKA guidelines for use of Potassium binders 2023

SZC: Sustained serum K^+ control for up to 1 year when used as maintenance therapy.

- **Once-daily maintenance dosing of SZC sustains normokalaemia (3.5-5.0 mmol/L) for up to one year.**[1,2]
- **88% of patients in the Extension Phase receiving SZC maintained an average serum K^+ of <5.1 mmol/L over 11 months.**[1,2]
- **No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations.**[1,2]

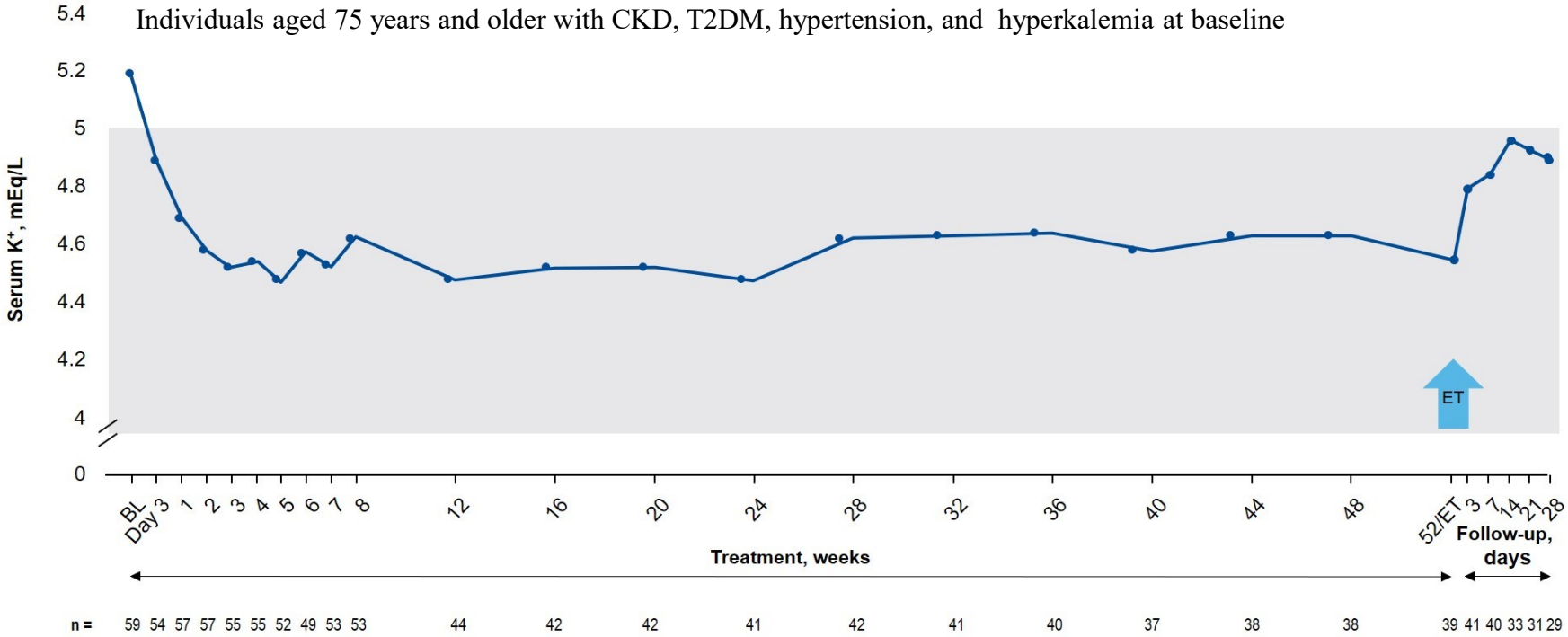


*Please note that the recommended starting dose for maintenance therapy with SZC is 5g once daily, which may be titrated to 10g once daily as needed. No more that 10g once daily should be used for maintenance therapy. The 5g once daily dose can be down titrated to 5g every other day.[1] The extended maintenance group contained a small proportion (11%) of patients who were treated with SZC 15g once daily.[3] The 15g dose is not approved for use in non-haemodialysis patients

1. AstraZeneca. Lokelma (Sodium Zirconium Cyclosilicate [SZC]). Summary of product characteristics. Available from: www.medicines.org.uk/emc Accessed: June 2020. **2**. Kosiborod M, et al. Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia. The HARMONIZE Randomized Clinical Trial. *JAMA* 2014;312:2223–2233; **3**. Data on File, AstraZeneca. HK/003/FEB2019

Adapted from: LOKELMA SmPC[1] and Kosiborod M, et al. (2014)[2]

AMETHYST-DN Main results on Potassium at each Time point after introction of Patiramor



Bakris G et al Am Med Assoc 2015;314:151-161

Patients	On RAASi[b] target dose[c]	Recommendation
Chronic or recurrent hyperkalaemia on RAASi therapy		• An approved K^+- binder may be initiated as soon as K^+ levels are confirmed as >5.0 mmol/L • Closely monitor K^+ levels. • Maintain treatment unless alternative treatable aetiology is identified
Chronic or recurrent hyperkalaemia	No	• RAASi should be optimised and an approved K^+ binders may be initiated as soon as confirmed K^+ levels are >5.0 mmol/L • Closely monitor K^+ level • Maintain treatment unless alternative treatable aetiology is identified
K^+ levels of 4.5 – 5.0 mEq/L	No	• Initiate/up-titrate RAASi therapy and closely monitor K^+ levels • If K^+ levels rise >5.0 mmol/L, initiate an approved K^+ binders
K^+ levels of >5.0 – ≤6.5 mEq/L	No	• Initiate an approved K binder • If K^+ levels <5.0 mol/L are detected, up-titrate RAASi and closely monitor K^+ levels • Maintain K^+ binder unless an alternative treatable aetiology for hyperkalaemia is identified
	Yes	• May initiate treatment with a K^+ binder • Closely monitor K^+ levels • Maintain K^+ binder unless an alternative treatable aetiology for hyperkalaemia is identified
K^+ levels of >6.5 mEq/L	Yes or No	• Discontinue/reduce RAASi therapy • May initiate treatment with a K^+ binder as soon as K^+ levels >5.0 mmol/L • Closely monitor K^+ levels

HYPERKALAEMIA IN CKD

Practice Point 3.11.5.1: Implement an individualized approach in people with CKD G3–G5 and emergent hyperkalaemia that includes dietary and pharmacologic interventions and takes into consideration associated comorbidities and quality of life (QoL). Assessment and education through a renal dietitian or an accredited nutrition provider are advised.

1st line: **Address correctable factors**	• Review non-RASi medications (e.g. NSAIDs, trimethoprim) • Assess dietary potassium intake (dietary referral) and consider appropriate moderation of dietary potassium intake
2nd line: **Medications**	Consider: • Appropriate use of diuretics • Optimize serum bicarbonate levels • Licensed potassium exchange agents
3rd line: **Last resort**	• Reduce dose or discontinue RASi/MRA (Discontinuation is associated with increased cardiovascular events. Review and restart RASi or MRA at a later date if patient condition allows.)