New ERA of Antihyperkalemic Treatment

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ESC European Society of Cardiology

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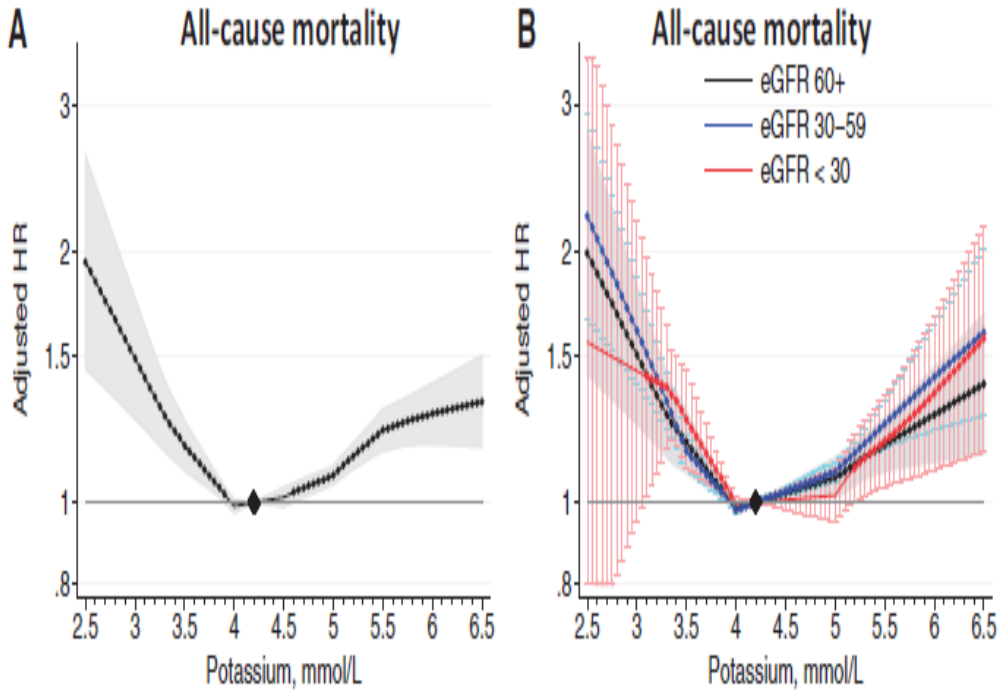
CLINICAL RESEARCH

Prevention and epidemiology

Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis



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Meta analysis

- Mortality Hazard ratio increased by 1.22 if K was >5.5 mmol/L
- Lowest mortality occurred when K was 4-4.5 mmol/L
- K below 4 was associated with increased cardiac events and mortality

HK is diagnosed based on serum K^+

K^+ level (mEq/L)	Diagnosis of HK[1,2]
>7.0	Severe HK
6.0–7.0	Moderate HK
5.0–<6.0	Mild HK

HK, hyperkalemia

1. American Heart Association. *Circulation* 2005;112(Suppl.):121–125; 2. Einhorn LM, et al. *Arch Int Med* 2009;169:1156–1162.

Abnormal serum K+ levels can cause ECG abnormalities, which may lead to cardiac arrest and death

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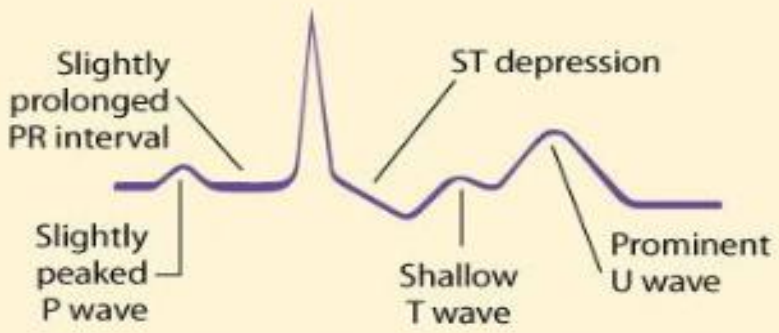
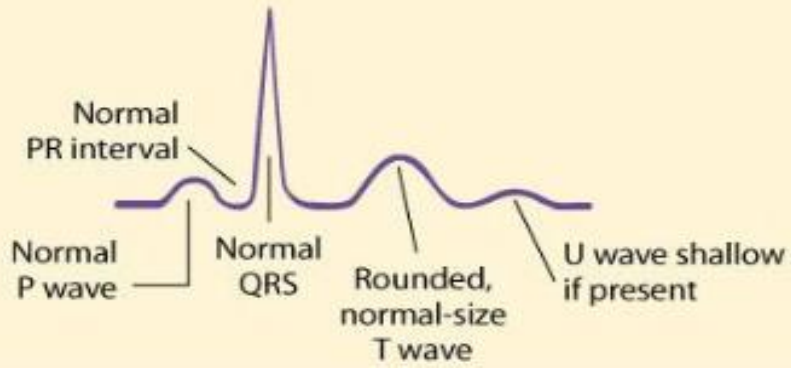
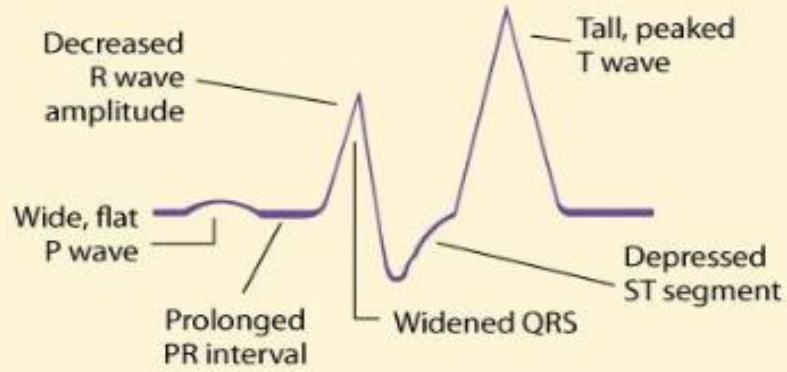
Hypokalaemia



Normal ECG with normal K⁺



Hyperkalaemia



ECG, electrocardiography; K⁺, potassium ion
Image reprinted from Mosby's Medical Dictionary, Elsevier, 2008.

Poor Sensitivity and Specificity of ECG as Diagnostic Test for Hyperkalemia

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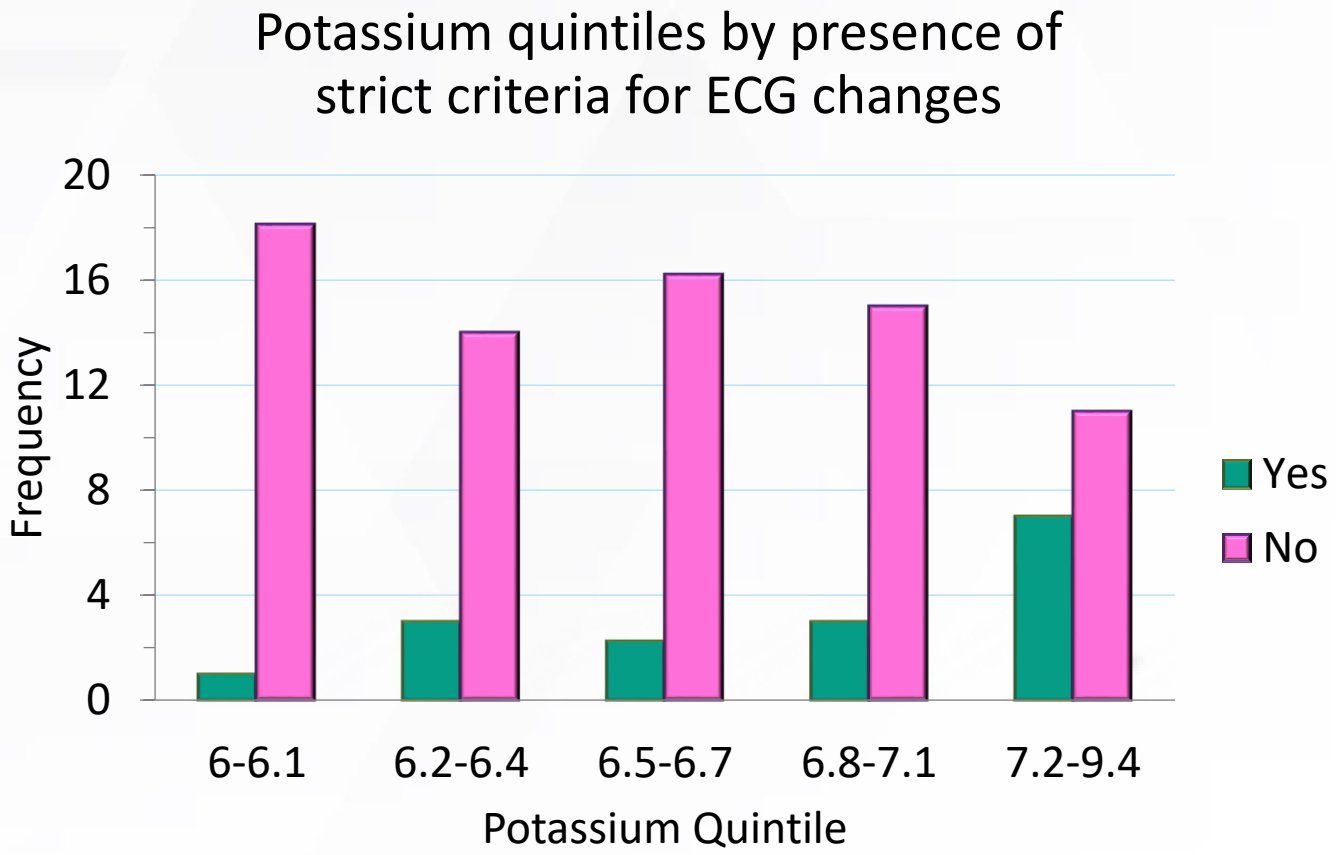
- In 127 patients with serum K^+ between 6-9.3 mEq/L, only 46% of ECGs noted to have changes[1]



1. Acker CG, et al. *Arch Intern Med.* 1998;158:917-924.
2. Montague BT, et al. *Clin J Am Soc Nephrol.* 2008;3:324-330.

Suddenly arrested

Transferred to Emergency Room !!

Cardiac Arrest: Brady- Asystole Patterns

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Mr. GAMAL

62 year old

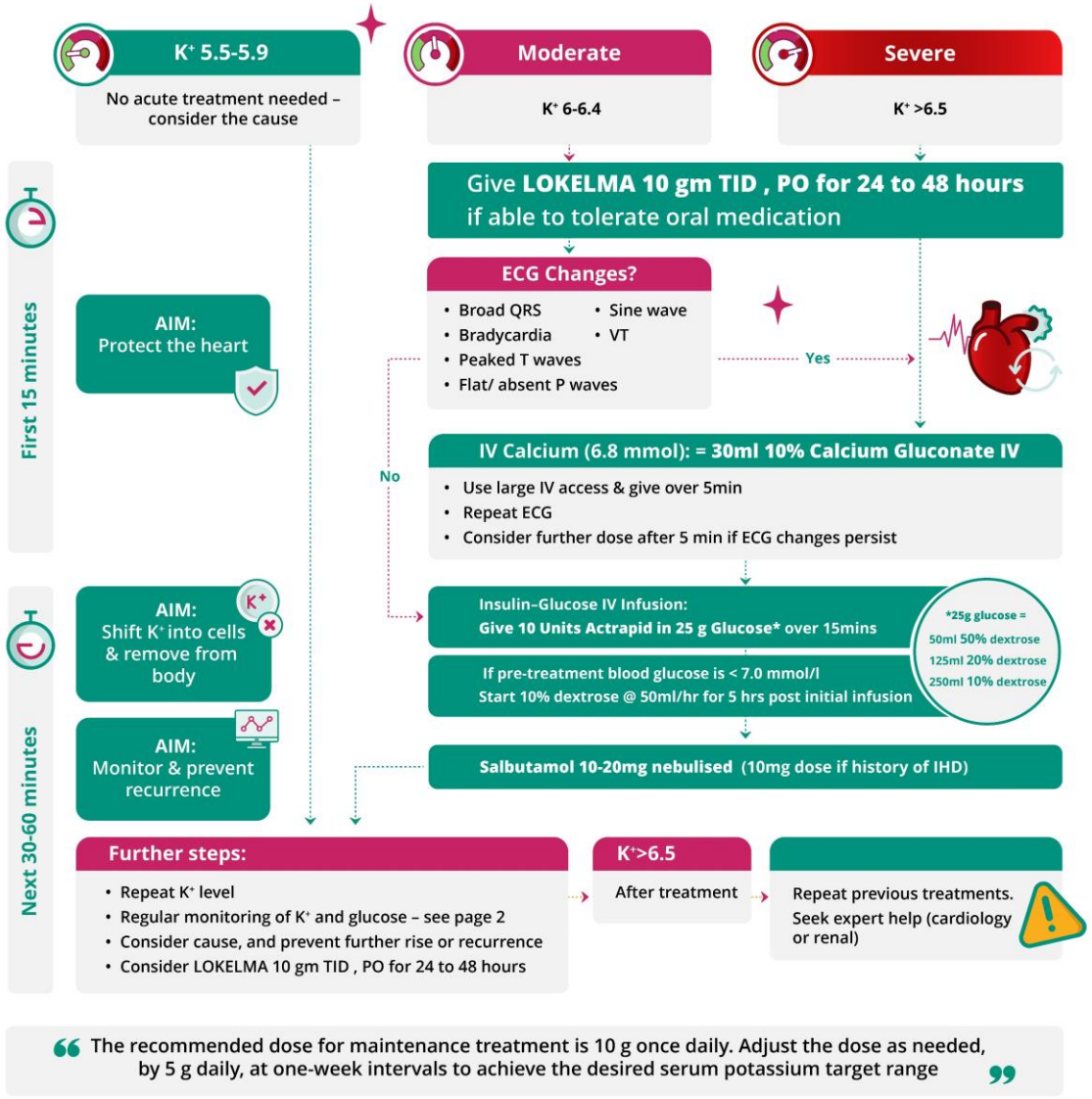
- Chronic kidney disease (Stage 4)
- Hypertension
- Recurring hyperkalemia

*From clinical case records

Voiceover:

Acute management of hyperkalemia

- Assess patient using ABCDE approach.
- 12-lead ECG and monitor cardiac rhythm if serum $K^+ \geq 6.0$ mmol/l.
- Exclude pseudo-hyperkalemia (check VBG K^+ if hemolysis suspected or send Lithium heparin tube sample).
- In cardiac arrest or life-threatening arrhythmias with suspected hyperkalemia follow ALS algorithms and treat as severe hyperkalemia with urgent IV calcium.



"The recommended dose for maintenance treatment is 10 g once daily. Adjust the dose as needed, by 5 g daily, at one-week intervals to achieve the desired serum potassium target range"

1.This Material is adapted and redesigned from Gloucestershire Hospitals NHS Foundation Trust,available at: https://www.gloshospitals.nhs.uk/media/documents/Inpatient_Hyperkalemia_Management_March_2023_W4sAT5O.pdf
2.LOKELMA® (sodium zirconium cyclosilicate) [package insert] AstraZeneca.2018

Behind the Scene: Last Follow up visits

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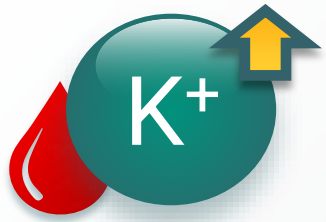
Blood pressure
Systolic >160 mm Hg

- Maximum dose: Amlodipine and Carvedilol
- Increased Losartan dose



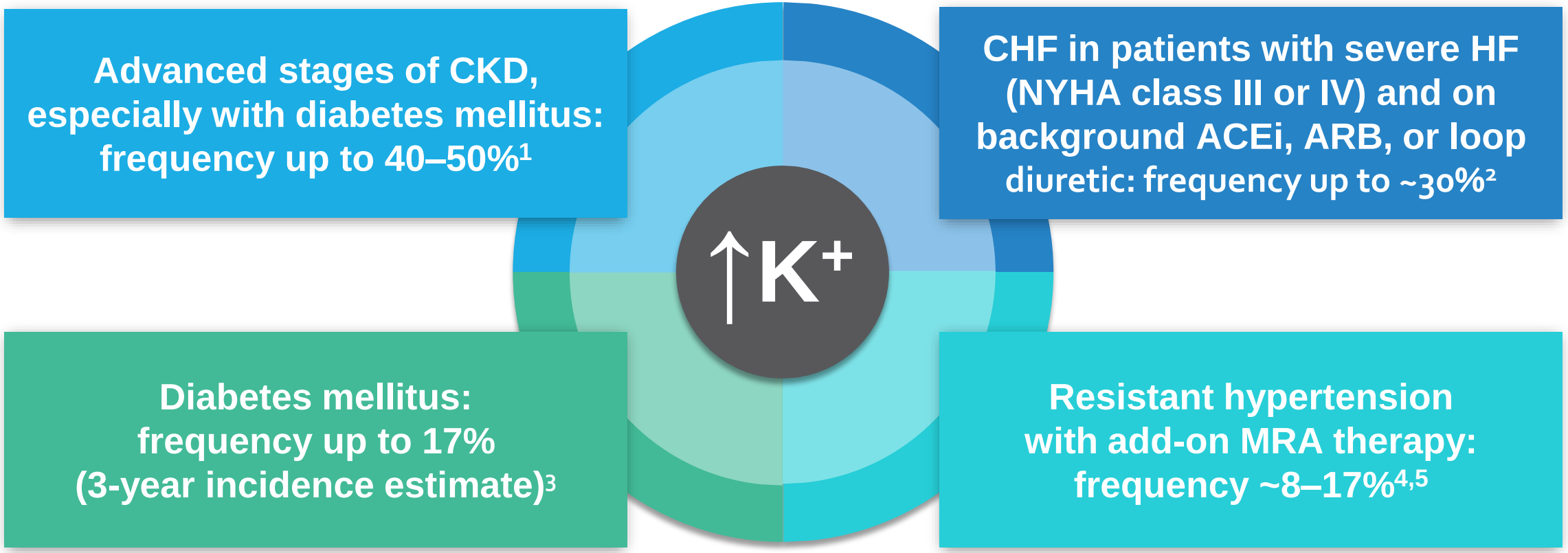
Serum potassium is >5 mEq/L

Is there a scope for dietary modifications?

Voiceover:

There is a high incidence of HK in certain patient subgroups

The incidence of HK in the general population is 2–3%[1]



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Causes of hyperkalemia in acutely ill patients

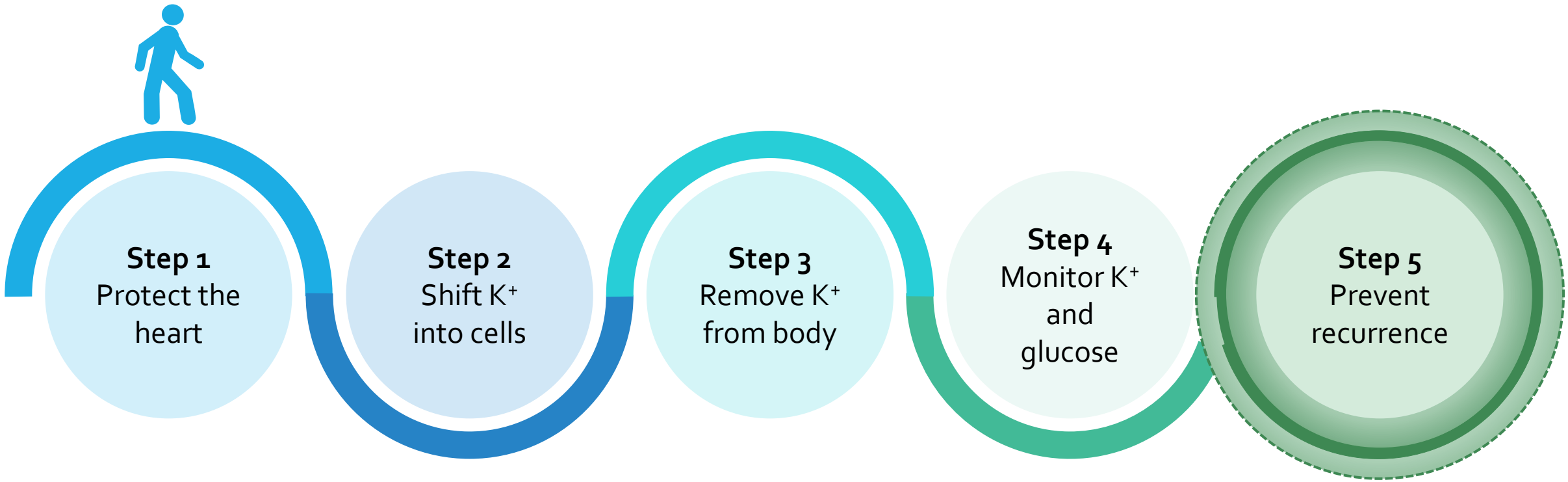
- Altered renal clearance
  - chronic kidney disease
  - acute kidney injury
  - Renin angiotensin aldosterone system inhibitors
- Release from intracellular space
  - Hemolysis
  - Rhabdomyolysis
  - Tissue injury
- Altered transfer to the intracellular space
  - Acidosis
  - insulin deficiency
  - beta blockers
  - heparin

Options

- Glucose insulin
  - **10 units of soluble insulin with 25g of glucose**.
- Nebulized Beta Agonist
- Calcium
- Furosemide
- RRT
- K exchange Resin

Treating HK: A systematic approach is recommended to enhance patient outcomes

- Guidelines from the UK Renal Association recommend a logical approach to managing HK, taking into account clinical priorities to reduce variability, enhance patient outcome, and reduce adverse events related to HK and its treatment



HK, hyperkalemia

UK Renal Association. Clinical Practice Guidelines: Treatment of Acute Hyperkalaemia in Adults 2014. Available at: https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf (Accessed February 2019)

Hyperkalaemia can be a chronic condition and an ongoing threat[13-15]

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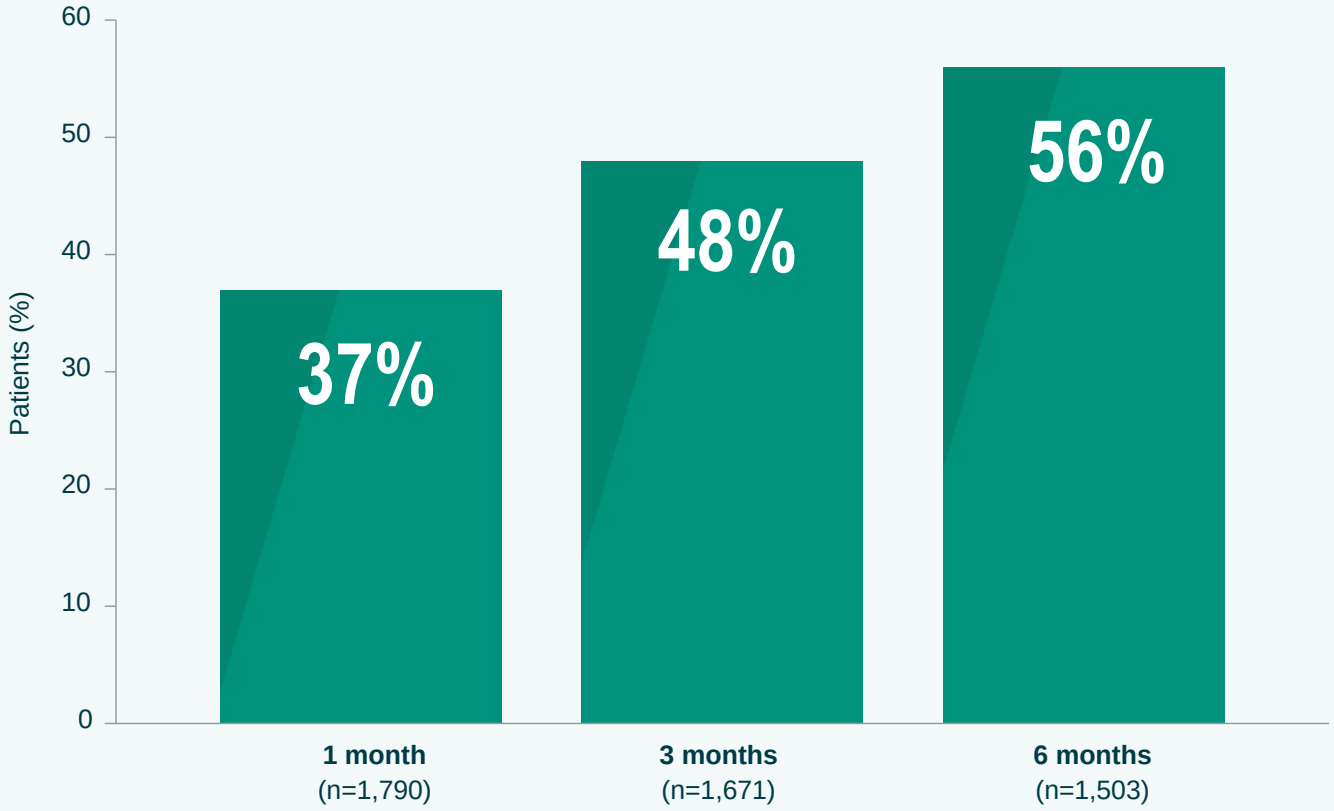
Over half of patients with CKD experienced hyperkalaemia recurrence within 6 months*[15]

Recurrent hyperkalaemia† in patients with CKD stage 3–4[15]



*REVOLUTIONIZE study design: A retrospective, observational study of US electronic health records that evaluated the recurrence of hyperkalaemia following a medical nutritional therapy visit (index date), within 30 days of lab confirmed HK diagnosis in adults with stage 3 or 4 CKD between January 2019 and October 2022. Patients were followed up for 6 months post-MNT.[15]
†Recurrent hyperkalaemia was defined as serum K^+ >5.0 mmol/L that was at least 7 days apart from a prior lab evidence of hyperkalaemia.[15]
CKD, chronic kidney disease; HK, hyperkalaemia; MNT, medical nutritional therapy.

Hyperkalaemia should no longer be a barrier to optimising RAASi therapy[5,6]

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For management of ACEi/ARB-associated hyperkalaemia,

KDIGO guideline* supports use of K^+ binder over ACEi/ARB decrease or discontinuation[5,6]

2022 KDIGO guideline update†

K^+ binders may be considered to decrease serum K^+ levels after other measures have failed, rather than decreasing or discontinuing ACEi or ARB treatment[6]

*KDIGO guideline relating to the management of blood pressure and to the management of diabetes in patients with chronic kidney disease.[5,6]
†2022 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.[6]
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; KDIGO, Kidney Disease Improving Global Outcomes; RASi, Renin–angiotensin system inhibitor.

LOKELMA crystal structure

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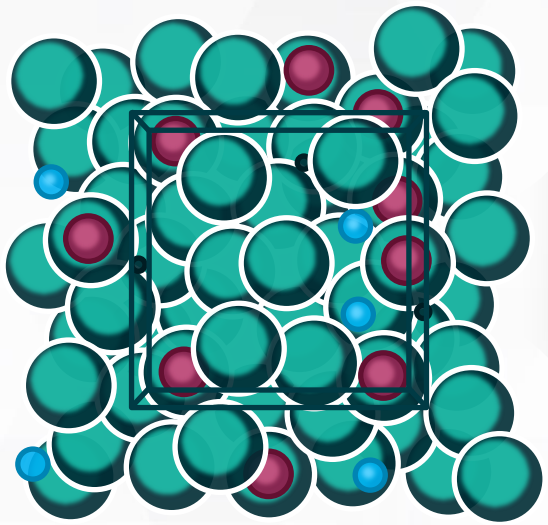
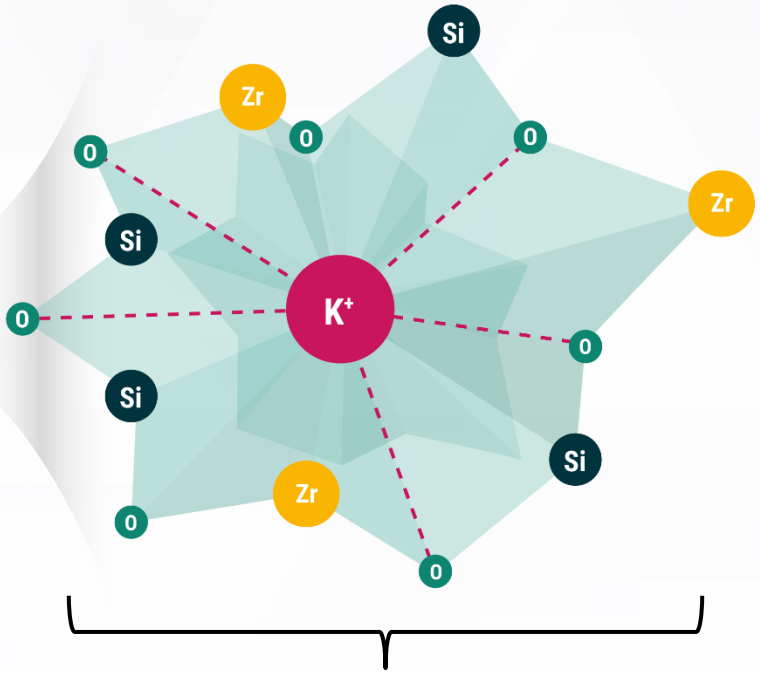
LOKELMA is indicated for the treatment of HK in adults[1]



Chemical formula:
$H_6Na_2O_9Si_3Zr^{+2}$



Average binding-site width: 3 Å

Key molecular characteristics:[1,3]

- Inorganic crystalline zirconium silicate compound
- Not a polymer
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- High affinity for K^+ [a]
- Exchanges Na^+ and H^+ for K^+

[a]In vitro activity does not always equate to clinical efficacy; images are illustrative only
HK, hyperkalemia

1. AstraZeneca AB. LOKELMA▼ EU Summary of Product Characteristics 2019; 2. US National Institutes of Health National Center for Biotechnology Information PubChem Open Chemistry Database. Compound summary: sodium zirconium cyclosilicate (CID 91799284). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/91799284#section=Top (Accessed February 2019); 3. Stavros F, et al. *PLoS One* 2014;9:e114686

LOKELMA and SPS: Selectivity for K^+

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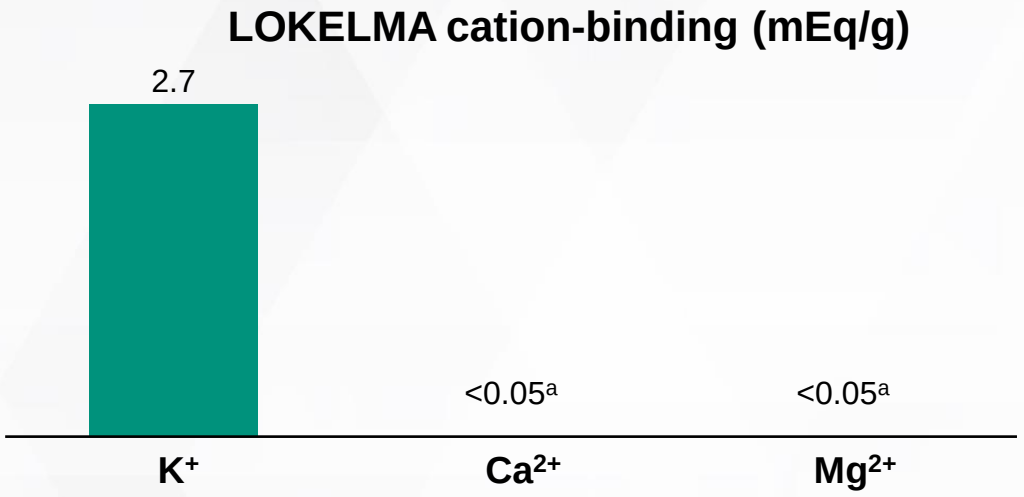
- In vitro studies were designed to examine the ion exchange capacities of LOKELMA and SPS
- K^+, Ca^{2+}, and Mg^{2+} concentration ratio of 1:1:1



- LOKELMA displayed **9.3**× more K^+-binding capacity than SPS
- LOKELMA was >**125**× more selective for K^+ than SPS
- SPS was more selective for Mg^{2+} and Ca^{2+} than for K^+
- LOKELMA and SPS have not been studied in head-to-head clinical trials and *in vitro* effects do not necessarily equate to efficacy, therefore no superiority of efficacy or other clinical benefit should be implied.

[a]Exchange capacity for Ca^{2+} and Mg^{2+} was <LOD (<0.05)
LOD, limit of detection; SPS, sodium polystyrene sulfonate
Adapted from: Stavros F, et al. *PLoS One* 2014;9:e114686

LOKELMA binds K^+ throughout the GI tract[a]

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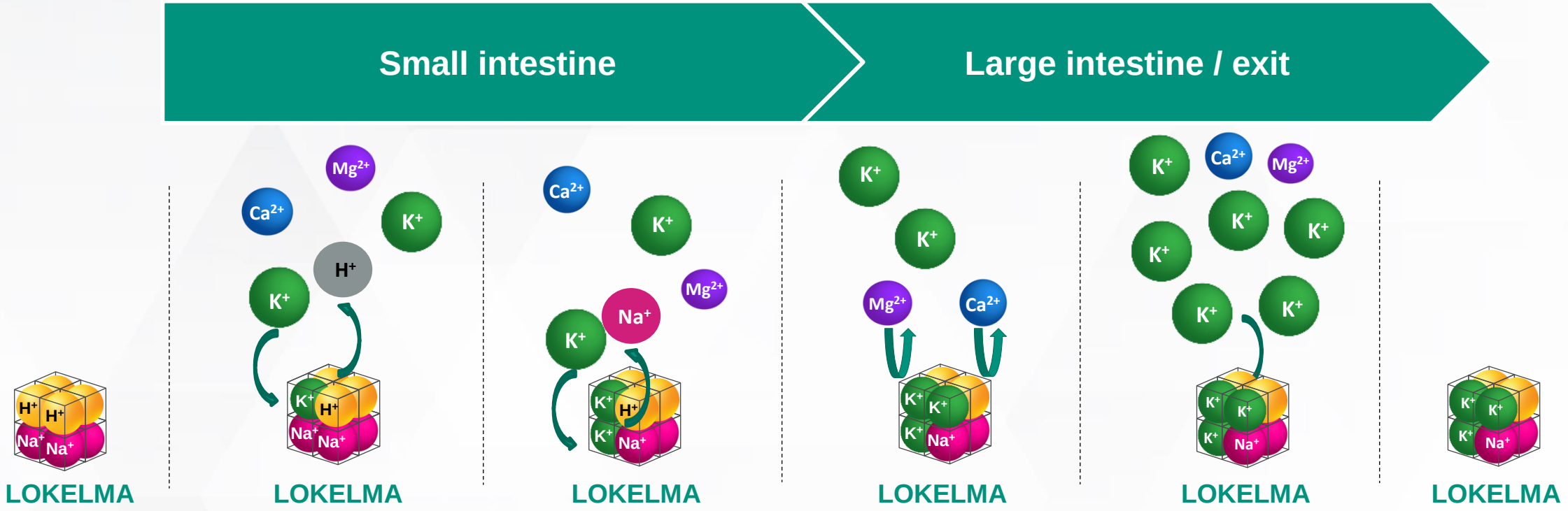

- Based on in vitro data, LOKELMA may begin working immediately in the small intestine to preferentially capture K^+
- K^+ is exchanged for sodium and hydrogen

[a]For illustrative purposes only
GI, gastrointestinal
Stavros F, et al. *PLoS One* 2014;9:e114686

Choose LOKELMA for rapid serum K^+ reduction as early as 1 hour*

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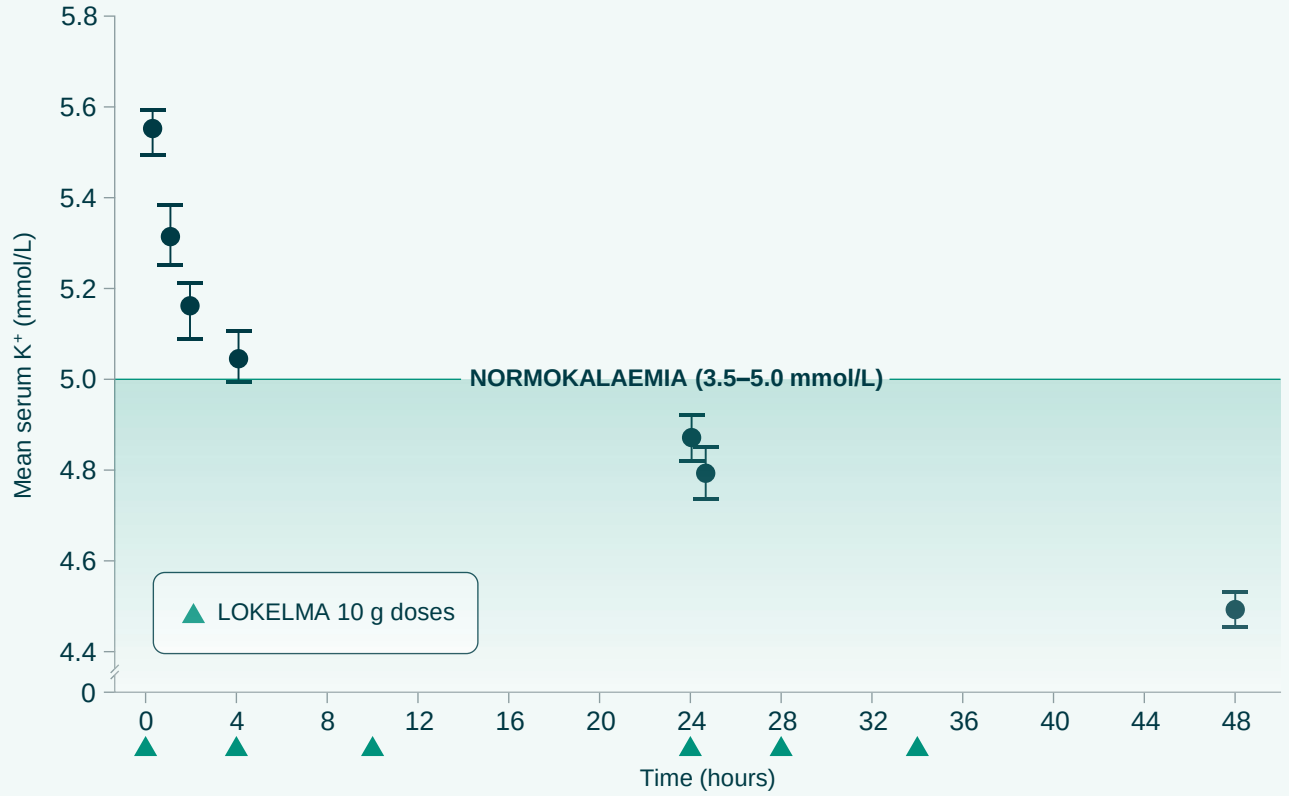
One dose of LOKELMA significantly reduced serum K^+ levels at 1 hour vs baseline ($P<0.001$)*[1]

Median time to normokalaemia was 2.2 hours (interquartile range, 1.0 to 22.3 hours)[4]

Mean serum K^+ levels with LOKELMA 10 g three times daily for 48 hours (n=258)[4]



98% of patients
achieved normokalaemia at 48 hours*[1]

After first dose of LOKELMA 10 g, the mean change in serum K^+ was –0.2 mmol/L at 1 hour (95% confidence interval; –0.3 to –0.2; $P<0.001$ vs baseline).[4]
*HARMONIZE (ZS004), a Phase III, multicentre, multiphase, placebo-controlled study in 258 patients with hyperkalaemia. Open-label phase: LOKELMA 10 g three times daily, administered for 48 hours, at which time patients (n=237) with normokalaemia (3.5–5.0 mmol/L) were randomised to LOKELMA or placebo once daily, 5 g, 10 g, or 15 g, for 28 days. Primary endpoint: mean serum K^+ level with LOKELMA vs placebo on Days 8–29. Eligible patients then continued treatment with LOKELMA 10 g, once daily, which could be titrated to 5 g or 15 g, in an 11-month, open-label extension study (ZS004E).[1,4,16]
Please note that LOKELMA 15 g is not approved for use in patients not on haemodialysis.

Stay with LOKELMA for sustained K^+ control for up to 1 year

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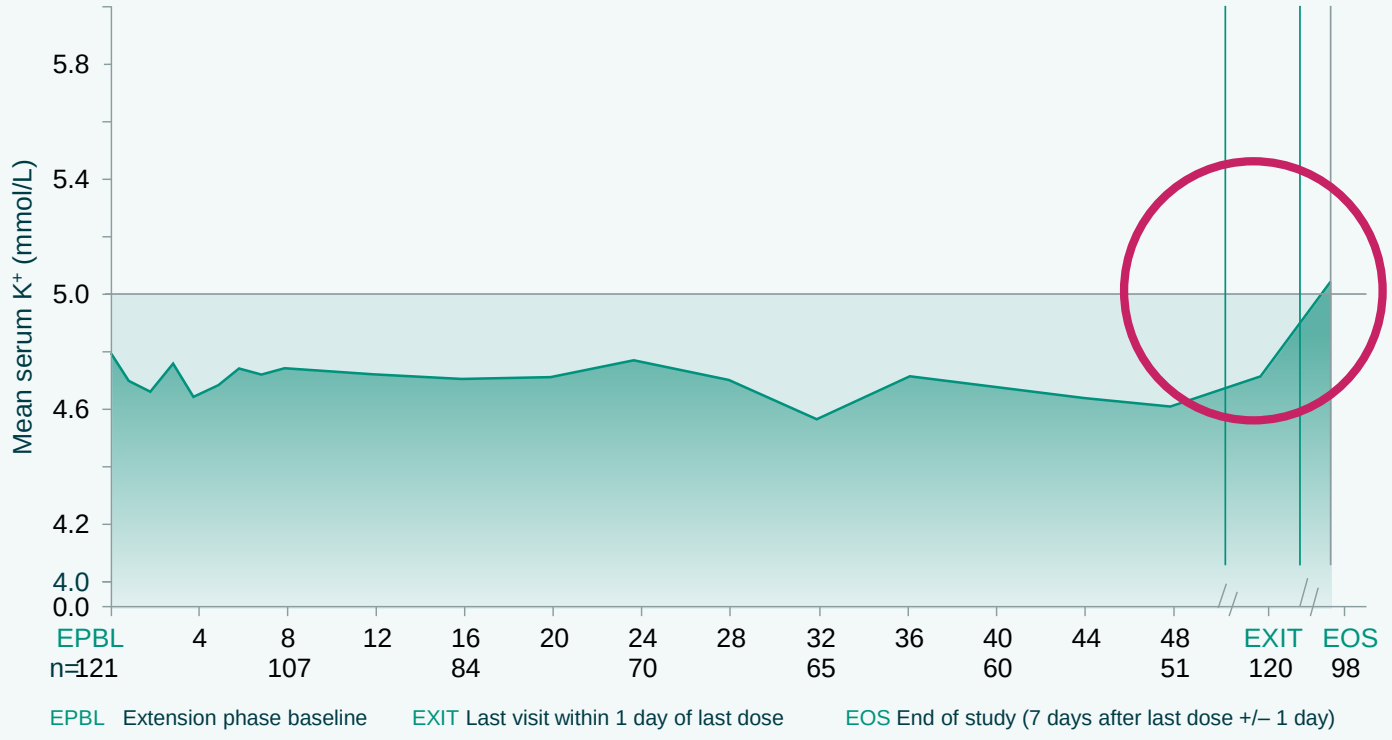
LOKELMA sustained normokalaemia with continued treatment up to one year[1]

Mean serum K^+ levels in patients who completed a 28-day randomised maintenance phase and continued on LOKELMA for 11 months[1]



Discontinuing LOKELMA resulted in increased K^+ levels[8]

Please note that LOKELMA 15 g is not approved for use in patients not on haemodialysis.

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For your CKD patients with hyperkalaemia

CHOOSE LOKELMA: Rapid K^+ reduction and sustained K^+ control* so you can focus on chronic kidney disease treatment goals

- **Rapid K^+ reduction** as early as 1 hour†[1,4]
- **Sustained K^+ control** over 1 year*[1]
- **Generally well tolerated** in clinical trials[1]

#1
branded K^+ binder globally‡[10]

KDIGO guideline¶[5,6]

For management of ACEi/ARB-associated hyperkalaemia, **KDIGO guideline supports use of a K^+ binder** over ACEi/ARB decrease or discontinuation[5,6]

Disclaimer: Individual is a model and not a real patient.
*Based on the maintenance phase of an 11-month, open-label study, following a 1-month placebo-controlled study (N=123).[1,4]
†Median time to K^+ normalisation was 2.2 hours (Interquartile range 1.0 to 22.3).[1,4]
‡As of March 2023.[10]
¶KDIGO guideline relating to the management of blood pressure and to the management of diabetes in patients with chronic kidney disease.[5,6]
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes.

What's next?

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01 Down-titrate Losartan

02 Continue RAASi optimization

Voiceover: Given this situation, a dilemma presents itself. Will we have to down-titrate Valsartan due to the increased serum potassium for this patient? Or, is it possible to continue RAAS inhibitor optimization in view of its cardiorenal benefits?

RAASi: Renin-angiotensin-aldosterone system inhibitors.

RAASi Down-titration or Discontinuation was Associated With Doubling of Mortality Across Patient Subtypes

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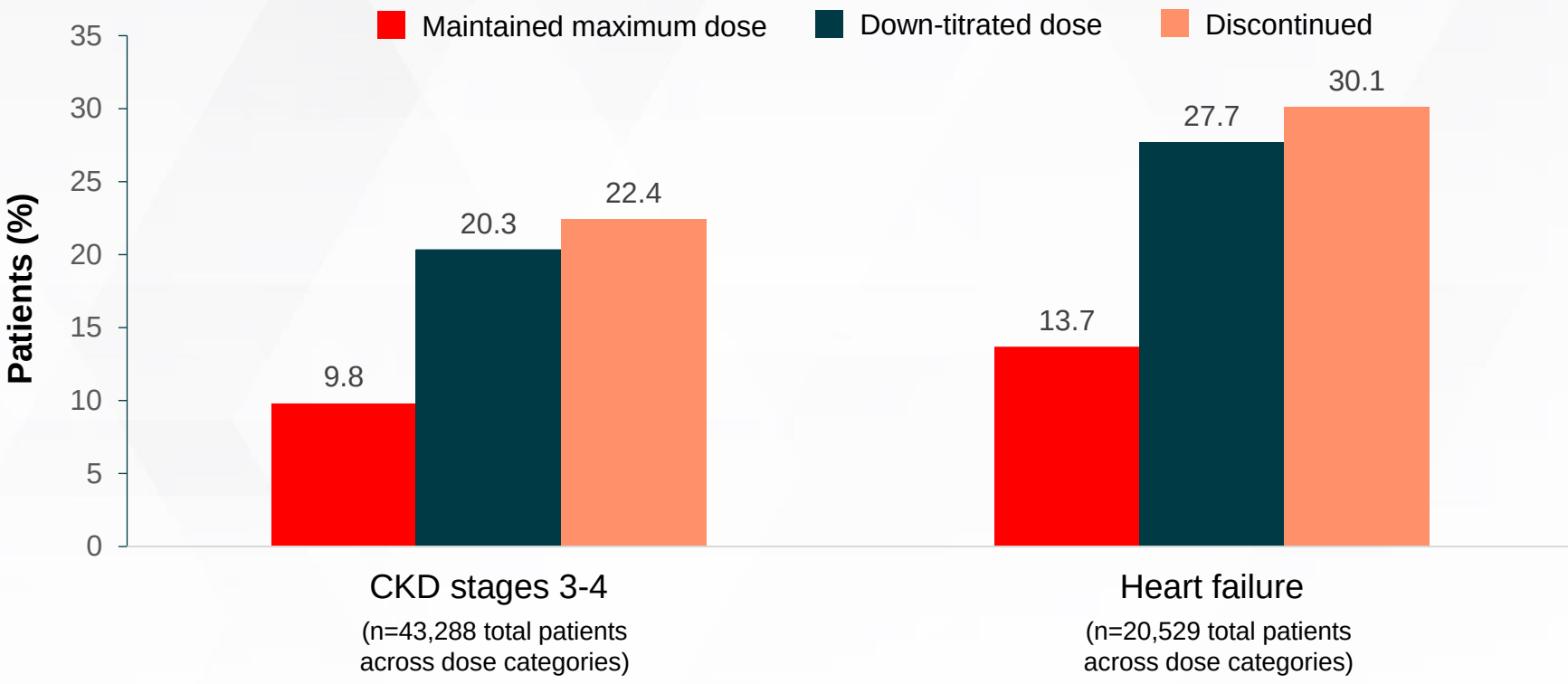
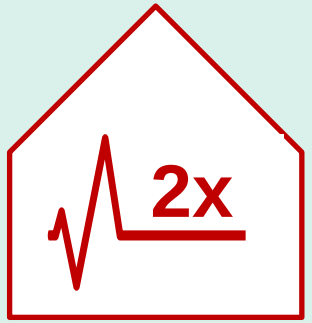
Mortality Rate in Patients Based on Last RAASi Dose[a]





Mortality rates doubled in cardiorenal patients whose RAASi was **down-titrated or discontinued**, compared to patients who maintained their maximum dose[b]

Note:A retrospective analysis of a US database of electronic health records (Humedica; N>200,000) of patients ≥5 years of age with various comorbidities and with at least 1 outpatient RAASi prescription and at least 2 serum K^+ readings from 2007-2012. RAASi included ACEi, ARB, direct renin inhibitor, and select MRA.
[a]RAASi dose level was defined as: maximum = labeled dose; down-titration = submaximum dose of any RAASi lower than the labeled dose; discontinued = absence of RAASi prescriptions for a period of more than 390 days subsequent to prior prescription. Patients RAASi dose were grouped based on their last dose prior to mortality event; [b]The cause of RAASi dose change was not specified.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; MRA = mineralocorticoid receptor antagonist;
RAASi = renin-angiotensin-aldosterone system inhibitor; US = United States.
Epstein M et al. *Am J Manag Care.* 2015;21(suppl 11):S212–S220.

Back To Our Patient

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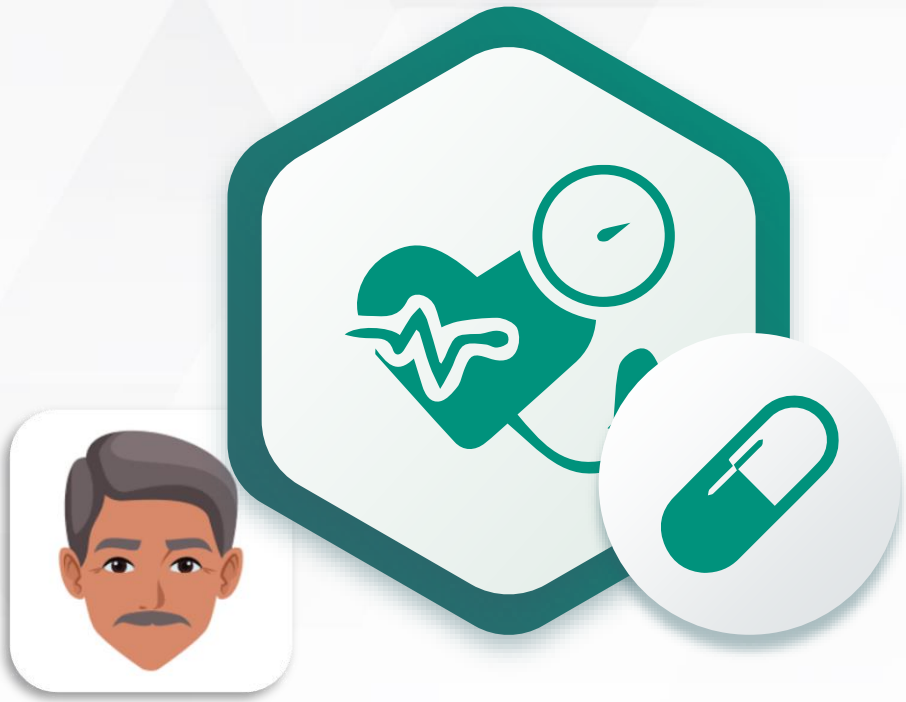

Prescribed LOKELMA 5g for maintenance

Diet is liberalized

Increased dose of Losartan is maintained

Voiceover: Coming back to the individual patient with persistent hypertension despite being on maximum dose of amlodipine and carvedilol, and hyperkalemia due to increase in valsartan. LOKELMA 5 g was initiated on non-dialysis days and diet was liberalized while maintaining the increased dose of valsartan.

Back To Our Patient

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BP <140 mm Hg

Continue heart healthy diet

Repeat
K^+ is < 5 mEq/L

Voiceover: With this approach, his systolic blood pressure is now consistently <140 mm Hg. The patient is able to enjoy a heart healthy diet. And repeat serum potassium levels have consistently been under 5.5 mEq/L.

BP: Blood pressure

Clinical implications for LOKELMA

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In long-term management of HK in chronic settings

Is Effective[1]

Is Generally Well-tolerated[1]

Allows RAASi optimisation[2]

Voice over: From our clinical and RWE audit, we suggest that the potassium-binder LOKELMA is effective and generally well-tolerated in chronic hemodialysis patients and allows for RAASi optimization.. Thank you for listening.

RWE: Real word evidence

1. Qu X, et al. Cureus. 2023;15(9):e45058. 2. Silva-Cardoso J, et al. Heart Fail Rev. 2021; 26(4): 891–896.

ALL in ALL

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- Hyperkalemia is common in the hospitalized and especially in the ICU patient.
- Several diseases including the heart the kidneys or both can lead to hyperkalemia.
- Diabetes end management of chronic disease also leads to hyperkalemia.
- Hyperkalemia is fatal and requires prompt management.
- Several steps can be made to treat acute hyperkalemia.
- The addition oh the new sodium zirconium cyclosilicate potassium exchange reason which works in one hour is an extremely beneficial to treat this fatal condition.

THANK YOU