XI congresso nazionale

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ROMA 24-26 MAGGIO 2018

Una nuova era per il trattamento dell'iperkaliemia?

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Overview

- Why is Hyperkalemia Relevant?
- Hyperkalaemia incidence and risk factors in patients with CKD and/or HF
- The clinical burden and resource utilisation
- Limitations of current treatment strategies
- Challenges in managing complex patients with hyperkalaemia

1. Why is Hyperkalemia Relevant?

Why is Hyperkalemia Relevant?

1. **Hyperkalemia, which is a serum K^+ level of >5.0 mEq/L, is potentially life-threatening**
2. **Elevated plasma K^+ decreases the ratio of intracellular to extracellular K^+, causing partial depolarization of the cell membrane that leads to:**
   - Muscle weakness / paralysis
   - Life-threatening effects on cardiac conduction
   - Arrhythmias
   - Sudden death
3. **Hyperkalemia is one of the greatest risk factors associated with all-cause mortality in patients with pre-existing CVD, patients with advanced CKD, patients without CKD, and patients undergoing dialysis**
4. **Hyperkalemia is an unfortunate adverse effect of a variety of commonly-used treatments in HF, CVD, and renal disease, including RAAS inhibitors**
5. **Hyperkalemia is associated with a huge economic cost burden, including increased emergency department visits and hospitalization**

Dunn JD, et al. *Am J Manag Care* 2015;21:S307–S315

Hyperkalemia is Diagnosed Based on Serum Potassium

Potassium level (mEq/L)	Diagnosis of hyperkalemia[1,2]
≥6.0	Severe hyperkalemia
5.5–<6.0	Moderate hyperkalemia
5.0–<5.5	Mild hyperkalemia
3.5 –<5.0	Normokalaemia

Clinical presentation[1]

- Often asymptomatic
- If present, symptoms may include heart palpitations, muscle weakness, muscle pain, paraesthesia, nausea, diarrhea, and vomiting
- Cardiac conduction abnormalities ranging from ECG changes to life-threatening arrhythmias may occur
- Severe hyperkalemia can be life-threatening

ECG=electrocardiogram

1. Rastergar A, Soleimani M. *Postgrad Med J* 2001;77:759–764; 2. Einhorn LM, et al. *Arch Int Med* 2009;169:1156–1162

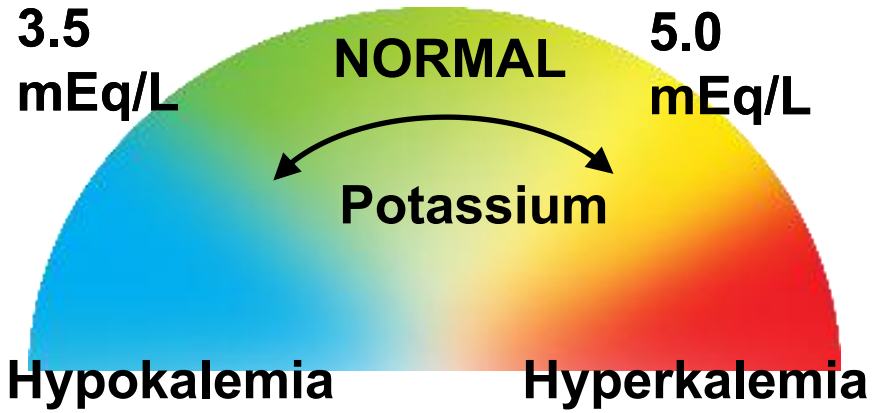
Hyperkalemia Can Be Acute or Chronic

ACUTE HYPERKALEMIA	RECURRENT (PERIODIC OR PERSISTENT) HYPERKALEMIA
Frequency Singular event[1]	**Frequency** >1 event per year[1]
Ongoing management No[1]	**Ongoing management** Yes[1]
Pathology • Abnormal net release of K^+ from cells due to trauma, metabolic acidosis, hemolytic states[1]	**Pathology** • Impaired K^+ excretion[1]
Treatment goals • To induce potassium flux into the intracellular space and remov K^+ from the body to prevent cardiac arrhythmias[1]	**Treatment goals** • To prevent development or recurrence of hyperkalemia by correcting the underlying disturbance in potassium homeostasis[1]
Treatment strategies[2] • Calcium gluconate can be used as first-line treatment in patient with EKG abnormalities or severe hyperkalemia to protect the cardiomyocytes • Insulin and β-agonists should be administered to shift potassiur into cells • Kayexelate and hemodialysis can be used to eliminate K^+ from the body	**Treatment strategies** • Eliminate precipitating factors, such as high K^+ intake or hyperkalemia-causing drugs if possible[1] • Prescribe a low potassium diet and avoid potassium-containing salt substitutes[1] • Prescribe thiazide (or loop diuretics if GFR <30mL/min and there is no evidence of volume depletion) [1] • Administer sodium bicarbonate to reduce acidosis[1]

EKG=electrocardiogram; GFR=glomerular filtration rate

1. National Kidney Foundation. Clinical Update on Hyperkalemia 2014; 2. Mushiyakh Y, et al. *J Community Hosp Intern Med Perspect* 2012;1:1–7

There are Many Causes of Hyperkalemia



Diet

- Increased dietary intake of potassium
- Salt substitutes

Diseases

- Chronic kidney disease
- Heart failure
- Diabetes

Drugs

- RAAS inhibitors
- NSAIDs
- β blockers
- Immuno-suppressants
- K^+-sparing diuretics
- Antibiotics
- Heparin
- Antifungals

NSAID=nonsteroidal anti-inflammatory drug; RAAS=renin–angiotensin–aldosterone system

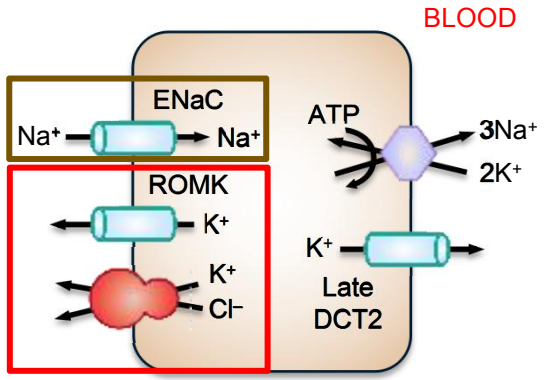
Hollander-Rodriguez J, Calvert JF Jr. *Am Fam Physician* 2006;73:283–290

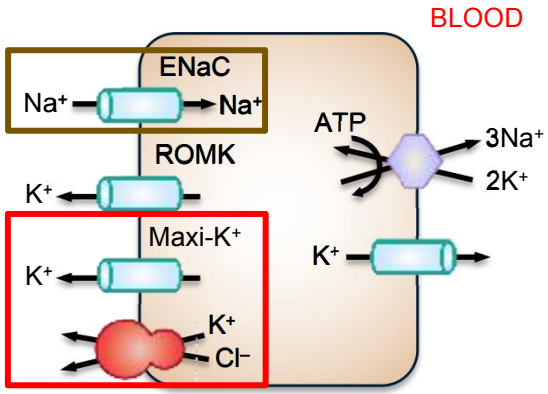
Decreased Tubular Flow and Renal Failure Decrease K^+ Excretion

- Damage to the distal tubules and collecting ducts reduces renal flow, which impairs sodium delivery to the distal regions of the nephron and reduces K^+ excretion
- Reduced tubular mass in CKD also reduces tolerance to acute K^+ challenges[1]

Decreased sodium delivery to the distal tubule reduces sodium influx to principal cells, which reduces the lumen-negative membrane potential that drives K^+ efflux

Damage to the distal tubules and collecting ducts diminishes potassium excretion





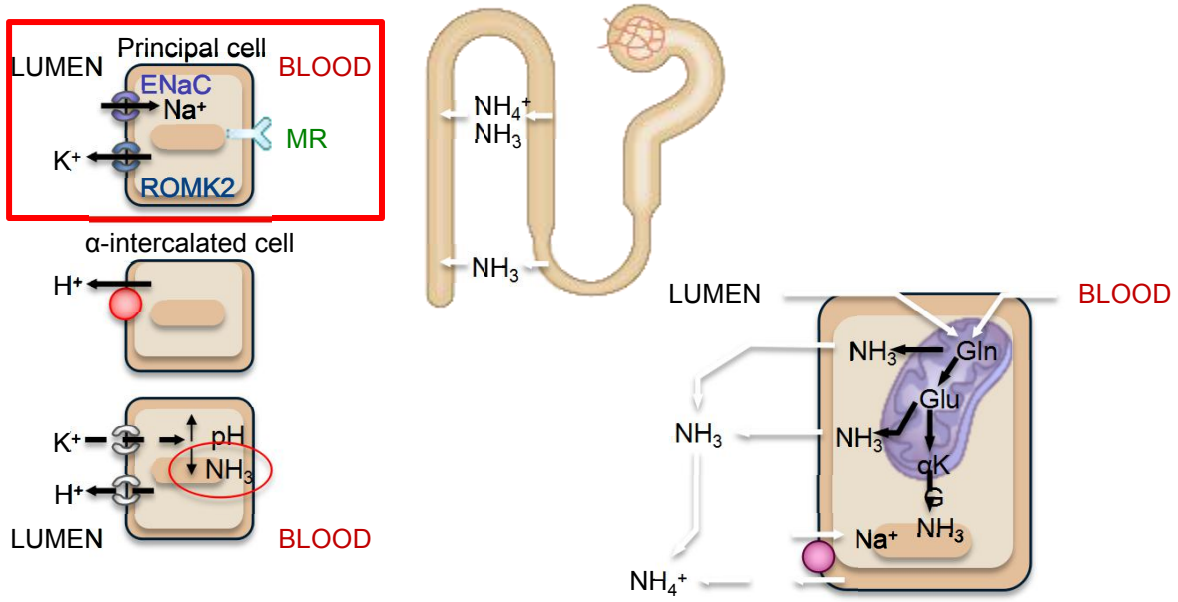
ATP=adenosine triphosphate; CKD=chronic kidney disease; DCT2=distal convoluted tubule 2; ENaC=epithelial sodium channel; ROMK=renal outer medullary potassium channel

1. Mushiyakh Y, et al. *J Community Hosp Intern Med Perspect* 2011;1:1–7; 2. Palmer BF. *Clin J Am Soc Nephrol* 2015;10:1050–1060

Impairments in the Renin–Aldosterone Axis Reduce K^+ Diffusion into the Tubular Fluid

- The majority of patients with hyperkalemia have low levels of aldosterone or an insufficient response to aldosterone by tubular cells
- Hyperkalemia is common in conditions associated with underproduction of renin, such as diabetes, and underproduction of aldosterone such as Addison's disease

Aldosterone deficiency reduces Na^+ reabsorption through the ENaC sodium channel on principal cells in the distal nephron and collecting duct, reducing the lumen-negative membrane potential that is essential for K^+ efflux



α-KG=α-ketoglutarate; ENaC=epithelial sodium channel; Gln=glutamine; Glu=glutamate; MR=mineralocorticoid receptor; ROMK2=renal outer medullary potassium channel 2

Karet FE, et al. *J Am Soc Nephrol* 2009;20:251–254

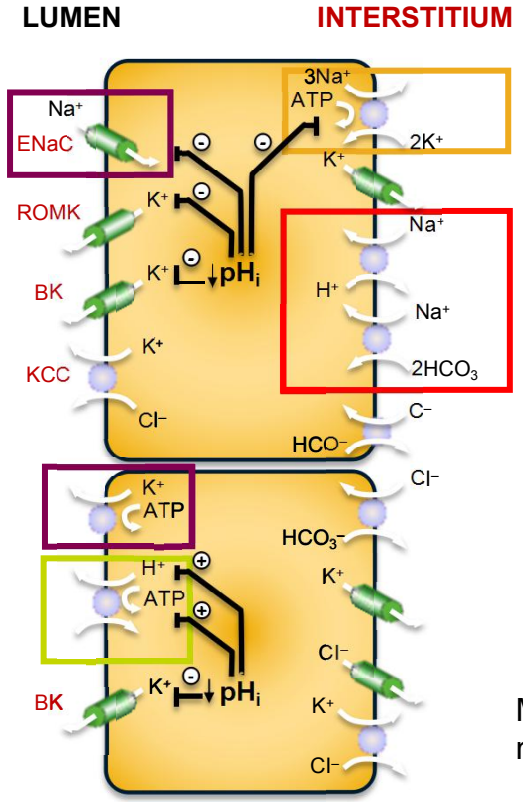
Metabolic Acidosis in Renal Disease Reduces K^+ Elimination

- Declining kidney function causes acid retention, which inhibits potassium excretion and enhances potassium reabsorption[1,2]

Abundance of ENaC channels decreases when pH is reduced

Stimulation of H^+ secretion by the vacuolar ATPase reduces the lumen-negative transepithelial potential difference

Upregulated H^+/K^+ ATPase in intercalated cells enhances reabsorption



Low intracellular pH reduces basolateral Na^+/K^+ ATPase activity, diminishing K^+ flux through ROMK and BK K^+ channels

Inhibited Na^+/H^+ exchange and Na^+/HCO_3^- cotransport reduces the activity of the Na^+/K^+ ATPase

Metabolic acidosis also reduces the lumen-negative transepithelial potential difference[1]

ATP=adenosine triphosphate; BK, big potassium; ENaC=epithelial sodium channel; ROMK=renal outer medullary potassium channel

1. Aronson PS, et al. *J Am Soc Nephrol* 2011;22:1981–1989; 2. Kovesdy CP. *Nephrol Dial Transplant* 2012;27:3056–3062

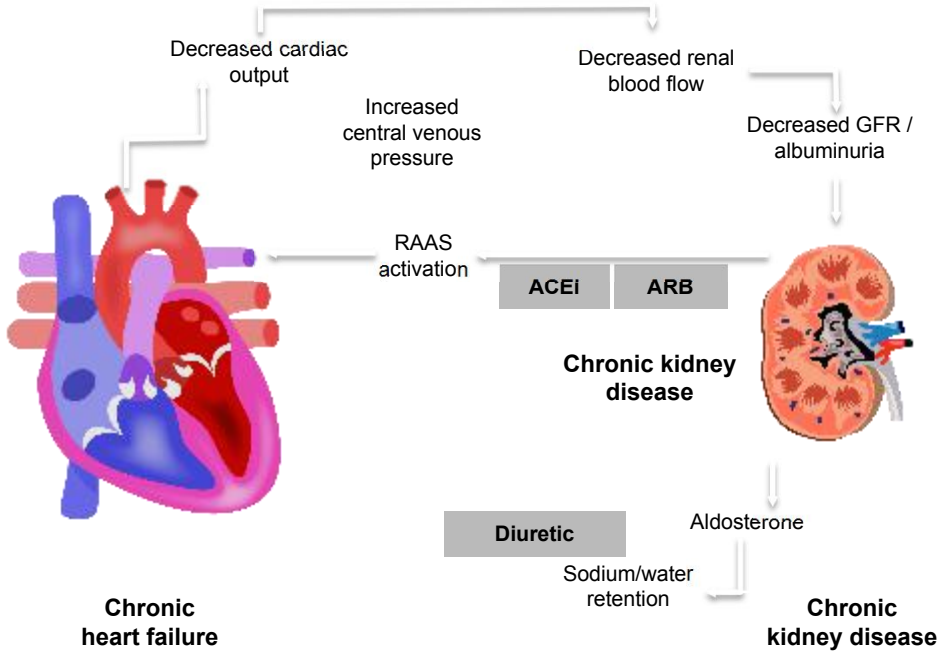
Hyperkalemia is Common in CHF

Renal function often declines with progressive CHF, and GFR is often reduced, reducing K^+ excretion[1]

Many commonly used CHF treatments, including ACE inhibitors, ARBs, and aldosterone receptor antagonists, predispose patients to hyperkalemia by decreasing aldosterone production or interfering with its effect, which reduces K^+ excretion[1]

Hyperkalemia also predisposes to cardiac arrhythmias and increases the risk of cardiac death[1]

Interaction between heart failure and renal dysfunction[2]



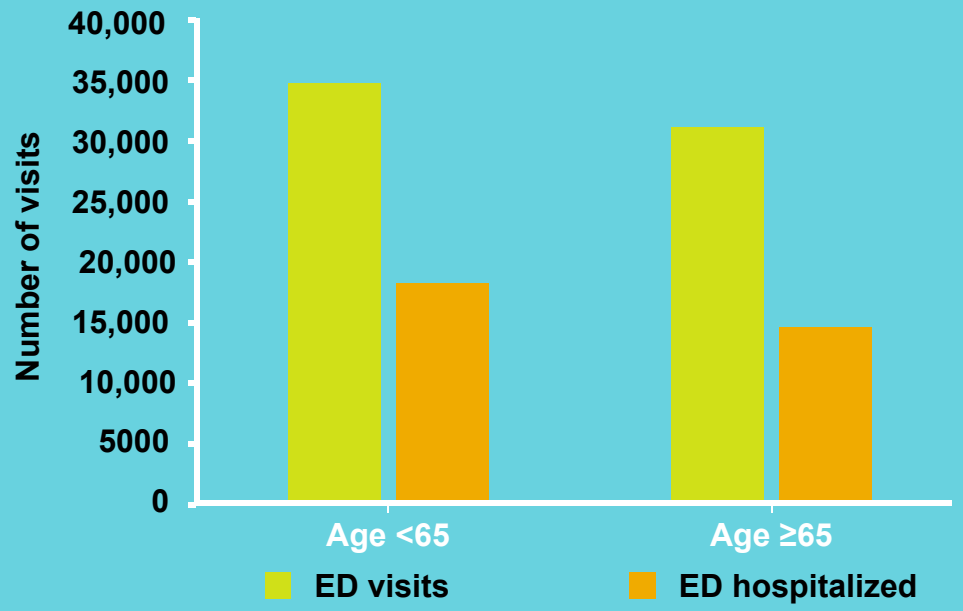
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CHF=congestive heart failure; GFR=glomerular filtration rate; RAAS=renin–angiotensin–aldosterone system

1. Sica D, et al. *Congest Heart Fail* 2003;9:224–229; 2. Damman K, et al. *J Am Coll Cardiol* 2014;63:853–871

Resource Utilization for Patients with Primary Diagnosis of Hyperkalemia is High

National Emergency Department Sample (NEDS)

~50% ED visits resulted in hospital admission



National Inpatient Sample (NIS)

- **Mean LOS 3.1 days**
- **Mean hospital charges $24K**
- **69% Medicare patients**
- **Discharge status:**
  - 15% to nursing home or rehab
  - 11% to home healthcare

ED=emergency department; LOS=length of stay

HCUP Databases. Healthcare Cost and Utilization Project (HCUP). 2012 Agency for Healthcare Research and Quality, Rockville, MD. Available at www.hcup-us.ahrq.gov/databases.jsp.

2. Incidence and risk factors of hyperkalaemia in patients with CKD and patients with HF

HiK is relatively uncommon in the general population

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

Diet[1,2]

- K^+ supplements
- Salt substitutes

Diseases[1]

- CKD
- HF
- Diabetes

Common medications[a]

- RAASi therapy[1,2]
- NSAIDs[2]
- β blockers[2]
- Immuno-suppressants[2]
- K^+-sparing diuretics[2]
- Heparins[2]
- Some antibiotics / antifungals[2]

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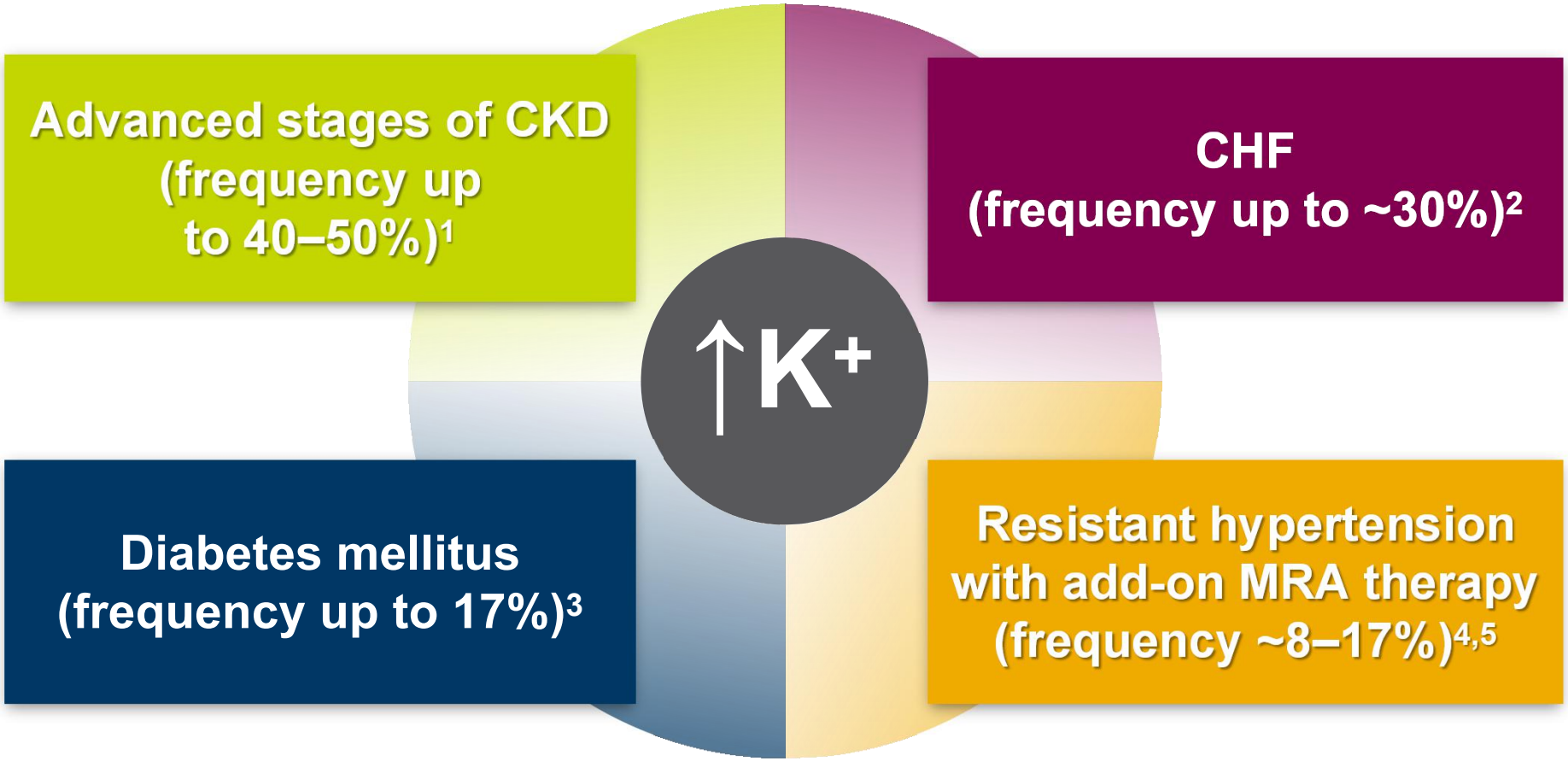
[a]This is not an exhaustive list

CKD, chronic kidney disease; HiK, hyperkalaemia; HF, heart failure; NSAID, non-steroidal anti-inflammatory drug; RAASi, renin–angiotensin–aldosterone system inhibitor

1. Kovesdy CP. *Nat Rev Nephrol* 2014;10:653–662; 2. Hollander-Rodriguez J, Calvert JF Jr. *Am Fam Physician* 2006;73:283–290

Patient subgroups with a high incidence of HiK

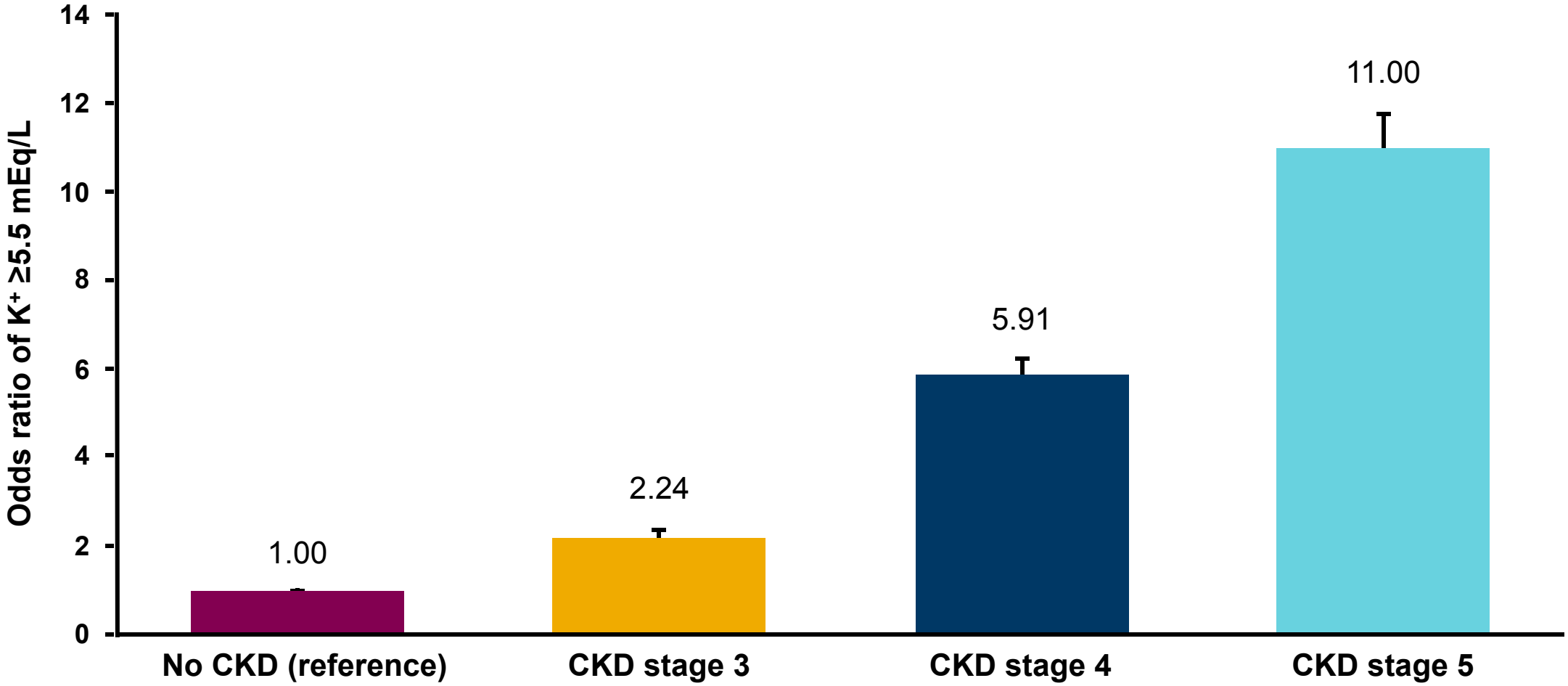


HiK is defined as K^+ >5.0 mEq/L[6]

CHF, chronic heart failure; CKD, chronic kidney disease; HF, heart failure; HiK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist

1. Kovesdy CP. *Nat Rev Nephrol* 2014;10:653–662; 2. Vardeny O, et al. *Circ Heart Fail* 2014;7:573–579; 3. Nilsson E, et al. *ERA-EDTA*, Madrid, 2017. Poster presentation SP313; 4. Chomicki J, et al. Presented at ASH Annual Scientific Meeting & Exposition; 16th–20th May 2014; New York, NY, USA; P-10; 5. Khosla N, et al. *Am J Nephrol* 2009;30:418–424; 6. Yancy CW, et al. Circulation. 2017;136:e137–e161.

HiK risk increases with CKD severity

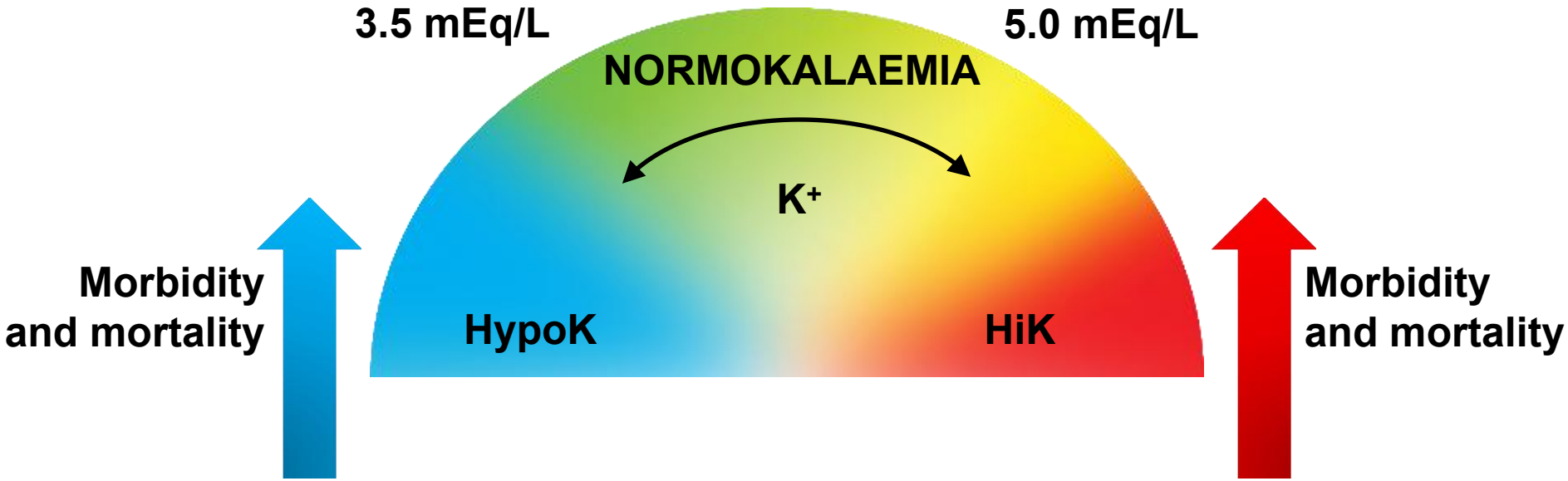


CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HiK, hyperkalaemia
Einhorn LM, et al. *Arch Intern Med* 2009;169:1156–1162

3. The clinical burden and resource utilisation associated with HiK

HiK is associated with increased morbidity and mortality

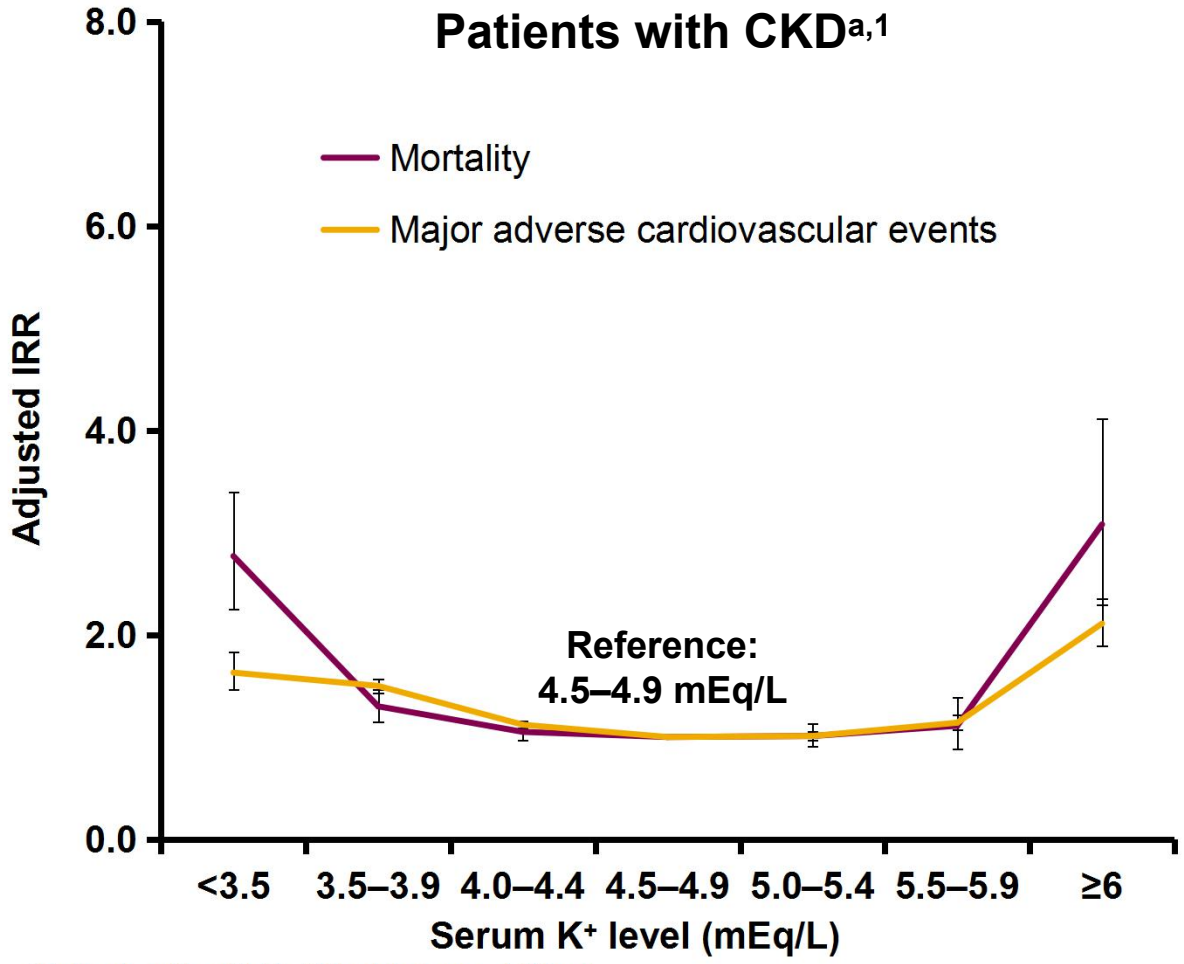
- As serum K^+ levels deviate from normal levels, rates of morbidity (including MACE) and mortality increase[1–5]

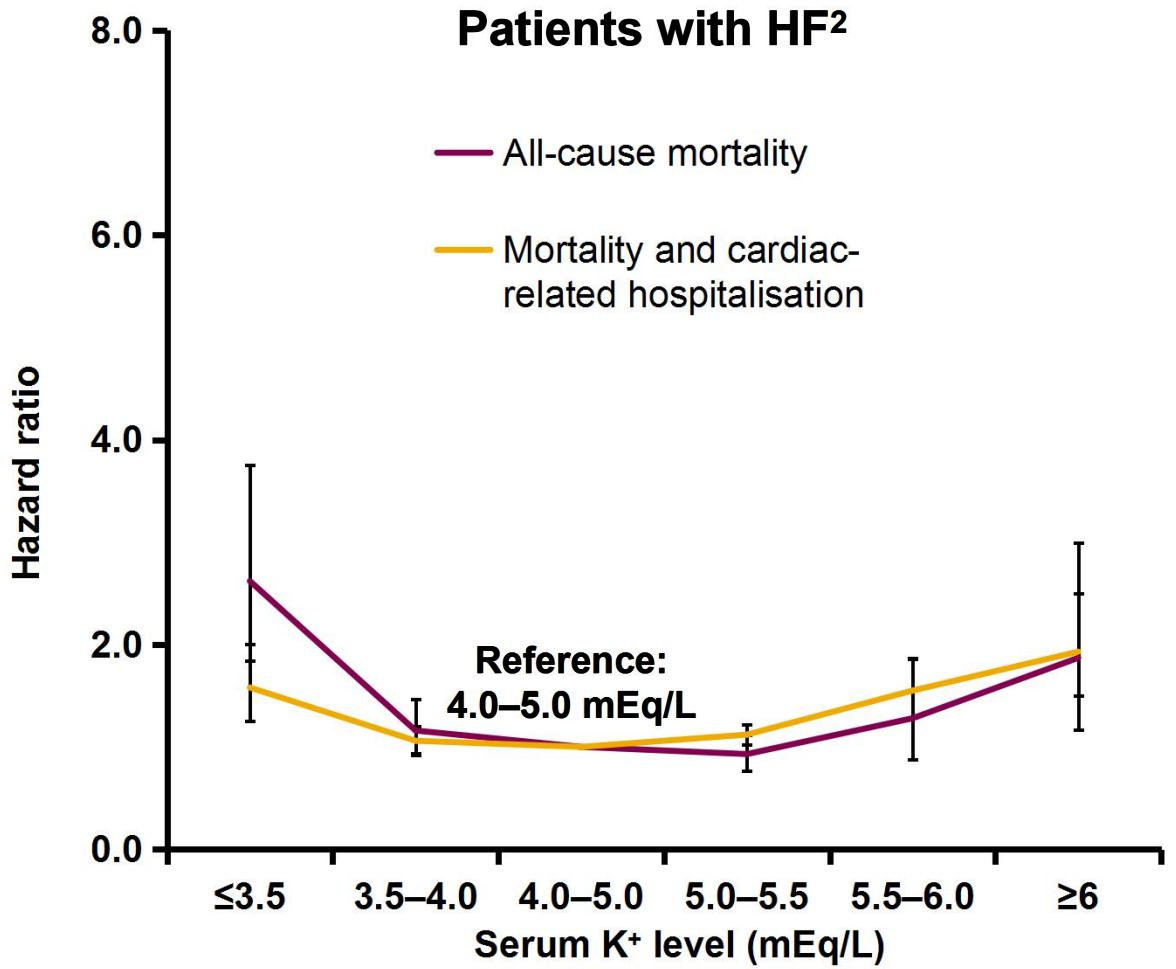


CV, cardiovascular; HiK, hyperkalaemia; HypoK, hypokalaemia; MACE, major adverse cardiovascular events

1. Luo J, et al. *Clin J Am Soc Nephrol* 2016;11:90–100; 2. McMahon GM, et al. *Intensive Care Med* 2012;38:1834–1842;
3. Hayes J, et al. *Nephron Clin Pract* 2012;120:c8–c16; 4. An JN, et al. *Crit Care* 2012;16:R225; 5. Goyal A, et al. *JAMA* 2012;307:157–164

High serum K^+ is associated with increased mortality and adverse outcomes in patients with CKD and those with HF



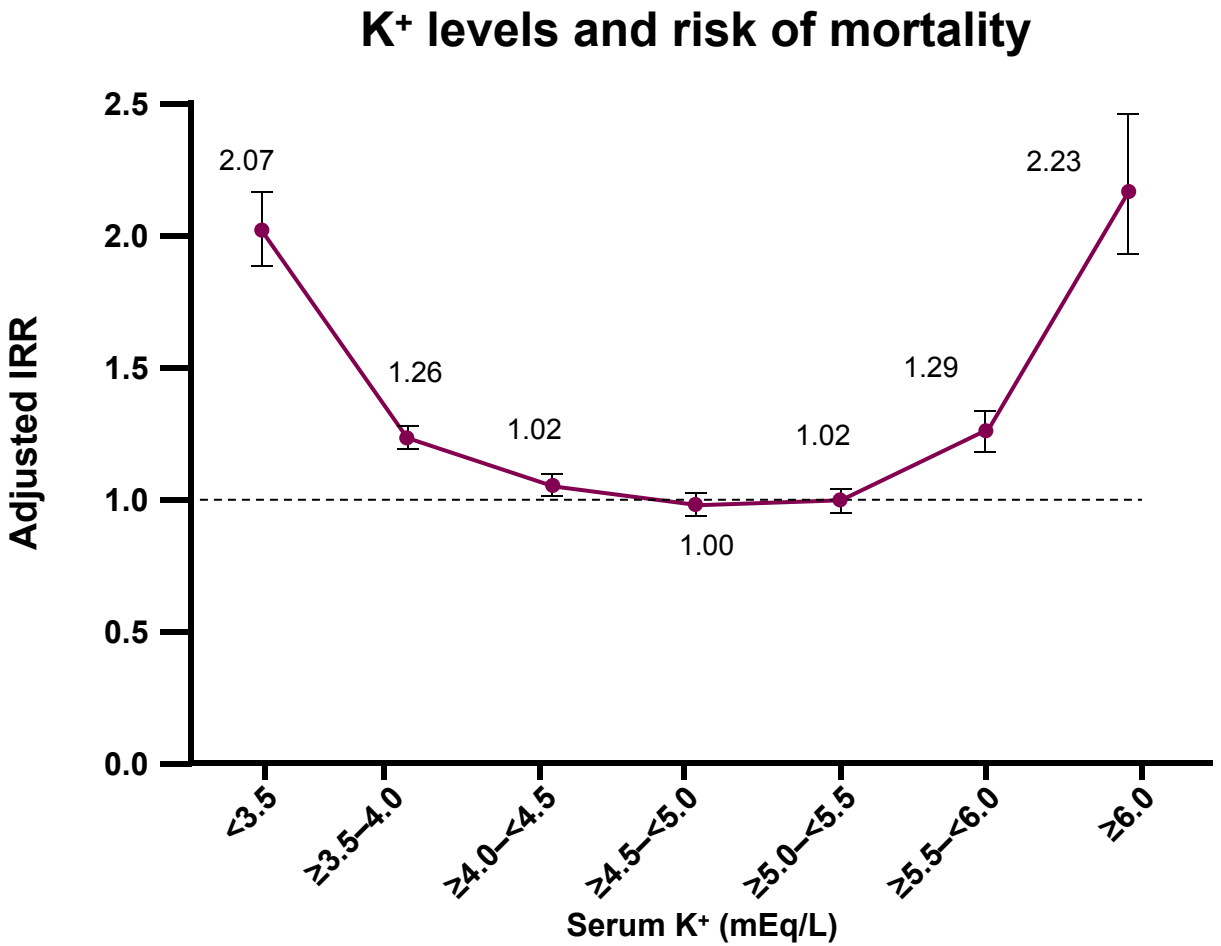


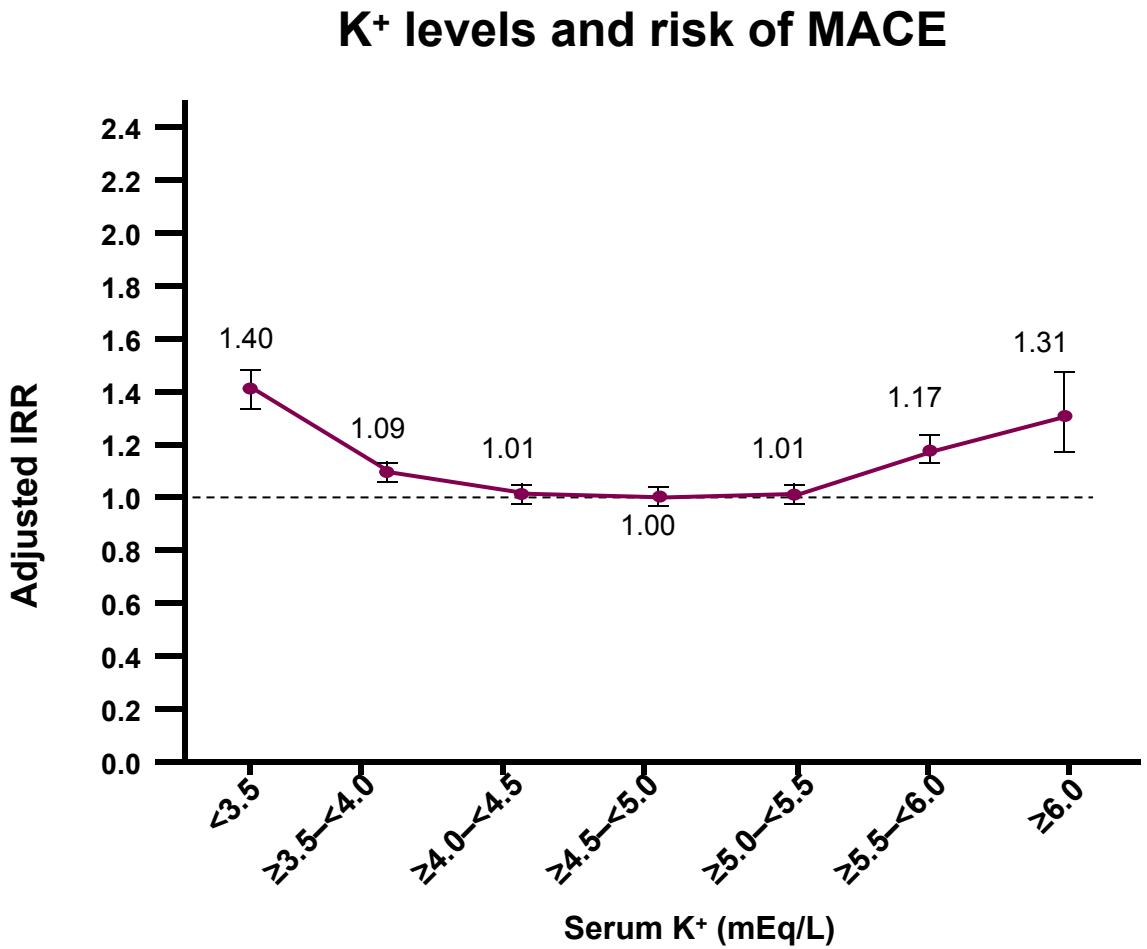
[a]Patients with eGFR <30 mL/min per 1.73 m^2

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IRR, incident rate ratio; MACE, major adverse cardiovascular events

1. Luo J, et al. *Clin J Am Soc Nephrol* 2016;11:90–100; 2. Hoss S, et al. *Am J Cardiol* 2016;118:1868–1874

Recent studies confirm high serum K^+ levels are associated with increased risk of mortality and MACE in CKD

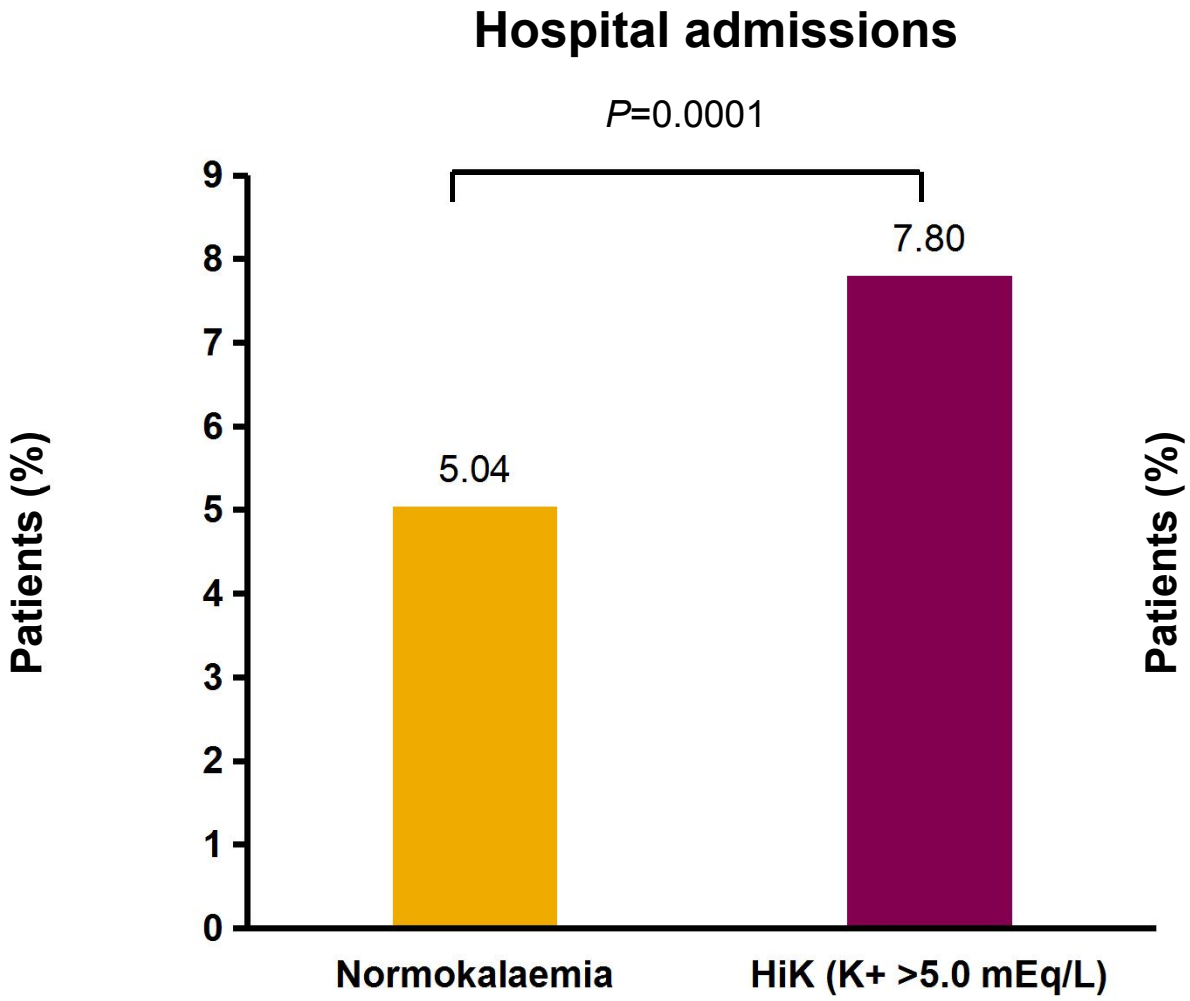


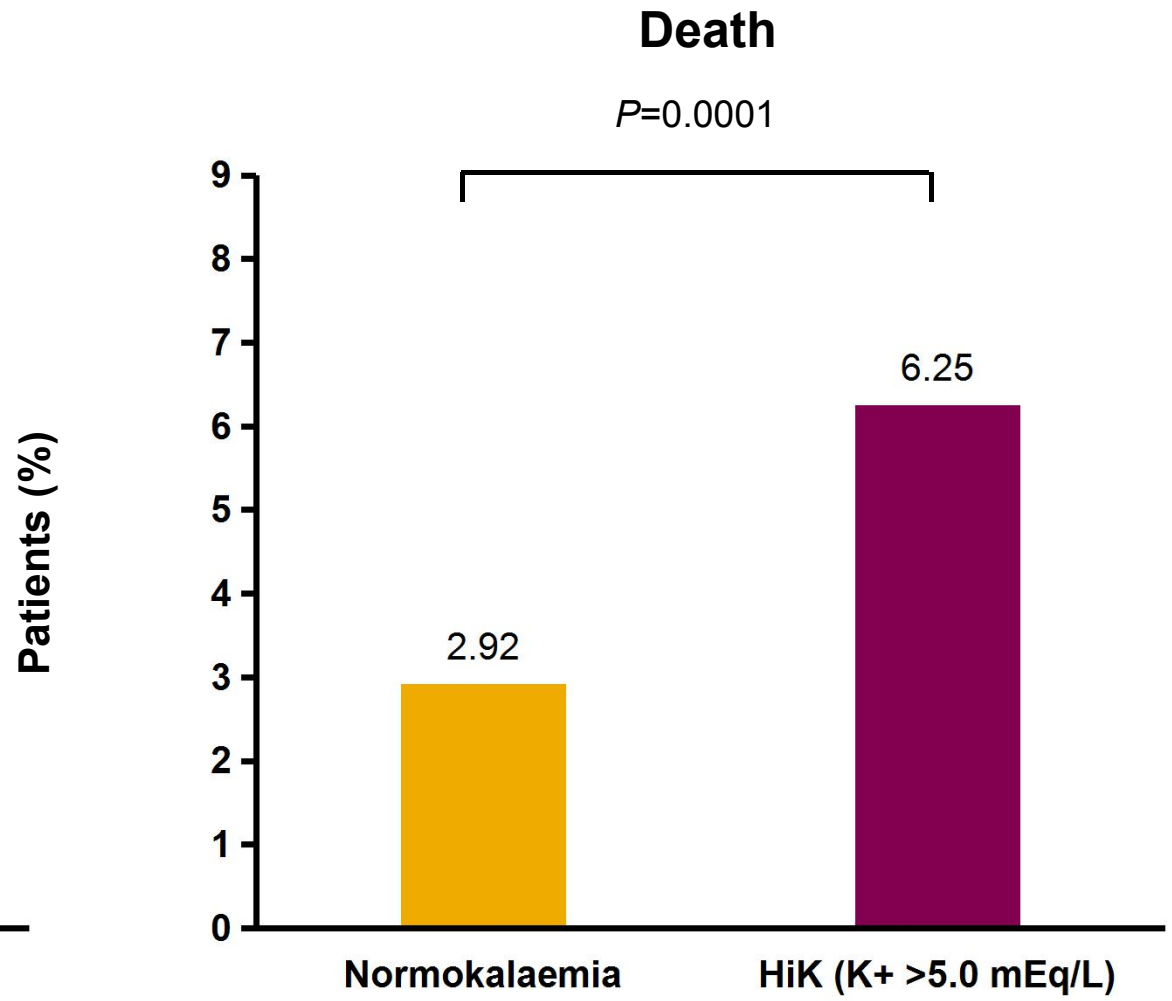


CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics; IRR, incident risk ratio; MACE, major adverse cardiovascular events

Adapted from Qin L, et al. Presented at ERA-EDTA, Madrid; 3rd–6th June 2017; Oral presentation MO067

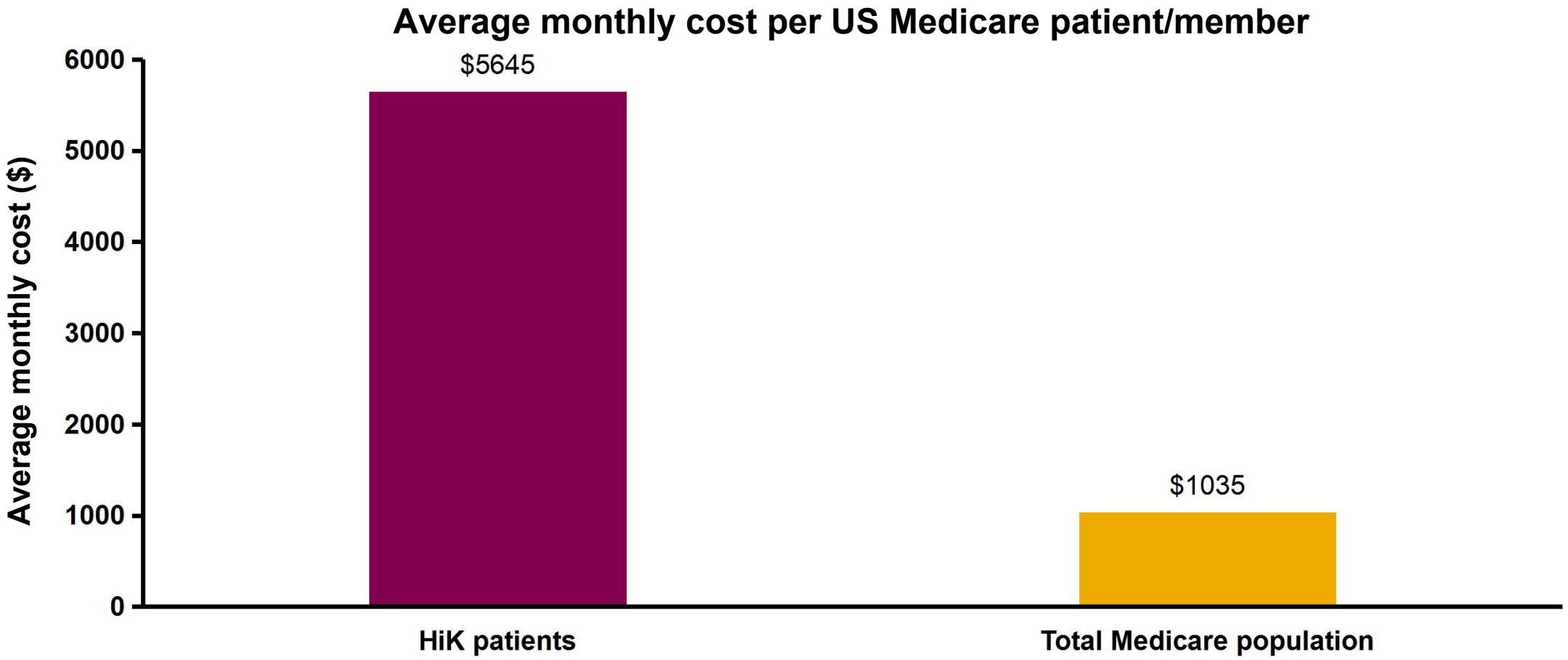
HiK is associated with a higher incidence of hospital admissions and death in patients with CVD[a]





[a]HF and hypertension
CVD, cardiovascular disease; HF, heart failure; HiK, hyperkalaemia
Jain N, et al. *Am J Cardiol* 2012;109:1510–1513

HiK is associated with higher healthcare costs



HiK, hyperkalaemia

Fitch K, et al. Presented at the AMCP 2016; 19th–22nd April 2016; San Francisco, CA, USA; E62

4. Limitations of current treatment strategies

Emergency treatments of HiK

Treatment strategy	Mechanism of action	Advantages	Limitations
Calcium gluconate	Membrane stabilisation	• Onset of action in 1–3 minutes • Efficacy can be monitored with ECG and dose can be repeated if no changes observed	• Short duration of effect (30–60 minutes) • Serum K^+ level is unaffected • Avoid in patients receiving digoxin (risk of digoxin toxicity) • Risk of hypercalcaemia
Insulin glucose	K^+ redistribution into the intracellular space	• Onset of action within 30 minutes • Effect lasts 4–6 hours	• Risk of hypoglycaemia • Does not reduce total K^+ levels
β-2-adrenergic agonists	K^+ redistribution into the intracellular space	• Onset of action (~30 minutes) • Effect is independent of insulin and aldosterone	• Short duration, inconsistent effect (2–4 hours) • Does not reduce total K^+ levels • Use with caution in ischaemic heart disease (risk of tachycardia)
Dialysis (haemodialysis, peritoneal dialysis)	K^+ elimination	• Onset of action within minutes • Effects lasting until end of dialysis or longer	• Concentration of K^+ in the dialysate can contribute to HiK • Limitations and complications inherent to each dialysis modality

ECG, electrocardiogram; HiK, hyperkalaemia

Adapted from Dunn J, et al. *Am J Manag Care* 2015;21:S307–S315

Treatments that can remove excess K^+

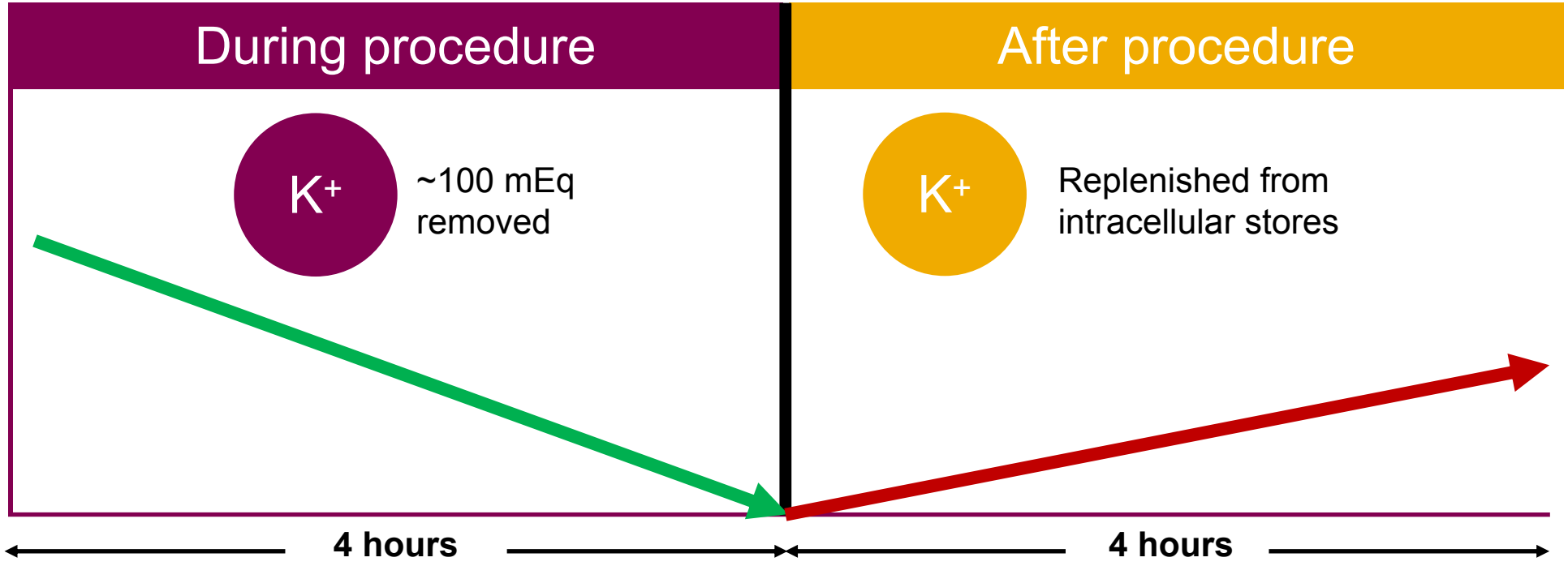
Treatment strategy	Mechanism of action	Advantages	Limitations
Diuretics	K^+ elimination	• Onset of action depends on start of diuresis • Beneficial in patients with volume expansion	• Efficacy depends on residual renal function • Increased risk for gout and diabetes • May worsen kidney function
Dialysis (haemodialysis, peritoneal dialysis)	K^+ elimination	• Onset of action within minutes • Effects lasting until end of dialysis or longer	• Concentration of K^+ in the dialysate can contribute to HiK • Limitations and complications inherent to each dialysis modality
Potassium binders (Sodium polystyrene sulphonate)	K^+ elimination	• Onset of action within 2 hours (oral) • Effects may last 4–6 hours or longer depending on ongoing K^+ intake or cellular redistribution	• No consistent evidence of efficacy[2] • Maximum effect may take 6 hours • Serious GI adverse events reported, including fatal cases of intestinal necrosis • Caution with sodium loads in patients with congestive HF, hypertension, or oedema • Appropriate for intermediate/subacute care only

GI, gastrointestinal; HF, heart failure; HiK, hyperkalaemia

Adapted from 1. Dunn J, et al. *Am J Manag Care* 2015;21:S307–S315; 2. Kayexalate US Prescribing Information (Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011287s022lbl.pdf, accessed 17 August 2017)

Dialysis is an effective treatment but it is often followed by rebound HiK

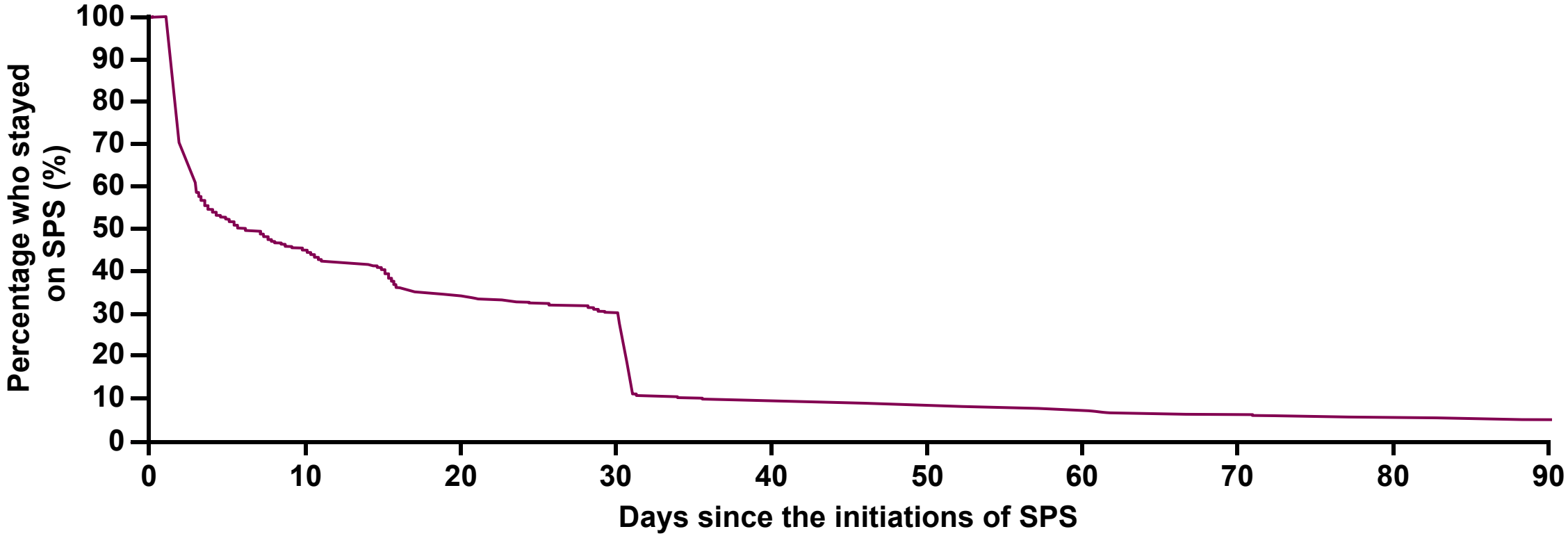
- Although in stable individuals it is possible to remove over 100 mEq of K^+ during a 4-hour dialysis session, the overall effectiveness of dialysis is limited by a rapid replenishment of K^+ from intracellular stores after the procedure



HiK, hyperkalaemia
Adapted from Sterns R, et al. *Kidney Int* 2016;89:546–554

Median SPS treatment duration was 7 days

- Long-term efficacy data from randomised controlled studies with SPS are limited[1,2]
- Discontinuation of SPS among 4559 patients from a large US claims database study (January 1st 2010 and December 31st 2014); patients had to have ≥1 SPS prescription fill and ≥31 days of continuous enrolment[3]



SPS, sodium polystyrene sulphonate

1. Chaitman M, et al. *P T* 2016;41:43–50; 2. Lepage L, et al. *Clin J Am Soc Nephrol* 2015;10:2136–2142; 3. Betts K, et al. Presented at ASN Kidney Week 2016; 15th–20th November 2016; Chicago, IL, USA; FR-PO786

Adherence to low-K^+ diet can be challenging

- Patients with CKD are counselled to adhere to dietary K^+ restrictions for the rest of their lives
- Some foods that are particularly rich in K^+ can be easily avoided, but because K^+ is present in many foods, knowing what is allowed can be confusing[1]
- In addition, many K^+-rich foods are considered 'heart healthy', so following a low-K^+ diet may contribute to the burden of CVD in these patients[2]
- Adherence of patients with CKD to dietary restrictions ranges from ~2 to ~40%[3]

CKD, chronic kidney disease; CVD, cardiovascular disease

1. Beto JA, et al. *Int J Nephrol Renovasc Dis* 2016;9:21–33; 2. Kalantar-Zadeh K, et al. *Semin Dial* 2015;28:159–168; 3. Herselman M, *S Afr J Clin Nutr* 2008;21

5. Challenges in managing complex patients with HiK

Ciclosilicato di sodio e zirconio

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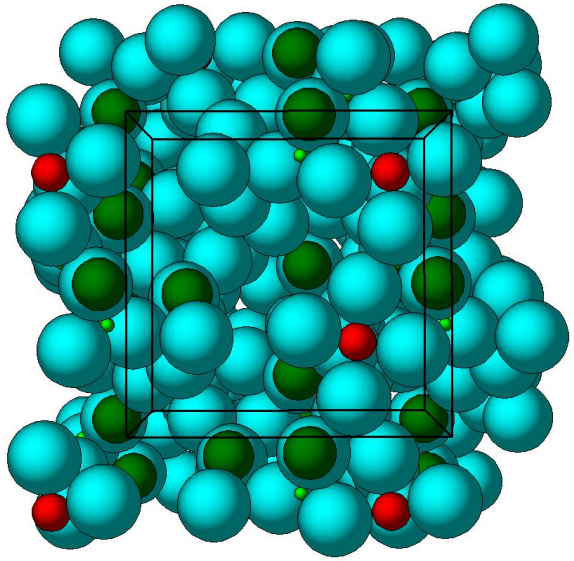
Crystal Structure

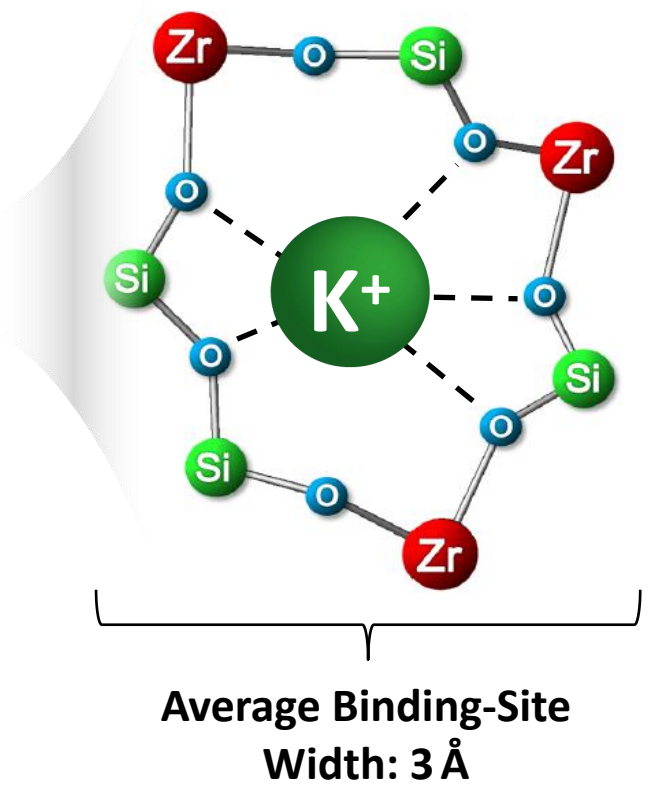
(Ciclosilicato di Sodio e Zirconio) (CSZ)



- Inorganic crystalline zirconium silicate compound
- Not a polymer
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed

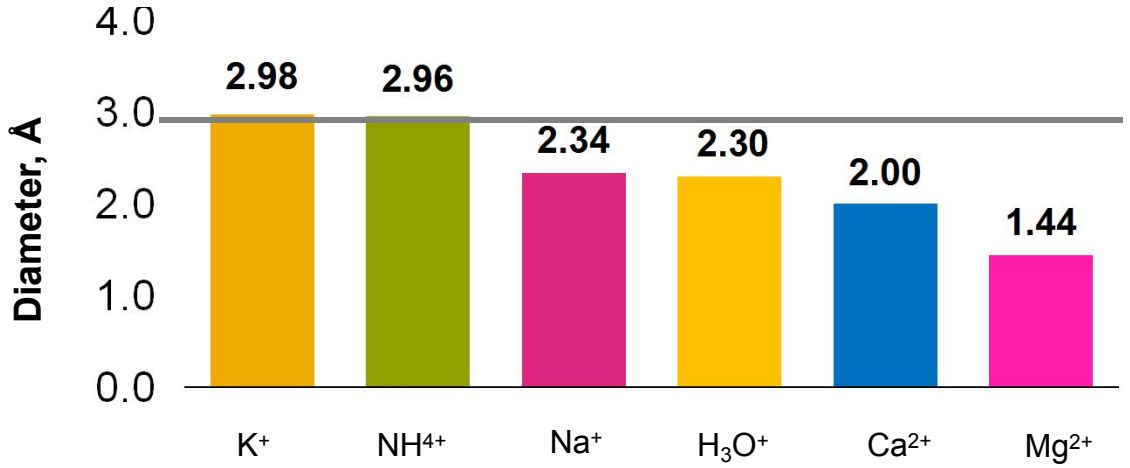
1. Adapted from Stavros F, et al. *PLoS One*. 2014;9:e114686.

Engineered to be Highly Selective for K^+



Average Binding-Site Width: 3 Å

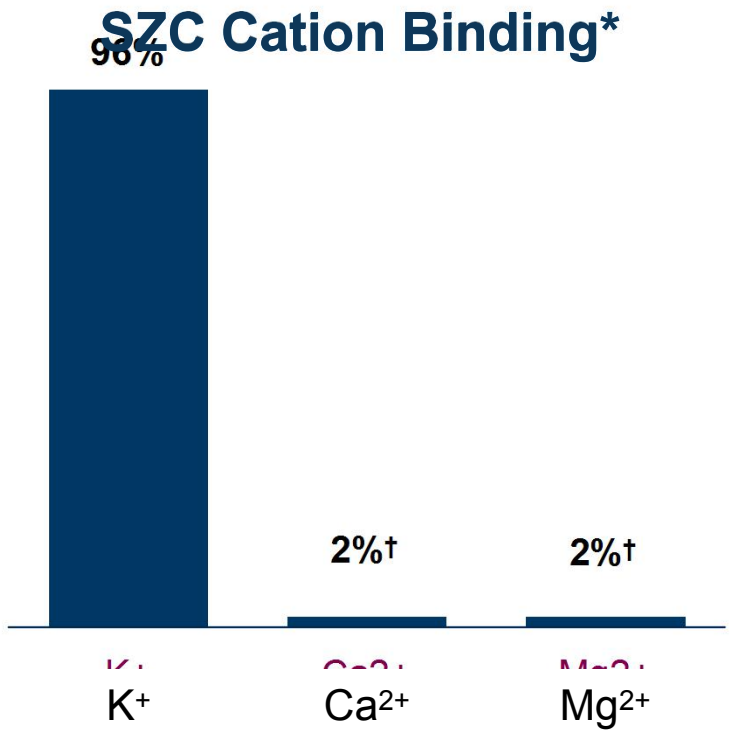
- Binding-site 3Å wide, designed to selectively fit K^+ ions
- Exchanges Na^+ and H^+ for K^+

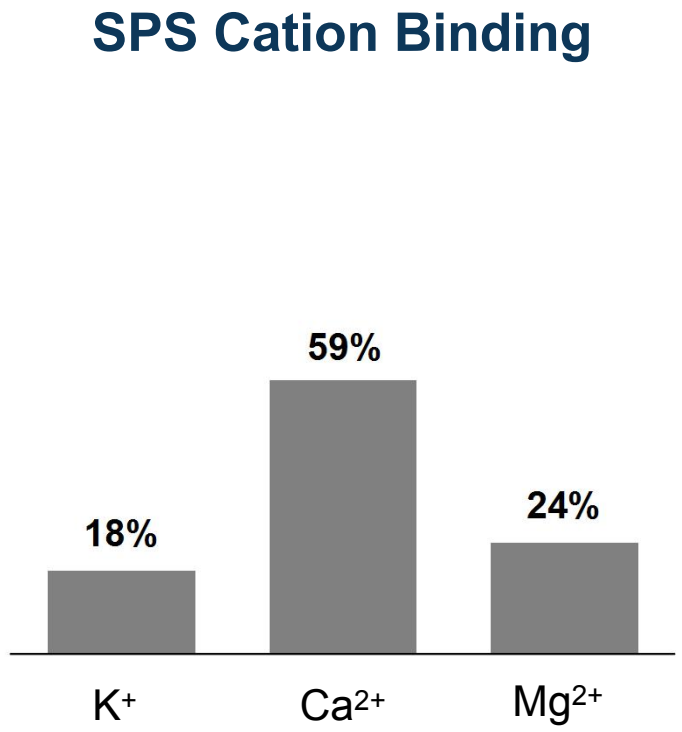


1. Adapted from Stavros F, et al. *PLoS One*. 2014;9:e114686.

SPS Shows Higher Selectivity for Ca^{2+} and Mg^{2+} than for K^+

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





*Graphs show the mEq/g and at the 1:1:1 line for SZC is 2.7/0.05/0.05 and for SPS, it is 0.3/1.0/0.4 (mEq/g). This translates into the percentages of 96/2/2 and 18/59/24, respectively.

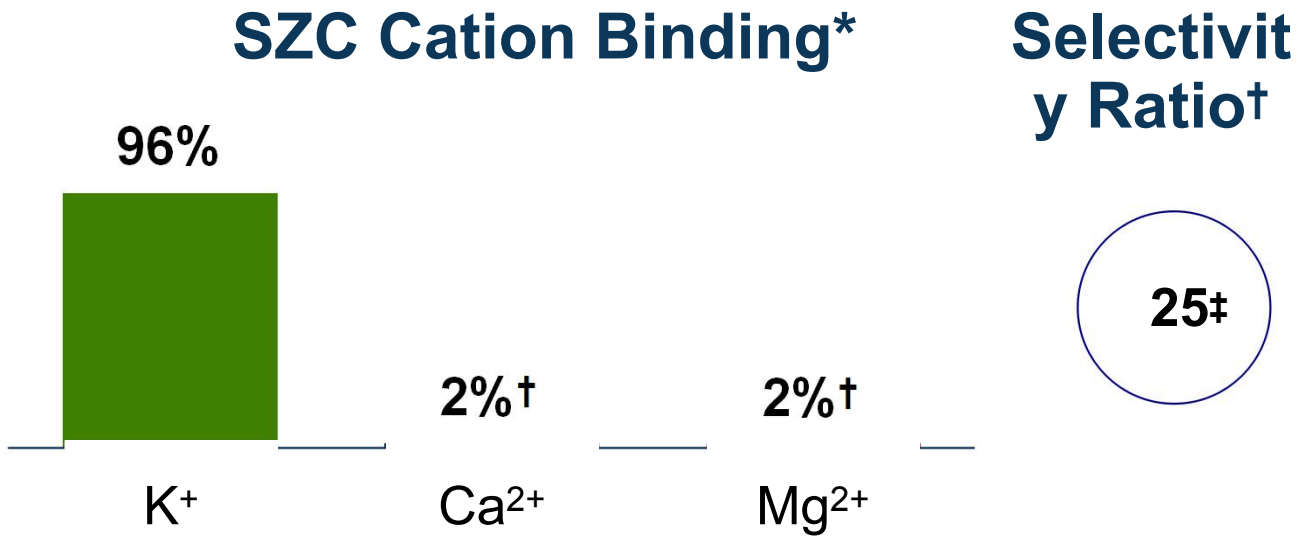
†Selectivity ratio = $[K^+] / [Ca^{2+}] + [Mg^{2+}]$

Exchange capacity of Ca^{2+} and Mg^{2+} was below the 0.05 detection limit; therefore, 0.05 was assumed for calculation purposes

1. Stavros F, et al. *PLoS One*. 2014;9:e114686.

Selectivity for Potassium (K^+)

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



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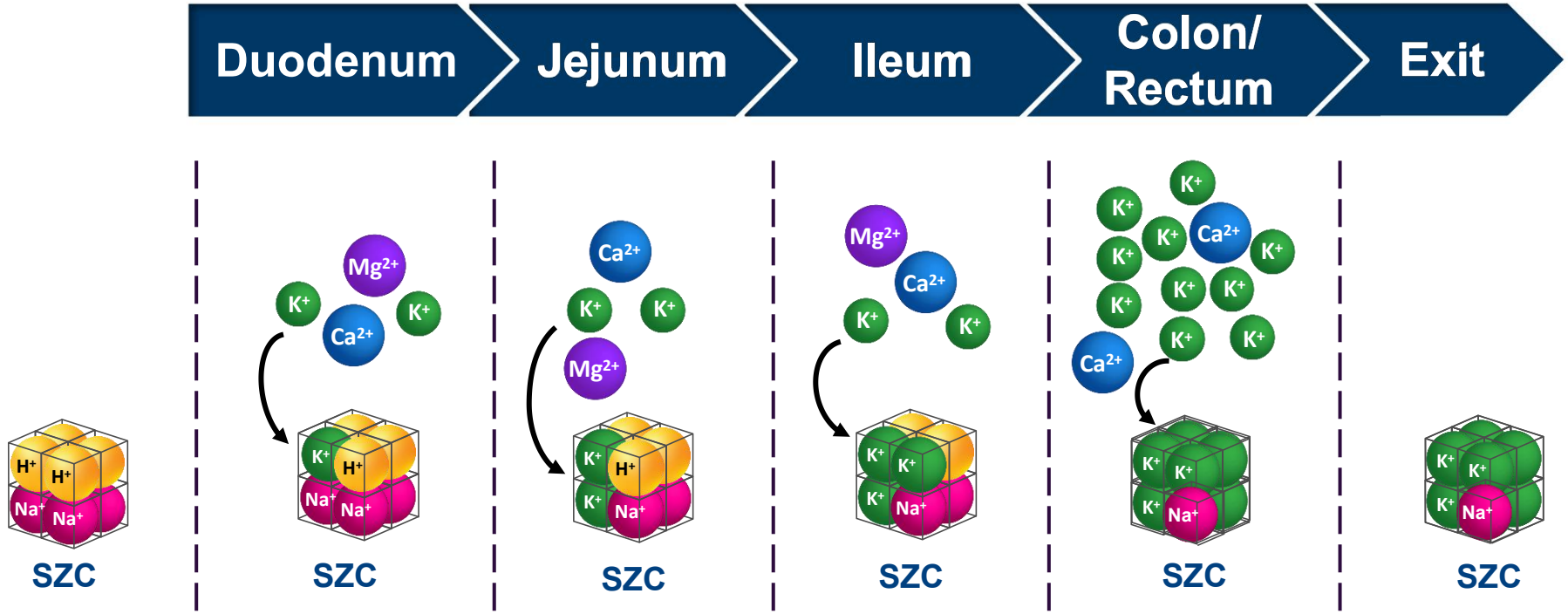
1. Stavros F, et al. *PLoS One*. 2014;9:e114686.

SZC Binds K^+ Throughout the GI Tract*



- Based on in vitro data, SZC may begin working immediately in the small intestine to preferentially capture K^+

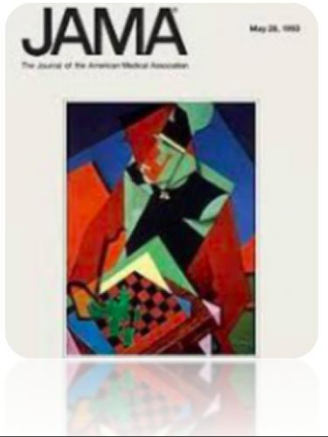
*For illustrative purposes only

1. McCullough PA et al. *Rev Cardiovasc Med*. 2015;16(2):140-155.
2. Adapted from Stavros F et al. *PLoS One*. 2014;9:e114686.

Original Investigation

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD



JAMA December 3, 2014 Volume 312, Number 21

HARMONIZE

Population:

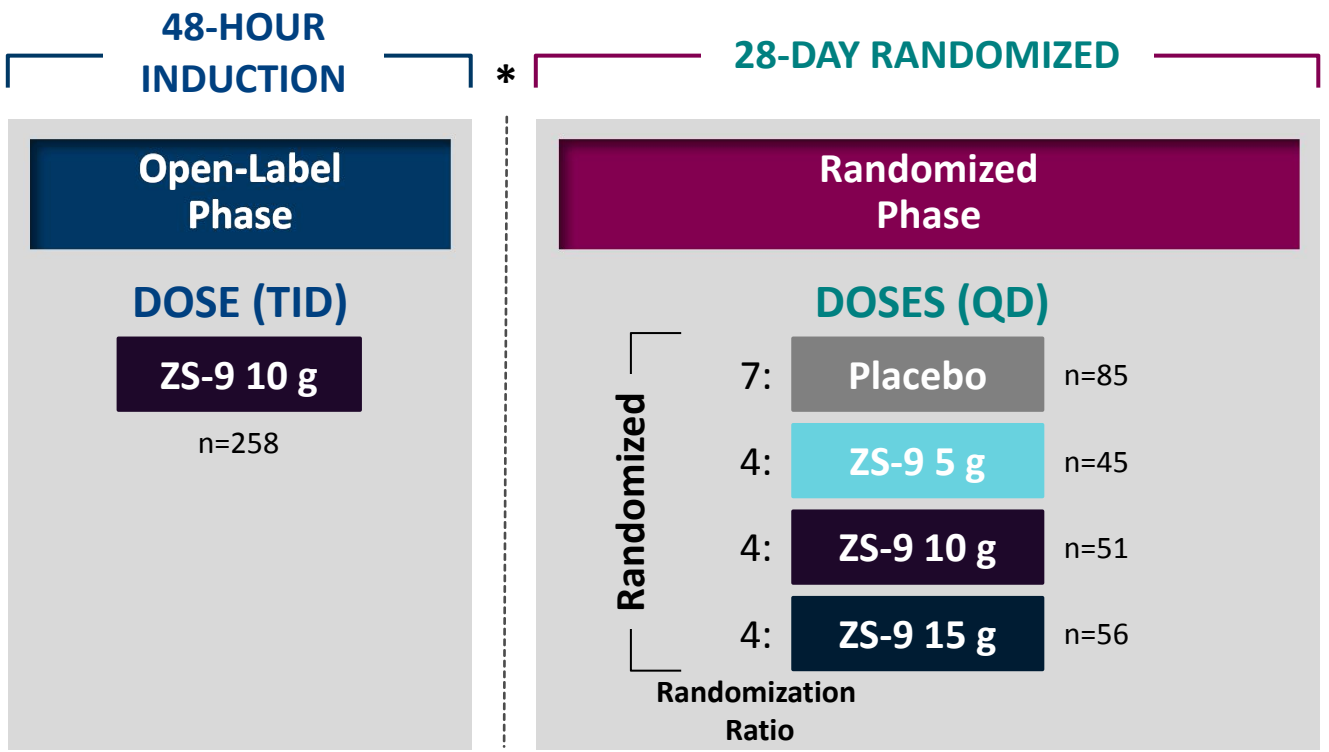
- 258 patients enrolled:
- CKD 66% population
- HF 36% population
- HK > 5.1 mEq/L without upper limit(mean baseline HK 5.6mEq/L)

Primary objective :

- To confirm the safety and efficacy of sodium zirconium cyclosilicate in restoring normokalemia over 48 hours
- To confirm the safety and efficacy of sodium zirconium cyclosilicate in maintaining normokalemia over 28 days

Kosiborod M, et al. *JAMA*. 2014;312:2223-2233.

HARMONIZE :Study Design



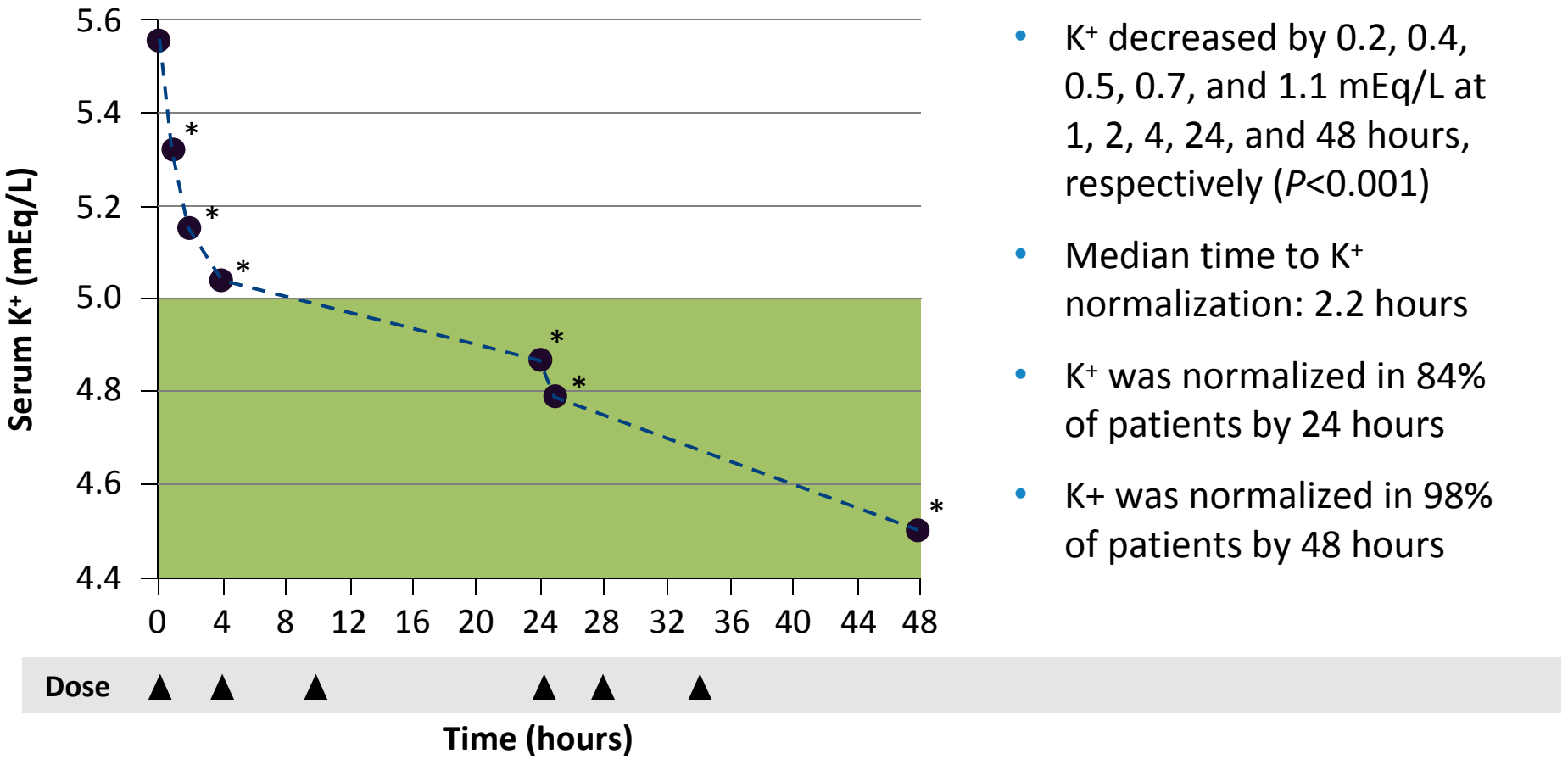
- 44 nephrology, cardiology, general research sites: US 80%; South Africa 12%; Australia 8%
- Entry criteria: serum K^+ ≥5.1 mEq/L
- **Primary endpoint: comparison of mean serum K^+ levels from day 8 to day 28**

*Proceeded to randomized phase if patient achieved normokalemia by morning of study day 3.

Adapted from Kosiborod M, et al. *JAMA*. 2014;312:2223-2233.

HARMONIZE Open-Label Phase: Mean Serum K^+

Mean Serum K^+ Levels with SZC 10 g TID



- K^+ decreased by 0.2, 0.4, 0.5, 0.7, and 1.1 mEq/L at 1, 2, 4, 24, and 48 hours, respectively (P<0.001)
- Median time to K^+ normalization: 2.2 hours
- K^+ was normalized in 84% of patients by 24 hours
- K+ was normalized in 98% of patients by 48 hours

ıEq/L.

Adapted from Kosiborod M, et al. *JAMA*. 2014;312:2223-2233.

HARMONIZE Other Laboratory Values and Vital Signs

- No clinically significant changes in serum Mg^{2+}, Ca^{2+}, or Na^{+}
- No dose-dependent increase in urinary Na^{+} excretion
- No significant changes in blood pressure, heart rate, or body weight at any dose level
- No clinically significant arrhythmias occurred in any of the ZS-9 groups or the placebo group
- Significant reductions in serum aldosterone in the ZS-9 groups

Kosiborod M, et al. *JAMA*. 2014;312:2223-2233.

HARMONIZE SAFETY :Oedema (Acute Phase + Maintenance Phase)

	Open-label, acute phase	Maintenance Phase			
	ZS 10g (n=258)	Placebo (n=85)	ZS 5 g (n=45)	ZS 10 g (n=51)	ZS 15 g (n=56)
Oedema*, n (%)	0	2 (2.4%)	1 (2.2%)	3 (5.9%)	8 (14.3%)

- None were deemed by the investigator as treatment-related

- In total, 66% of patients had chronic kidney disease, 36% had heart failure, 66% had diabetes mellitus, and 70% were receiving a RAAS inhibitor
- A total of 14 patients reported oedema*: 7.9% of patients (12/152) in the ZS groups and 2.4% of patients (2/85) in the placebo group
  - One case of generalized oedema was considered a serious adverse event
- Of the 14 patients who developed oedema, 7 did not require changes in therapy
- Thirteen of 14 patients who developed oedema completed the study

Included terms oedema and peripheral oedema as treatment-emergent adverse event

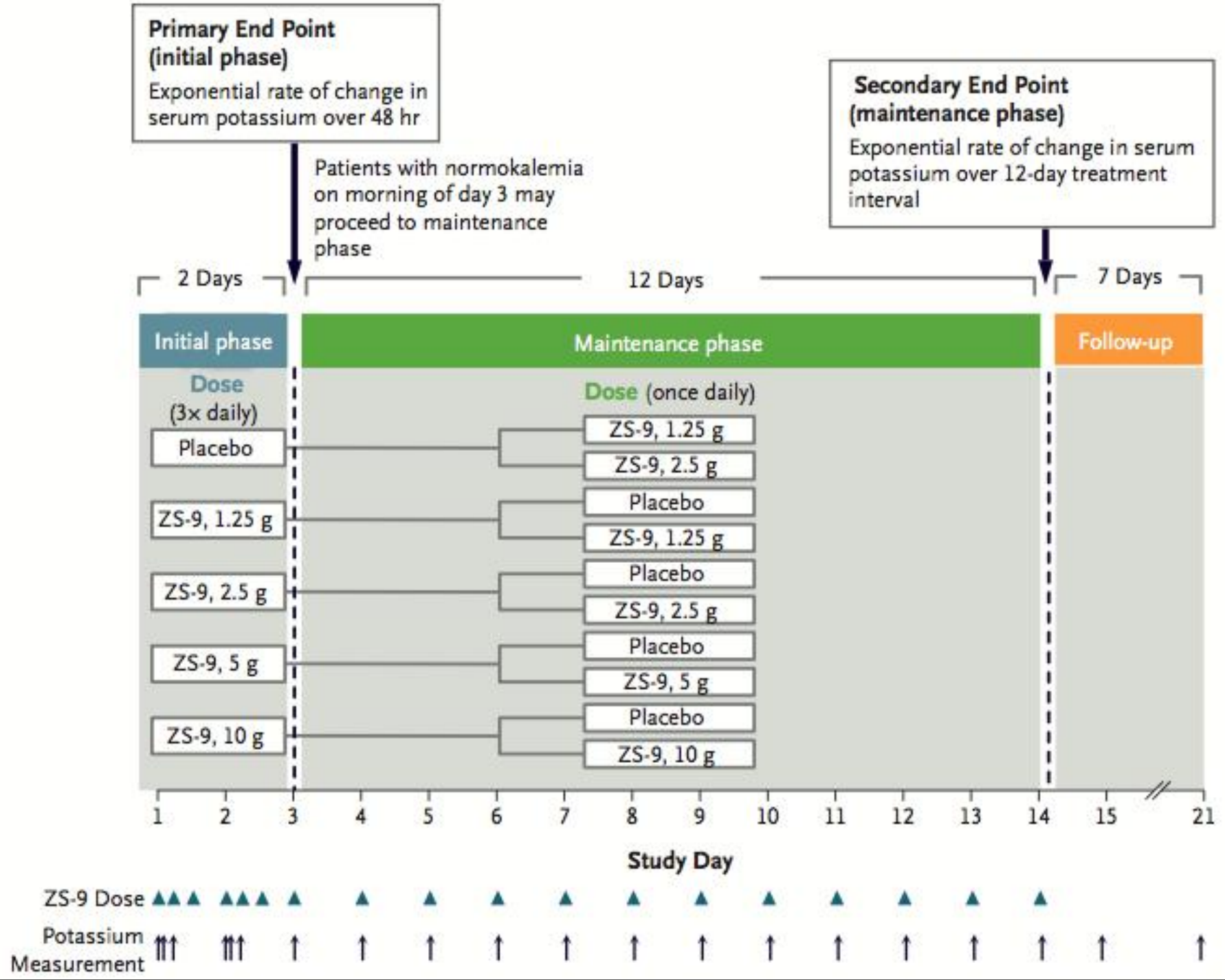
Kosiborod M et al. *JAMA*. 2014;312:2223-2233

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.


Primary End Point
(initial phase)
Exponential rate of change in serum potassium over 48 hr
Patients with normokalemia on morning of day 3 may proceed to maintenance phase
Secondary End Point
(maintenance phase)
Exponential rate of change in serum potassium over 12-day treatment interval
2 Days
12 Days
7 Days
Initial phase
Maintenance phase
Follow-up
Dose
(3× daily)
Dose (once daily)
Placebo
ZS-9, 1.25 g
ZS-9, 2.5 g
ZS-9, 5 g
ZS-9, 10 g
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 21
Study Day
ZS-9 Dose
Potassium Measurement

Conclusions

Patients with hyperkalemia who received ZS-9, as compared with those who re- ceived placebo, had a significant reduction in potassium levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy.
(Funded by ZS Pharma; ClinicalTrials.gov number, NCT01737697.)

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ENERGIZE)

4. STUDY DESIGN

4.1 Overall design

The study is designed to determine if ZS 10g administered up to three times over 10h added to insulin and glucose in patients presenting with hyperkalaemia will prove tolerable and efficacious by performing a multicentre, international, randomized, double-blind, placebo-controlled, prospective, parallel-group study.

The study will recruit patients with S-K ≥6.0 mmol/L. Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1 ratio to ZS or placebo.

The study includes a single treatment visit no longer than 24h followed by a single follow up contact 7 days later.

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the reduction of potassium at 4 hours after start of dosing	Mean absolute change in S-K from baseline until 4h after start of dosing
Secondary objectives:	**Endpoint/variable:**
To assess the effect of ZS vs placebo when added to insulin and glucose on the response to therapy	Fraction of patients responding to therapy with responders to therapy defined as • S-K <6.0mmol/L between 1 and 4h and S-K <5.0mmol/L at 4h AND • No additional therapy administered for hyperkalaemia from 0 to 4h with exception of the initial insulin treatment administered at 0h
To assess the effect of ZS vs placebo when added to insulin and glucose on the change in serum potassium at 1h and 2h after start of dosing	Mean absolute change in S-K from baseline to 1 and 2h after start of dosing
To assess the effect of ZS vs placebo when added to insulin and glucose on achieving normokalaemia	The fraction of patients achieving normokalaemia 1, 2 and 4h after start of dosing

To assess the effect of ZS vs placebo when added to insulin and glucose on achieving S-K <5.5mmol/l and <6.0mmol/l

The fraction of patients achieving S-K <5.5mmol/l and <6.0mmol/l 1, 2, and 4h after start of dosing

To assess the need for additional therapies for hyperkalaemia between ZS and placebo when added to insulin and glucose

The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 0 to 4h. The considered therapies are:

- 2nd dose of insulin
- Beta-agonists
- Diuretics
- Dialysis
- Sodium bicarbonate

Safety objective:	**Endpoint/variable:**
To characterize the safety of ZS when added to insulin and glucose	Adverse events (AEs) and serious AEs (SAEs) Changes in vital signs (VS), physical examinations, and ECGs Changes in clinical laboratory parameters, including assessment of hypokalaemia using S-K measurements and of hypoglycaemia using P-glucose measurements

Take home message

- Hyperkalaemia is prevalent in patients with CKD, HF, diabetes and in those treated with RAASi therapy
- High serum potassium levels are associated with increased hospitalisations and mortality, and may limit the use of life-saving RAASi therapy
- Current treatments for hyperkalaemia have limitations:
  - Most emergency therapies do not remove excess potassium and have short durations of action
  - Treatments that can remove potassium also have disadvantages, e.g. diuretics, dialysis and SPS
  - Long-term management may involve low-potassium diets, which are difficult to follow, lowering RAASi dosing, which may increase mortality, and potassium binders

Take home message

- ZS-9 resulted in significantly lower serum K^+ than placebo
- Results were consistent for all patient subgroups, including those with CKD, HF, and DM, or on RAASi therapy

GRAZIE

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