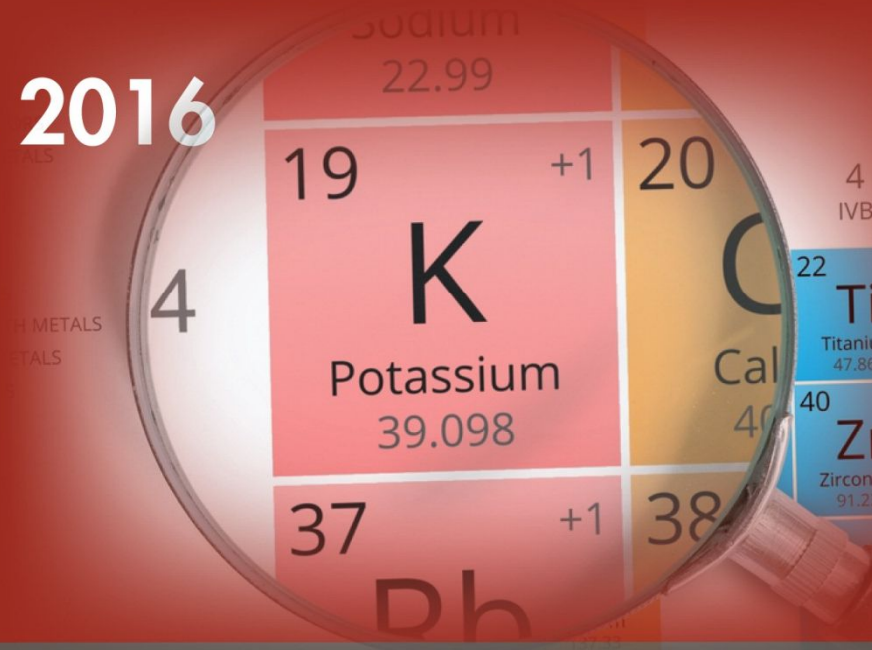
OPTIMIZING OUTCOMES IN HYPERKALEMIA:

An Update for Health-System Pharmacists

Wednesday, December 7, 2016
11:30 AM to 1:00 PM

Mandalay Bay,
North Convention Center



University of Tennessee College of Pharmacy

Advanced Studies in Pharmacy®

A Midday Symposium conducted at the 51st ASHP Midyear Clinical Meeting and Exhibition.

Food and beverage are no longer provided at Midday.

This activity is supported by an educational grant from ZS Pharma

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- ***Albuterol***
- ***Calcium chloride***
- ***Calcium gluconate***
- ***Insulin***
- ***Loop diuretics***
- ***Sodium bicarbonate***
- ***Sodium zirconium cyclosilicate***

Agenda

Overview and Activity Goals
Kristy N. Greene, PharmD, BCPS, BCCCP

Overview of Hyperkalemia
Kristy N. Greene, PharmD, BCPS, BCCCP

Correcting Hyperkalemia
Kelly Harbourt, PharmD, BCPS, BCCCP

Pharmacist Strategies to Optimize Hyperkalemia Outcomes
Kristy N. Greene, PharmD, BCPS, BCCCP, and Kelly Harbourt, PharmD, BCPS, BCCCP

Concluding Remarks/Question and Answer Session
Kelly Harbourt, PharmD, BCPS, BCCCP

Learning Objectives

- **RECOGNIZE** precipitating factors, including clinical conditions and medication therapy, that contribute to the development of hyperkalemia.
- **IDENTIFY** and compare available treatment options for acute and chronic hyperkalemia, including novel agents.
- **APPLY** pharmacist-driven strategies to optimize treatment for hyperkalemia.

CPE Information

INTENDED AUDIENCE – This activity is designed for health-systems pharmacists. No prerequisites required.

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Educational Grant

The University of Tennessee
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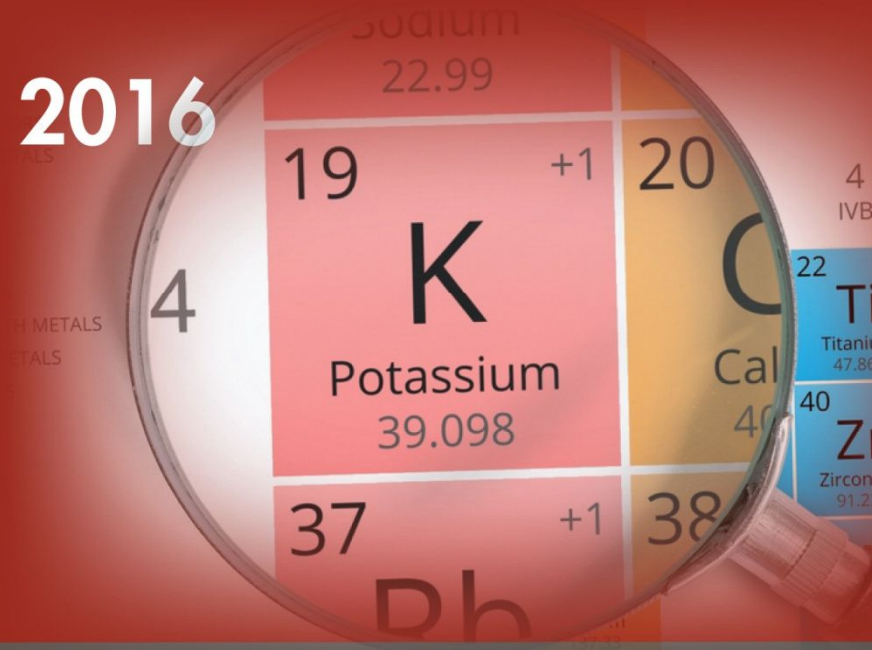

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Optimizing the Management of Hyperkalemia: *An Update for Health-System Pharmacists*

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Overview of Hyperkalemia

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Learning Agenda

- Review potassium homeostasis
- Identify factors promoting potassium shifts including the renin-angiotensin-aldosterone system (RAAS)
- Discuss etiologies and risk factors associated with hyperkalemia
- Describe electrocardiogram (ECG) changes associated with hyperkalemia

Hyperkalemia

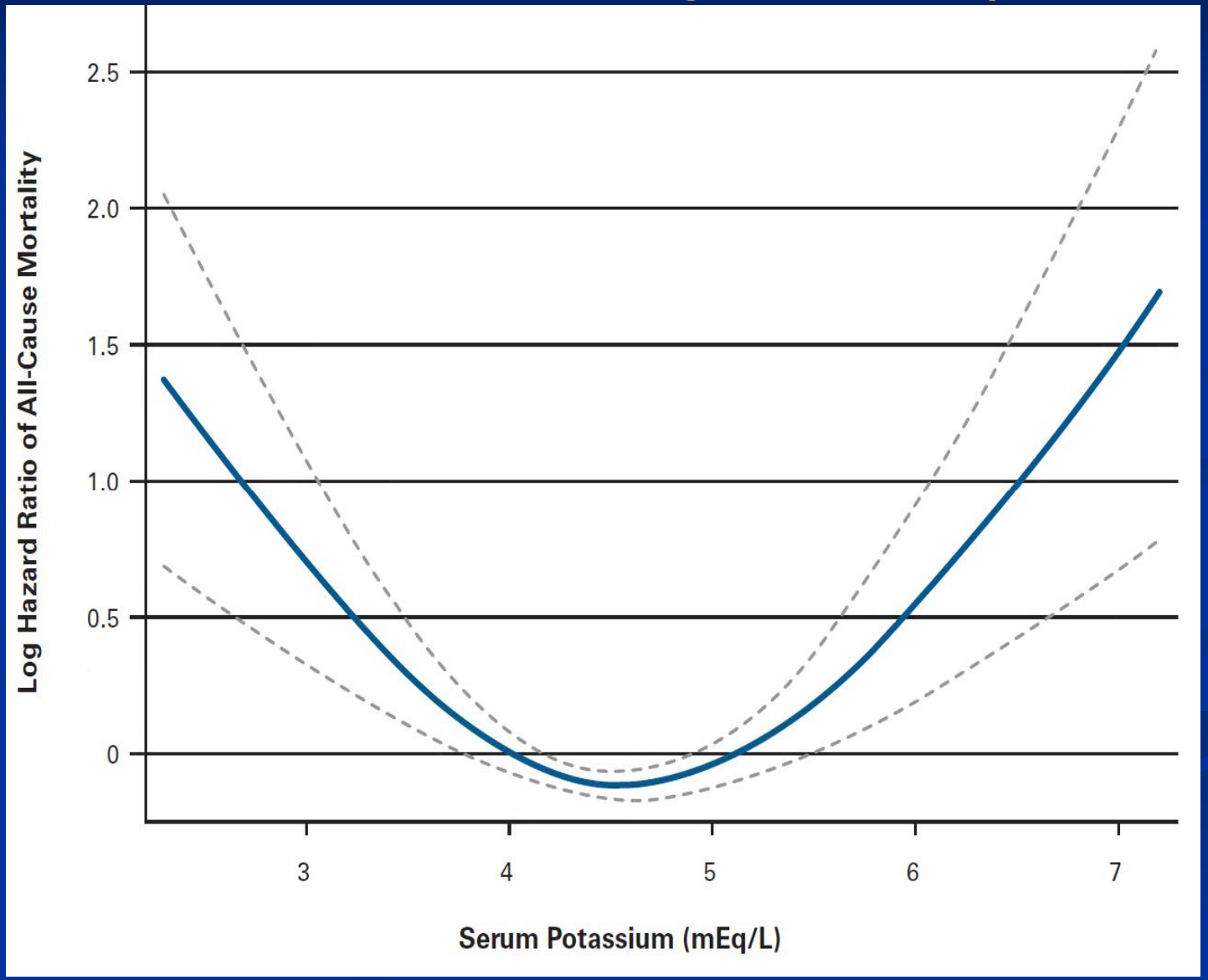
- Defined as a serum potassium level above the reference range, >5.0 mEq/L
- Associated with muscle weakness, paralysis, and life-threatening effects on cardiac conduction
- Incidence and prevalence rates are reported between 1 and 10 per 100 patients.
- A hyperkalemic episode in a CKD patient increases the odds of mortality within 1 day of the event.

Hyperkalemia Frequency (%)	
General Population	CKD
2–3	40–50

CKD = chronic kidney disease.

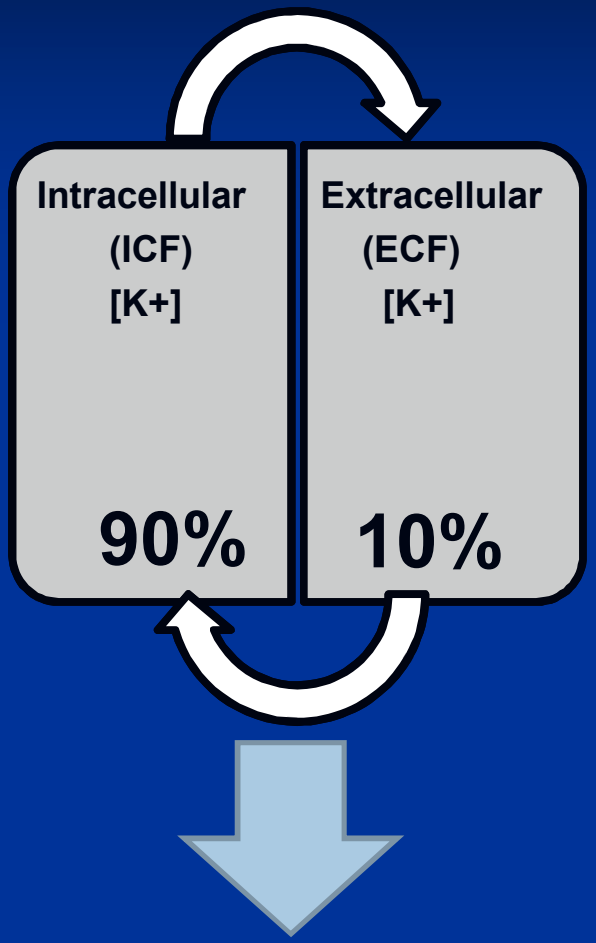
Arch Intern Med. 2009;169:1156-1162; *Nat Rev Nephrol*. September 16, 2014.

All-Cause Mortality Associated with Serum Potassium Levels in Non-Dialysis-Dependent Patients with Chronic Kidney Disease (*n* = 1227)



Clin Pract. 2012;120(1):C*-C16. For educational purposes only.

Potassium Homeostasis

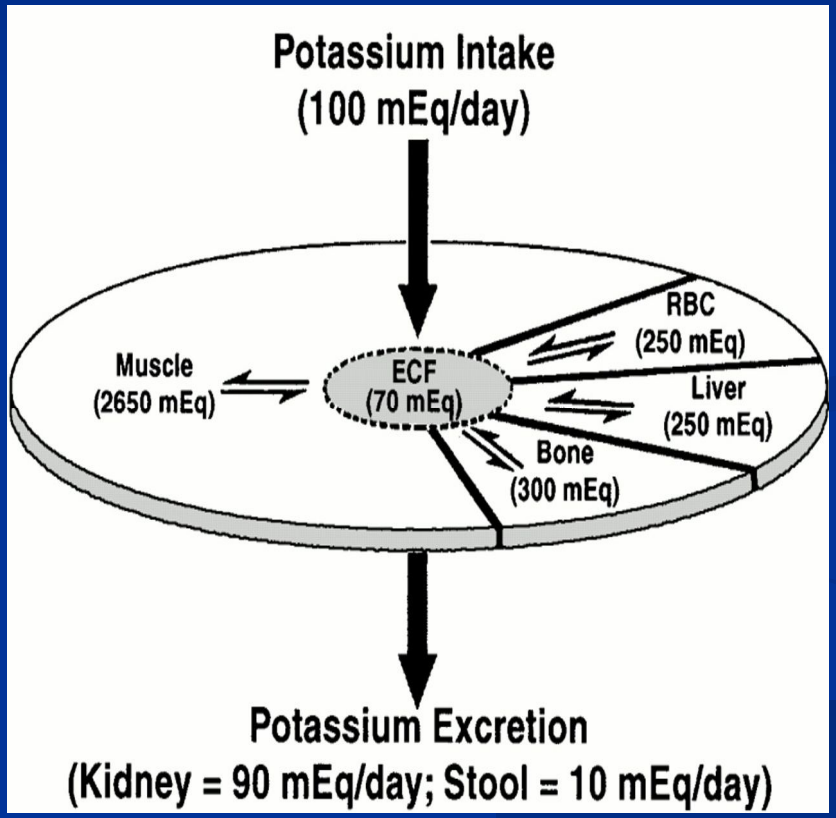


Factors Stimulating Potassium Shifts	
ECF to ICF	ICF to ECF
Insulin release	Mineral acidosis
Catecholamines	Hyperosmolarity
Metabolic alkalosis	Nonselective beta blockade
Anabolic state	Alpha-1 stimulation

ECF = extracellular fluid; ICF = intracellular fluid.

Electrolyte Blood Press. 2013;11(1):9-16.

Potassium Homeostasis

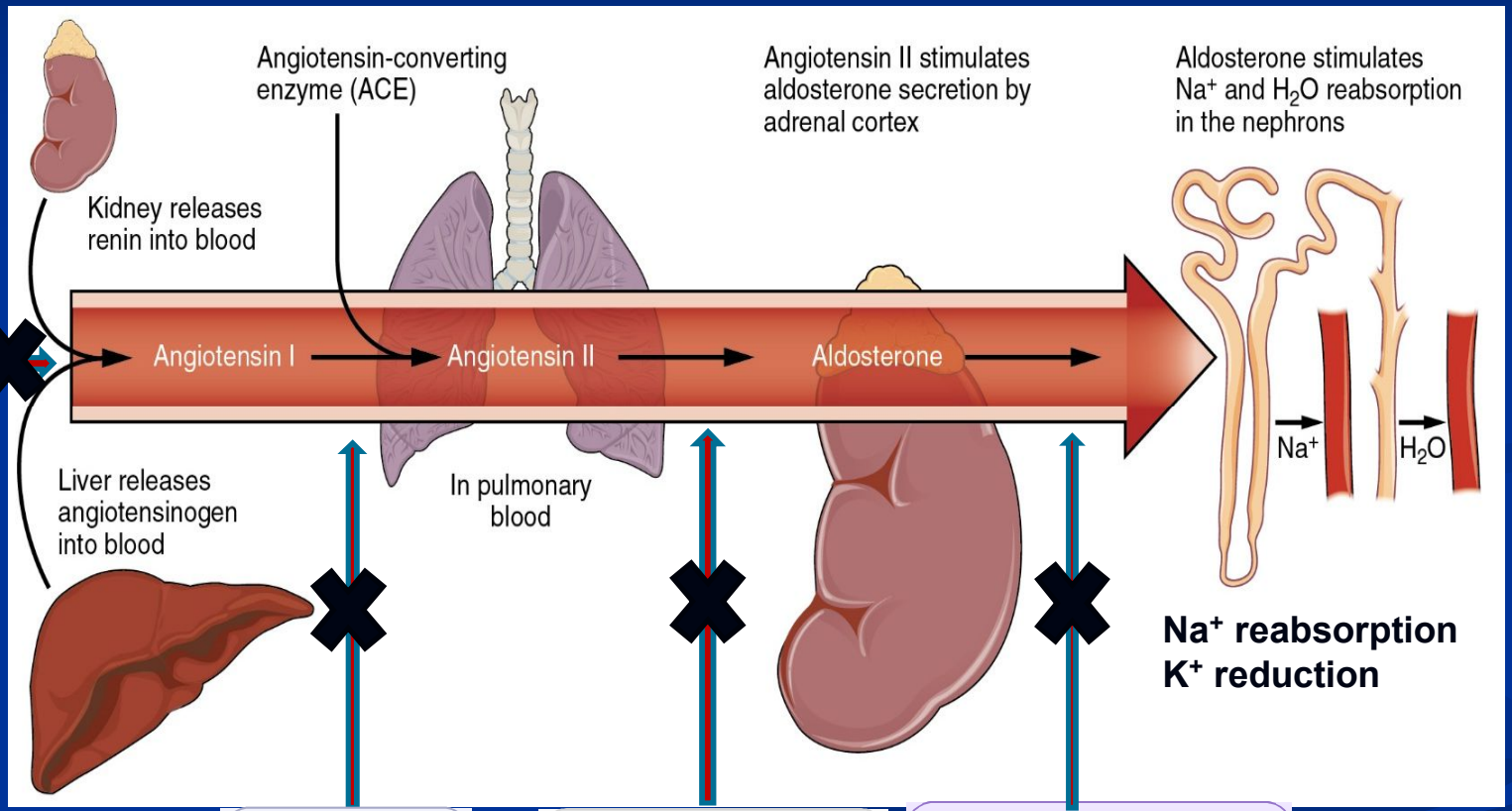


Internal balance

External balance

RBC = red blood cell.
For educational purposes only.

Renin-Angiotensin-Aldosterone System



Renin inhibitors

ACE inhibitors (ACE-I)

Angiotensin-receptor blockers (ARBs)

Aldosterone receptor antagonists

Electrolyte balance. archive.cnx.org. Available at: http://archive.cnx.org/contents/ca0c80ce-7586-419b-a890-6bdad12ec809@4/electrolyte-balance. For educational purposes only.

Etiologies

Impaired Renal Excretion	Extrinsic Factors	Intracellular to Extracellular Potassium Shift	Diet
• Renal insufficiency or failure	• Exogenous potassium intake • Medications	• Metabolic acidosis • Hemolytic states • Tissue damage	• Orange juice, nectarines, kiwis, raisins, dried fruit, bananas, cantaloupe, honeydew, prunes

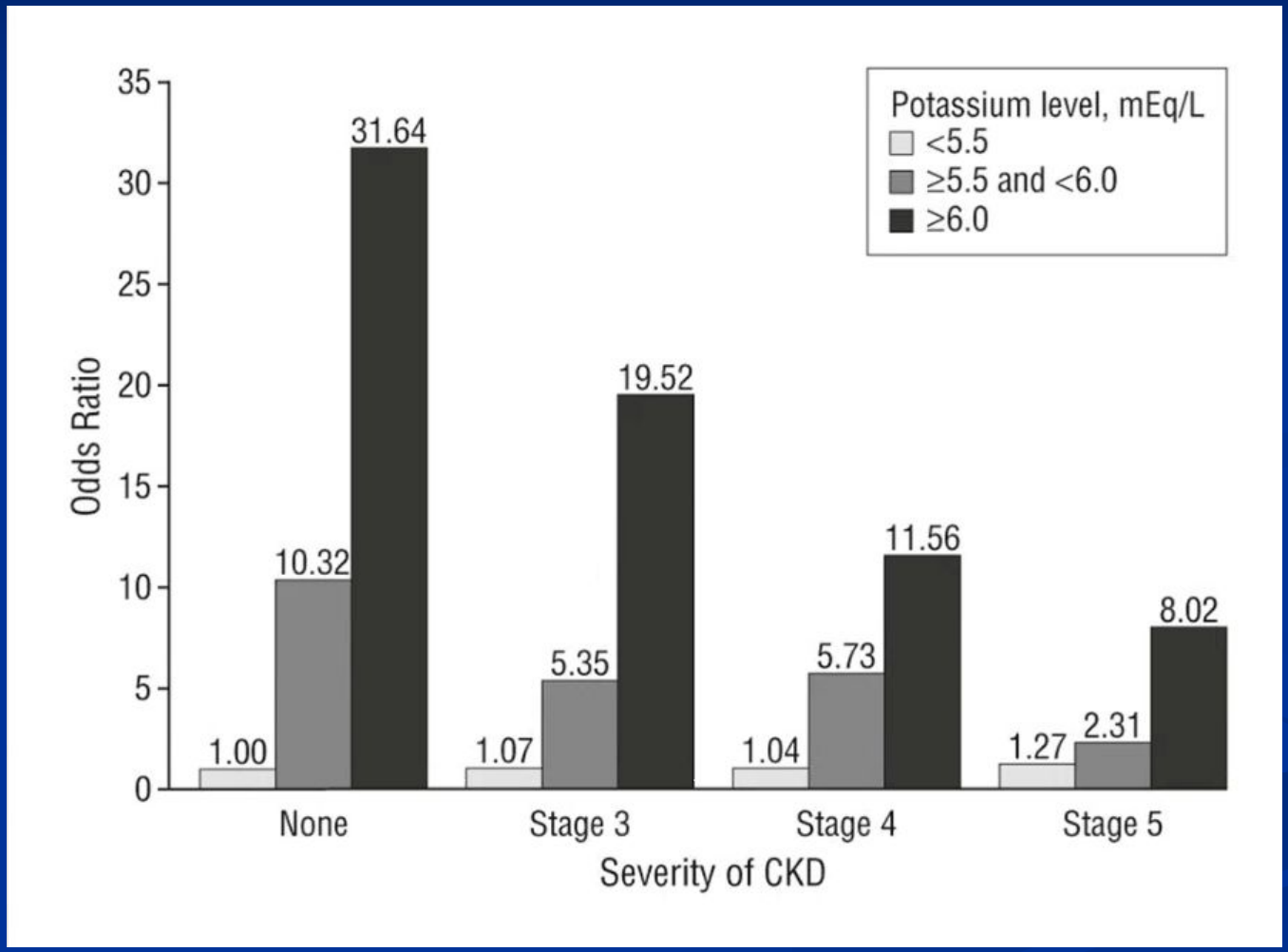
J Am Soc Nephrol. 1998;9:1535-1543; *Am J Manag Care*. 2015;21:S307-S325.

Risk Factors

- Age
- Renal insufficiency or CKD
- Diabetes
- Hypertension (HTN)
- Congestive heart failure (CHF)
- High protein intake
- Medications promoting potassium retention
  - Use of RAAS inhibitors (RAASi) – with increased risk if presence of HTN, CKD, or CHF

Clin J Am Soc Nephrol. 2010;5:531–548; *Postgrad Med J*. 1995;71(839):551-552; *Curr Hypertens Rep*. 2016;18:55.

Hyperkalemia Risk (with and without CKD)



***P* < .001** for all moderate and severe hyperkalemia groups

***P* < .05** for Stage 5 with normokalemia vs reference group

Normokalemia <5.5 mEq/L; moderate ≥5.5 mEq/L and <6.0; severe ≥6.0 mEq/L

Arch Intern Med. 2009;169:1156-1162.

Conditions

- Hyperkalemia secondary to type IV renal tubular acidosis includes the following:
  - Diabetes mellitus
  - Sickle cell disease or trait
  - Lower urinary tract obstruction
  - Adrenal insufficiency
  - Primary Addison's disease due to autoimmune disease, tuberculosis, or infarct
  - Enzyme deficiencies
  - Genetic disorders
- Burns (electrical and thermal)

Agents Causing Hyperkalemia

Causes	Medication
Drugs that promote transmembrane potassium shift	Nonselective beta-blockers (eg, propranolol, labetalol, carvedilol), digoxin intoxication, mannitol
Drugs that affect aldosterone secretion	ACE inhibitors (eg, benazepril, lisinopril), direct renin inhibitors (eg, aliskiren), NSAIDs and COX-2 inhibitors (eg, ibuprofen, celecoxib), calcineurin inhibitors (cyclosporine, tacrolimus)
Drugs that cause tubular resistance to action of aldosterone or renin release	Aldosterone antagonists (eg, spironolactone, eplerenone) and other potassium-sparing diuretics (eg, amiloride, triamterene), trimethoprim, pentamidine, heparin
Agents that contain potassium	Salt substitutes and alternatives, penicillin G, stored blood products
Other	Succinylcholine, herbal supplements

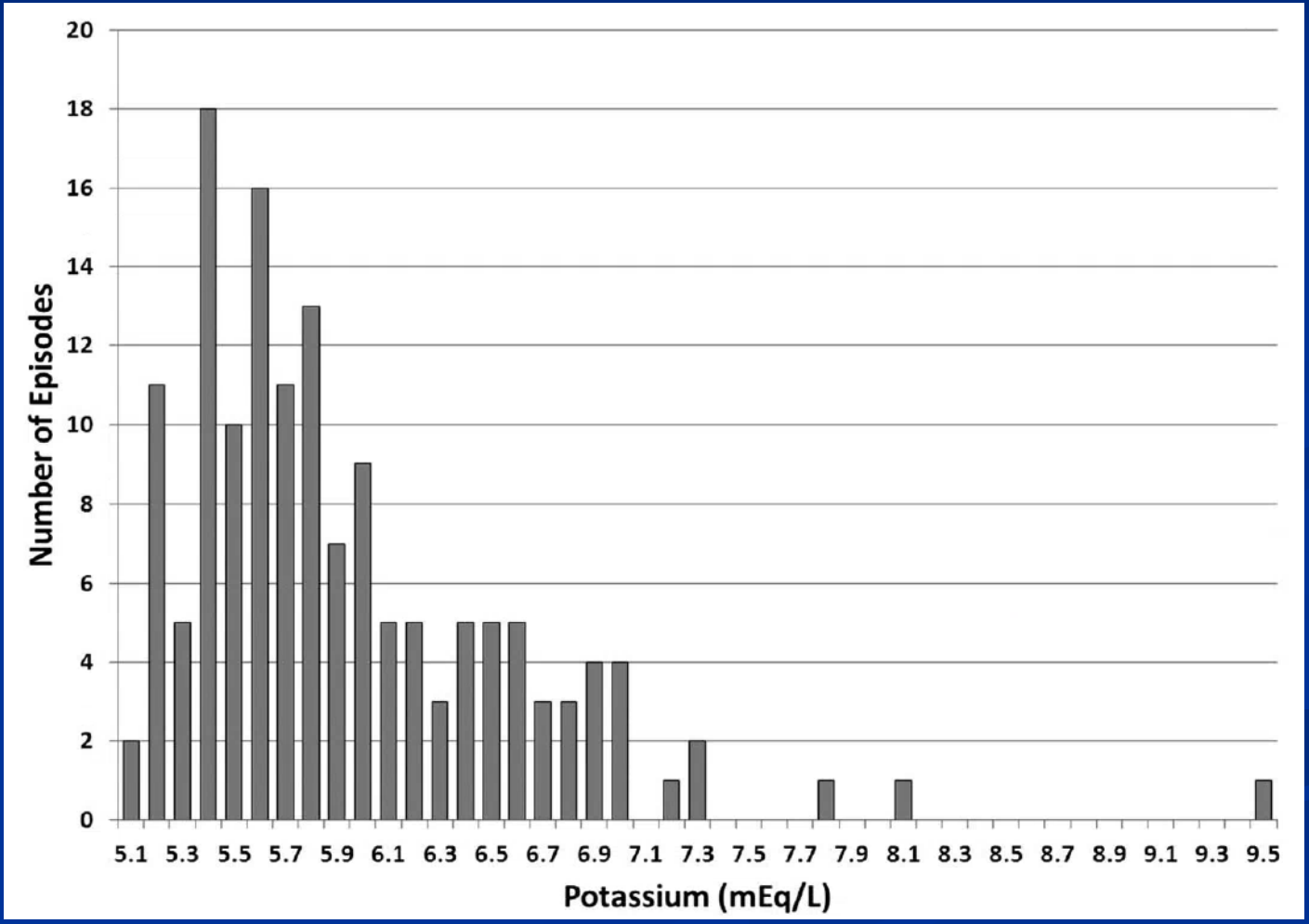
COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal anti-inflammatory drugs.

Drug Saf. 2014;37:677-692; *Am J Manag Care*. 2015;21:s307-s325.

Signs and Symptoms

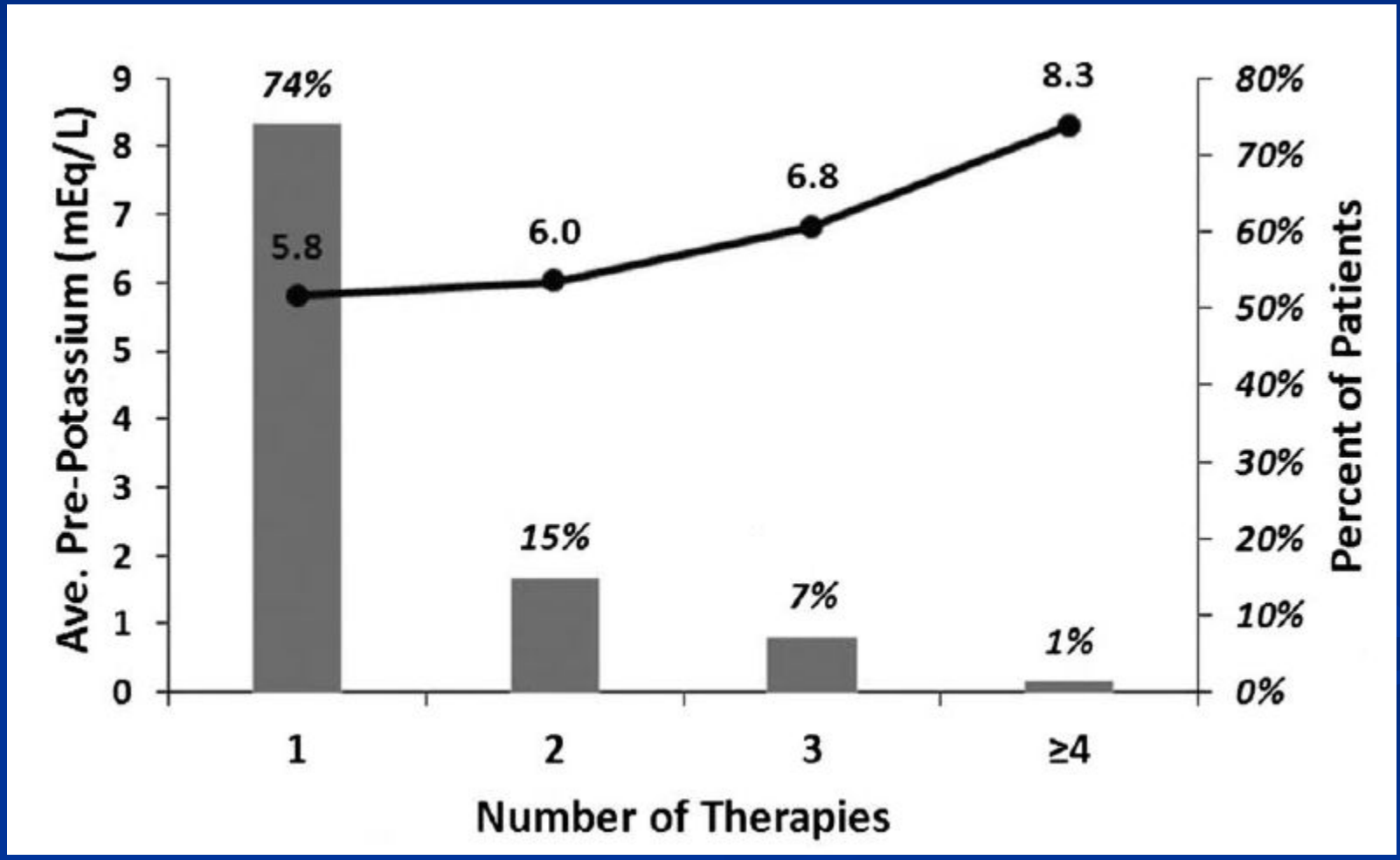
- Frank muscle paralysis
- Dyspnea
- Palpitations
- Chest pain
- Nausea or vomiting
- Paresthesias

Pretreatment Potassium Concentrations



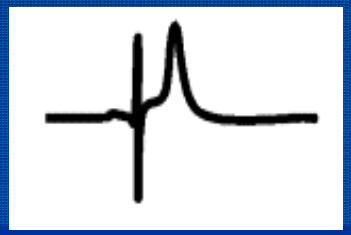
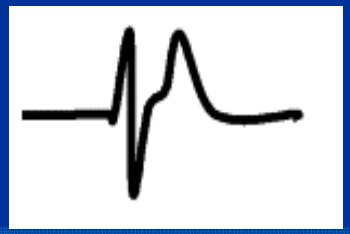
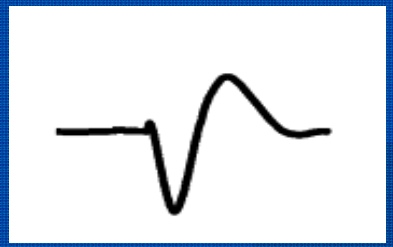
Am J Med Sci. 2014;347:93-100. For educational purposes only.

Mean Pretreatment Potassium Concentration Prompting Treatment



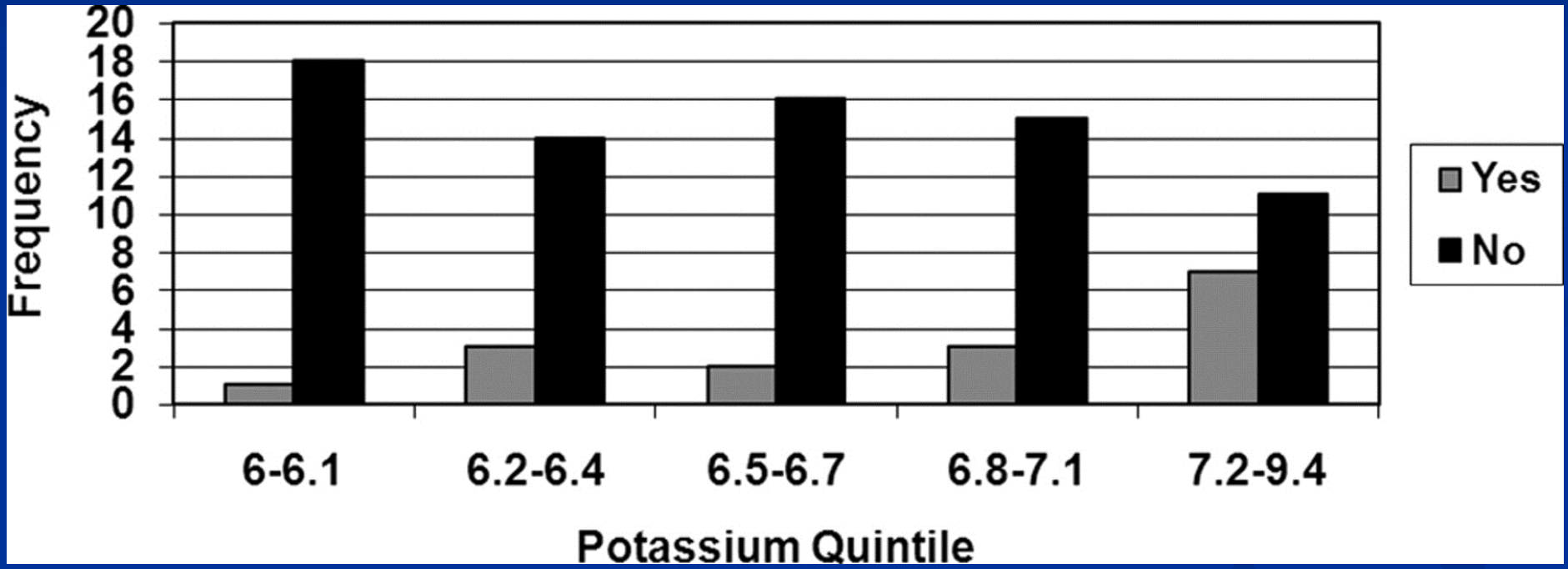
Am J Med Sci. 2014;347:93-100. For educational purposes only.

Electrocardiogram Changes

Serum Potassium	Typical ECG Appearance	Possible ECG Abnormalities
Mild (5.6–6.4 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5–8.0 mEq/L)		Loss of P wave Prolonged QRS complex ST-segment elevation Ectopic beats and escape rhythm
Severe (>8.0 mEq/L)		Progressive widening of QRS sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

Emerg Med. 2004;27:153-160.

ECG Changes



Clin J Am Soc Nehprol. 2008;3:324-330. For educational purposes only.

Hyperkalemia in Hospitalized Patients

	No. of ECGs Performed	Potassium Concentration (mEq/L)	No ECG-Related Changes (%)
Fordjour KN, Walton TW, Doran JD, et al.	70	≥6.5	50
Acker CG, Johnson JP, Palevsky PM, et al.	54	≤6.8	57

Am J Med Sci. 2014;347(2):93-100; *Arch Intern Med.* 1998;158:917-924.

Identification

- Vital signs are usually normal (exceptions: bradycardia or tachypnea).
- Muscle weakness and flaccid paralysis
- Depressed or absent deep tendon reflexes

Identification

Blood samples from a vein or line into which potassium is being infused

Laboratory error

Pseudohyperkalemia

(hemolysis, leukocytosis, thrombocytosis)

Repeated clenching of fist during phlebotomy

Uncommon genetic syndromes

Crit Care Clin. 2001;18:273-288; *Nephron.* 2002;92:40.

Identification

- Investigate pathophysiologic mechanisms
- Rule out spurious elevations
- Determine existing predispositions to hyperkalemia
- If absence of contributing factors, repeat blood test

Factors Requiring Treatment

- Presence of clinical symptoms
- Presence of ECG changes

Laboratory Testing

ECG

Urine potassium, sodium, osmolality

Complete blood count

Metabolic profile

Glucose level

Digoxin level

Arterial or venous blood gas

Urinalysis

Cortisol and aldosterone levels

Serum uric acid and phosphorus

Serum creatinine phosphokinase

Urine myoglobin

Clin J Am Soc Nephrol. 2011;6:1963-1972.

Correcting Hyperkalemia

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Department of Clinical and Administrative Sciences
Notre Dame of Maryland University School of Pharmacy
Clinical Pharmacy Specialist Multitrauma ICU
University of Maryland Medical Center
Baltimore, Maryland

Learning Agenda

- Discuss management of underlying causes of hyperkalemia
- Review traditional methods to correct acute and chronic hyperkalemia
- Describe novel agents for treatment of hyperkalemia including patiromer sorbitex calcium and sodium zirconium cyclosilicate (ZS-9)

Treatment of Underlying Cause

- Impaired renal excretion of potassium
  - Supportive care for management of acute and/or chronic kidney disease
- Extrinsic factors
  - Removal of offending agent
  - Discontinuation of exogenous potassium supplementation
- Treatment of disease states that cause extracellular shifting of potassium
  - Acidosis
  - Rhabdomyolysis
  - Tumor lysis syndrome

Acute Hyperkalemia

- Singular event constituting a medical emergency
- Characterized by a rapid increase in potassium
- Requires immediate evaluation and rapid reduction in potassium but no ongoing treatment
- Three phases of management
  - Stabilization of myocardium
  - Shifting of potassium to the intracellular space
  - Elimination of potassium

Clinical Updates in Hyperkalemia. National Kidney Foundation; 2014. Available at: www.kidney.org.

Stabilization of Myocardium

- Obtain and evaluate patient 12-lead ECG
- Prompt administration of IV calcium
  - Stabilizes myocardium by increasing threshold potential thereby preventing ventricular arrhythmias
  - Does not change potassium concentration
  - Calcium chloride 1 g IV or calcium gluconate 2–3 g IV
  - Central venous access is preferred for administration of calcium chloride.

IV = intravenous.

Kidney Int. 2016;89:546-554.

Shifting of Potassium to Intracellular Space

- All agents that shift potassium intracellularly are temporary solutions.
- Insulin
  - Insulin regular 10 units IV + dextrose 50% IV 50 mL (25 g)
  - Coadministration of dextrose prevents hypoglycemia.
  - Duration of effect: ~4–6 hours
- $Beta_2$ agonists
  - Albuterol 10–20 mg nebulization
  - Decrease serum K+ by 0.3–0.6 mEq/mL in 30 minutes

Activate Na/K+ ATPase pumps

- Sodium bicarbonate
  - Sodium bicarbonate 50–100 mEq IV x 1 dose
  - Varying data regarding duration of action (~2 hours)

Causes Na/H+ exchange, in turn

Am J Med. 2015;128:1281-1287; *Kidney Int.* 2016;89(3):546-554.

Elimination of Potassium

- Decrease/eliminate all potassium intake
- Increase urinary elimination
  - Loop diuretics
  - Requires adequate renal function for drug to reach site of action
  - Efficient diuresis is required for sufficient kaliuresis.
- Increase fecal elimination
  - Sodium polystyrene sulfonate (SPS)
- Dialysis
  - Resource intensive
  - Poses risk to patient – particularly those not already on chronic dialysis

Kidney Int. 2016;89:546-554.

Sodium Polystyrene Sulfonate

- FDA approval in 1958
- Mechanism of action
  - Exchanges sodium ions for potassium ions in the large intestine, which are then excreted in feces
  - Onset of action: 2–24 hours
- Efficacy
  - Patient-dependent
  - May decrease K^+ by up to 0.9 mEq/L
- Warnings/Precautions
  - May cause intestinal necrosis and/or fecal impaction, particularly when administered with sorbitol
  - Not appropriate for long-term use

FDA = US Food and Drug Administration.

Kidney Int. 2016;89:546-554; Sodium polystyrene sulfonate [package insert]. Sanofi-Aventis; 2009.

Acute Hyperkalemia Treatment Summary

Medication	Dose	Route	Onset of Action	Duration of Effect*	Mechanism of Action
Calcium chloride 10% or Calcium gluconate 10%	6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate)	IV	1–3 minutes	30–60 minutes	Cardiac membrane potential stabilization
Sodium bicarbonate	50–100 mEq	IV	5–10 minutes	~2 hours	Intracellular shift of K^+
Insulin regular	10 units	IV	30 minutes	4–6 hours	Intracellular shift of K^+
Albuterol	10–20 mg	Inhalation	30 minutes	2–4 hours	Intracellular shift of K^+
Loop diuretics	40 mg furosemide or equivalent	IV	5–10 minutes (varies with start of diuresis)	As long as diuresis is present	Renal excretion of K^+
Dialysis	N/A	Hemodialysis or CRRT	Within minutes of starting therapy	Patient-dependent	Removal of K^+

*Duration of effect for agents that eliminate potassium depend on ongoing potassium redistribution and/or ongoing potassium intake.

CRRT = continuous renal replacement therapy; N/A = not applicable.

Adapted from: *Pharmacy Times.* 2016:109-117.

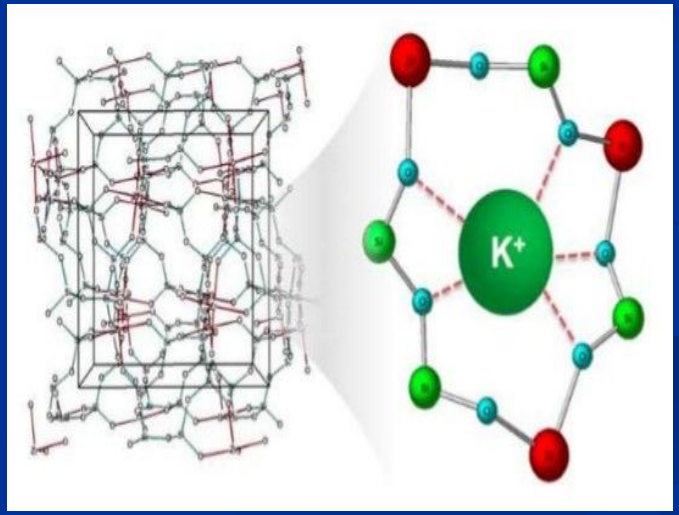
Chronic Hyperkalemia

- Greater than one event per year requiring ongoing management
- Caused by chronic impairment of potassium excretion
- Patients at greatest risk
  - CKD
  - Receiving medications that cause RAAS inhibition
- Goals of therapy
  - Prevent development and recurrence of hyperkalemia by correcting underlying cause

Clinical Updates in Hyperkalemia. National Kidney Foundation; 2014. Available at: www.kidney.org.

Novel Agents for Hyperkalemia

- Patiromer sorbitex calcium
- Sodium zirconium cyclosilicate (ZS-9)



Patiromer Sorbitex Calcium

- FDA approval date: October 21, 2015
- Mechanism of action
  - Non-absorbed, cation-exchange polymer containing a calcium-sorbitol counterion; binds potassium in lumen of GI tract resulting in reduction of potassium levels
- Adult dose
  - 8.4 g PO once daily
  - May increase dose at ≥1-week intervals by 8.4 g (maximum dose: 25.2 g/day)

STATUS

November 27, 2016

FDA approves a supplemental New Drug Application with updates to the label of patiromer for oral suspension. The label no longer includes a Boxed Warning regarding the separation of patiromer and other oral medications. The updated label recommends patients take patiromer at least 3 hours before or 3 hours after other oral medications.

GI = gastrointestinal; PO = by mouth.

Patiromer sorbitex calcium [package insert]. Redwood City, CA: Relypsa; 2015.
FDA Approves Supplemental New Drug Application for Veltassa Removing Boxed Warning Regarding Drug-Drug Interactions. Relypsa Web site. Available at: http://www.relypsa.com/newsroom/press-releases/112716/. Accessed on: December 13, 2016.

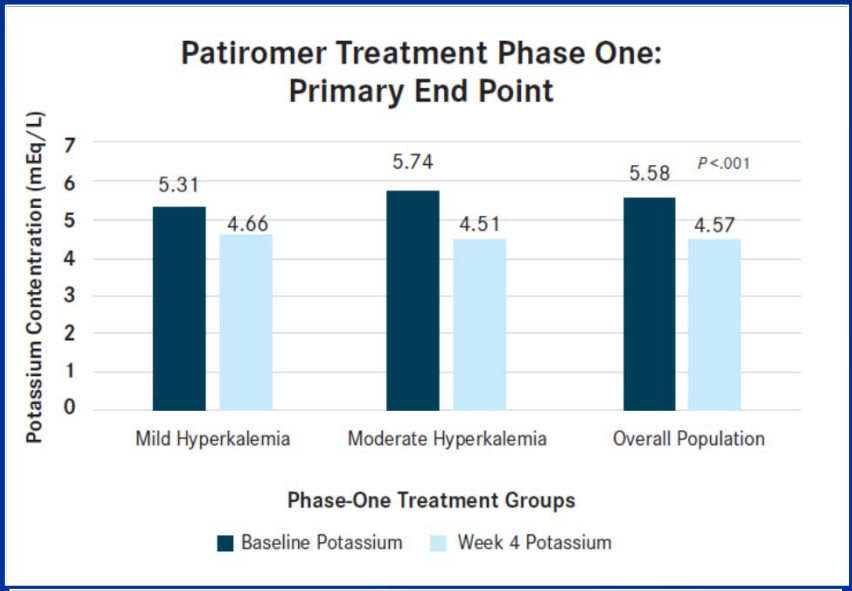
Patiromer Sorbitex Calcium

- Precautions
  - Avoid use in patients with severe constipation, bowel obstruction, or impaction
  - May worsen GI conditions
- Adverse effects
  - Hypomagnesemia (5%–9%)
  - Constipation (7%), diarrhea (5%), abdominal distress/flatulence (2%)
- Average wholesale price
  - 8.4 g (4): $142.80
  - 16.8 g (1): $23.80
  - 25.2 g (1): $23.80

Patiromer sorbitex calcium [package insert]. Redwood City, CA: Relypsa, 2015.

Patiromer – Clinical Efficacy & Safety Data

OPAL-HK	
Study Design	Two-phase, single-blind, randomized withdrawal study
Population	243 patients with CKD and hyperkalemia receiving ≥1 RAAS-inhibiting drug
Intervention	Phase 1: Patiromer x 4 weeks titrated to maintain K+ 3.8–5.1 mEq/L Phase 2: One arm crossover to placebo to evaluate persistence of effect; remaining patients continued on patiromer for 4 additional weeks
Outcomes	Primary outcome: reduction in potassium at 4 weeks and 8 weeks
Results	Phase I: reduction of 1.01 mEq/L in overall population ($P < .001$) Phase II: recurrence 60% in placebo vs 15% in patiromer group ($P < .001$)



Reduction of potassium in OPAL-HK phase I

N Engl J Med. 2015;372:211-221. For educational purposes only.

Patiromer – Clinical Efficacy & Safety Data

PEARL-HF	
Study Design	Randomized, double-blind, placebo-controlled trial
Population	*N* = 105; patients had indication for spironolactone therapy + either CKD with GFR <60 mL/min OR history of hyperkalemia that led to discontinuation of a RAASi
Exclusion Criteria	Severe GI disorders, unstable arrhythmias, obstructive or restrictive cardiomyopathy, ACS, TIA, QTc >500 ms, receiving or anticipating needing dialysis, SBP >170 or <90, LFTs >3 x ULN
Intervention	• Randomized to patiromer 30 g once daily or placebo for 4 weeks • Spironolactone initiated on day 1 and titrated to 25 mg on day 15 if potassium is ≤5.1 mEq/L
Outcomes	• Serum potassium levels at 4 weeks • Incidence of hyperkalemia • Rate of successful titration of spironolactone
Results	• Serum potassium reduced by 0.45 mEq/L more in patiromer vs placebo (*P* < .001) • Incidence of hyperkalemia 7.3% patiromer vs 24.5% placebo (*P* =.015) • Proportion of patients having successful up-titration of spironolactone: 91% vs 74% (*P* = .019) • Incidence of hyperkalemia in CKD patients: 6.7% vs 38.5% (*P* = .041)

ACS = acute coronary syndrome; GFR = glomerular filtration rate; LFT = liver function test; SBP = systolic blood pressure; TIA = transient ischemic attack; ULN = upper limit of normal.

Eur Heart J. 2011;32:820-828.

Patiromer – Clinical Efficacy and Safety Data

AMETHYST-DN	
Study Design	Phase II, randomized, multicenter, open-label, dose-ranging trial conducted at 48 sites in Europe from June 2011 to June 2013
Patient Population	• 306 outpatients with diabetes, kidney disease (GFR 15–60 mL/min) and hyperkalemia • All patients received RAAS-inhibitors prior to and during study (ACE inhibitor or ARB + spironolactone)
Intervention	Patients were stratified by baseline serum potassium level • Mild hyperkalemia (5 to 5.5 mEq/L) received patiromer 4.2 g, 8.4 g, or 12.6 g twice daily • Moderate hyperkalemia (>5.5 to <6 mEq/L) received patiromer 8.4 g, 12.6 g, or 16.8 g twice daily • Patiromer was titrated to maintain serum potassium level ≤5.0 mEq/L
Outcomes	Primary efficacy: Mean change in serum potassium level from baseline to week 4 Primary safety: Adverse events through 52 weeks Secondary efficacy: Mean change in serum potassium level through 52 weeks
Results	Primary efficacy outcome *Mild hyperkalemia group*: -0.35 mEq/L for the 4.2 g group; -0.51 mEq/L for the 8.4 g group; and 0.55 mEq/L for the 12.6 g group *Moderate hyperkalemia*: -0.87 mEq/L for the 8.4 g group, -0.97 mEq/L for the 12.6 g group, and -0.92 mEq/L for the 16.8 g group • *P* <.001 for all changes vs baseline Primary safety outcome: Hypomagnesemia (7.2%), mild to moderate constipation (6.3%) and hypokalemia <3.5 mEq/L (5.6%) Secondary efficacy outcome: Statistically significant mean decreases in K+ at every monthly check point in both groups

AMETHYST-DN = Patiromer in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy.

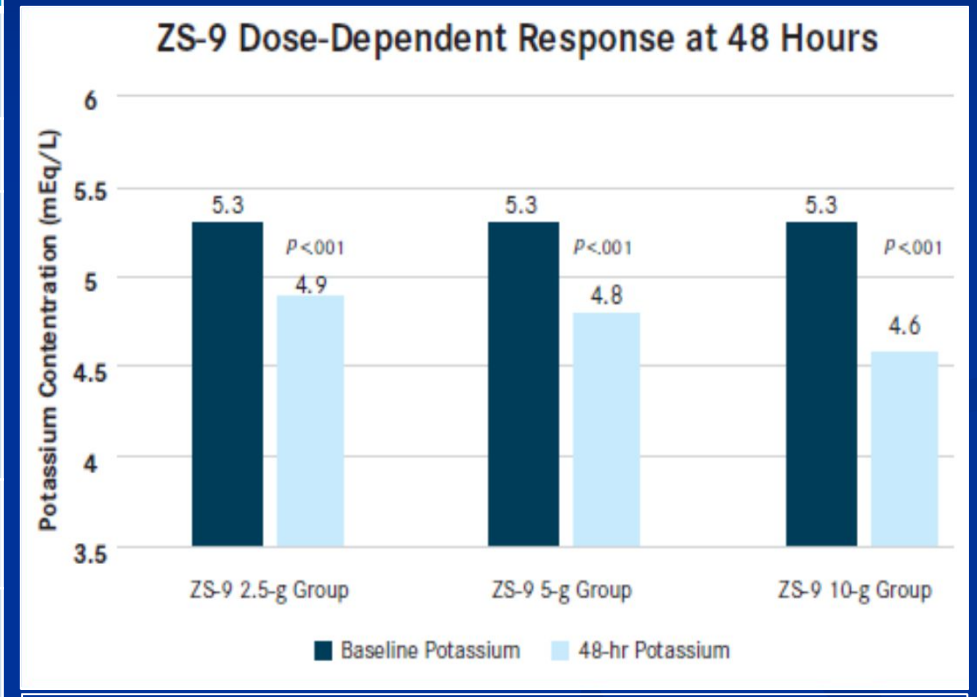
JAMA. 2015; 314 :151-161.

Sodium Zirconium Cyclosilicate (ZS-9)

- FDA status: pending
- Mechanism of action
  - Selective cation exchanger that binds potassium in exchange for hydrogen and sodium ions
- Dose range studied: 1.25–15 g PO once daily
- Adverse effects
  - Mild GI effects (nausea, diarrhea, constipation, abdominal pain)
  - Mild edema and hypokalemia in high-dose groups when studied

ZS-9 – Clinical Efficacy & Safety Data

Sodium Zirconium Cyclosilicate in Hyperkalemia	
Study Design	**Multicenter, 2-stage, double-blind, phase III trial**
Population	**753 patients with hyperkalemia**
Intervention	**Stage 1: ZS-9 or placebo TID for 48 hours Stage 2: patients with normokalemia were randomized to either ZS-9 or placebo once daily for the remaining 2 weeks**
Outcomes	**Exponential rate of change in mean potassium at 48 hours**
Results	**• Mean reduction in potassium at 48 hours was -0.3 mEq/L. • Potassium remained at 4.7 and 4.5 mEq/L for the 5-g and 10-g groups, respectively.**
AEs	**GI effects (2%–8%)**



Reduction of potassium in ZS-9 phase III trial

AE = adverse effects; TID = 3 times a day.

N Engl J Med. 2015;372:222-231. For educational purposes only.

ZS-9 – Clinical Efficacy & Safety Data

HARMONIZE	
Study Design	Phase III, multicenter, randomized, double-blind, placebo-controlled
Population	258 patients with potassium >5.1 mEq/L over 28-day period
Intervention	• All patients received ZS-9 10 g PO TID x 48 hours during initial open-label period. • Normokalemia was achieved in 237 patients who were then randomized to ZS-9 5, 10, 15 g or placebo once daily x 28 days. • 65% CKD patients, 35% heart failure; >50% remained on RAAS-inhibiting therapy
Outcomes	Serum potassium levels at 48 hours and 28 days
Results	• At 48 hours, mean reduction in potassium = 1.1 mEq/L ($P < .001$). • At 28 days, all doses of ZS-9 resulted in significant decrease in potassium and maintenance of reduction ($P < .001$ for all groups). • More patients on placebo returned to hyperkalemia during 28-day period.
Adverse Effects	Similar between ZS-9 and placebo groups; hypokalemia developed in the 10-g and 15-g groups

Eur J Heart Fail. 2015;17:1050-1056.

Sodium Zirconium Cyclosilicate (ZS-9)

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STATUS

- May 27, 2016: FDA sent Complete Response Letter (CRL) to AstraZeneca.
  - Cited observations in a preapproval manufacturing inspection
  - Acknowledged receipt of additional material that required review
- October 18, 2016: AstraZeneca submitted complete resubmission of NDA to FDA for sodium zirconium cyclosilicate.

NDA = New Drug Application.

AstraZeneca receives CRL from FDA [news release]. Redwood City, CA: ZS Pharma; May 27, 2016. https://www.astrazeneca.com/media-centre/press-releases/2016/astrazeneca-receives-complete-response-letter-from-us-fda-for-sodium-zirconium-cyclosilicate-zs-9-for-oral-suspension-for-treatment-of-hyperkalaemia-27052016.html. Accessed November 10 2016.

Comparison of Potassium-Binding Agents

Medication	Dose	Route	Onset of Action	Potassium-Lowering Effect	FDA Approval Status
Sodium polystyrene sulfonate	15 g given 1–4 times daily	PO/ rectal	3–4 hours	-0.9 mEq/L in 24 hours	Yes (1958)
Patiromer sorbitex calcium	8.4 g once daily, titrated weekly (maximum dose: 25.2 g)	PO	Not defined	-1.01 mEq/L over 4 weeks	Yes (2015)
Sodium zirconium cyclosilicate (ZS-9)	Studied in doses of 1.25, 2.5, 5, and 10 g	PO	2–3 hours	-1.1 mEq/L in 48 hours	No (NDA resubmitted October 2016)

Adapted from: *Pharmacy Times.* 2016:109-117.

Role in Therapy for Novel Agents

- Both agents have been shown to be effective in reducing and preventing hyperkalemia in patients with CKD and heart failure.
  - Included patients remaining on RAAS-inhibiting therapy
- May have a role in prevention and treatment of chronic hyperkalemia, allowing patients to remain on RAAS-inhibiting therapy
- Continuation of ACE inhibitors, ARBs, and/or spironolactone may enable patients to retain clinical outcome benefits proven with these medication classes.

Future Directions for Novel Agents

- Long-term safety and efficacy are unclear due to short duration of clinical trials.
  - Patiromer: maximum duration 52 weeks
  - ZS-9: maximum duration 28 days
- Additional trials are needed to assess clinical outcomes when patients are able to continue RAAS-inhibiting therapy.
  - CKD: cardiovascular-related mortality, progression of CKD
  - Heart failure: decreased HF hospitalizations, decreased mortality
- Further trials are needed to assess safety when used for longer durations.

N Engl J Med. 1992;327(10):685-691; *JAMA*. 2009;302:1658-1665; *Clin J Am Soc Nephrol*. 2010;5(3):531-548; *Ren Fail*. 2012;34(9):1095-1099. *JAMA*. 2015; 314:151-61.

Pharmacist Strategies to Optimize Hyperkalemia Outcomes

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Hyperkalemia Management - Four Steps

- Antagonize the effects of hyperkalemia
- Identify and remove sources of potassium
- Decrease serum potassium levels by promoting intracellular shifts
- Remove potassium from the body

Hyperkalemia Treatments

Medication	Dose	Potassium Reduction (mEq/L)	Clinical Pearls
Calcium chloride 10% or calcium gluconate 10%	6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate)	N/A	Does not affect potassium concentrations Can worsen digoxin toxicity Effective in normocalcemic patients Must give infusion in patients that do not have a central line.
Sodium bicarbonate	50–100 mEq	0.7	When administered by infusion, effect is delayed. Significant sodium load Can worsen acidosis in patients with respiratory insufficiency
Insulin regular	10 units	0.6–1.0	Give 50 mL of 50% dextrose 5% for normoglycemic patients (blood glucose <250 mg/dL). Consider 5% dextrose solution infusion to prevent hypoglycemia with repeated doses.

Am Fam Physician. 2006;73:283-290; *J Am Soc Nephrol*. 1998:1535-1543.

Hyperkalemia Treatments

Medication	Dose	Potassium Reduction (mEq/L)	Clinical Pearls
Albuterol	10–20 mg	0.62–0.98	Underdosing is common. Dose necessary for potassium reduction is 2–8 times that given via nebulizer and 50–100 times the dose by metered dose inhalers.
Loop diuretics	40 mg furosemide or equivalent	—	Caution in volume-depleted patients Limited efficacy in moderate-to-severe kidney disease
Dialysis	N/A	Dialysis dependent	Barriers: time, access (in nondialysis patients), invasive nature

Am Fam Physician. 2006;73:283-290; *J Am Soc Nephrol*. 1998:1535-1543.

A Pharmacist's Role in Hyperkalemia

- Identifying patients at risk
  - Clinical decision tools
  - Flags within electronic health record
- Treatment recommendations
  - Indirect
    - Hyperkalemia kits in automated dispensing cabinets
    - Order sets
  - Direct
    - Clinical recommendations during direct patient care
    - Participation in code/resuscitation events
- Prevention of recurrence
  - Identifying potential cause
  - Pharmacotherapy recommendations
  - Role of novel agents?

AMIA Annu Symp Proc. 2005:989.

Case Study 1

JM is a 64-year-old female with history of HTN, diabetes, GERD, CHF (EF = 30%), and left leg ulcer, now with purulent secretions and pain in lower extremities. She reports poor intake due to not feeling well for the past 2 days. Upon admission, examination and testing reveals the following:

Laboratory Results	
Sodium	132 mEq/L
Potassium	5.8 mEq/L
BUN	34 mg/dL
Serum creatinine	1.9 mg/dL
Glucose	316 mg/dL

Medications	
Amlodipine 5 mg PO daily	Carvedilol 25 mg PO twice daily
Lisinopril 40 mg PO daily	Spironolactone 25 mg PO twice daily
Metformin 500 mg PO twice daily	Multivitamin PO once daily
Pantoprazole 40 mg PO daily	Furosemide 20 mg PO daily

BUN = blood urea nitrogen; EF = ejection fraction; GERD = gastroesophageal reflux disease.

Discussion Question

What risk factors does JM have for hyperkalemia?

- Renal insufficiency
- Diabetes
- Medications: beta-blocker and RAASi
- HTN and CHF (in the presence of RAASi)

Discussion Question

What additional information would be helpful to determine if treatment is necessary?

- ECG
- Vital signs
- Arterial blood gas
- Compliance with medications

Management

Medication	Dose	Route	Onset of Action	Duration of Effect*	
Calcium chloride 10% or calcium gluconate 10%	6.8 mmol elemental calcium (1 g calcium chloride or 3 g calcium gluconate)	IV	1–3 minutes	30–60 minutes	Pending vital sign assessment or ECG changes
Sodium bicarbonate	50–100 mEq	IV	5–10 minutes	~2 hours	
Insulin regular	10 units	IV	30 minutes	4–6 hours	Considering elevated serum glucose
Albuterol	10–20 mg	Inhalation	30 minutes	2–4 hours	
Loop diuretics	40 mg furosemide or equivalent	IV	5–10 minutes (varies with start of diuresis)	As long as diuresis is present	
Dialysis	N/A	Hemodialysis or CRRT	Within minutes of starting therapy	Patient-dependent	

*Duration of effect for agents that eliminate potassium depend on ongoing potassium redistribution and/or ongoing potassium intake.

Adapted from: *Pharmacy Times*. 2016:109-117.

Medication Management

- Initiate treatment with regular insulin ± calcium administration
- Recheck blood glucose
- Follow up basic metabolic panel to confirm potassium reduction
- Perform detailed medication history with compliance status
- Determine if modifications to current medication regimen are necessary

Case 2 – Part 1

DM is a 58-year-old male with HTN, CKD Stage 3 (baseline SCr: 2.1), and hyperlipidemia. He presented to the ED today with altered mental status, reported decreased oral intake, and nausea. Per his wife, his blood pressure control has been poor on only one agent and his primary care physician recently prescribed lisinopril 20 mg once daily in addition to his prior HTN regimen. Shortly after arrival in the ED, DM has a cardiac arrest and you are the pharmacist responding to the code.

Laboratory Results	
Sodium	136 mEq/L
Potassium	6.9 mEq/L
BUN	56 mg/dL
Serum creatinine	3.7 mg/dL
Glucose	138 mg/dL

Medications	
Amlodipine 5 mg PO daily	Renal multivitamin PO daily
Atorvastatin 40 mg PO daily	Omeprazole 20 mg PO daily
Lisinopril 20 mg PO daily (started 10 days prior)	Tamsulosin 0.4 mg PO daily

12-lead ECG: tachycardic, peaked T waves, widened QRS

ED = emergency department; SCr = serum creatinine.

Case 2 – Part 2

DM was successfully resuscitated following 1 round of CPR, calcium gluconate 2 g IV x 1 dose, insulin regular 10 units IV x 1 dose, and dextrose 25 g IV x 1 dose. He also received 3 L of 0.9% NaCl for fluid resuscitation. He was admitted to the ICU for monitoring post-cardiac arrest, however was extubated the following day, is hemodynamically stable, and discharge planning has begun. The team involves you as their clinical pharmacist to help with outpatient medication management.

Laboratory Results	
Sodium	139 mEq/L
Potassium	4.8 mEq/L
BUN	30 mg/dL
Serum creatinine	2.4 mg/dL
Glucose	128 mg/dL

Vital Signs	
T	37.3°C
BP	164/92 mm Hg
HR	86 bpm
RR	14 bpm
O_2 Sat	99% on 2 L NC

BP = blood pressure; CPR = cardiopulmonary resuscitation; HR = heart rate; ICU = intensive care unit; NC = nasal cannula; RR = respiration rate; T = temperature.

Summary

- Identifying patients at risk
  - Clinical conditions
  - Medications
- Treatment recommendations
- Prevention of recurrence
  - Identifying potential cause
  - Pharmacotherapy recommendations
  - Role of novel agents
    - Patiromer sorbitex calcium
    - Sodium zirconium cyclosilicate