



Overcoming the Causes (and Consequences) of Chronic Hyperkalemia

OVERVIEW

Chronic hyperkalemia has several possible causes, including impaired renal excretion of potassium due to a decrease in mineralocorticoid activity, often resulting from renin-angiotensin-aldosterone system inhibitor (RAASi) therapy. While limiting potassium intake and avoiding the use of RAASi therapy are common strategies to manage patients who develop chronic hyperkalemia, both have important negative consequences on patient outcomes, particularly related to the kidneys. Sodium polystyrene sulfonate has often been used to bind potassium, but limited effectiveness and gastrointestinal toxicity limit its use. In the past few years, 2 additional potassium-binding agents have become available with evidence of effectiveness and safety. In addition, a nonsteroidal mineralocorticoid receptor antagonist with reduced potential for hyperkalemia has recently become available. This case-based activity touches on the diagnostic and clinical challenges faced in the primary care management of patients with chronic hyperkalemia, with suggestions for integrating the evolving options into practice to improve patient outcomes.

TARGET AUDIENCE

This activity is intended for family medicine physicians and other healthcare professionals who work in the family medicine/primary care setting.

LEARNING OBJECTIVES

- List common causes of hyperkalemia
- Describe the clinical benefits of renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in patients with chronic kidney disease and heart failure
- Compare and contrast patiromer and sodium zirconium cyclosilicate for the treatment of chronic hyperkalemia, including safety and efficacy data
- Identify opportunities to treat patients with potassium-binding agents, in accordance with the latest guidance, to help optimize the use of RAASi therapy

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My name is Dr. Biff Palmer and I'm a professor of internal medicine at the University of Texas Southwestern Medical Center. I appreciate the opportunity to make this presentation. I'm going to begin by just providing a brief outline of what is going to be covered. We're going to start off with a case presentation. We'll talk a little bit about the pathophysiology of hyperkalemia and its management. We'll talk about acute treatment of the disease. We'll talk also about the discharge planning in the individual that we'll present as a case discussion and review the concept of when and how best to start drugs that block the renin angiotensin system. We'll also talk about the role of potassium binding therapy. And then lastly, we'll concentrate on emerging treatment data, reviewing some recent clinical trials, and also talk about what is in the future in terms of case management for chronic management of hyperkalemia, the role of drug treatment, and the importance of coordinating clinical care.

INTRODUCTION

Let's talk about the individual as a case study. A 64-year-old man presents with new onset weakness. His medical history is noteworthy for type 2 diabetes, hypertension, and stage 3b chronic kidney disease (CKD). We note that he had a myocardial infarction 6 months ago, complicated by heart failure with a reduced ejection fraction. His current medications include lisinopril, metoprolol, insulin, and furosemide. And also, of importance, we note that he was started on spironolactone 25 mg a week ago by his cardiologist.

Case Study: Meni

- A 64 yo man presents with new onset weakness
- Medical history
 - T2DM, HTN, stage 3b CKD
 - MI 6 mos ago complicated by HF rEF (EF 35%)
 - Had been taking
 - Lisinopril 10 mg/d
 - Metoprolol succinate 50 mg/d
 - Insulin
 - Furosemide 20 mg twice daily until 1 week ago, when he was started on spironolactone 25 mg/d by his cardiologist

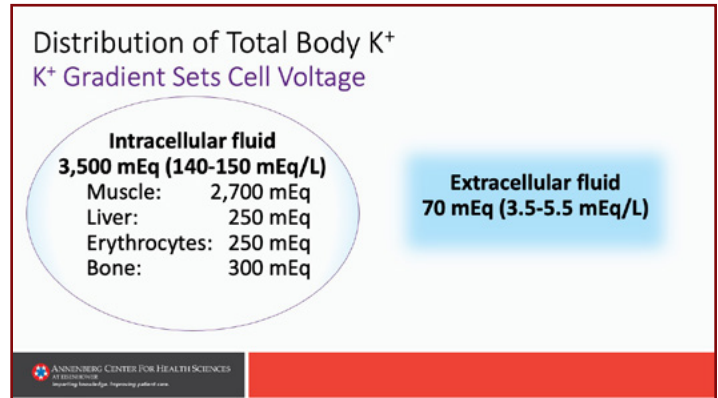
Two days ago, he noted generalized weakness that has worsened over the last 24 hours. Review of the basic metabolic profile reveals that he now has a potassium of 6.8 mEq/L. He also has evidence of a normal gap metabolic acidosis, his serum creatinine concentration is 2.0 mg/dL, and his glucose is 184 mg/dL. Upon discovery of these derangements in the metabolic profile, he was instructed to go to the emergency department.

Case Study: Meni

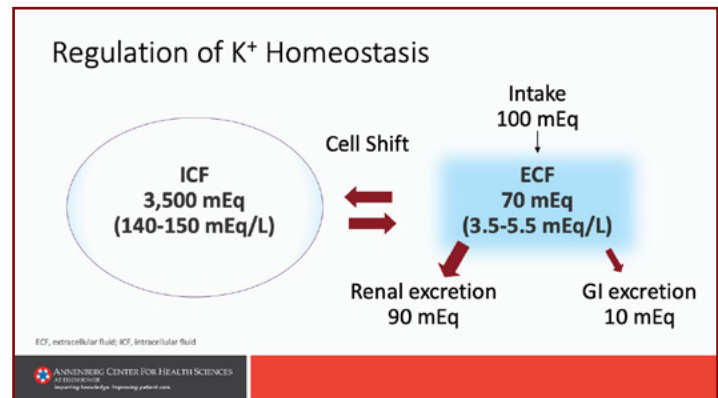
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- Two days ago, he noticed generalized weakness which has worsened over the last 24 hours
- A basic metabolic profile obtained by his PCP shows
 - Na⁺ 139 mEq/L
 - K⁺ 6.8 mEq/L
 - Cl⁻ 107 mEq/L
 - HCO₃⁻ 18 mEq/L
 - SCr 2.0 mg/dL
 - Glucose 184 mg/dL
- The patient is instructed to go to the emergency department

Let's talk a little bit about potassium homeostasis. This is just an overview to remind us that, in a typical 70 kg individual, we have roughly 3,500 mEq of total body potassium. The majority of that is found in skeletal muscle, with a smaller quantity in liver and red blood cells. And then there's about 70 mEq of potassium in the extracellular fluids. This very large inward to outward gradient is important in determining the cell voltage and this is why derangements in serum potassium primarily give rise to manifestations in excitable tissues, such as neuromuscular tissue as well as cardiac tissue.



With respect to potassium homeostasis, imagine that somebody ingests 100 mEq of potassium. The kidney is the main route by which that potassium is excreted. There is a small contribution of the gastrointestinal (GI) tract, primarily in the colon. Now, the ability of the kidney to excrete potassium is not instantaneous. It takes several hours. To guard against excessive rises in extracellular potassium concentration following a load, there's initially a shift of potassium into the cell to allow the kidney enough time to reestablish total body potassium balance. The 2 most important factors physiologically affecting potassium shift into the cell are the release of insulin and also beta-adrenergic stimulation.



Hyperkalemia is a common disorder. It's been found to be present in up to 40% to 65% of patients who have CKD, even in clinics that are specialized to care for these individuals. The annual mortality rate can be as high as 25%.

Here are data that are retrospective in nature from a study where they looked at the relationship of a serum potassium and mortality within a 24-hour period after discovery of that serum potassium. The graph shows a graded relationship between the rise in the extracellular potassium concentration and 24-hour mortality. The greater the serum potassium, the greater mortality. These data demonstrate that hyperkalemia is not a benign disorder.

When we see a patient who has hyperkalemia, how do we approach that individual? Listed here are several main categories of what causes

Epidemiology of Hyperkalemia

- Prevalence as high as 40%-65% in patients with CKD
- Even in specialized CKD clinics, the prevalence is as high as 55%
- Annual mortality rate 25%

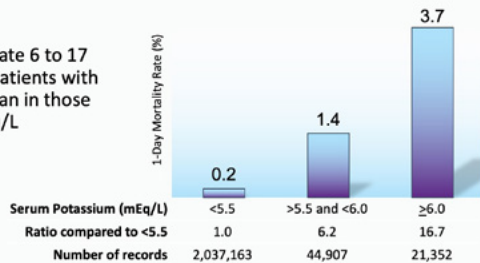
CKD, chronic kidney disease

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Forbes LM, et al. *Arch Intern Med*. 2009;169:1150-1162.
Horns L, et al. *Am J Med Sci*. 2012;343:418-424.
Sarafidis PA, et al. *Clin J Am Soc Nephrol*. 2012;7:1234-1241.
O'Riordan S, et al. *Ann Intern Med*. 2012;156:200-207.

Mortality Rate Within 1 Day of a Hyperkalemia Event

1-day mortality rate 6 to 17 times higher in patients with $K^+ \geq 5.5$ mEq/L than in those with $K^+ < 5.5$ mEq/L



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Differential Diagnosis of Hyperkalemia

- Pseudohyperkalemia
- Excess K^+ intake
- Cell shifts
- Impaired renal excretion
 - Only cause of sustained hyperkalemia
 - Primary decrease in mineralocorticoid activity

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hyperkalemia. One of the things we always want to exclude is so-called pseudohyperkalemia. That is when the potassium is high in a test tube, but not in the individual. This obviously occurs in somebody who has had fist clenching during the phlebotomy technique, the use of a tourniquet. If you ever suspect pseudohyperkalemia, it's best to have the patient repeat the value using a green topped tube and also without a tourniquet.

Excess potassium intake can certainly be a contributor to hyperkalemia, however, this will only really occur if you have depressed kidney function. In the setting of normal kidney function, you can actually ingest quite a large amount of potassium and never get hyperkalemia. The normal kidney has a large capacity to excrete potassium. Excess potassium intake plays a role in individuals with decreased kidney function.

Cell shifts can cause hyperkalemia. This is usually transient in nature. Causes include metabolic acidosis, insulin deficiency, or alpha-adrenergic stimulation. These are just some of many factors that can cause a shift of potassium out of the cell. Cell injury, by the way, is another potential cause.

Perhaps the most common cause, though, of hyperkalemia, either in the inpatient or the outpatient setting, is impaired kidney excretion. This is really the main cause of sustained hyperkalemia. While several factors

are involved, many of the factors tend to center around disturbances in the renin-angiotensin-aldosterone system (RAAS).

The main causes of impaired kidney excretion can be divided into several categories. One category is people who have decreased mineralocorticoid activity. Another is a primary decrease in the amount of sodium being delivered to the distal nephron. This might occur, for example, in decompensated heart failure where you have avid proximal sodium reabsorption and, therefore, less sodium delivery. Other causes of reduced sodium being delivered to the distal nephron include oliguric acute kidney injury and acute glomerulonephritis. Hyperkalemia tends to be much more common with these 2 latter causes.

Impaired Renal K^+ Excretion

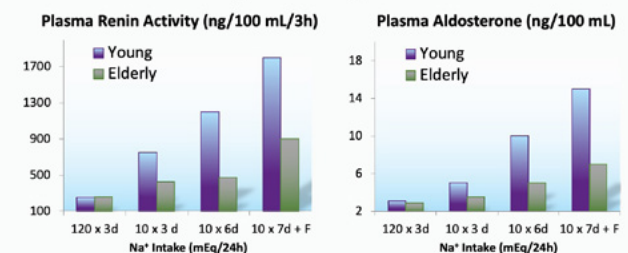
- Primary decrease in mineralocorticoid activity
- Primary decrease in distal Na^+ delivery
 - Decompensated heart failure
 - Oliguric acute renal failure
 - Acute glomerulonephritis
- Abnormal cortical collecting duct
 - Drugs
 - Tubulointerstitial nephritis
 - Urinary obstruction

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Another cause of impaired kidney excretion is anything that primarily disrupts function at the collecting ducts. This can be due to a variety of medications. Another cause is tubulointerstitial renal disease. Here, the primary pathologic process is attacking the tubules. Urinary obstruction is also a common cause of hyperkalemia. In fact, I always remind clinicians that if you have unexplained hyperkalemia, it's always worthwhile considering if the patient has an obstructive uropathy.

One of the other risk factors for impaired kidney excretion is older age. As individuals age, there is an age-related decrease in the ability to make renin and aldosterone. In this particular study, you can see that, on the left-hand panel, as you progressively reduce sodium intake to try to contract extracellular fluid volume, young individuals have a robust increase of plasma renin activity in comparison to otherwise healthy elderly subjects. And that's also reflected in serum aldosterone. Even when augmented with a dose of furosemide, young individuals have a much more robust increase in aldosterone as compared to elderly subjects. This age-related impairment perhaps contributes to the higher risk of hyperkalemia when older subjects are placed on drugs that target the RAAS.

Change in PRA and Aldosterone With Na^+ Restriction in Young vs Elderly

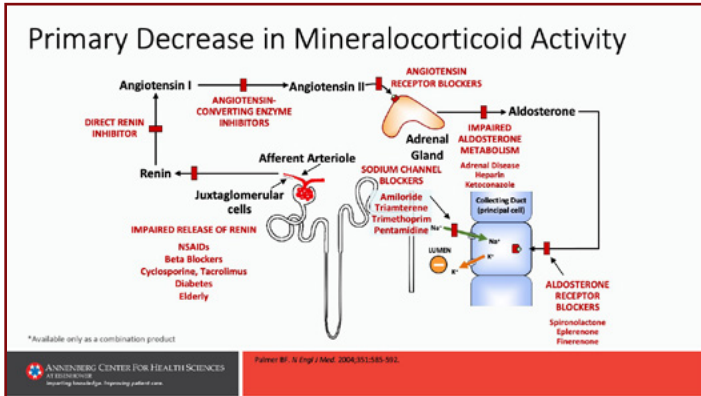


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Verbruggen P, et al. *Kidney Int*. 1978;12:225-233.

I emphasize the idea that disease states or medications that disrupt the renin angiotensin system are common causes of hyperkalemia. If we go back here to the beginning, remember that aldosterone acts by stimulating sodium movement into the cell of the collecting duct. That

creates a negative charge and that's one of the big driving forces for potassium secretion. Anything that disrupts the activity of aldosterone, or the formation of aldosterone, tends to quickly result in hyperkalemia. Aldosterone receptor antagonists include spironolactone, eplerenone, and a new mineralocorticoid receptor antagonist called finerenone.



Drugs that block the epithelial sodium channels, such as amiloride, triamterene, the antibiotics trimethoprim-sulfamethoxazole or pentamidine, block sodium movement, thereby limiting the generation of the negative charge, which is why potassium secretion is impaired.

There are entities that limit the formation of aldosterone from the zona glomerulosa of the adrenal gland. In addition to intrinsic adrenal disease, the drug heparin reversibly interferes with aldosterone biosynthesis, as does the azole antifungal, ketoconazole.

The angiotensin receptor blockers (ARBs) block the angiotensin-1 receptor on the zona glomerulosa cells and that's why ARBs cause hyperkalemia because they limit aldosterone production. The angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II and, therefore, lower aldosterone levels. Aliskiren is a direct renin inhibitor that blocks serum renin activity blocker. Aliskiren limits the formation of angiotensin I and subsequently lowers aldosterone levels.

There is also a variety of processes that block the release of renin. They include, most commonly, the nonsteroidal anti-inflammatory drugs (NSAIDs), as well as beta-blockers. Both prostaglandins and adrenergic input stimulate renin release, thus blocking either prostaglandins with NSAIDs or administration of a beta-blocker will lower renin levels. The calcineurin inhibitors, such as cyclosporine and tacrolimus, have a variety of effects on potassium homeostasis, but one of the things they tend to do is lower the renin levels in the blood. Individuals with diabetes frequently have hyporeninemic hypoaldosteronism due to microvascular disease of the juxtaglomerular cells, and I already alluded to the idea that elderly subjects have this age-related defect in production of both renin and aldosterone.

Among the clinical consequences of hyperkalemia, cardiac toxicity is the most commonly appreciated toxicity and so we have to be aware of the electrocardiogram (ECG) changes that can occur with hyperkalemia. These are peaking of the T-wave and prolongation of the PR and QRS intervals. Muscle weakness is also a manifestation. I always remind people that if you ever were called to the emergency department for a dialysis patient, for example, and they complain that they have weakness, you always have to be suspicious of hyperkalemia. And lastly, hyperkalemia can be associated with secondary development of an acidification defect. Hyperkalemia suppresses ammoniogenesis in the proximal tubule, thereby limiting buffer availability for distal hydrogen ion secretion. That's why hyperkalemia and normal gap acidosis frequently coexist, as in the patient I presented earlier.

Clinical Consequences of Hyperkalemia

- Cardiac toxicity
- Muscle weakness
- Impaired renal acidification

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 1. Adick CJ, et al. *Ann Intern Med*. 1998;128:927-934.
 2. Managaya ST, et al. *Clin J Am Soc Nephrol*. 2008;2:124-130.

With regard to ECG manifestations, it is worthwhile to note that there's oftentimes a poor correlation between having ECG changes and the degree of hyperkalemia. This was a study where individual values were obtained and a cardiologist actually read the ECG in these patients. As shown by the graph, it is only when the serum potassium rises to a very high level that there is a fairly high frequency of seeing the typical ECG changes. Note that in individuals who had a serum potassium level only slightly above 6 mEq/L, ECG changes were frequently not present at all. And indeed, when you look at the individuals who had the most severe manifestations, arrhythmias or even a cardiac arrest, only 1 of these individuals had ECG changes typical of hyperkalemia. The point is that we can't necessarily rest and feel comfortable in somebody who has an elevated serum potassium level and normal ECG since the ECG or cardiac status can quickly deteriorate, even in the absence of classic changes.

Poor Sensitivity and Specificity of ECG as Diagnostic Test for Hyperkalemia

- In 127 patients with serum K⁺ between 6-9.3 mEq/L, only 46% of ECGs noted to have changes¹
- In 90 cases, only 24 noted to have characteristic T-wave changes as read by a cardiologist²
- Only 1/14 who presented with arrhythmias or arrest had strict criteria²

ECG, electrocardiogram

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 1. Adick CJ, et al. *Ann Intern Med*. 1998;128:927-934.
 2. Managaya ST, et al. *Clin J Am Soc Nephrol*. 2008;2:124-130.

RAAS Inhibitor Therapy

How do we manage hyperkalemia? The first thing we need to do is look at the patient's medication profile and ask ourselves, are they taking one of those medications that disrupt the RAAS and is there an opportunity to alter that medication in order to lower the risk of hyperkalemia? Dietary potassium counseling is also an option. Obviously, there are certain foods that are enriched in potassium, and if we could curtail those foods, that might also have a beneficial effect. As I will subsequently talk about, though, that oftentimes comes with a catch-22 in that we need to remember that most foods that are enriched in potassium are also heart-healthy. On the one hand, by restricting potassium-enriched foods, you might also be restricting foods that could potentially be heart-healthy.

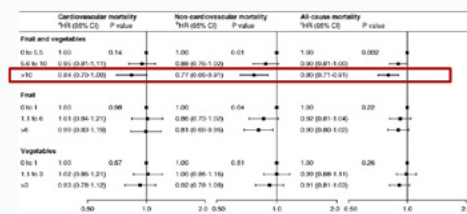
Thirdly, effective diuretic therapy is also quite useful in the management of hyperkalemia. I always remind clinicians that when your estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73 m², loop diuretics really become a required therapy. If furosemide is chosen as

Management of Hyperkalemia

- Review medications
- Dietary K⁺ counseling
- Effective diuretic therapy
 - Loop diuretics when estimated glomerular filtration rate <30mL/min/1.73 m²
 - Use furosemide twice daily
- NaHCO₃ tablets (650-mg tablet, 8 mEq)
- Decrease or discontinue renin-angiotensin-aldosterone system blocker

the loop diuretic, also remember it's a short-acting drug that should be used twice daily. Correcting metabolic acidosis with sodium bicarbonate tablets can also be of utility. This is thought to work by increasing distal sodium delivery, but also by raising the blood pH, you shift potassium back into cells. We can also decrease or discontinue RAAS inhibitors if the patient is on these medications and, as you well know, these drugs cause hyperkalemia. But again, as I will subsequently allude to, this also comes with a catch-22 because these drugs have favorable effects on cardiovascular outcomes. Therefore, one has to be at least cognizant of the catch-22 that exists.

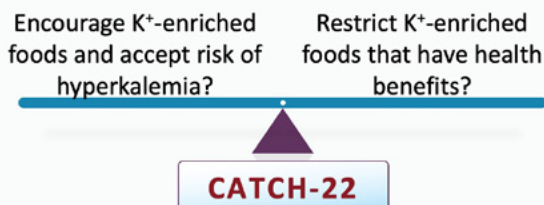
Higher Intake of Fruits and Vegetables Associated With Lower All-Cause Mortality



9757 patients across European and South American countries in the: Dietary Intake, Death and Hospitalization in Adults with ESKD Treated with Hemodialysis Study

There is a drawback restricting fruits and vegetables as a way to manage hyperkalemia. Once again, fruits and vegetables are enriched in potassium, but as illustrated in this study of dialysis patients, those individuals who were ingesting the greatest amounts of fruits and vegetables had more favorable effects on cardiovascular mortality, noncardiovascular mortality, and even all-cause mortality. Again, if you simply restrict these foods that are enriched in potassium, you're giving up the cardiac or health benefits of those foods, and so perhaps we need to be a little bit more nuanced as to how we recommend restricting dietary potassium.

Dietary K⁺ Restriction: A Catch-22 of Managing Diseases That Benefit From K⁺-Enriched Foods



Clinical Guidelines Recommend RAASi Therapy for Treatment of Acute and Chronic Heart Failure

2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF

Intervention	Recommendation
ACEi	Class I Recommended in addition to a β -blocker, for symptomatic patients with HF \neq EF
	Class I Recommended in patients with asymptomatic LV systolic dysfunction
	Class IIa Recommended in patients with stable CAD
ARBs	Class I Recommended to symptomatic patients with HF unable to tolerate an ACEi (patients should also receive a β -blocker and an MRA)
Aldosterone blockade	Class I Recommended for patients with HF \neq EF, who remain symptomatic despite treatment with an ACEi and a β -blocker

Class recommendation I – recommended/indicated; Class recommendation IIa – should be considered
 ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; ESC, European Society of Cardiology; HF, heart failure; HF \neq EF, heart failure with reduced ejection fraction; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor

The other thing I mentioned was this catch-22 with regards to either using suboptimal doses of RAAS inhibitors or even discontinuing them altogether.

Remember that various guidelines include use of ACE-I/ARBs and aldosterone antagonists as a class I recommendation for patients with heart failure because there are multiple studies showing that these drugs provide a mortality benefit.

KDIGO Recommends RAASi Therapy for Managing Patients With CKD

ND-CKD patients without diabetes mellitus

- We recommend that an ARB or ACEi be used in adults without diabetes with ND-CKD and urine albumin excretion >300 mg per 24 hours (or equivalent) in whom treatment with BP-lowering drugs is indicated (1B)

ND-CKD patients with diabetes mellitus

- We recommend that an ARB or ACEi be used in adults with diabetes and ND-CKD with urine albumin excretion >300 mg per 24 hours (or equivalent) (1B)

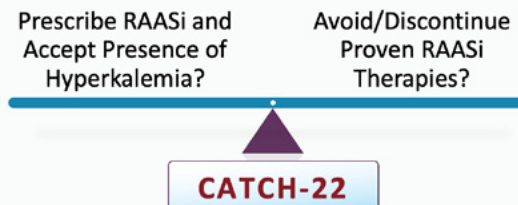


ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; ND-CKD, non-dialysis chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor

A similar story plays out in individuals who have CKD. In a class I category, various guidelines tell us we should manage patients with CKD with ACE-I or ARBs whether they have diabetes mellitus or not because, again, we have clinical trial data that show that these drugs slow the progression of CKD, particularly when you have large amounts of proteinuria.

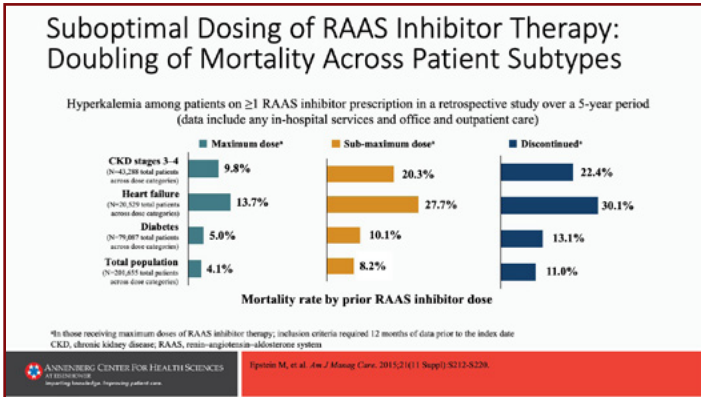
Again, we have this catch-22 situation where, on the one hand you can lower the dose and even discontinue RAAS inhibitor therapy and that may have a favorable effect on the serum potassium level, but at the same time, then you're giving up on proven therapies that may have beneficial effects, both on the kidney disease progression and the presence of their underlying cardiovascular disease. The idea is if we had a tool that would

Hyperkalemia vs RAASi: The Catch-22 of Managing Diseases That Benefit From RAASi Therapy!

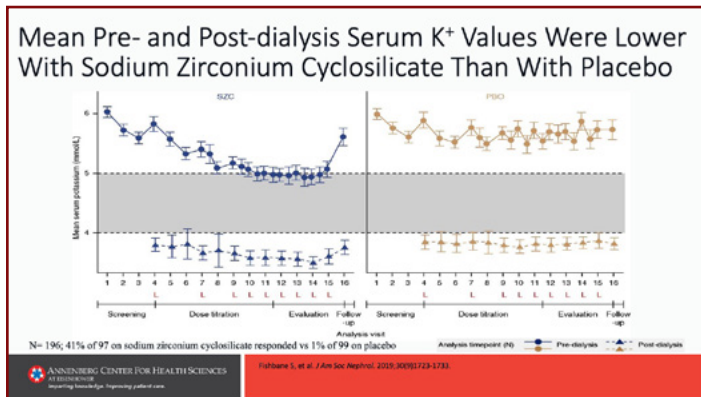


enable us to use these drugs and yet avoid the metabolic complication of hyperkalemia, this would have great clinical utility.

The evidence that using suboptimal dosing or discontinuing RAAS inhibitors has an adverse effect is shown in a study by Epstein et al. Notice that if you compare individuals who have CKD in advanced stages, heart failure, diabetes, and all of these groups mixed together, the mortality rate, when they're on maximal doses, is much less than when they're treated with either submaximal doses or if the drugs had been discontinued altogether.



I'm going to talk a little bit about the use of potassium-binding drugs. One of the areas where potassium-binding drugs have now proven great utility is in the management of patients on dialysis who have persistent predialysis hyperkalemia. This is a study looking at 1 of these drugs called sodium zirconium cyclosilicate. A group of approximately 200 or so patients on dialysis who had predialysis hyperkalemia were randomized to either receive sodium zirconium cyclosilicate or managed in a typical way. Notice that when the sodium zirconium cyclosilicate was given on nondialysis days, the predialysis hyperkalemia was corrected with no real incidence of postdialysis worsening hypokalemia as compared to the placebo group that remained hyperkalemic.



It should be noted that, in this particular study, the use of sodium zirconium cyclosilicate was not associated with any change in interdialytic weight gain or worsening in blood pressure control. The reason is the sodium zirconium cyclosilicate exchanges potassium for sodium, but there were no adverse events with regard to salt overload, noted in this dialysis study.

Let me just summarize to this point by saying that hyperkalemia is common in patients who have CKD, particularly in those with underlying conditions that disrupt the RAAS. This is a long-term concern, given the epidemiologic data to show that hyperkalemia is associated with worse outcomes. Hyperkalemia is associated with several side effects about which we need to be aware. Obviously, the cardiac events that we discussed. Hyperkalemia can cause muscle weakness and this frequent coexistence of hyperkalemia and a normal gap acidosis may

Summary

- Hyperkalemia is common in patients with CKD and in those with conditions that disrupt the renin-angiotensin-aldosterone system
 - It is a long-term concern
- Hyperkalemic events are associated with worse outcomes
 - Cardiac events
 - Muscle weakness
 - Impaired acidification
- Strategies to limit development of hyperkalemia would be useful clinically

be related, in that hyperkalemia suppresses ammoniogenesis, thereby secondarily impairing kidney acidification. Given these adverse events of hyperkalemia, we need to have strategies to limit the development of hyperkalemia that can be clinically useful.

Let's go back to our case. Remember this is an individual recently started on spironolactone. He had developed a serum potassium level of nearly 6.8 mEq/L, so he was referred to the emergency department. Once there, he was treated with dextrose 50% in water, insulin, and nebulized beta-adrenergic agent. Six hours later, the serum potassium level had decreased to 5.1 mEq/L. At that time, lisinopril and spironolactone were discontinued. The question is, in going back to this catch-22, is that really an optimal way to manage and is there anything else that can be done to prepare this patient for ultimate discharge?

Case Study (continued)

- Meni is admitted to the hospital and is treated with
 - 1 amp D50W
 - 10 units insulin
 - 10 mg of nebulized albuterol
- 6 hours later → K⁺ 5.1 mEq/L
- Lisinopril and spironolactone are discontinued

How should this patient be managed once ready for discharge?

D50W, 50% dextrose in water

There are some concepts in terms of continuing care to keep in mind when managing individuals with chronic hyperkalemia. Once hospitalized, the transition into the outpatient setting must be started. This is going to require patient education as to diet adherence. We have to educate the patient on treatment, medications to avoid, for example of nonsteroidal anti-inflammatory drugs. We need to educate the patient about recognizing symptoms of hyperkalemia, weakness that can sometimes

Continuing Care for Patients With Chronic Hyperkalemia

- If hospitalized for hyperkalemia, begin transition to outpatient early
- Patient education
 - Treatment, diet adherence
 - Symptom recognition
 - Action plan
- Health care team
 - Physicians: hospitalist, cardiologist, nephrologist, general internist/primary care
 - Nurse, NP, PA, pharmacist, case manager

occur, and formulate an action plan with patient involvement—not only with the patient— but also the other members of the healthcare team.

To emphasize, in an individual like this, we're going to have multiple clinicians involved, the hospitalist, the cardiologist. This patient had CKD, therefore, it's quite likely a nephrologist would be involved and then, of importance as well, the primary care physician. The nurses on the healthcare team are going to be integrally involved, as is the dietician, perhaps a physician extender, a physician assistant, pharmacist, and case managers. There's absolutely no question that when we think about the various comorbidities that cause chronic hyperkalemia, a healthcare team involved in the care of this individual really is going to involve a broad array of specialists and other healthcare professionals.

The Continuum of Hyperkalemia

- Acute treatment may be needed for unrecognized chronic hyperkalemia
- Signs/symptoms should be closely monitored following an episode of acute hyperkalemia
 - Do not discharge until hyperkalemia has resolved
- Hospitalist will need to decide if
 - Current medications can be continued
 - Disease-modifying treatment needs to be initiated
- Patient recognition of signs/symptoms is important
- Coordinated care is essential

The acute treatment of hyperkalemia is oftentimes needed, as it was in this individual. The fact that this patient presented with life-threatening hyperkalemia at 6.8 mEq/L is why signs and symptoms of hyperkalemia need to be recognized. These patients need to be followed closely and certainly not discharged until the hyperkalemia has resolved. In a patient such as this, who might have been under the care of a hospitalist, that individual, along with the other members of the healthcare team, will need to decide how the outpatient regimen might need to be modified. Are there—and what are—the issues in modifying that outpatient regimen?

Once again, I want to emphasize that we do need to educate the patient of the signs and symptoms. Hyperkalemia can be asymptomatic and perhaps it's asymptomatic in the majority of individuals, but on occasion it can present with symptoms. Again, coordinated care is clearly essential. All of the members of the healthcare team will need to be involved in the care of an individual such as the one we've talked about.

Remember that in this patient who presented, the lisinopril and the spironolactone, 2 drugs that have been shown to not only slow progression of CKD, but also provide a mortality benefit in the setting of heart failure, simply discontinuing them or using them at suboptimal doses presents this catch-22. Yes, it may help prevent hyperkalemia recurrence, but at the

Hyperkalemia vs RAASi: The Catch-22 of Managing Diseases That Benefit From RAASi Therapy!

Prescribe RAASi and Accept Presence of Hyperkalemia?

Avoid/Discontinue Proven RAASi Therapies?

RAASi, renin-angiotensin-aldosterone system inhibitor

same time, we're giving up on a proven therapy that has cardiovascular benefit. We need to, with the members of the healthcare team, discuss this issue and ask ourselves are there strategies that could potentially allow us to use these drugs and help minimize the likelihood of this metabolic side effect, that being the hyperkalemia?

Drugs that target the RAAS can be both kidney-saving and lifesaving, particularly in patients who are most at risk for hyperkalemia, including the patient with CKD, heart failure, or diabetes mellitus.

RAASi Promotes Kidney-Saving and Life-Saving Benefits in Patients With CKD, Heart Failure, or Diabetes Mellitus

CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor

This is an older study simply showing that these RAAS inhibitors cause hyperkalemia and the risk of hyperkalemia becomes additive when you use them together. Notice that in this trial, as compared to the placebo group, hyperkalemia increases when you add an ARB, that's the middle line in red, and then when you add spironolactone, the risk is even higher. This makes it clear that these are drugs that increase the risk for hyperkalemia.

Mean Serum K⁺ Concentration Was Significantly Higher With MRA vs ARB

Hyperkalemia (serum K⁺ >6.0 mEq/L) occurred at least once in 2, 13, and 14 subjects in the placebo, ARB, and MRA groups, respectively (MRA [spironolactone] vs placebo, P<.001; ARB [losartan] vs placebo, P<.009). ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist

Miksis LF, et al. J Am Soc Nephrol. 2009;20(12):2641-2650

Having said that, though, remember these drugs provide cardiovascular benefits. The RALES study was a classic study in which the addition of 25 mg of spironolactone to ACE inhibitor therapy provided a mortality benefit. The results of RALES really revolutionized the therapy of heart failure and

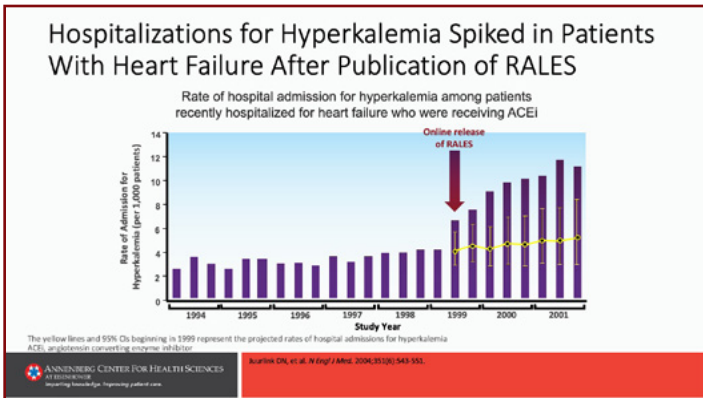
RALES/EMPHASIS-HF: MRAs Improved Survival in Patients With Heart Failure

MRAs, mineralocorticoid receptor antagonists

Fitz S, et al. N Engl J Med. 1999;341(10):769-775

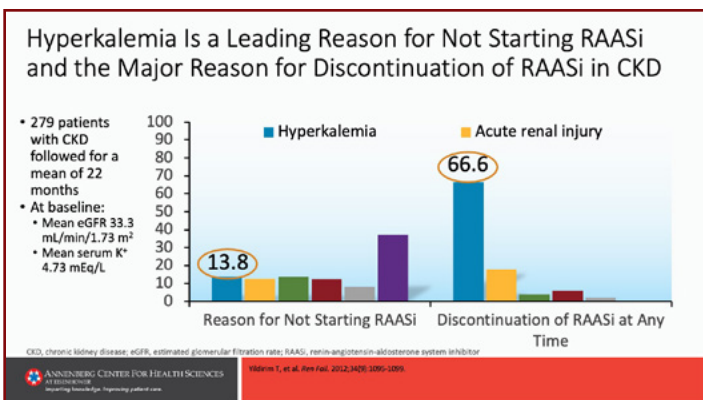
has really become a standard of care using aldosterone antagonists in people who have reduced ejection fraction.

Interestingly, soon after the publication of the RALES study, there was a spike in hospital admissions for hyperkalemia. When you think about a clinical trial, like the RALES study, the clinicians involved in that trial took great care, and frequent monitoring was employed, to make sure that hyperkalemia did not develop. In other words, people with advanced CKD were excluded. People were frequently educated about the avoidance of other drugs that could cause hyperkalemia. Under the conditions of a clinical trial, hyperkalemia was not very common in the RALES trial. But once the data was released and clinicians embraced the use of aldosterone antagonists in patients with heart failure, this spike was observed because suddenly people were being started on the drug but not receiving the kind of follow-up that was done in the clinical trial. Many of these people, probably without good education, were taking drugs that may have further increased their risk of hyperkalemia.



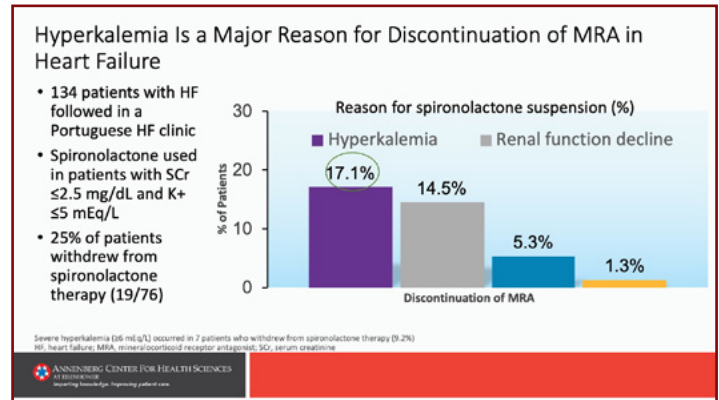
The results of this study highlight the idea that we need to be diligent when using these drugs, be aware of the risk and provide good patient education and good follow-up, so that we minimize the kind of spike that was noted here in this trial.

Again, hyperkalemia is often cited as a reason for not starting a RAAS inhibitor. This is a study of 279 subjects, where in 13.8% of the subjects, hyperkalemia was cited as the reason for not using a RAAS inhibitor. The other big category was if somebody had evidence of acute kidney injury.



Hyperkalemia is also a major reason for discontinuation of either ACE-I or mineralocorticoid antagonists in patients with heart failure. Here are the results from a study in Europe of patients with heart failure. Seventeen percent of the time hyperkalemia was cited for the reason that spironolactone was not used in these individuals. Again recall, heart failure with reduced ejection fraction, there's great data that mineralocorticoid

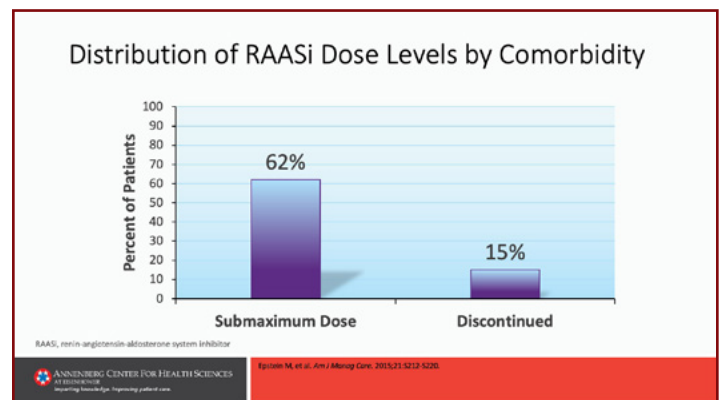
receptor antagonists provide cardiovascular benefits. But here we see an example of a metabolic side effect limiting the utilization of this drug. Once again, going back to the idea that if we had strategies that could help minimize this metabolic side effect, this would be of potential clinical benefit.



This is a study that looked at the distribution of RAAS inhibitor dose by comorbidity. The large percentage of patients were using submaximal doses, and in 15% the drugs were discontinued. The results show that there's a large population of patients that could be benefitting from these drugs if used maximally, but yet the clinical experience is that oftentimes they're on submaximal doses or the drugs are discontinued altogether.

Current guidelines have actually tended to lessen the use of full-dose RAAS inhibitors because of concerns related to hyperkalemia.

If we look at the KDOQI guidelines, they say ACE-I or ARBs should be used in patients with CKD, and at the highest tolerated dose. If hyperkalemia develops, the dose can be reduced or the medication discontinued. This was the current state-of-the-art.



Current Guidelines Tend to Lessen the Use of Full Recommended Doses of Renin-Angiotensin-Aldosterone System Inhibitors Because of Concerns Related to Hyperkalemia

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Hyperkalemia Prevents Use of Guideline-Recommended RAASi Therapy to Delay Progression to ESRD

Kidney Disease Outcomes Quality Initiative, Guideline 11: Use of ACEis and ARBs in CKD

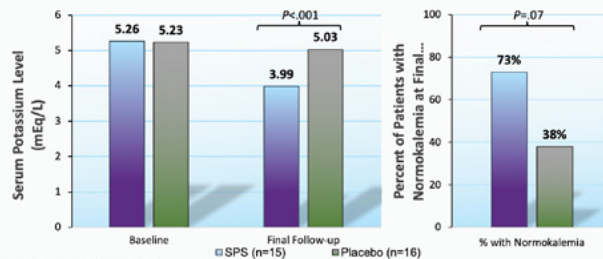
- In general, highest tolerated dose of RAASi (ACEi or ARB) is recommended
- If hyperkalemia develops
 - **Reduce** dose of ACEi or ARB and/or
 - **Discontinue** ACEi or ARB

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ESRD, end-stage renal disease; RAASi, renin-angiotensin-aldosterone system inhibitor

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KID08. <https://doi.org/10.1177/0885066610374240>

Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD



CKD, chronic kidney disease; SPS, sodium polystyrene sulfonate

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LePage L, et al. *Clin J Am Soc Nephrol*. 2015;10(12):2136-2142

Potassium-binding Medications

Now, I've alluded to that it would be of great clinical utility if we had drugs that could limit the development of hyperkalemia, allowing use of RAAS inhibitors. When you think about that strategy, potassium-binding agents come to mind. Now, for the last 50 years, the only potassium-binding agent that we had was sodium polystyrene sulfonate, which was actually approved back in 1958. But, interestingly, there's really no evidence that this drug has a great potassium-lowering effect beyond the sorbitol with which it is frequently co-administered. That is, if you look at the data critically, the ability of sodium polystyrene sulfonate to lower potassium can be largely explained by the increase in stool volume that's brought about by the co-administration of sorbitol. And, in fact, because of the diarrhea, the stool volume effect of sorbitol, this has really become an irrational way to chronically manage hyperkalemia. It's a very poorly tolerated drug and rarely can be associated with adverse and serious gastrointestinal side effects.

Sodium Polystyrene Sulfonate: Limited Data to Substantiate Efficacy

Approved in 1958, before well-controlled studies were required¹
Indicated for the treatment of hyperkalemia²

"...no convincing evidence that SPS increases fecal K⁺ losses in experimental animals or humans and no evidence that adding sorbitol to the resin increases its effectiveness..."¹

There is concern that SPS may not be effective without osmotically active amounts of sorbitol^{3,4}

SPS, sodium polystyrene sulfonate

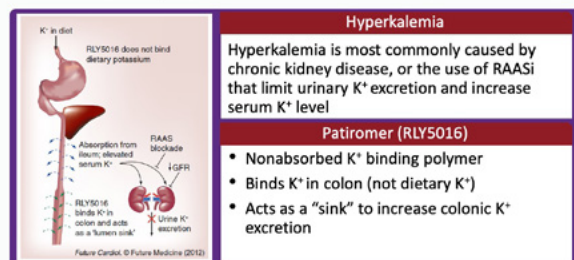
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1. Sterns RH, et al. *J Am Soc Nephrol*. 2012;23(2):393-395.
2. Kurokawa T, et al. *Am J Med*. 1998;104(1):1-7.
3. Kurokawa T, et al. *Am J Med*. 1998;104(1):1-7.
4. Gray R, et al. *J Am Soc Nephrol*. 1998;9(12):2136-2142.

The only clinical trial that's ever been done was only about a month in duration and it's shown here. They took a group of individuals who had mild hyperkalemia. They were able to show that the sodium polystyrene sulfonate did have a lowering effect, but I would just mention to you that there was only about 30 or so subjects in this trial and it was of very short duration. And again, I would just hazard to say that, chronically, sodium polystyrene sulfonate is very poorly tolerated and, as I alluded to, can be associated with severe GI side effects.

Because of this limitation, there's been a need for newer potassium-binding drugs that are effective and well tolerated. And we now have 2 newer agents. The first one is patiomer. This is a polymer. It binds potassium in the lumen of the GI tract. It does so in exchange for calcium. There have now been several trials showing that the utilization of this drug can enable the use of RAAS inhibitors and limit the development of hyperkalemia. Patiomer binds potassium in the lumen of the GI tract

Patiomer Is a Polymer That Binds Potassium in the Colon



GFR, glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor

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Reiser M, et al. *Future Cardiol*. 2012;8(1):17-28

by lowering the free potassium in the lumen. It now creates a favorable gradient for blood potassium to diffuse into the colon where, again, it binds to the polymer.

There are several trials that have been conducted to show the efficacy and tolerability of patiomer. The first one was conducted by Matt Weir and colleagues and published in *The New England Journal of Medicine*. Patients with CKD who were on RAAS inhibitors were treated for 4 weeks at various doses. The study demonstrated a favorable effect on reducing the serum potassium level with patiomer. Patients underwent a withdrawal phase where, of those who were controlled, they either had patiomer discontinued or they were continued on patiomer for an additional 8 weeks.

Patiomer in Patients With Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

- Patients with CKD on RAAS inhibitors (n=243) with hyperkalemia (5.1 to <6.5 mEq/L) at baseline
- Phase 1 (treatment phase)
 - Treatment with patiomer for 4 weeks
 - 4.2 g twice daily if K⁺ 5.1 to <5.5 mEq/L
 - 8.4 g twice daily if K⁺ 5.5 to <6.5 mEq/L
- Phase 2 (withdrawal phase):
 - Eligible patients (n=107) were those with baseline K⁺ of 5.5 to 6.4 mEq/L in whom the K⁺ level decreased to 3.8 to 5.0 mEq/L
 - Randomized to continue patiomer (at same dose) or switch to placebo for 8 weeks

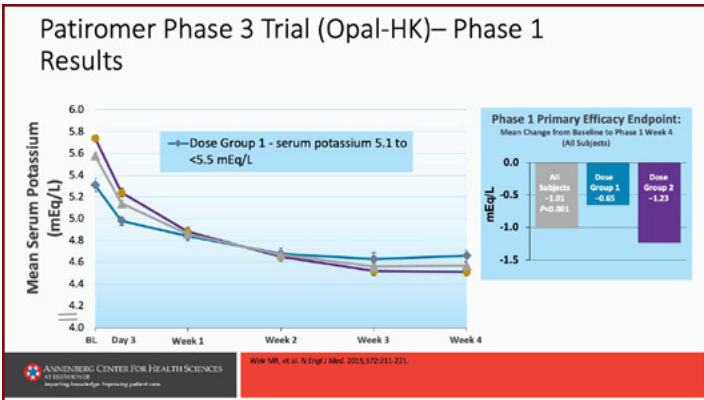
CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor

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Weir MR, et al. *N Engl J Med*. 2015;373:211-221

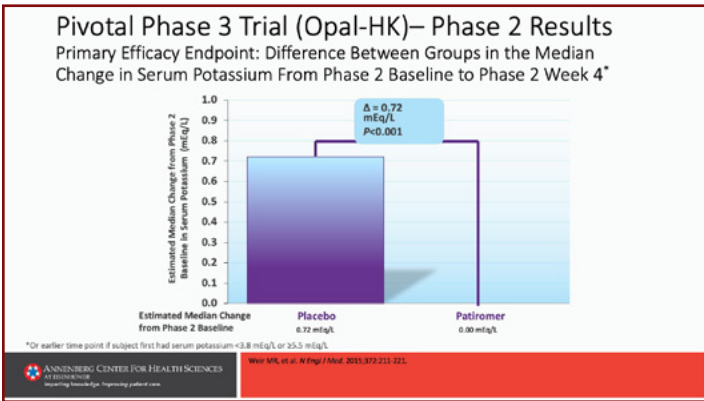
During the treatment phase, at varying subgroups of elevated serum potassium level, all of these individuals had control of their serum potassium by the end of the 4 weeks. This, I would like to emphasize, occurred despite the fact that 100% of these individuals were taking RAAS inhibitors. Despite the use of ongoing RAAS inhibitor therapy, patiomer was able to control the serum potassium level.

In the withdrawal phase, of those who were controlled at the end of that 4-week period, you can see that in the placebo group, that is those



The efficacy of patiromer during the withdrawal phase was uniform across all of these subgroups. It made no difference if the patient had diabetes or heart failure, the potassium level at baseline, maximum dose of RAAS inhibitor, age, or sex. The patiromer-treated patients were able to better maintain control of the serum potassium level compared to a placebo group across all of these baseline characteristics.

In terms of tolerability, patiromer was well tolerated. There are patients who experience some GI side effects, such as constipation or diarrhea. In the clinical trial data, about 3% developed hypomagnesemia; thus, monitoring the serum magnesium level is recommended. In general, patiromer is a very well-tolerated drug.



Adverse Events During the Initial Treatment Phase and Through the Safety Follow-up Period* for That Phase

Adverse Event	No. of Patients (%)
≥ 1 Adverse event	114 (47)
Constipation	26 (11)
Diarrhea	8 (3)
Hypomagnesemia	8 (3)
Nausea	8 (3)
Anemia	7 (3)
Chronic renal failure	7 (3)
≥ 1 Serious adverse event	3 (1)

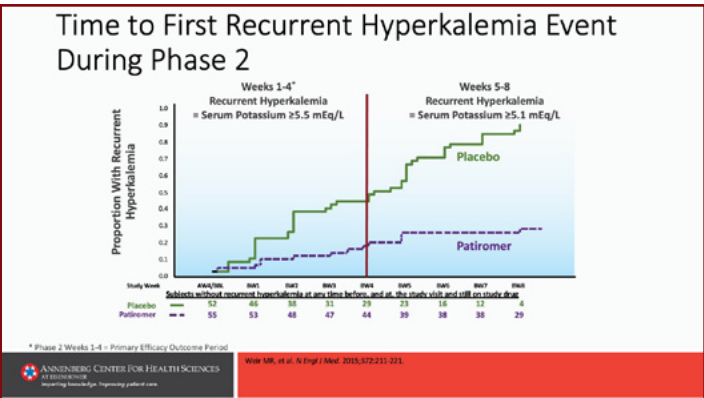
*1-2 weeks after discontinuation of study drug

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individuals who stopped patiromer, the serum potassium level significantly increased as compared to those who remained on patiromer.

After controlling the serum potassium level, if you stopped it, ie, the placebo group, the hyperkalemia recurred, whereas it was much better controlled if the patient remained on patiromer. Once again, it's worthwhile emphasizing that all of these individuals were on RAAS inhibitors.

Adverse events that were noted during the withdrawal phase were similar. A small number of individuals experienced constipation or diarrhea, but there were no clinically important differences with the placebo group in terms of adverse or serious adverse events.



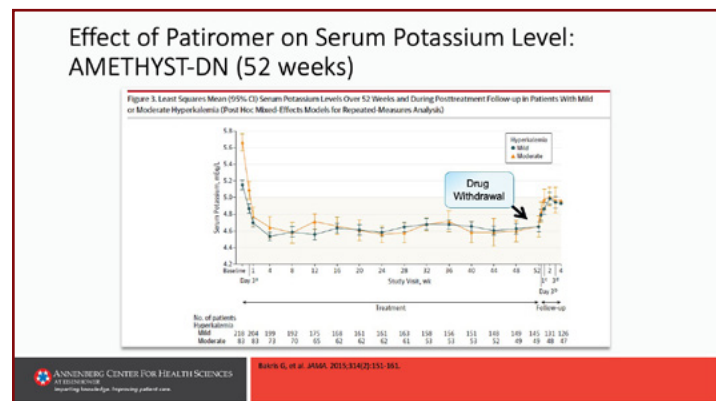
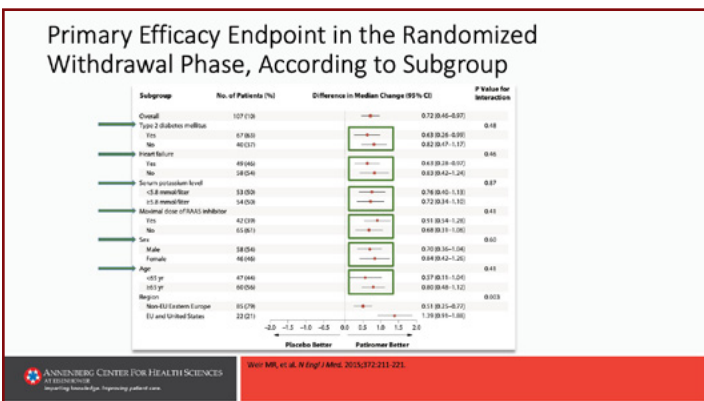
Adverse Events During the Randomized Withdrawal Phase and Through the Safety Follow-up Period* for That Phase

Adverse Event	Placebo (n=52)	Patiromer (n=53)
≥ 1 Adverse event	26 (50)	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Nausea	0	2 (4)
≥ 1 Serious adverse event	1 (2)	0

*1-2 weeks after discontinuation of study drug; Data are presented as number of patients (%).

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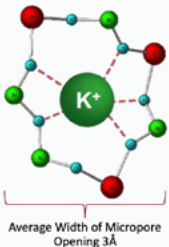
Now, Bakris and his colleagues asked the question, would patiromer be useful on a chronic basis? To answer this question, they conducted this 52-week trial in a cohort of patients who had diabetes. Once again, all of these individuals were taking RAAS inhibitors. Note that the serum



potassium level could be reduced to the normal range in a group of people who came in with hyperkalemia. The 52-week study also showed the durability of this effect. It is also important to note that when patiromer was stopped after 52 weeks, the hyperkalemia tended to reoccur. This trial provided long-term data showing that patiromer can enable the use of RAAS inhibitors and enable the use of these drugs in such a way that hyperkalemia is prevented.

The other drug that's now become available is sodium zirconium cyclosilicate. This again is a crystalline structure that binds potassium in exchange for sodium. It is taken by mouth, but is not systemically absorbed. As it binds the potassium, it lowers the free potassium concentration in the lumen of the GI tract, allowing potassium now to diffuse from blood into the lumen, causing a reduction in the serum concentration. It's a crystalline structure designed to be highly specific for potassium. The only other cation it seems to bind to is ammonium ion.

Sodium Zirconium Cyclosilicate: A Novel, Selective K⁺ Binding Agent



Average Width of Micropore Opening 3Å

Sodium Zirconium Cyclosilicate Properties

- Microporous zirconium silicate compound
- Insoluble, highly stable
- 9.3x more K⁺ binding capacity than sodium polystyrene sulfonate (Kayexalate™)
- >125x more selective for K⁺ than sodium polystyrene sulfonate

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 REPORTING: HARMONIZE-01; TREATING: PATIROMER

Richard M, et al. JAMA. 2014;312(21):2221-2231

Several trials have now shown the efficacy of sodium zirconium cyclosilicate. The HARMONIZE study was a double-blind, placebo-controlled trial involving subjects with hyperkalemia. The drug was given 3 times per day over the initial 48 hours and then once a day thereafter. The HARMONIZE study investigated sodium zirconium cyclosilicate at several doses.

HARMONIZE Trial

- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluating sodium zirconium cyclosilicate 3 times daily in an initial 48-hour open-label phase (N=258)
- Patients (n=237) achieving normokalemia (3.5-5.0 mEq/L) were randomized to once-daily treatment for 28 days with
 - Sodium zirconium cyclosilicate
 - 5 g (n=45)
 - 10 g (n=51), or
 - 15 g (n=56) or
 - Placebo (n=85)

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Richard M, et al. JAMA. 2014;312(21):2221-2231

Patients with a variety of comorbidities were enrolled, including heart failure and diabetes. About two-thirds were taking RAAS inhibitors.

If we look at the efficacy of the drug over the initial 48 hours when the drug was being given 3 times per day, again as compared to the placebo group, notice how the potassium was rendered into the normal range, again across a wide range of underlying risk factors, CKD, eGFR reduction, heart failure, RAAS inhibitor therapy, and various levels of baseline potassium. In all of these groups, the drug was quite efficacious in controlling the serum potassium level.

HARMONIZE Trial (continued)

- In the open-label phase:
 - Congestive heart failure: 36.4%
 - Diabetes mellitus: 65.9%
 - RAASi therapy: 69.8%

RAAS, renin-angiotensin-aldosterone inhibitor

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Richard M, et al. JAMA. 2014;312(21):2221-2231

HARMONIZE Trial: Serum Potassium Levels During the Open-Label Phase (48 hours) by Demographics

Demographic	0 hours (n)	48 hours (n)
All	258	251
CKD History	169	163
CKD eGFR	179	172
Heart Failure	94	92
Diabetes	170	166
Taking RAASi	180	173
Baseline Potassium Level, mEq/L	119	115
<5.5	100	99
5.5-6.0	39	37
>6.0		

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Richard M, et al. JAMA. 2014;312(21):2221-2231

Let's look at the results by the dose of sodium zirconium cyclosilicate used. The 15-g dose is not particularly used commonly, more the 5- and the 10-g doses. The trial results showed that there is somewhat of a dose-response relationship.

HARMONIZE Trial: Serum Potassium Levels During the Randomized Phase (Days 8–29) According to Study Group

Zirconium Cyclosilicate Dose	No. of patients	Mean baseline potassium, mEq/L
Placebo	82	5.55
5-g	45	5.53
10-g	50	5.58
15-g	54	5.55

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Richard M, et al. JAMA. 2014;312(21):2221-2231

In terms of side effects, sodium zirconium cyclosilicate is very well tolerated. In fact, there were no real side effects other than a dose-dependent increase in edema. This may be related to the sodium load of the drug. As I mentioned, the 15-g dose is not utilized very commonly. Interestingly, hypokalemia, either with patiromer or sodium zirconium cyclosilicate, is quite uncommon despite the fact that these are potassium-lowering drugs. Hypokalemia can occur, but it's distinctly uncommon.

A second study by Packham and colleagues looked at sodium zirconium cyclosilicate in a group of individuals with hyperkalemia at baseline. Patients were initially treated with sodium zirconium cyclosilicate or placebo 3 times per day for 48 hours and then switched to once-a-day therapy. After controlling the serum potassium level, patients entered a withdrawal phase to look at what would happen if you stop sodium zirconium cyclosilicate vs continue on it.

HARMONIZE Trial: Adverse Events Occurring in ≥5% of Patients in Any Group

Adverse Events	No. (%)				
	Open-Label Phase Zirconium Cyclosilicate, 10g (n = 258)	Randomized Phase			
		Placebo Group (n = 85)	Zirconium Cyclosilicate Dose Group 5g (n = 45)	10g (n = 51)	15g (n = 56)
Any event	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)	25 (44.6)
Blood and lymphatic system disorders					
Anemia	0	0	0	0	3 (5.4)
Gastrointestinal disorders					
Constipation	2 (0.8)	0 (7.1)	0	1 (2.0)	1 (1.8)
General disorders and administration site conditions					
Edema*	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Metabolic and nutrition disorders					
Hyperkalemia (all)	0	0	0	5 (9.8)	6 (10.7)
Hyperkalemia (reported as adverse event)	0	0	0	0	1 (1.8)
Infectious and infestations					
Upper respiratory tract infection	1 (0.4)	1 (1.2)	3 (6.7)	1 (2.0)	1 (1.8)

Kushnir M, et al. *JAMA*. 2014;312(12):2222-2231.

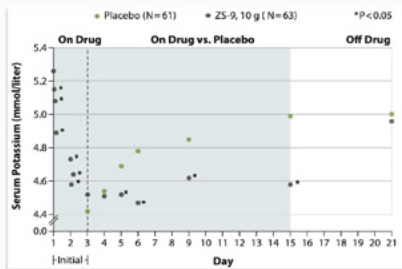
Sodium Zirconium Cyclosilicate in Hyperkalemia

- Multicenter, double-blind phase 3 trial of patients (N=754) with hyperkalemia
- Phase 1
 - Patients randomly assigned to receive thrice-daily treatment for 48 hours with:
 - Sodium zirconium cyclosilicate (1.25 g, 2.5 g, 5 g, or 10 g) or
 - Placebo
- Phase 2
 - Patients achieving normokalemia (3.5-4.9 mEq/L) (N=543) were randomly assigned to once-daily treatment from days 3 through 11 with:
 - Sodium zirconium cyclosilicate (1.25 g, 2.5 g, 5 g, or 10 g) or
 - Placebo

Fackham DK, et al. *N Engl J Med*. 2015;373(2):222-231.

In the first 48 hours, the serum potassium level rapidly fell. In this particular trial, as early as 1 hour, there was already a statistically significant reduction in the serum potassium level with sodium zirconium cyclosilicate compared with placebo. During the withdrawal phase, patients who remained on sodium zirconium cyclosilicate maintained control of their serum potassium level, whereas if you stopped it, the hyperkalemia tended to recur.

Potassium Levels With Sodium Zirconium Cyclosilicate 10 g Once-Daily During Phase 2



Fackham DK, et al. *N Engl J Med*. 2015;373(2):222-231.

Adverse Events During Initial Phase and Maintenance Phase

Table 2. Adverse Events during Initial Phase and Maintenance Phase*									
Adverse Events in Initial Phase	ZS-9, 1.25 g		ZS-9, 2.5 g		ZS-9, 5 g		ZS-9, 10 g		No. of patients
	Placebo	158	154	141	157	143			
Adverse event — no. (%)									
Any	17 (10.8)	25 (16.2)	13 (8.2)	22 (14.0)	17 (11.9)				
Gastrointestinal disorder†	8 (5.1)	7 (4.5)	3 (2.1)	6 (3.8)	5 (3.5)				
Cardiac disorder‡	0	1 (0.6)	0	3 (1.9)	2 (1.4)				
Urinary tract infection	0	3 (1.9)	0	1 (0.6)	0				
Adverse Events in Maintenance Phase	ZS-9, 1.25 g	ZS-9, 2.5 g	Placebo	ZS-9, 1.25 g	Placebo	ZS-9, 2.5 g	Placebo	ZS-9, 5 g	ZS-9, 10 g
No. of patients	46	50	41	49	46	54	68	65	61
Adverse event — no. (%)									
Any	10 (21.7)	12 (24.0)	13 (31.7)	14 (28.6)	9 (19.6)	11 (20.4)	14 (21.3)	15 (24.6)	21 (33.3)
Gastrointestinal disorder†	4 (8.7)	2 (4.0)	1 (2.4)	0	2 (4.3)	4 (7.4)	5 (7.7)	5 (7.7)	0
Cardiac disorder‡	0	0	0	0	1 (1.9)	1 (1.5)	2 (3.1)	1 (1.6)	2 (3.2)
Urinary tract infection	2 (4.3)	1 (2.0)	2 (4.9)	1 (2.0)	0	1 (1.9)	1 (1.5)	3 (4.6)	0

Fackham DK, et al. *N Engl J Med*. 2015;373(2):222-231.

Adverse events during the initial 48 hours and in the withdrawal phase showed sodium zirconium cyclosilicate was well tolerated. The adverse events were really no different than with placebo. Once again, the only adverse event that's been noted with sodium zirconium cyclosilicate is a dose-dependent increase in the peripheral edema.

Other Treatment Considerations

There are now data employing a new mineralocorticoid antagonist called finerenone. This is a nonsteroidal drug. It's a unique drug that has a unique structure compared to spironolactone. It also has a very short half-life. The results of the FIDELIO-DKD study were recently published. In this study, a large cohort of individuals were screened and then 5,000 or so were randomized to either finerenone or placebo, on top of standard-of-care, and what I mean by that, these patients were all on RAAS inhibitors or remained on that standard-of-care. The primary outcome was a kidney outcome, looking at further reductions in eGFR, need for dialysis, or renal death and a secondary outcome looking at cardiovascular benefits.

FIDELIO-DKD: Study Design



Hierarchical endpoints

- Kidney composite: Time to kidney failure, sustained ≥40% decrease in eGFR from BL, or renal death
- CV composite: Time to CV death, non-fatal MI, non-fatal stroke or hospitalization for HF
- Death from any cause
- Hospitalization for any cause
- Change in UACR
- Second kidney composite

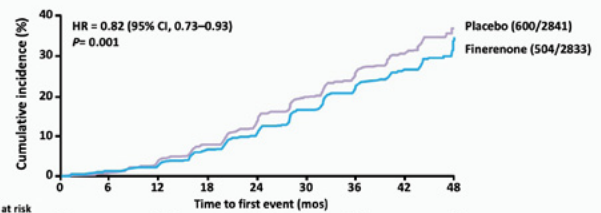
*10 mg if screening eGFR <60 mL/min/1.73 m² and 20 mg if >60 mL/min/1.73 m²; up-titration encouraged from month 1 if serum potassium <4.8 mEq/L and eGFR stable

Barkh CR, et al. *N Engl J Med*. 2020;383(23):2219-2228.

In terms of the primary outcome, the finerenone group had a statistically significant reduction. I would like to emphasize that in this study, finerenone was used on top of standard-of-care and the placebo group all are treated with standard-of-care, meaning ACE-I or ARB. Adding finerenone seems to confer an additional benefit, compared with placebo, over this 48-month period.

FIDELIO-DKD: Primary Endpoint

Kidney Failure*, Sustained >40% Decrease in eGFR from BL, or Renal Death



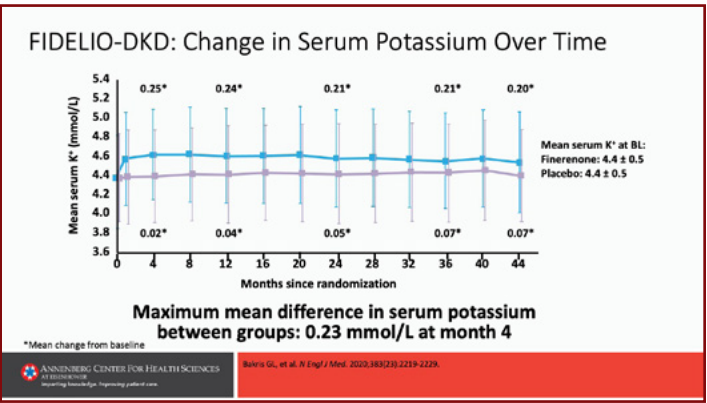
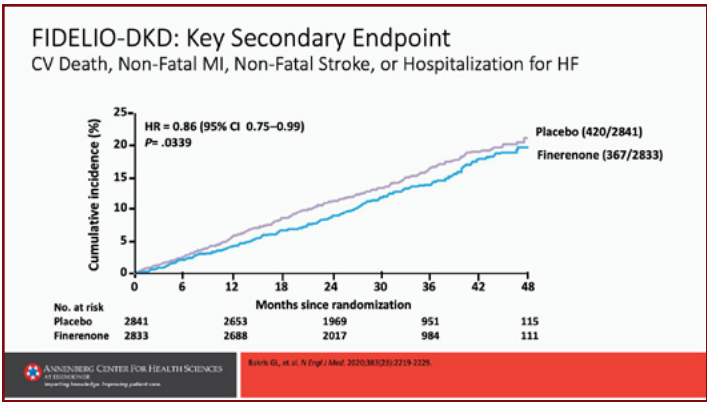
No. at risk
Placebo 2841
Finerenone 2833

*ESRD or eGFR <15 mL/min/1.73 m²

Barkh CR, et al. *N Engl J Med*. 2020;383(23):2219-2228.

The study also had a secondary outcome, which was the cardiovascular component, looking at cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Once again, adding finerenone to a standard-of-care has additional benefit in this secondary outcome. And this drug now has an FDA indication to be utilized as a way to both slow CKD progression and provide cardiovascular benefit in our patients with diabetes mellitus who have kidney disease.

Interestingly, hyperkalemia can occur, as you might expect, but it tends to be much less common than what we typically think of with spironolactone.



Many people believe this may be related to the short half-life of finerenone compared to spironolactone, which has a half-life close to 48 hours. The half-life of finerenone is measured in hours.

Our various strategies to minimize hyperkalemia include dietary potassium restriction, but remember to do so in a somewhat nuanced way, given that many of the foods that are enriched in potassium are heart-healthy. We definitely want to look at and avoid medications that cause hyperkalemia and we can discontinue without untoward events. Avoidance of nonsteroidal anti-inflammatory drugs can be quite useful, avoiding potassium-sparing diuretics if we are able to, the calcineurin inhibitors. That's not always possible because calcineurin inhibitors are often utilized in transplant patients. There's now data actually trying to examine whether these potassium-binding drugs can be safely used in the setting of calcineurin inhibitor therapy without altering the drug levels.

Strategies to Mitigate Hyperkalemia

- Dietary potassium restriction
- Avoid drugs that can cause or potentiate hyperkalemia
 - NSAIDs
 - K⁺-sparing diuretics
 - Calcineurin inhibitors
 - Other
- Concomitant use of potassium binders such as patiromer, sodium zirconium cyclosilicate, sodium polystyrene sulfonate

NSAIDs = non-steroidal anti-inflammatory drugs

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And again, we now have this new class of agents. Patiromer and sodium zirconium cyclosilicate, which are very well tolerated, are options to manage hyperkalemia in the setting of RAAS inhibitor use. I would also add that sodium polystyrene sulfonate is a very poorly tolerated agent and not a viable drug to use in the long-term management of hyperkalemia.

Let's go back to the case study. Remember that the patient had been successfully treated in the hospital. His serum potassium level had been lowered to a much safer level. The serum creatinine actually also was back to baseline and the serum potassium level was even better 1 week following hospital discharge. His discharge medications were carvedilol, a long-acting loop diuretic, the dihydropyridine calcium channel blocker amlodipine, a restricted potassium diet. There was communication with the primary care clinician about these changes within 1 week of discharge. At that time, the repeat serum potassium and creatinine levels were stable. Recognizing that this patient had a lot of underlying comorbidities that might benefit from an ACE-I, the primary care clinician did restart the ACE-I with the plan that the serum potassium level would be repeated in 2 weeks. If the serum potassium level increased, one could consider dietary counseling, as well as the use of one of these more novel potassium-binding drugs, patiromer or sodium zirconium cyclosilicate.

Case Study (continued)

Outcome of patient in hospital

- Patient SCr returns to baseline, repeat K⁺ 4.5 mEq/L
- Discharge medications include carvedilol, torsemide, amlodipine, insulin, restricted potassium diet
- Coordinated care with PCP with follow-up 1 week post-discharge
 - Repeat SCr stable, K⁺ 4.3 mEq/L
 - Restart lisinopril 20 mg/d
- Repeat levels in 2 weeks; if K⁺ increased, consider diet counseling, oral K⁺ binding agent
- Restart spironolactone when K⁺ stable

PCP, primary care provider; SCr, serum creatinine

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The primary care physician, again with communication from the hospital team, was also going to consider restarting spironolactone since this individual had heart failure with reduced ejection fraction and would, indeed, benefit from being on a mineralocorticoid antagonist. This case illustrates the nice communication between the hospital team, the outpatient setting, and the need to at least revisit the idea of restarting drugs that might have cardiovascular benefit, recognizing that we have now strategies that could enable the utilization of these drugs, whereas that was not really feasible before.

Some tips for good team care. Both the team members, as well as the patient, must have the same goal, that is, a good outcome. The patient should be involved in the decision making and that involves providing good education to the patient about what's being done and what the potential side effects are. Good communication is absolutely essential between the various healthcare team members, not only while the patient is in the hospital, but between the team members in the hospital and the outpatient clinician, so that revisiting, for example, the reinitiation of ACE-I or ARB, can be undertaken. And the patient has to be able to communicate with the healthcare team at all times.

Tips for Good Team Care

- Healthcare team members and patient must share the same goal
- Education provided to the patient must be consistent among healthcare team members
- Good communication is essential
 - Among healthcare team members
 - Between patient and healthcare team members
- The patient must know how to communicate with the healthcare team

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