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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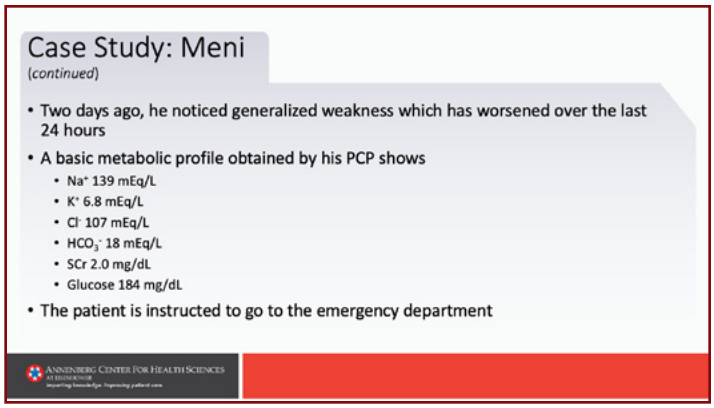
My name is Dr. Biff Palmer and I'm a professor of internal medicine at the University of Texas Southwestern Medical Center. I appreciate the opportunity to make this presentation. I'm going to begin by just providing a brief outline of what is going to be covered. We're going to start off with a case 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.

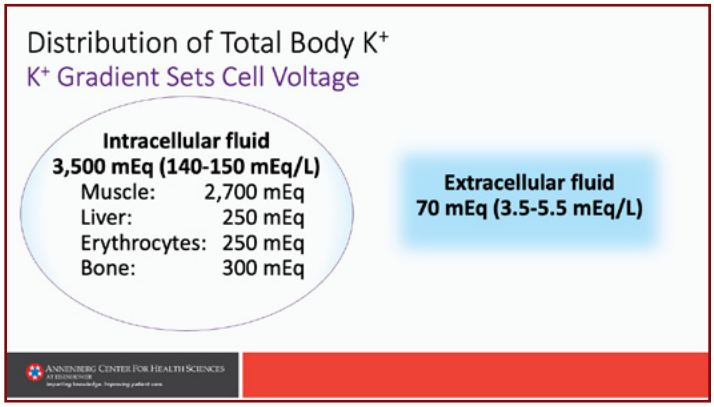
INTRODUCTION

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.

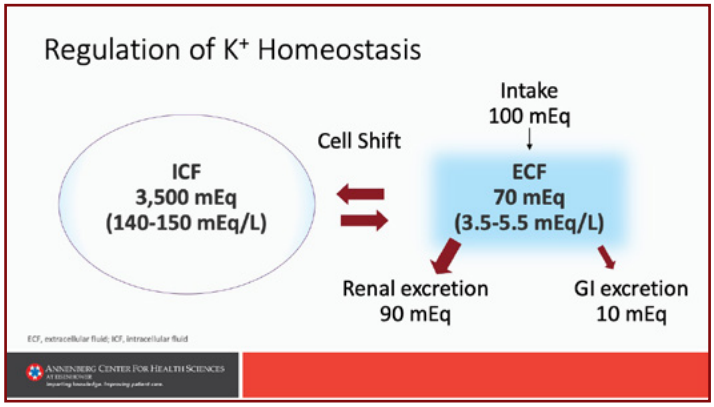
Two days ago, he noted generalized weakness that has worsened over the last 24 hours. Review of the basic metabolic profile reveals that he now has a potassium of 6.8 mEq/L. He also has evidence of a normal gap metabolic acidosis, his serum creatinine concentration is 2.0 mg/dL, and his glucose is 184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



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.



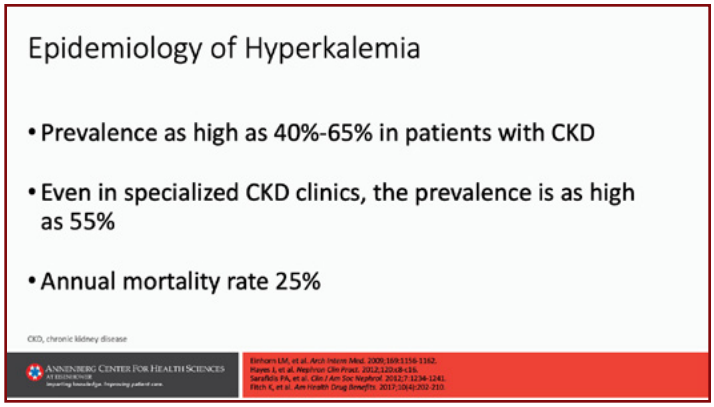
With respect to potassium homeostasis, imagine that somebody ingests 100 mEq of potassium. The kidney is the main route by which that potassium is excreted. There is a small contribution of the gastrointestinal (GI) tract, primarily in the colon. Now, the ability of the kidney to excrete potassium is 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.

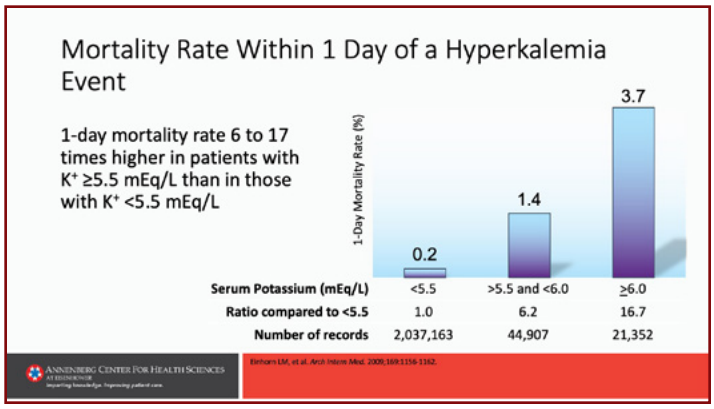


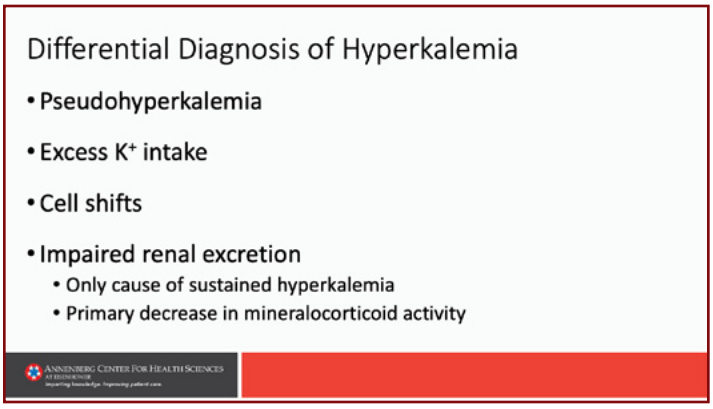
Hyperkalemia is a common disorder. It's been found to be present in up to 40% to 65% of patients who have CKD, even in clinics that are specialized to care for these individuals. The annual mortality rate can be as high as 25%.

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







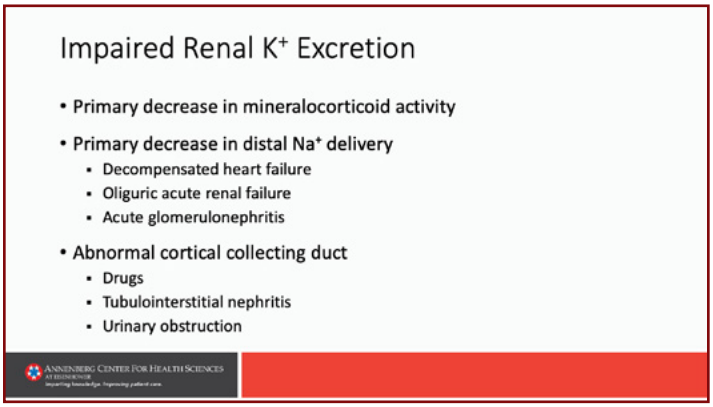
hyperkalemia. One of the things we always want to exclude is so-called pseudohyperkalemia. That is when the potassium is high in a test tube, but not in the individual. This obviously occurs in somebody who has had fist clenching during the phlebotomy technique, the use of a tourniquet. If you ever suspect 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.

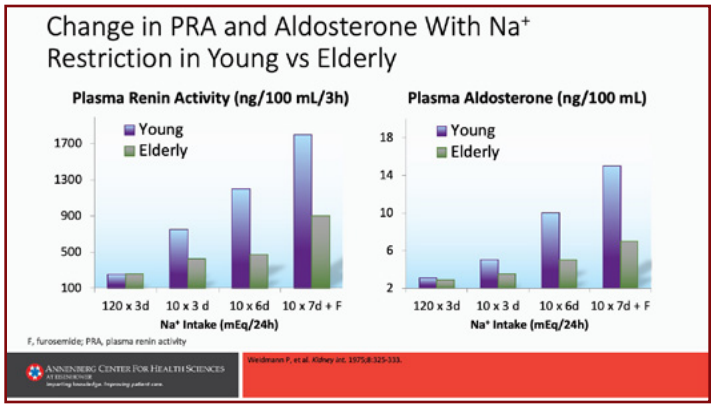
Perhaps the most common cause, though, of hyperkalemia, either in the inpatient or the outpatient setting, is impaired kidney excretion. This is really the main cause of sustained hyperkalemia. While several factors are involved, many of the factors tend to center around disturbances in the renin-angiotensin-aldosterone 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.



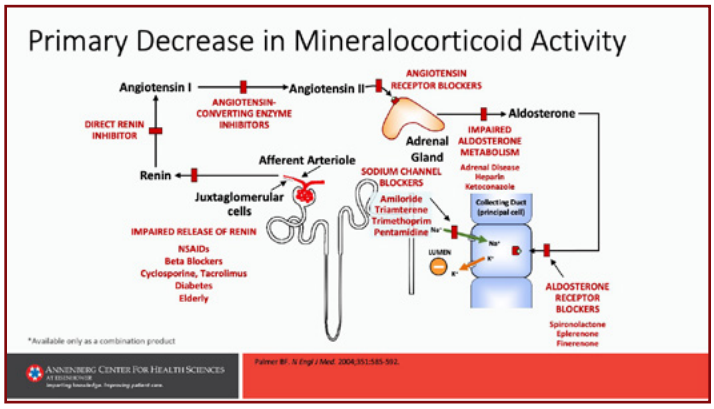
Another cause of impaired kidney excretion is anything that primarily disrupts function at the collecting ducts. This can be due to a variety of medications. Another cause is tubulointerstitial renal disease. Here, the primary pathologic process is attacking the tubules. Urinary obstruction is also a 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.



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.



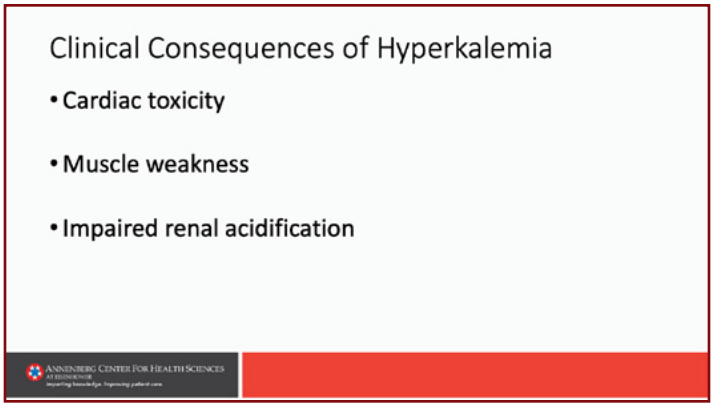
Drugs that block the epithelial sodium channels, such as amiloride, triamterene, the antibiotics trimethoprim-sulfamethoxazole or pentamidine, block sodium movement, thereby limiting the generation of the negative charge, which is why potassium secretion is impaired.

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.

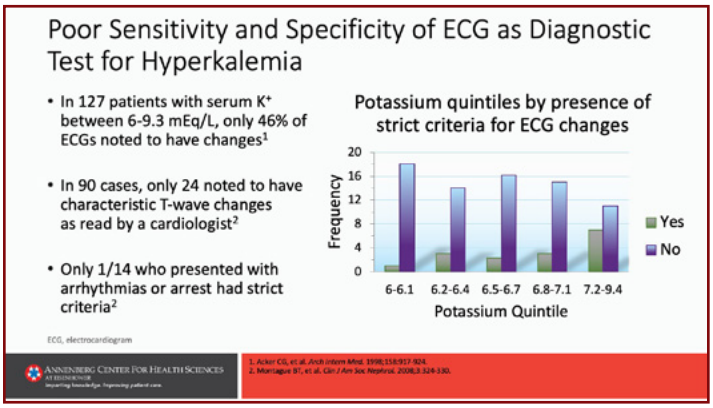
The angiotensin receptor blockers (ARBs) block the angiotensin-1 receptor on the zona gluomerulosa cells and that's why ARBs cause hyperkalemia because they limit aldosterone production. The angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II and, therefore, 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 hyphoaldosteronism 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 ammoniagenesis 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.



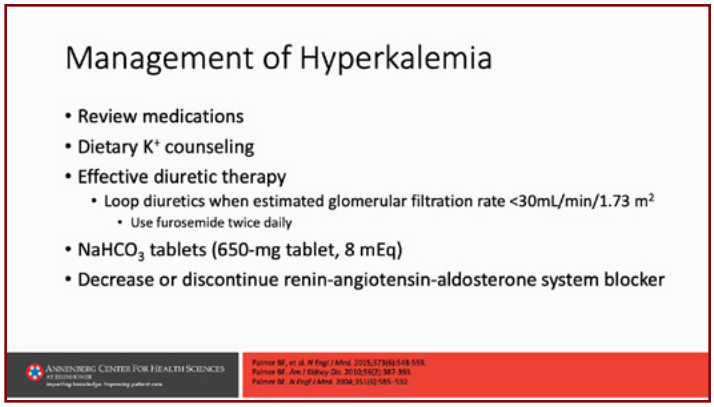
With regard to ECG manifestations, it is worthwhile to note that there's oftentimes a poor correlation between having ECG changes and the degree of hyperkalemia. This was a study where individual values were obtained and a cardiologist actually read the ECG in these patients. As shown by the graph, it 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.



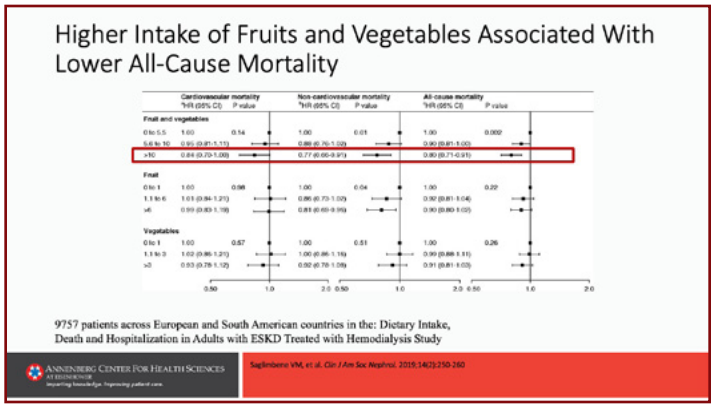
RAAS Inhibitor Therapy

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.

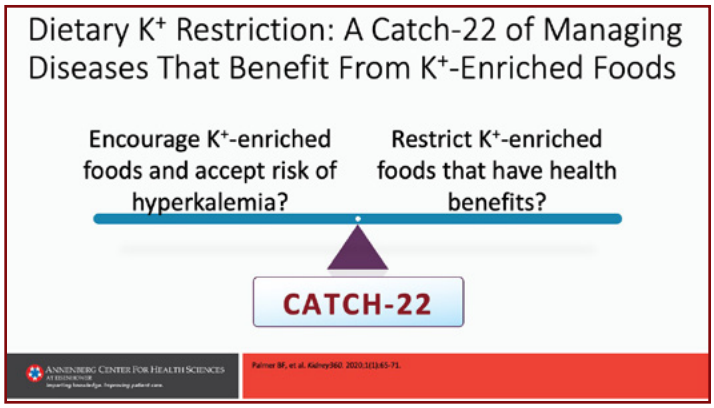
Thirdly, effective diuretic therapy is also quite useful in the management of hyperkalemia. I always remind clinicians that when your estimated glomerular filtration rate (eGFR) falls below 30 mL/min/1.73 m^2, loop diuretics really become a required therapy. If furosemide is chosen as

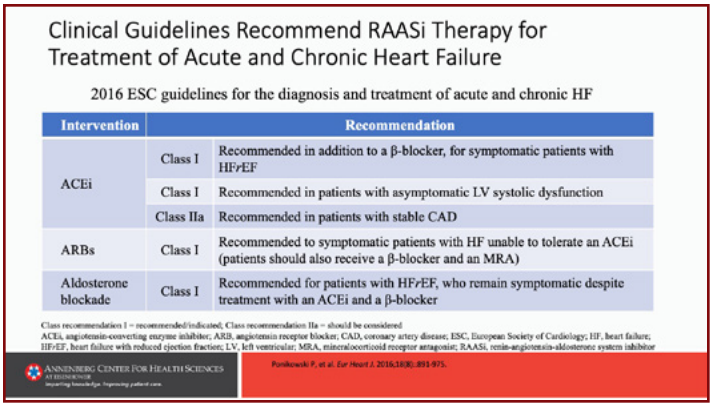


the loop diuretic, also remember it's a short-acting drug that should be used twice daily. Correcting metabolic acidosis with sodium bicarbonate tablets can also be of utility. This is thought to work by increasing distal sodium delivery, but also by raising the blood pH, you shift potassium back into 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.



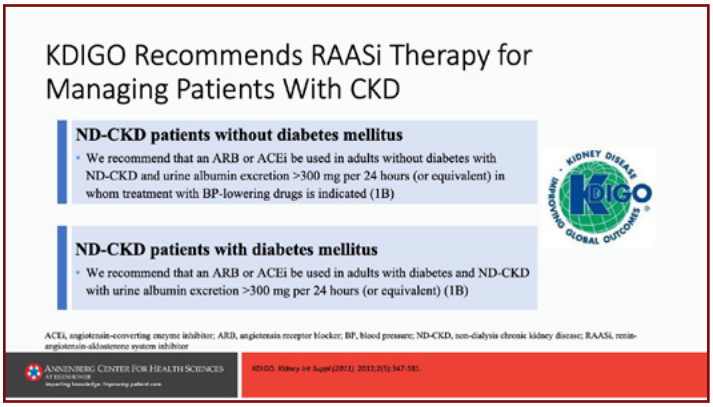
There is a drawback restricting fruits and vegetables as a way to manage hyperkalemia. Once again, fruits and vegetables are enriched in potassium, but as illustrated in this study of dialysis patients, those individuals who were ingesting the greatest amounts of fruits and vegetables had more favorable 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.





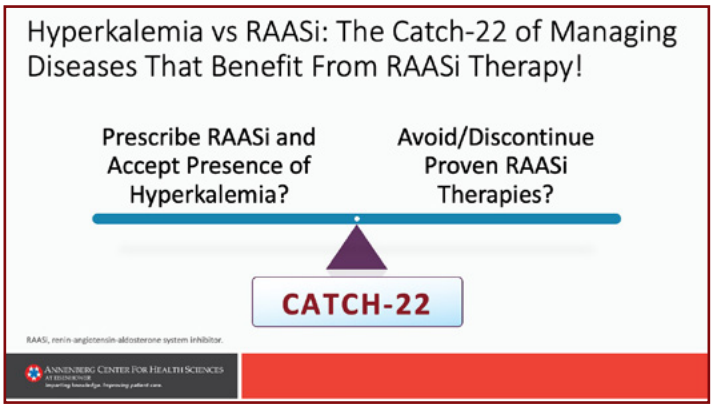
The other thing I mentioned was this catch-22 with regards to either using suboptimal doses of RAAS inhibitors or even discontinuing them altogether.

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.



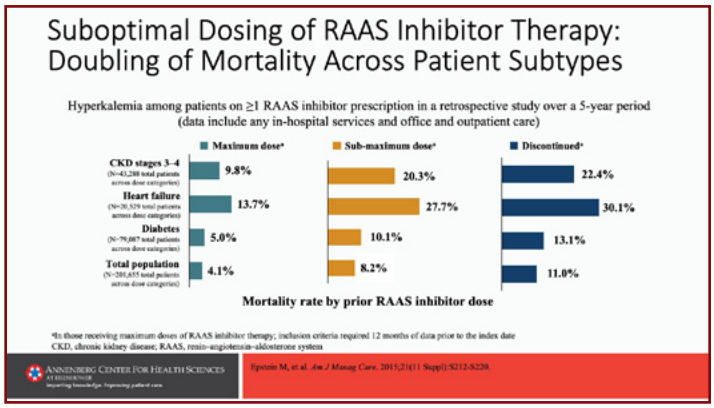
A similar story plays out in individuals who have CKD. In a class I category, various guidelines tell us we should manage patients with CKD with ACE-I or ARBs whether they have diabetes mellitus or not because, again, we have clinical trial data that show that these drugs slow the progression of CKD,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

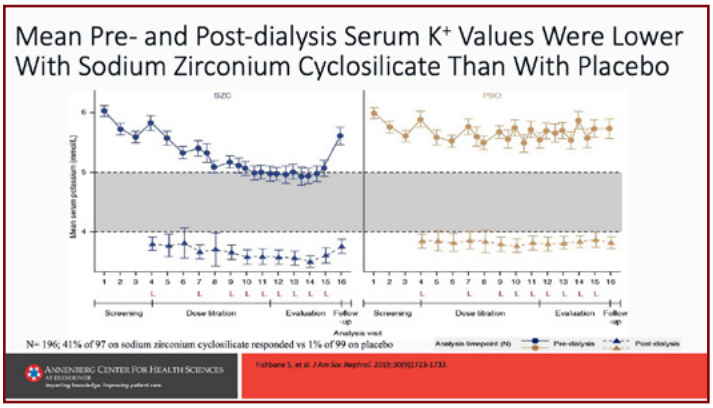


enable us to use these drugs and yet avoid the metabolic complication of hyperkalemia, this would have great clinical utility.

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.

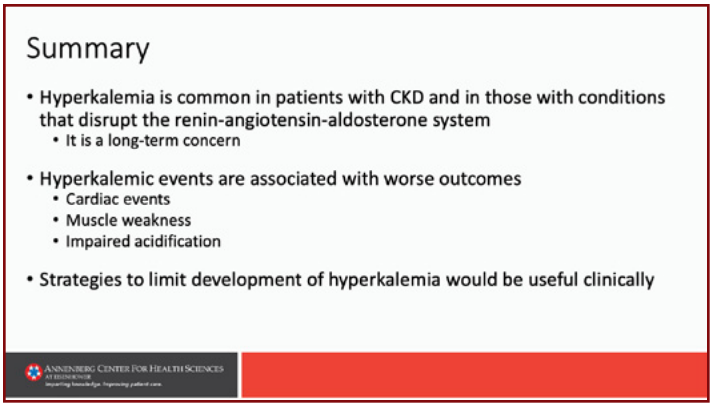


I'm going to talk a little bit about the use of potassium-binding drugs. One of the areas where potassium-binding drugs have now proven great utility is in the management of patients on dialysis who have persistent predialysis hyperkalemia. This is a study looking at 1 of these drugs called sodium zirconium 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.



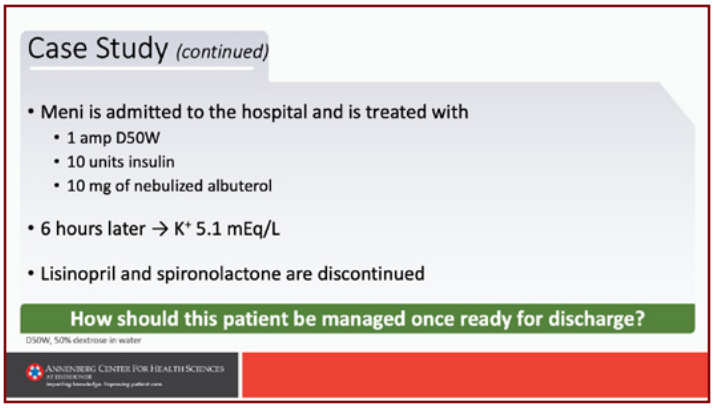
It should be noted that, in this particular study, the use of sodium zirconium cyclosilicate was not associated with any change in interdialytic weight gain or worsening in blood pressure control. The reason is the sodium zirconium cyclosilicate exchanges potassium for sodium, but there were no adverse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

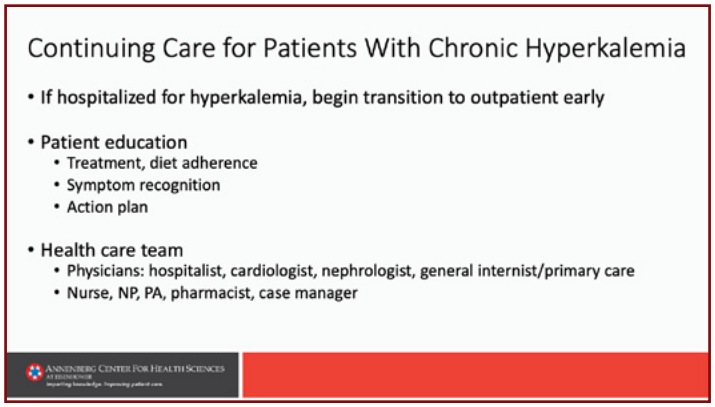


be related, in that hyperkalemia suppresses ammoniagenesis, thereby secondarily impairing kidney acidification. Given these adverse events of hyperkalemia, we need to have strategies to limit the development of hyperkalemia that can be clinically useful.

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?

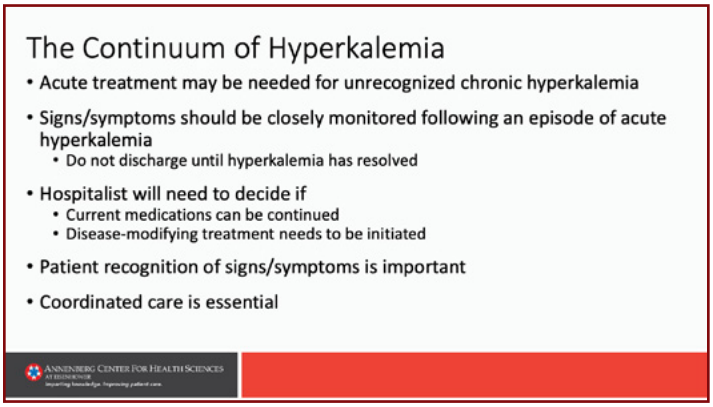


There are some concepts in terms of continuing care to keep in mind when managing individuals with chronic hyperkalemia. Once hospitalized, the transition into the outpatient setting must be started. This is going to require patient education as to diet adherence. We have to educate the patient on treatment, 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



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.

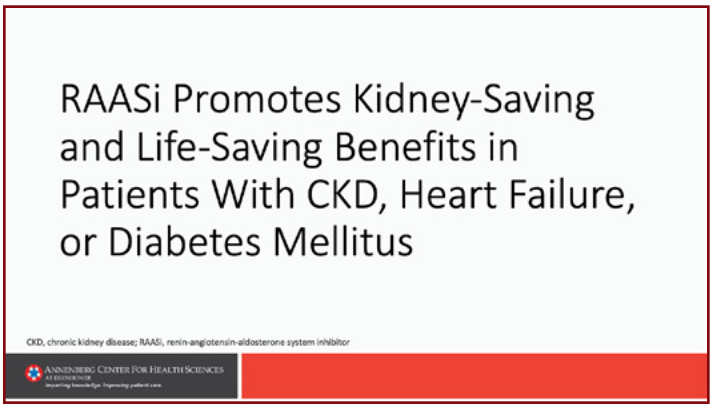


The acute treatment of hyperkalemia is oftentimes needed, as it was in this individual. The fact that this patient presented with life-threatening hyperkalemia at 6.8 mEq/L is why signs and symptoms of hyperkalemia need to be recognized. These patients need to be followed closely and certainly not discharged 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?

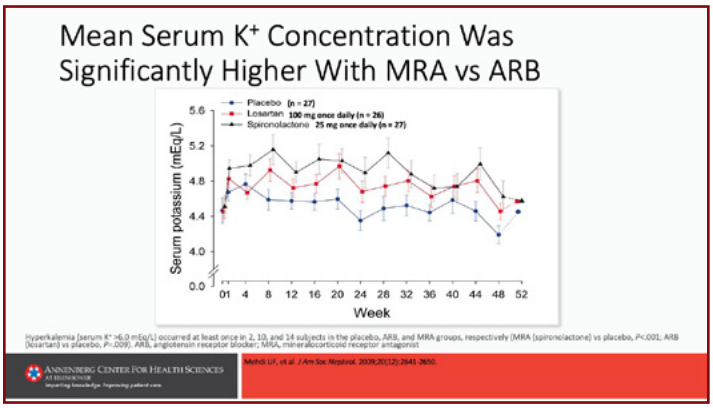
Once again, I want to emphasize that we do need to educate the patient of the signs and symptoms. Hyperkalemia can be asymptomatic and perhaps it's asymptomatic in the majority of individuals, but on occasion it can present with symptoms. Again, coordinated care is clearly essential. All of the members 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 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?

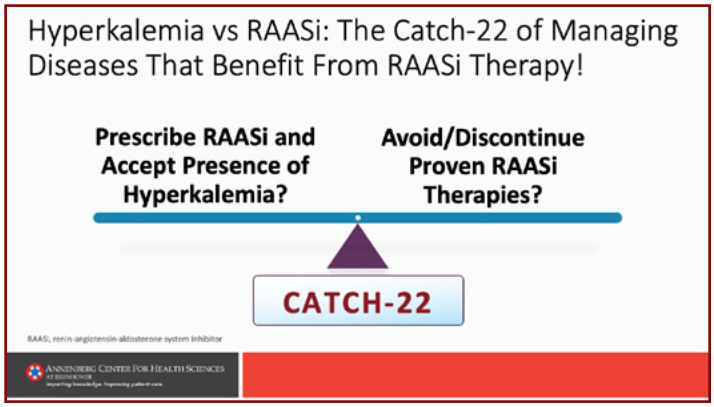
Drugs that target the RAAS can be both kidney-saving and lifesaving, particularly in patients who are most at risk for hyperkalemia, including the patient with CKD, heart failure, or diabetes mellitus.

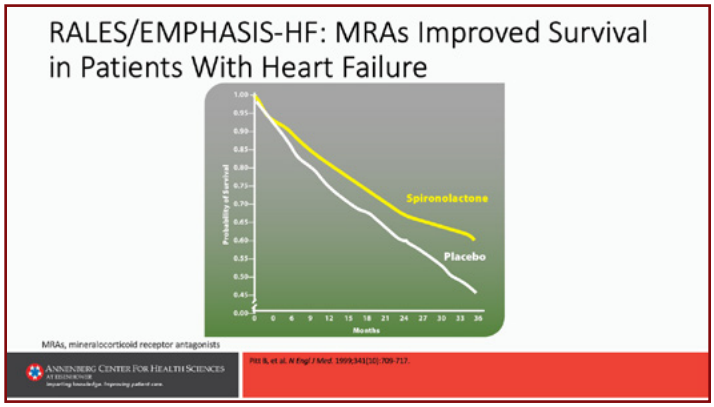


This is an older study simply showing that these RAAS inhibitors cause hyperkalemia and the risk of hyperkalemia becomes additive when you use them together. Notice that in this trial, as compared to the placebo group, hyperkalemia increases when you add an ARB, that's the middle line in red, and then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



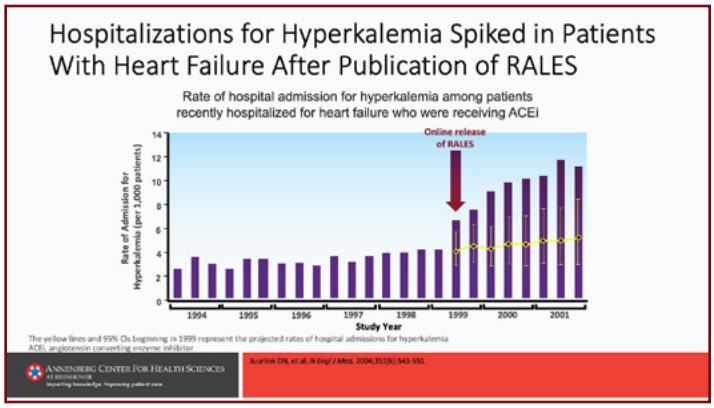
Having said that, though, remember these drugs provide cardiovascular benefits. The RALES study was a classic study in which the addition of 25 mg of spironolactone to ACE inhibitor therapy provided a mortality benefit. The results of RALES really revolutionized the therapy of heart failure and





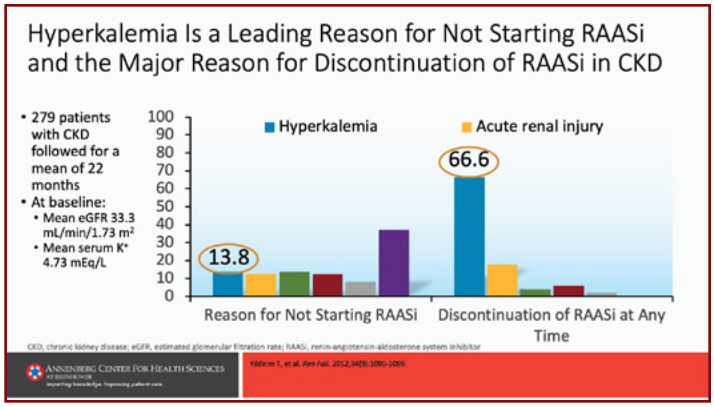
has really become a standard of care using aldosterone antagonists in people who have reduced ejection fraction.

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.

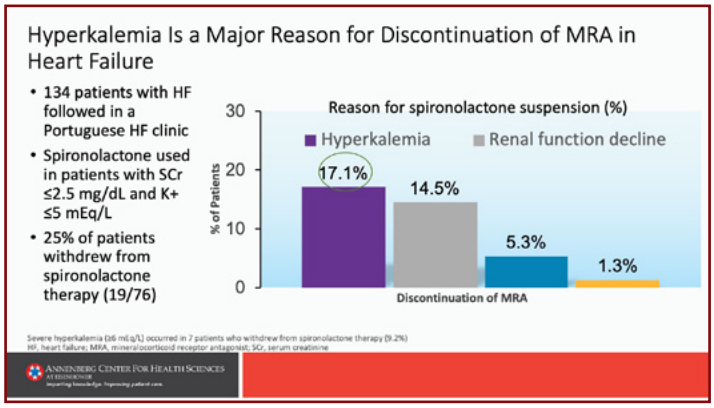


The results of this study highlight the idea that we need to be diligent when using these drugs, be aware of the risk and provide good patient education and good follow-up, so that we minimize the kind of spike that was noted here in this trial.

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.



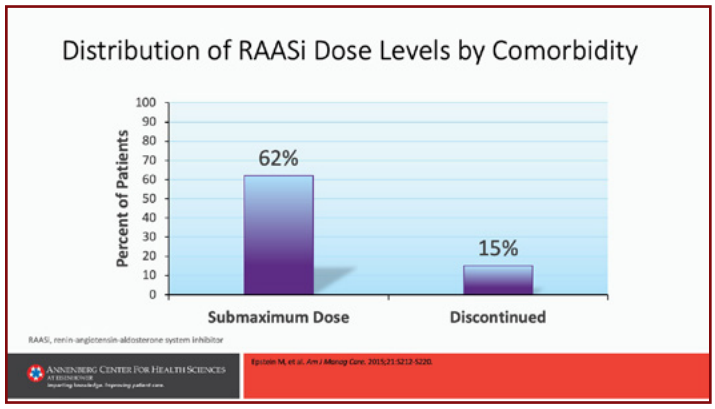
Hyperkalemia is also a major reason for discontinuation of either ACE-I or mineralocorticoid antagonists in patients with heart failure. Here are the results from a study in Europe of patients with heart failure. Seventeen percent of the time hyperkalemia was cited for the reason that spironolactone 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.

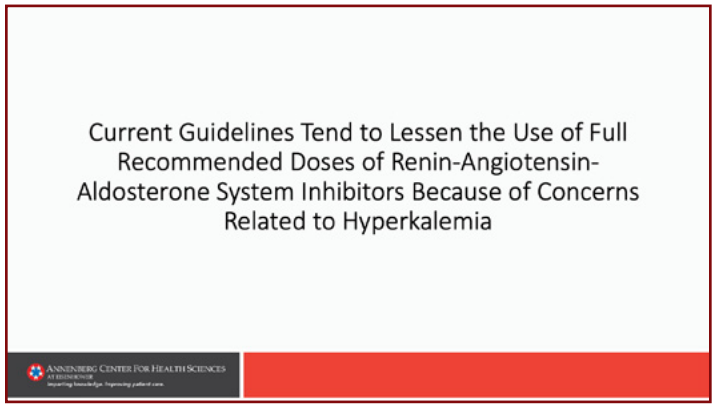


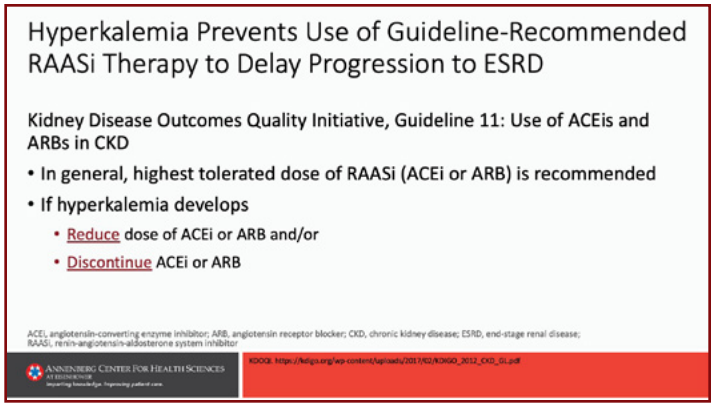
This is a study that looked at the distribution of RAAS inhibitor dose by comorbidity. The large percentage of patients were using submaximal doses, and in 15% the drugs were discontinued. The results show that there's a large population of patients that could be benefitting from these drugs if used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

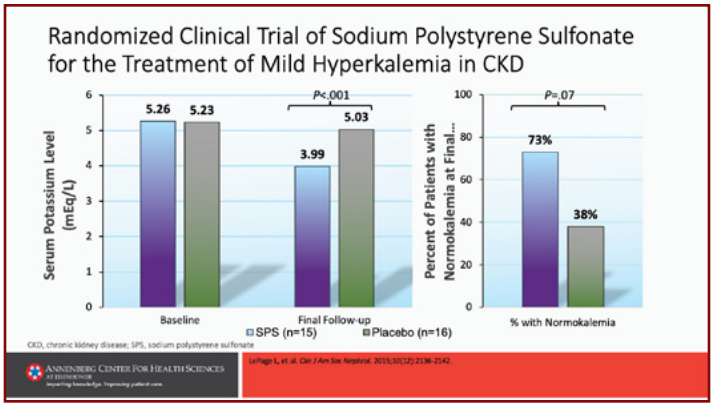
Current guidelines have actually tended to lessen the use of full-dose RAAS inhibitors because of concerns related to hyperkalemia.

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.



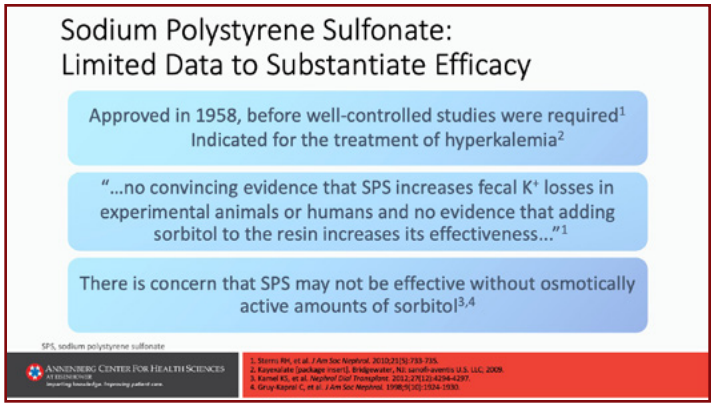






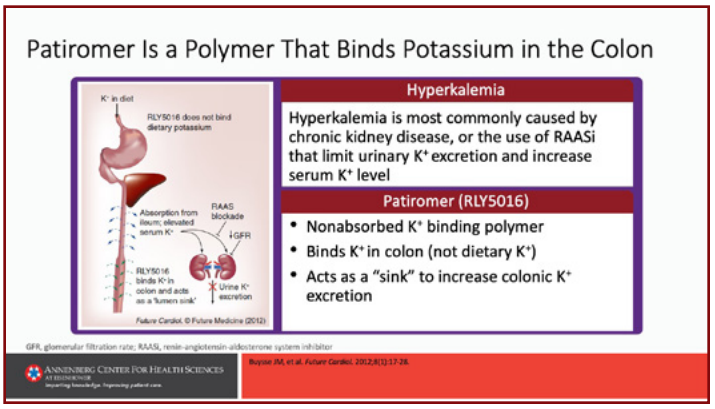
Potassium-binding Medications

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.



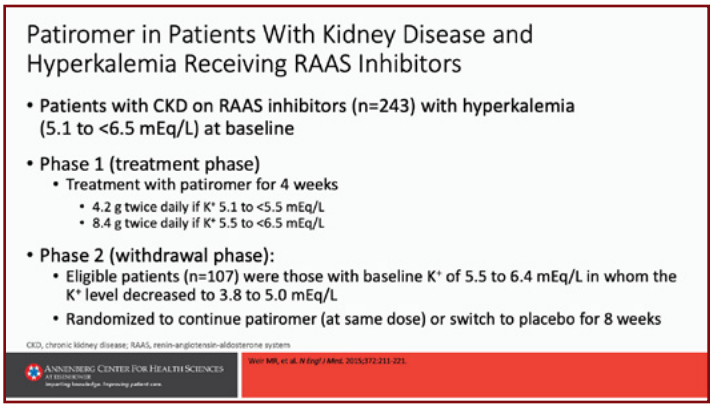
The only clinical trial that's ever been done was only about a month in duration and it's shown here. They took a group of individuals who had mild hyperkalemia. They were able to show that the sodium polystyrene sulfonate did have a lowering effect, but I would just mention to you that there was only 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 patiromer. 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. Patiromer binds potassium in the lumen of the GI tract



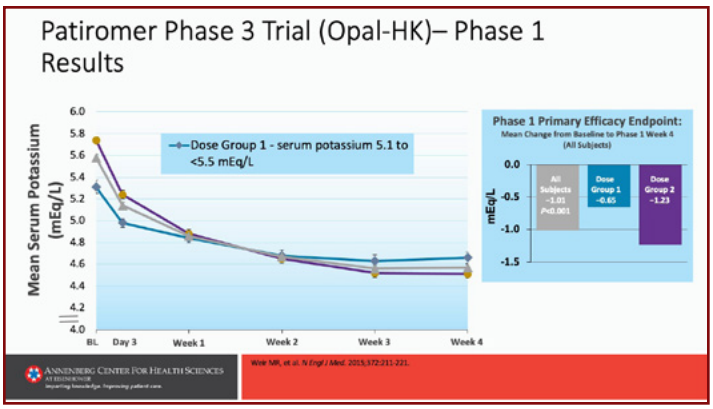
by lowering the free potassium in the lumen. It now creates a favorable gradient for blood potassium to diffuse into the colon where, again, it binds to the polymer.

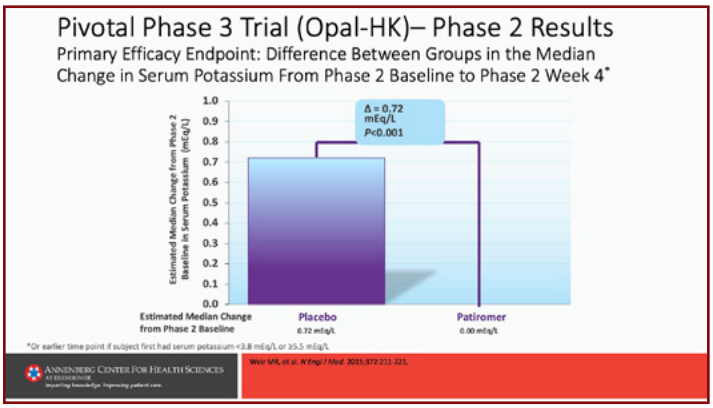
There are several trials that have been conducted to show the efficacy and tolerability of patiromer. The first one was conducted by Matt Weir and colleagues and published in *The New England Journal of Medicine*. Patients with CKD who were on RAAS inhibitors were treated for 4 weeks at various doses.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



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, patiromer was able to control the serum potassium level.

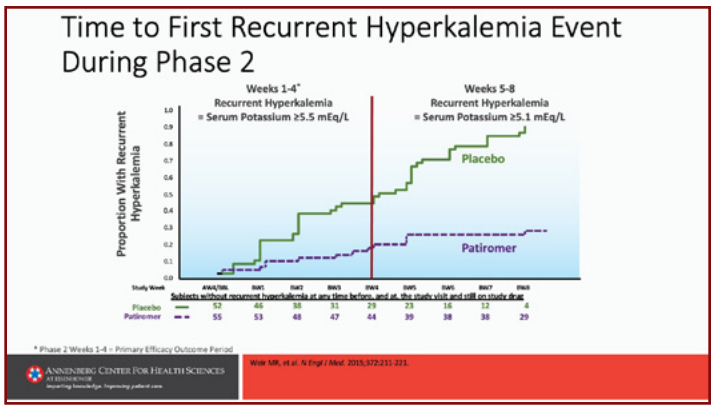
In the withdrawal phase, of those who were controlled at the end of that 4-week period, you can see that in the placebo group, that is those

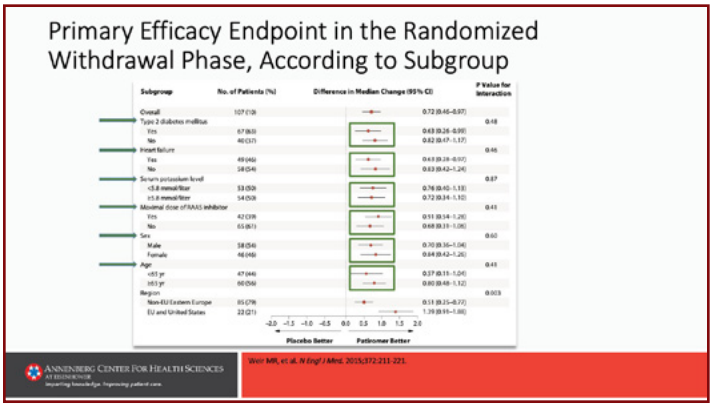




individuals who stopped patiromer, the serum potassium level significantly increased as compared to those who remained on patiromer.

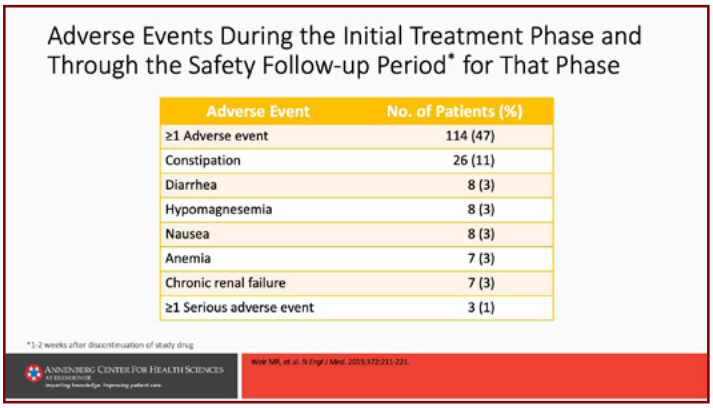
After controlling the serum potassium level, if you stopped it, ie, the placebo group, the hyperkalemia recurred, whereas it was much better controlled if the patient remained on patiromer. Once again, it's worthwhile emphasizing that all of these individuals were on RAAS inhibitors.



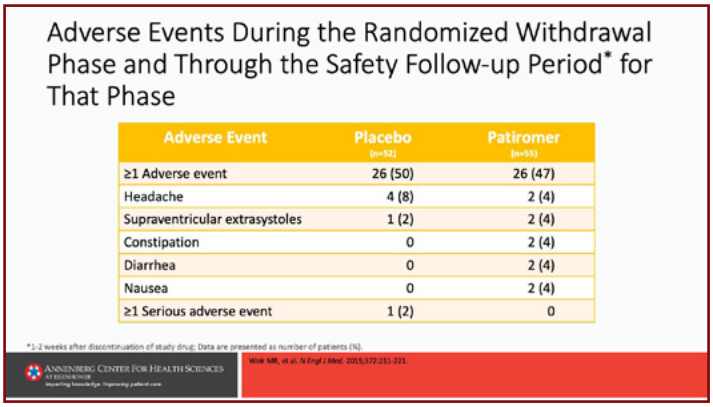


The efficacy of patiromer during the withdrawal phase was uniform across all of these subgroups. It made no difference if the patient had diabetes or heart failure, the potassium level at baseline, maximum dose of RAAS inhibitor, age, or sex. The patiromer-treated patients were able to better maintain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

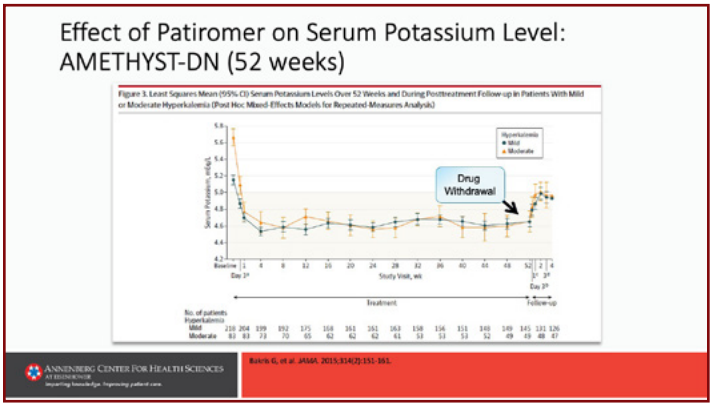
In terms of tolerability, patiromer was well tolerated. There are patients who experience some GI side effects, such as constipation or diarrhea. In the clinical trial data, about 3% developed hypomagnesemia; thus, monitoring the serum magnesium level is recommended. In general, patiromer is a very well-tolerated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



Adverse events 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.

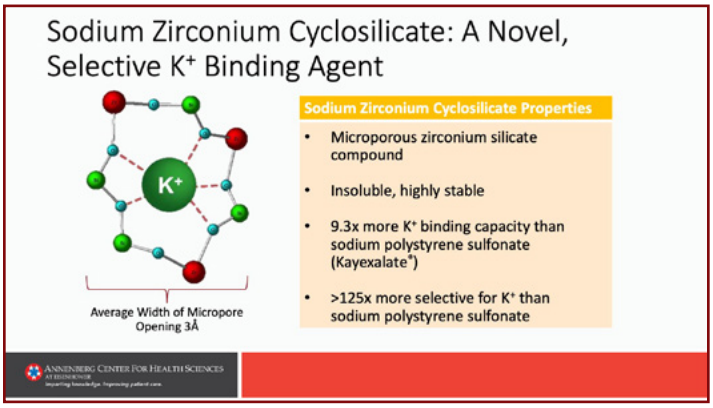


Now, Bakris and his colleagues asked the question, would patiromer be useful on a chronic basis? To answer this question, they conducted this 52-week trial in a cohort of patients who had diabetes. Once again, all of these individuals were taking RAAS inhibitors. Note that the serum

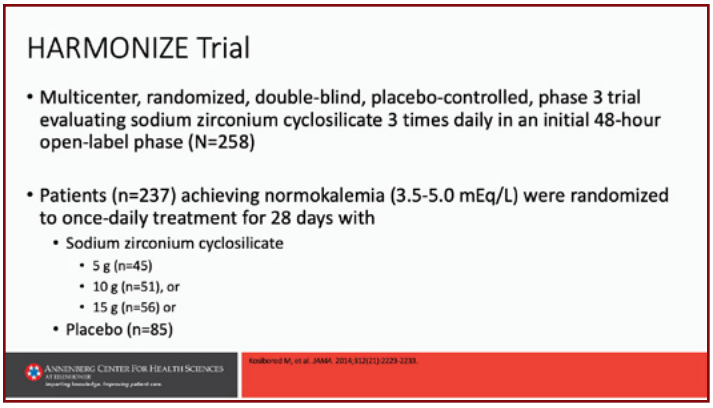


potassium level could be reduced to the normal range in a group of people who came in with hyperkalemia. The 52-week study also showed the durability of this effect. It is also important to note that when patiromer was stopped after 52 weeks, the hyperkalemia tended to reoccur. This trial provided long-term 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.

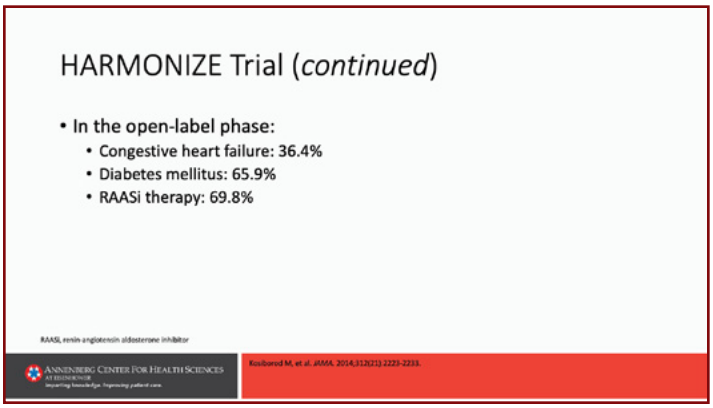


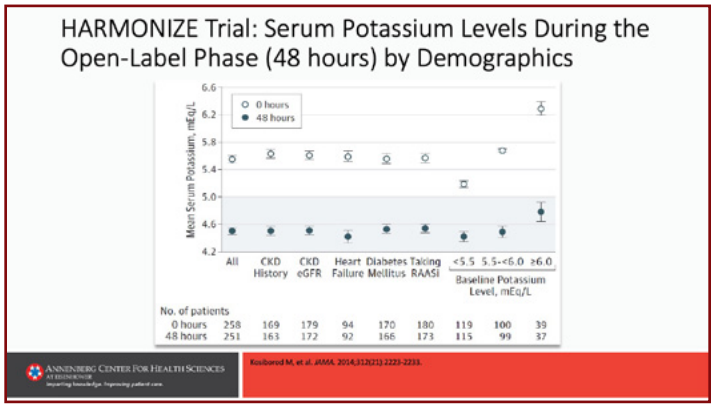
Several trials have now shown the efficacy of sodium zirconium cyclosilicate. The HARMONIZE study was a double-blind, placebo-controlled trial involving subjects with hyperkalemia. The drug was given 3 times per day over the initial 48 hours and then once a day thereafter. The HARMONIZE study investigated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



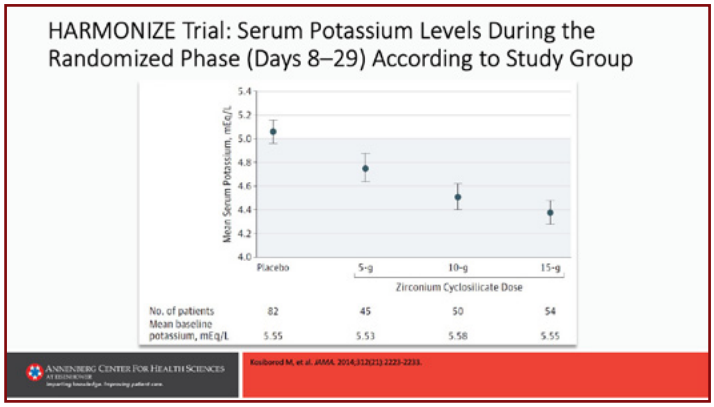
Patients with a variety of comorbidities were enrolled, including heart failure and diabetes. About two-thirds were taking RAAS inhibitors.

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.



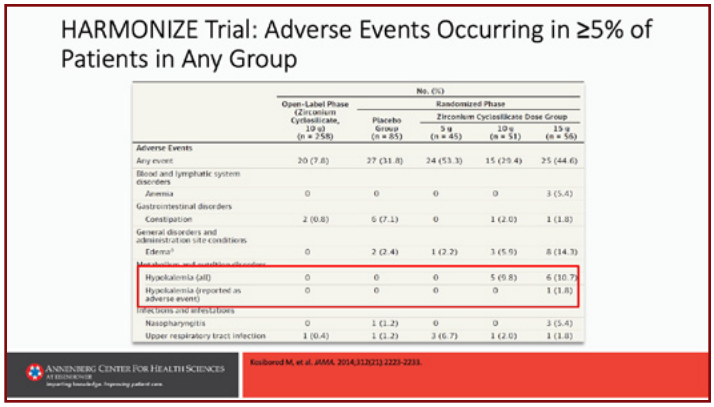


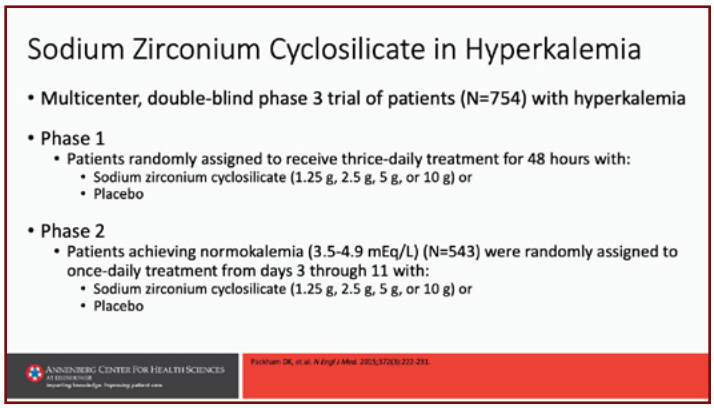
Let's look at the results by the dose of sodium zirconium cyclosilicate used. The 15-g dose is not particularly used commonly, more the 5- and the 10-g doses. The trial results showed that there is somewhat of a dose-response relationship.



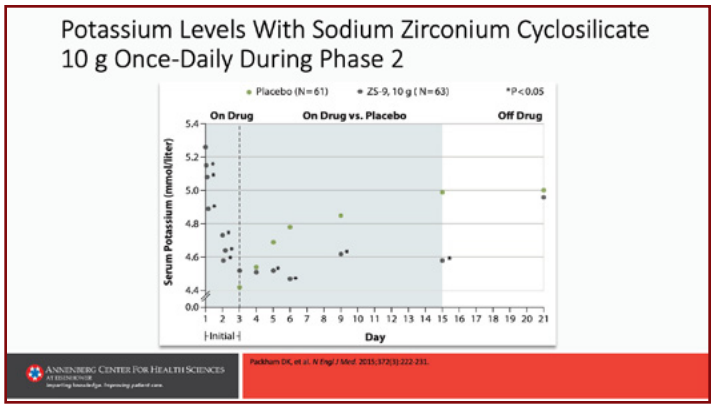
In terms of side effects, sodium zirconium cyclosilicate is very well tolerated. In fact, there were no real side effects other than a dose-dependent increase in edema. This may be related to the sodium load of the drug. As I mentioned, the 15-g dose is not utilized very commonly. Interestingly, hypokalemia, 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.

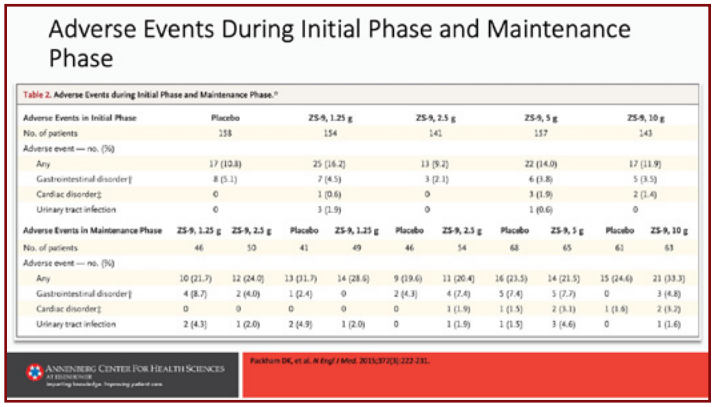
A second study by Packham and colleagues looked at sodium zirconium cyclosilicate in a group of individuals with hyperkalemia at baseline. Patients were initially treated with sodium zirconium cyclosilicate or placebo 3 times per day for 48 hours and then switched to once-a-day therapy. After controlling 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.





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.

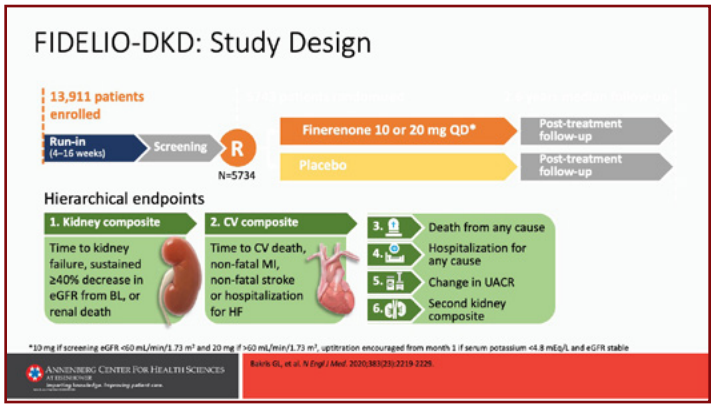




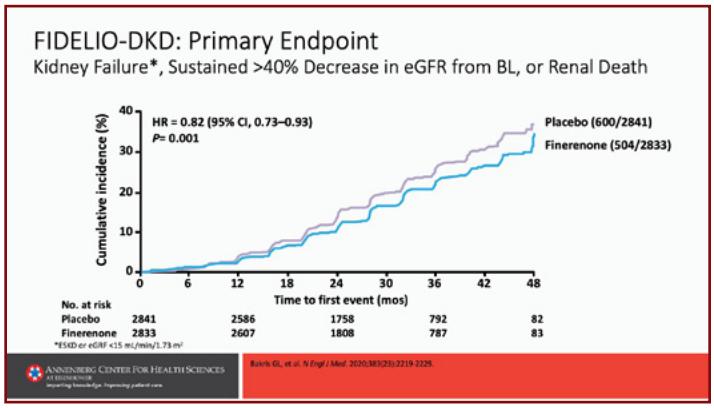
Adverse events during the initial 48 hours and in the withdrawal phase showed sodium zirconium cyclosilicate was well tolerated. The adverse events were really no different than with placebo. Once again, the only adverse event that's been noted with sodium zirconium cyclosilicate is a dose-dependent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

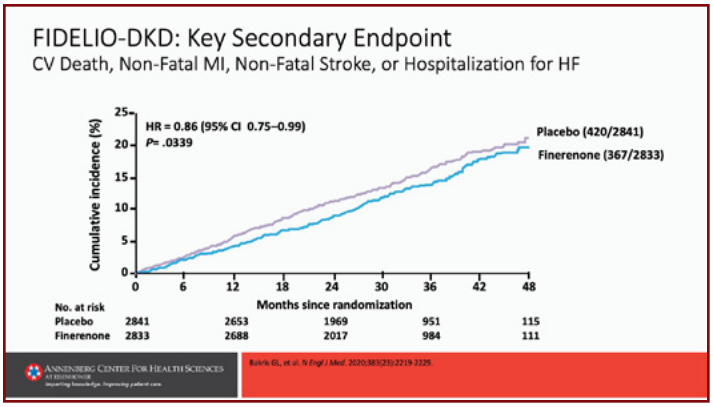


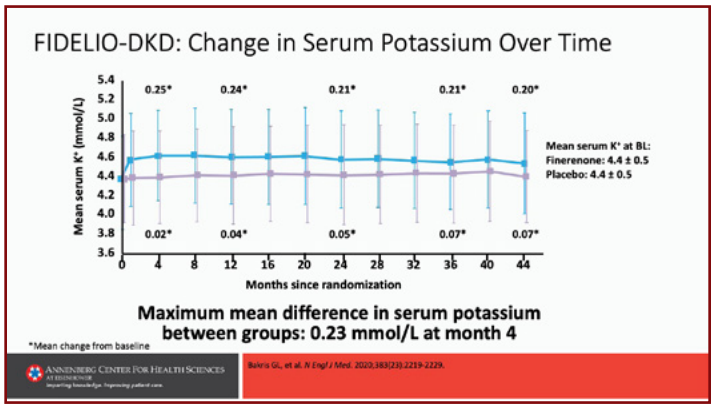
In terms of the primary outcome, the finerenone group had a statistically significant reduction. I would like to emphasize that in this study, finerenone was used on top of standard-of-care and the placebo group all are treated with standard-of-care, meaning ACE-I or ARB. Adding finerenone seems to confer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



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.

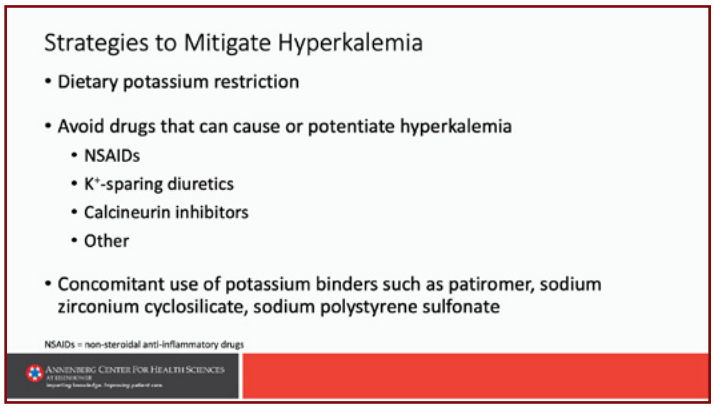
Interestingly, hyperkalemia can occur, as you might expect, but it tends to be much less common than what we typically think of with spironolactone.





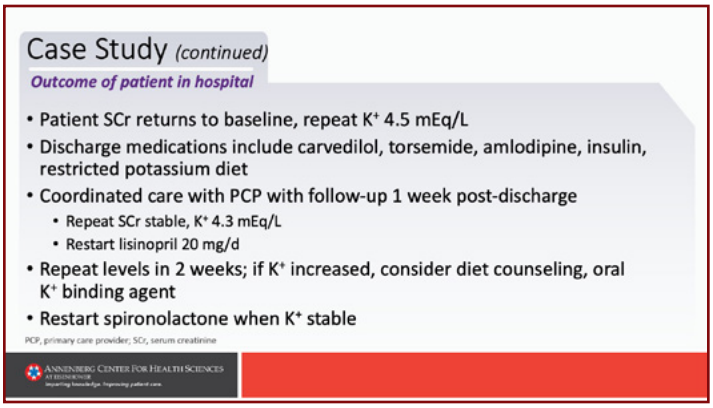
Many people believe this may be related to the short half-life of finerenone compared to spironolactone, which has a half-life close to 48 hours. The half-life of finerenone is measured in hours.

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.



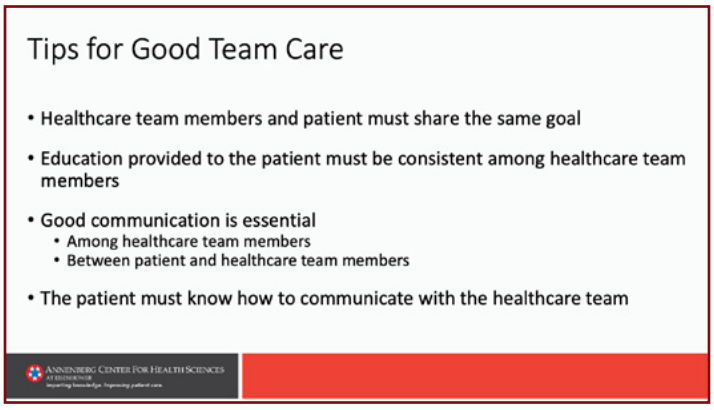
And again, we now have this new class of agents. Patiromer and sodium zirconium cyclosilicate, which are very well tolerated, are options to manage hyperkalemia in the setting of RAAS inhibitor use. I would also add that sodium polystyrene sulfonate is a very poorly tolerated agent and not a viable drug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



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.



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