Message From the Course Director

Dear Colleague,

Hyperkalemia is a potentially life-threatening condition that occurs in many clinical settings, including heart failure, diabetes mellitus, and chronic kidney disease. It contributes to mortality and can limit the use of cardioprotective and renoprotective renin-angiotensin-aldosterone blockers in high-risk patients. With increased knowledge of traditional management algorithms and emerging options for hyperkalemia, physicians can confidently apply evidence-based practices for diagnosis, treatment, and long-term monitoring of patients with this condition.

In this two-part CME activity, I review the clinical burden of hyperkalemia and challenges of managing it in routine practice as well as the latest evidence on effective new therapies. Please join me for this educational activity, which I hope you will find useful in your daily practice.

Sincerely,

Bertram Pitt, MD

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Activity Description and Educational Objectives

In this activity, an expert in hyperkalemia discusses standard of care and challenges with current management options in patients with hyperkalemia and the clinical role of new effective therapies.

Upon completion of this activity, participants should be better able to:

• Recognize the common risk factors for and clinical manifestations of hyperkalemia
• Assess current treatment strategies for hyperkalemia, challenges in management, and potential for improvement
• Summarize the latest trial data and the clinical role of recently approved and emerging treatment options for different patient populations with hyperkalemia
• Employ evidence-based approaches for the diagnosis and individualized management of patients with mild to severe hyperkalemia

Target Audience

This activity has been designed to meet the educational needs of primary care physicians, cardiologists, endocrinologists, and other clinicians involved in the management of hyperkalemia.

Requirements for Successful Completion

In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: May 16, 2016 - May 15, 2017
Time to Complete: 30 minutes

Faculty & Disclosure / Conflict of Interest Policy

Before the activity, all faculty and anyone who is in a position to have control over the content of this activity and their spouse/life partner will disclose the existence of any financial interest and/or relationship(s) they might have with any commercial interest producing healthcare goods/services to be discussed during their presentation(s); honoraria, expenses, grants, consulting roles, speakers bureau membership, stock ownership, or other special relationships. Presenters will inform participants of any off-label discussions. All identified conflicts of interest are thoroughly vetted by Medical Learning Institute, Inc. for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations.

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Bertram Pitt, MD, has a financial interest/relationship or affiliation in the form of:
Shareholder in AstraZeneca; Bayer Corporation; KBP BioSciences Co., Ltd., and Relypsa, Inc.
Bertram Pitt, MD does intend to discuss either non-FDA-approved or investigational use for the following products/devices: ZS-9 in the management of hyperkalemia and Patiomer.

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Donald DiPette, MD, has no financial interests/relationships or affiliations in relation to this activity.
Advancing the Care of Patients With Hyperkalemia: Integrating New Options Into Standard of Care

Hyperkalemia: Clinical Manifestations and Challenges in Clinical Practice

Bertram Pitt, MD
University of Michigan School of Medicine
Ann Arbor, Michigan

Dr. Pitt: Hello, I’m Doctor Bertram Pitt from the University Of Michigan School of Medicine, and I’d like to welcome you to this educational activity where we’re going to talk about advancing the management of hyperkalemia with new treatment options. After you complete this activity, I’d like you to access the post-test and evaluation form by clicking the red “Get Certificate” button. And afterwards I encourage you to download any of the slides, Practice Aids, and any other features that may interest you.

Hyperkalemia: Pathophysiology

So let’s go to the next slide, which talks about the ranges of potassium. But in general we’ve classified hyperkalemia as mild, moderate, and severe. I think most of us get pretty nervous when the potassium reaches 6.0, and, at that point, there’s a high risk of ventricular arrhythmias and we move toward more urgent therapy.

A lot of people think hypokalemia is only when you have a potassium below 3.5, but we have increasing evidence that in patients with heart failure, as well as in hypertension, that a potassium below 4.0 is also associated with increase in risk. So there’s actually a pretty narrow range, between about 4.0 to 5.0, that we should keep potassium and when it goes below or above, that can be trouble.

AA: aldosterone antagonist; ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; CKD: chronic kidney disease; HF: heart failure; K+: potassium; RAASi: renin-angiotensin aldosterone system inhibition.

So let’s get started. We’re going to talk about the clinical manifestations and the challenges in clinical practice of hyperkalemia. Of course, we all know that hyperkalemia is associated with ventricular arrhythmias and sudden death. And it’s become unfortunately common because of our increasing use of RAAS inhibitors and especially when we add them together (eg, when we add an MRA to an ACE or an ARB). And hyperkalemia has had a major effect on our clinical practice. First of all, it has dissuaded many people from using RAAS inhibitors in appropriate patients. And often when they start, because of hyperkalemia, they drop the dosage or discontinue the use of RAAS inhibitors, thereby, for instance, in patients with heart failure and reduced ejection fraction, they’re taking away lifesaving therapy.
Hyperkalemia: Causes and Clinical Manifestation

Development of hyperkalemia requires a defect in one or more of the mechanisms that maintain potassium homeostasis.

- Increased potassium load (dietary)
- Intracellular to extracellular shifts (uncommon)
- Decreased renal elimination (the most common cause)

Hyperkalemia is often asymptomatic and discovered on routine laboratory tests.

Clinical manifestations of acute and chronic hyperkalemia are related to changes in neuromuscular and cardiac arrhythmias.

- Muscular weakness or flaccid paralysis
- Ileus
- Characteristic ECG changes

Incidence of Hyperkalemia in CKD Patients

And I think we know that there are a number of precipitating factors for hyperkalemia. It could be dietary, or if you had an accident or muscle trauma, you can be shifting intracellular to extracellular potassium. But that’s pretty rare.

The major association is chronic kidney disease. You can have a high potassium load in your diet, and if you have normal renal function, for the most part, you’re going to be able to eliminate that potassium. But once you have renal disease or type 2 diabetes, it becomes more difficult, and the kidneys can’t excrete the potassium. And often it’s asymptomatic and discovered on routine laboratory evaluation when people come for a follow-up visit or are admitted to the hospital for something else. But it can cause muscle weakness and flaccid paralysis. And we see the same thing in the GI tract—you can get paralytic or weakness of the motility. You can also get ileus.

And I think you all know about the classic ECG changes of hyperkalemia, but I’d like to point out that you can have severe hyperkalemia leading to ventricular arrhythmias without any ECG changes. You shouldn’t be reassured just because the ECG is normal because you can be in big trouble independent of an ECG change.

And as I just mentioned, chronic kidney disease is one of the underlying causes of hyperkalemia. And as you can see in the box in the upper left of the slide, as you get more severe renal disease, the incidence of hyperkalemia increases. And as you can see in the graph to the right, it’s related not only to the presence of CKD but also to the use of RAAS inhibitors. So when you’re using a RAAS inhibitor and have CKD, then you have the greatest chance of having hyperkalemia, and especially if you’re using multiple RAAS inhibitors, let’s say an ACE or an ARB and an MRA, then you’ve increased the risk of hyperkalemia considerably.

Adjusted Mortality Based on Serum Potassium Levels in Patients With CKD

And this is taken from a very large insurance database. The lower curve comes from normal individuals, over 90,000 people. You can see it’s pretty flat.

But if you look at the upper curve, which is from people with chronic renal disease, class 3 to 5, then you can see the curve is shifted upward. There’s a pretty tight range between 4.0 and 5.0. And as you go above 5.0 or below 4.0, you have an increased risk in mortality.
patients were randomized in RALES to spironolactone or a placebo and in EMPHASIS to eplerenone or placebo. The incidence of serious hyperkalemia was pretty low, around 2%, 2.5%, but in the real world, people found a much higher percentage, 6% or 12%, and sometimes greater.

There are lots of reasons for that. Sometimes in the real world, people are not following the strict criteria we use in the trials [for inclusion/exclusion]. They're giving an MRA to people who have worse renal function than in the trials. And these people at baseline may have a higher potassium or a lower GFR. And sometimes they use much higher doses [than] in the major trials. We found in clinical practice that there was a big increase in hyperkalemia, and many of those patients got much higher doses of spironolactone, up to 100 mg, rather than the 12.5 to 50 mg that we used in the RALES trial.

So in the real world, there is a higher incidence of hyperkalemia. And you have to be careful when you use these drugs and especially you have to be willing and the patient has to be willing to have their potassium monitored. But if you do, and you pay attention to the inclusion and exclusion criteria, you can still get hyperkalemia, but you can see from these major trials that the incidence is pretty low.

As we look to the next slide, the bottom line is the control group, but the line above is those people with comorbidities, which include heart failure, CKD, or diabetes, and age 65. You can see there's a much higher risk of hyperkalemia. And when you get to 5.0, you already had a pretty significant increase in the risk of death, and conversely, if you go below 4.0.

So these data and data from several other sources are telling us that we should, in people who have comorbidities (e.g., renal disease, heart failure, diabetes, and the elderly), keep our potassium pretty tight in the 4.0 to 5.0 range. And anything out of that range we should start to worry.

MRA: mineralocorticoid receptor antagonist.

Now let's go to the next slide, and this looks at hyperkalemia defined as a potassium over 6.0, which is pretty serious hyperkalemia. In the critical trials of the MRAs—RALES, which was in people with severe heart failure and a reduced ejection fraction, and EMPHASIS Heart Failure, which was in people with heart failure and reduced ejection fraction but with mild symptoms—

PARADIGM-HF: Hyperkalemia in Patients With Heart Failure

| Hyperkalemia Rates in CHF Patients on MRA in Clinical Trials Versus Real-World Studies |
|------------------|------------------|------------------|
| **Clinical Trials** | **Real World** |
| RALES\(^1\) N = 822 | EMPHASIS\(^2\) N = 1,364 | Shah 2005\(^3\) N = 840 | Bozkurt 2003\(^4\) N = 104 |
| 2 | 2.5 | 6 | 12 |


eGFR: estimated glomerular filtration rate.

So let's go on to the next slide. And all of you know that we've had in the last year or so great data from the PARADIGM trial showing that LCZ-696 has improved survival compared to the ACE inhibitor, enalapril. And many people are beginning to switch from an ACE inhibitor to LCZ-696.

But even though LCZ-696 has marked advance, as you look, the incidence of hyperkalemia, at least over 5.5, was very similar. So I think if you're dealing with patients with heart failure who have a class I indication for an ACE inhibitor or an ARB and an MRA, you are going to see hyperkalemia.
Advancing the Care of Patients With Hyperkalemia: Integrating New Options Into Standard of Care

### Association Between Aldosterone Antagonist Therapy and Risk of Readmission for Hyperkalemia

**Table 1:**

<table>
<thead>
<tr>
<th>Days After Discharge</th>
<th>Cumulative Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20%</td>
</tr>
<tr>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td>20</td>
<td>60%</td>
</tr>
<tr>
<td>30</td>
<td>80%</td>
</tr>
</tbody>
</table>

Aldosterone Antagonist Therapy
--- No
--- Yes

Gray Test \( P < .001 \)


### Standard Treatment Options for Hyperkalemia

#### Therapy
- Emergent
- Intermediate
- Maintenance


#### Hyperkalemia: Effect on Healthcare Costs

- **Primary Diagnosis of Hyperkalemia**
  - **2011 ED Visits, n:**
    - **All Patients:** 80,000
    - **Medicare Members:** 60,000
  - **2011 Hospitalizations, n:**
    - **All Patients:** 40,000
    - **Medicare Members:** 30,000

- **Hospitalizations Discharged to Another Hospital, Institution, or Home Healthcare:**
  - **All Patients:** 5,000
  - **Medicare Members:** 4,000

- **In 2011,** the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$607 million
- **Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay**
- **One-third were discharged to another short-term hospital, institution, or home healthcare**


### HFrEF: Heart Failure With Reduced Ejection Fraction

And let’s move to the next slide. This is just one study showing that certainly when you take people with heart failure, with reduced ejection fraction, and you add an MRA, there is a higher incidence of hyperkalemia than without it. But there’s also a reduction in total mortality. So there’s a price to be paid, but overall, there’s clearly a net benefit from the addition of an MRA.

### Hyperkalemia: Effect on Healthcare Costs

Now let’s go on to the next slide and it shows that if you have hyperkalemia, there’s a marked increase in visits to the emergency room and people hospitalized. And there’s a tremendous cost associated with this. So if we could do something to eliminate or minimize the incidence of hyperkalemia, I think we’d have some reasonable effect on our economic burden of heart failure.

### SPS: Sodium Polystyrene Sulfonate

So let’s go on to the next slide which is the treatment options for hyperkalemia. If you have urgent arrhythmias, a very high potassium level, you can give them insulin and glucose. You can give them beta adrenoreceptor [antagonists], and then gradually give them calcium gluconate or sodium bicarbonate. You can give them diuretics, but that takes a little longer. And if nothing else is working, you certainly can go to dialysis.

Now if they are in the intermediate- or the long-term chronic maintenance phase, we’ve reduced the dose of the RAAS inhibitors or we’ve stopped them. We put the patient on a low-potassium diet; that’s easier said than done, but that’s something we should all try to do. If you’re going to deal with these patients, I think it pays to take a look and learn which foods are rich in potassium and what you can avoid and what’s low in potassium.

And we’ve had for a long time SPS, sodium polystyrene sulfonate. But unfortunately, although that’s been effective and around for a long time, it’s poorly tolerated.
Advancing the Care of Patients With Hyperkalemia: Integrating New Options Into Standard of Care

Current Management Challenges

<table>
<thead>
<tr>
<th>Acute Therapies*</th>
<th>Do not remove excess K+</th>
<th>Impractical in outpatient setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary K+ Restriction</td>
<td>K+ is common ingredient in many foods</td>
<td>Limits healthy food choices Met by nonadherence</td>
</tr>
<tr>
<td>Sodium Polystyrene Sulfonate (SPS)*</td>
<td>Uncertain efficacy (no rigorous clinical trials)</td>
<td>Poor tolerability May not be effective without sorbitol; however, sorbitol has been reported to cause intestinal complications, including colonic necrosis and perforation in immunocompromised patients</td>
</tr>
</tbody>
</table>

* IV calcium, sodium bicarbonate, insulin and dextrose, nebulized β-adrenergic agonists.

Now let’s go to the next slide, and it talks about some of the limitations and challenges with our current therapies. And, of course, the acute therapies just transiently lower potassium and lower the risk of arrhythmias but don’t really get rid of the excess potassium. And they’re really things that we can do in the hospital, such as dialysis and some of these other things, rather than in an outpatient setting.

And we mentioned diet, but it’s very hard to get a low-potassium diet because a lot of the things we think are a healthy choice diet are rich in potassium. And when you try to put people on a low-potassium diet, often they’re nonadherent.

And as I mentioned, sodium polystyrene sulfonate has been around for a long time but it’s been associated with really serious toxicity. There’s been bowel necrosis reported alone and with sorbitol, and that has really been a major problem. And it’s also just very poorly tolerated.

And as we go to the next slide, this is a little bit more detail about some of the risks of sodium polystyrene sulfonate. It talks about the intestinal necrosis. But I’d also like to point out that SPS exchanges potassium for sodium, and there can be some absorption of sodium, which can lead to volume overload. So in patients who have heart failure, this could be a real problem. Even patients with renal disease often have a volume overload. So this is a real limitation. And as you’ll see with some of the newer agents, this may be an advantage.

Clinical Attributes of a Potassium Binder

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Substantially lower serum K+ levels</td>
<td>• Palatable drug with good patient acceptance of dosage form</td>
</tr>
<tr>
<td>• Works in diverse populations (CKD, diabetes, HF, elderly, and combinations of these)</td>
<td>• Compatible with commonly used drugs in target population</td>
</tr>
<tr>
<td>• Works in a matter of hours and maintains its efficacy long term (months to years)</td>
<td>• Low AE rates and clear long-term safety</td>
</tr>
</tbody>
</table>

So we’re going to talk about what would be the ideal attributes of a drug that lowers potassium. And if you think about efficacy, we’d like to have a drug that would have clear and sustained efficacy. It should lower potassium levels to normal kalemic levels within hours. It should work across a number of indications, whether the patient has diabetes, renal disease, is elderly, or any combination of those. And we’d like it to work fairly quickly—within an hour.

And as far as safety, we’d like them to be tolerable and to be able to be maintained over the long run. We’d like the patients to feel comfortable taking them. And they shouldn’t ideally interfere with other drugs. And they should be safe and not have any off-target effects.

Na: sodium.

Sodium Polystyrene Sulfonate: Warnings and Precautions Highlighted in FDA-Approved Label

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>1958</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warning</td>
<td>Intestinal necrosis, which may be fatal, and other serious gastrointestinal AEs (bleeding, ischemic colitis, perforation) have been reported in association with SPS use Concomitant use of sorbitol with SPS has been implicated in cases of colonic intestinal necrosis</td>
</tr>
<tr>
<td>Precaution</td>
<td>SPS exchanges K+ for Na2+, leading to Na2+ volume overload Use caution when administering SPS to patients who cannot tolerate even a small increase in sodium loads (eg, severe congestive heart failure, severe hypertension, marked edema)</td>
</tr>
</tbody>
</table>

Bertram Pitt, MD
University of Michigan School of Medicine
Ann Arbor, Michigan

Latest Evidence on Effective New Therapies for Hyperkalemia

**Novel K+ Binders**

**Patiromer**
- Orally administered
- Homogenous, spherical beads
- Nonabsorbed, cation-exchange polymer that contains a calcium counterion
- Increases fecal potassium excretion through binding of potassium in the GI tract, predominantly in the lumen of the colon, where concentration of potassium is highest
  - Binds potassium in exchange for calcium and magnesium
  - FDA approved in 2015

**Sodium zirconium cyclosilicate (ZS-9)**
- Investigational agent awaiting approval

K: potassium.

**Dr. Pitt:** I’d like to talk about some of the latest advances with new therapies for hyperkalemia. There are two new agents. One is patiromer, which was approved by the FDA in October 2015 and became available in January of 2016. And the other one is sodium zirconium cyclosilicate (ZS-9), which has, at the moment, has not yet been approved, but we expect it will be approved somewhere in 2016. And both have been shown to be effective and really an advance for the treatment of hyperkalemia.

Patiromer is a polymer, and there are sort of these spherical beads, and they are pretty uniform. If you would look at a picture of light microscopy of SPS, you’d find very ragged crystalline fragments, so that may be why SPS causes bowel necrosis, whereas patiromer has these very round, pretty uniform beads, which have not been associated with any bowel necrosis. And it exchanges potassium for calcium and magnesium. And it acts mainly in the colon, where the highest concentration of the potassium is. And it’s really not pulling the potassium out of the food; it’s pulling the potassium out of the blood in the colon. And then it’s eliminating.

**OPAL-HK: Phase 3 Pivotal Study Design**

<table>
<thead>
<tr>
<th>Part A: Treatment Phase (Single Blind)</th>
<th>Part B: Randomized Withdrawal Phase (Single Blind)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects With CKD* on RAASi (N = 243)</td>
<td>Randomization</td>
</tr>
<tr>
<td>* Subjects with moderate to severe HK</td>
<td></td>
</tr>
<tr>
<td>Serum K+ 3.8 to &lt;5.1 mmol/L at part A week 4</td>
<td></td>
</tr>
<tr>
<td>Still on patiromer</td>
<td></td>
</tr>
<tr>
<td>Still on RAASi</td>
<td></td>
</tr>
<tr>
<td>(n = 107)</td>
<td>Patiromer, continued RAASi (n = 56)</td>
</tr>
<tr>
<td>Placebo, continued RAASi (n = 52)</td>
<td></td>
</tr>
<tr>
<td>Baseline Part A</td>
<td>Week 4 Part A Primary End Point</td>
</tr>
<tr>
<td>Week 8 Part B Primary End Point</td>
<td>Week 8 Part B Secondary End Point</td>
</tr>
</tbody>
</table>

BID: twice a day; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HK: hyperkalemia; RAASi: renin-angiotensin aldosterone system inhibition.

And there have been several major pivotal trials showing its safety and efficacy. The OPAL Hyperkalemia trial took people who were hyperkalemic, either they had mild hyperkalemia, from a potassium of 5.1 to a little less than 5.5 or they had moderate to severe hyperkalemia, and they could have a potassium level from 5.5 to less than 6.5 mmol/L. And both of those groups were given...
patiromer, in the mild, 4.2 grams twice-daily dosage; in the more severe, it was 8.4, and they took this for about 4 weeks.

The people in the moderate to severe group, if you got down to normal kalemia, and you stayed there, and you were still on a RAAS inhibitor, then you were randomly withdrawn.

Now, that is one of the proofs that the drug worked, but it also has some clinical implications. So when you keep people on a RAAS inhibitor, and if for some reason they were to stop patiromer while they were taking the RAAS inhibitor, they would have this marked increase in serum potassium and go to hyperkalemic levels pretty quickly.

So if you’re going to use this drug, patient education is really important. If they were to be taking enalapril, let’s say, or losartan and then they were also on patiromer to keep the potassium down, and one day they decided well, they think something’s bothering them, and they stop the patiromer, within a few days, they could have serious hyperkalemia and be at risk for sudden death.

So it’s important to use these drugs, but use them with patient education and make sure the patients understand the pluses and minuses of these drugs.

In the next slide we look at that 4-week period, the initial period. And you can see from the graph or the bar graph that both the mild and the people with moderate to severe had a really pretty striking reduction in serum potassium. Three-quarters of the patients had a serum potassium within the target range of 3.8 to 5.1 at week 4. And that was a very nice result.

Then we’re going to go on to the next slide. And it just shows that the people who received patiromer didn’t require much dose adjustment compared to placebo. And many more people were able to stay on their RAAS inhibitor if they were on patiromer than if they weren’t in the randomized withdrawal. So 94% at the end of that randomized withdrawal could stay on their RAAS inhibitor versus only 48% in the placebo group.

This is the randomized withdrawal. So if you had moderate to severe, and you were normalized, then you were randomly withdrawn. And those people that were withdrawn and went on placebo had a marked rise in serum potassium, about 0.72 mEq/L, compared to the people on patiromer, who stayed down.
Advancing the Care of Patients With Hyperkalemia: Integrating New Options Into Standard of Care

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HF: heart failure.

And this is part of the same study, but this is looking at a subset of people in that study who had heart failure. And we were reassured that regardless of whether you had heart failure or not, there was a striking reduction in potassium. And then when we withdrew the drug, it went up the same way. And the tolerability and the efficacy were very similar in people with or without heart failure. So that has lots of implications for the future.

And this is another study with patiromer, but this looks at its long-term effect. So in this case, people were treated for hyperkalemia over a year. And you can see that they were able to stay on the patiromer regardless of whether they had mild hyperkalemia or moderate to severe over that year. And once again, at the 52-week interval when it was withdrawn, the potassium bounces up as we saw in the previous slide. So this is very well tolerated over the year.

AA: aldosterone antagonist; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotension receptor blocker; βB: beta blocker; BL: baseline; Spiro: spironolactone.

Now patiromer is approved for the treatment of hyperkalemia, and the PEARL study is looking at the prevention, which is not an FDA use of the potassium-lowering agents. These were people that we’ve looked at that had either chronic renal disease or they had a history of hyperkalemia and they had stopped their ACE inhibitor or angiotension receptor blocker or a beta blocker or an aldosterone antagonist and weren’t on them at the moment.

LS: least square.

The people who had mild or moderate hyperkalemia could really stay on this and had a reduction in potassium. Not shown here, when we looked at the people who had CKD and got spironolactone, if they were on placebo, they had a marked increase in hyperkalemia, somewhere around 39%, 40%, versus about 9% on patiromer. So we could prevent hyperkalemia, but as I emphasized, this is really not indicated at the moment, and far
more studies would need to be done to have this approved. But it’s something, I think, for the future.

![Adverse Reactions Reported in ≥2% of Patients in Patiromer Clinical Trials](image)

Mg: magnesium.

And these are the side effects in the trials of patiromer that were seen in greater than 2% of patients. And I mentioned that potassium was exchanged for calcium and magnesium. And there was about a 9% incidence of hypomagnesemia of less than 1.4 mg/dL. But I’d like to emphasize that despite the reduction in serum magnesium levels, people didn’t go below a level of 1.0, and there were no arrhythmias associated with this. There was about a 7% incidence of constipation. There were a few episodes of diarrhea, and there were a few people that had hypokalemia. But once again, there’s not been any arrhythmias seen with this. We don’t like to see hypokalemia—you could always correct—but for the most part when you’re treating people who have a very high potassium, you don’t get to this range. There is some nausea, some abdominal discomfort, and flatulence. But for the most part, as you can see from that 52-week study, this was pretty well tolerated.

Before clinical studies were done, there were a number of in vitro binding studies, and it was found that patiromer interfered with the absorption or the binding of other drugs. And that led the FDA to suggest that you shouldn’t take another drug within 6 hours of patiromer.

<table>
<thead>
<tr>
<th>Test Drug</th>
<th>Administered at the Same Time</th>
<th>Administered 3 Hours After Test Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>No clinically meaningful reduction in absorption (AUC)</td>
<td>No impact on peak concentration (C_{max})</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>No impact on peak concentration (C_{max})</td>
<td>No impact on absorption (AUC)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Some reduction in peak concentration (C_{max})</td>
<td>No impact on peak concentration (C_{max})</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Reduced absorption (AUC)</td>
<td>Reduced peak concentration (C_{max})</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Not tested in humans (quinidine rarely used; thiamine commonly present in food)</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Reduced absorption (AUC)</td>
<td>Reduced peak concentration (C_{max})</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Reduced peak concentration (C_{max})</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
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<td>Levothyroxine</td>
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<tr>
<td>Metoprolol</td>
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AUC: reduced absorption; C_{max}; peak concentration.

There are a number of drugs in vivo where there’s been no effect whatsoever on absorption, and some where there’s been a slight effect, and some where there’s been a more severe effect.

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Cyclosilicate (ZS-9) exchanges potassium for hydrogen and potassium for calcium and magnesium, sodium zirconium it traps potassium. And in contrast to patiromer, which exchanges sodium in the intestine.

When sodium zirconium cyclosilicate (ZS-9) was discontinued, hyperkalemia potassium went down pretty quickly and stayed down.

And as you go to the next slide, you can see the results—that potassium went down pretty quickly and stayed down.

Patiromer Drug Interactions\(^1\) (Cont’d)

RAASi (lisinopril, spironolactone, valsartan)
Cholesterol-lowering drugs (atorvastatin)
Anticoagulants and antiplatelets (apixaban, aspirin, rivaroxaban)
Cardiac glycoside (digoxin)
Antidiabetics (glipizide)
Antigout drug (allopurinol)
Antibiotics (amoxicillin, cephalaxin)
Antiepileptic (phenytoin)
Vitamin (riboflavin)

These are the drugs that had no interaction. Some of our antihypertensive RAAS inhibitors like lisinopril, spironolactone, and valsartan were not affected. Atorvastatin was not affected. Some of the anticoagulants were not affected. Some of the antibiotics, allopurinol, some of the anticoagulants, and vitamins. And we think that it might be safe to wait about 3 hours, but I think we’re going to have to wait for the FDA ruling on that at the moment. The label still says 6 hours, and one should stick to that and not give patiromer less than 6 hours after some of these drugs.

Sodium Zirconium Cyclosilicate (ZS-9): Novel First-in-Class Compound Designed to Trap Potassium\(^1\)

- Oral administration, tasteless, odorless
- Nonabsorbed, inorganic crystalline zirconium silicate compound
- Exchanges K\(^+\) for hydrogen and sodium in the intestine
  - High K\(^+\) specificity attributable to chemical composition and diameter of the micropores
  - 125 times more selective for K\(^+\) compared with SPS

SPS: sodium polystyrene sulfonate.

We’d like to talk about the other agent, sodium zirconium cyclosilicate (ZS-9), which has also, as I mentioned, been shown to be effective and safe. This has a little bit different mechanism of action. It’s a crystal in structure, and because of the pore sizes it traps potassium. And in contrast to patiromer, which exchanges potassium for calcium and magnesium, sodium zirconium cyclosilicate (ZS-9) exchanges potassium for hydrogen and sodium. It’s not absorbed and easy to take. It’s tasteless, odorless, and it’s very selective for potassium.

Phase 3 Sodium Zirconium Cyclosilicate (ZS-9) Study Design\(^1\)

- Primary end point: exponential rate of change in serum potassium over 48 hours
- Secondary end point: exponential rate of change in serum potassium over 12-day treatment interval

Phase 3 Sodium Zirconium Cyclosilicate (ZS-9) Study Results\(^1\)

- Normokalemia maintained in patients who received sodium zirconium cyclosilicate (ZS-9) 5 g or 10 g
- Potassium levels increased to hyperkalemic levels in placebo group
- When sodium zirconium cyclosilicate (ZS-9) was discontinued, hyperkalemia redeveloped within 1 week


And as you go to the next slide, you can see that there's sort of a dose effect. That the higher the dose, the more effective sodium zirconium cyclosilicate (ZS-9) is.

You can see that there's a dose-dependent reduction in serum potassium, and that reduction with sodium zirconium cyclosilicate (ZS-9) was seen pretty rapidly, within the first few hours, and is sustained over time. Sodium zirconium cyclosilicate (ZS-9) is also being studied over the long-term, just as patiromer was, and looks like it's very effective and pretty well tolerated over the 52 weeks.

And if we go to the next slide, this is another study with sodium zirconium cyclosilicate (ZS-9), HARMONIZE, where there was an open-label phase and then a randomized phase with placebo and sodium zirconium cyclosilicate (ZS-9) at 5, 10 and 15 mg, once again looking at the potassium reduction.

And if we go to the next slide, the people who have looked at sodium zirconium cyclosilicate (ZS-9) have taken out the subset of patients with heart failure, and showed that it's effective in heart failure just as well as without heart failure. And it looks like it has important implications.
As we go to the next slide, there is a little difference though between the side effect profile of sodium zirconium cyclosilicate (ZS-9) and patiromer. So at the highest doses of sodium zirconium cyclosilicate (ZS-9), there has been some peripheral edema. And as I mentioned, it's nonabsorbed, but it does exchange sodium for potassium. And we're not quite sure why that edema is—whether it's because some sodium is absorbed or not—but there is an increase in edema that's been seen—a small increase. And there has been some increase in blood pressure. Just like with patiromer, there's some hypokalemia, depending where you start, and some GI effects.

I think until we have head-to-head trials, which may or may not happen, we'll not know exactly how these two differ. But I would say the bottom line is they're both very effective in reducing serum potassium into the normal kalemic range if you have hyperkalemia and pretty well tolerated over a year. So I think they're going to have a major effect on our clinical practice compared to where we were just a short time ago when all we had was SPS.

As I've said, patiromer and sodium zirconium cyclosilicate (ZS-9) are both effective in reducing serum potassium to normal kalemic levels in patients with hyperkalemia. They're well tolerated over a year and very different than with SPS. They don't have bowel necrosis associated with them, and they're just as good in people with heart failure or without heart failure.

And I think that having these new agents is going to make a marked improvement on our clinical management of hyperkalemia. And we hope it's going to enable us to keep RAAS inhibitors, ACEs, and ARBs, and MRAs over the long term. If you're dealing with a patient with HF-RF, where we know that ACEs, ARBs, and MRAs have all been lifesaving and associated with reduction in mortality, once we start reducing the dose and stopping them, we're losing all those benefits. And even more importantly, many people have never started on them because of the fear of hyperkalemia.

But we certainly need more long-term clinical outcome studies to show that this strategy really does result in a reduction in mortality and morbidity compared to our past strategy, where we just reduced the dose or stopped it. But these new drugs will open up a number of opportunities. One can think of exploring higher doses of the RAAS inhibitors, looking at people who were contraindicated previously because of bad renal disease, where there is a very high risk. So there's a tremendous opportunity for clinical research in the future, but right now we have two new drugs that look very effective for the treatment of hyperkalemia and I think can have a major role in our everyday practice.

Disclaimer: The faculty has referred to sodium zirconium cyclosilicate as ZS-9, its trade name; no bias is inferred.
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