Kendall Williams, MD: Welcome everyone to the Penn Primary Care Podcast. I'm your host, Dr. Kendall Williams. So, one of the most common things and the most important things we manage in primary care is congestive heart failure. It's very serious business because it has high morbidity and mortality, and it's very important that we manage it properly. There's been a lot of movement in the treatment of heart failure in the last five or 10 years, particularly related to Entresto and SGLT2 inhibitors. And now, there are new guidelines in 2022 for the treatment of heart failure. So, it's worth our time to review all of that.

In order to do that, I brought onto the podcast two experts in congestive heart failure. Dr. Lee Goldberg is the Section Chief of Advanced Heart Failure and Cardiac Transplant at Penn. He also has a background and interest in informatics and is the vice-chair within the Department of Medicine for Informatics, and he is a Professor of Medicine at Penn. Lee, thanks for coming.

Lee Goldberg: Thank you very much for having me.

Kendall Williams, MD: Dr. Stuart Prenner is the program director for the Fellowship of Advanced Heart Failure and an Assistant Professor of Medicine at Penn. Stu is also an expert on heart failure with preserved ejection fraction, which we're going to talk about. Stu, thanks for being here.

Stuart Prenner: Thanks for having me.

Kendall Williams, MD: So, I think the first thing we just want to go over is the difference between HFpEF and HFrEF. We all know that, but there's also some new definitions out there that came out with the new guidelines. So, Stu, maybe I'll just throw this to you. How does HFpEF differ from HFrEF?

Stuart Prenner: Yeah, it's a great question. In general, these conditions are all defined mostly by the ejection fraction. And there are various cut points that separate these conditions. And so in general, an ejection fraction of over 50% accompanied by heart failure symptoms is labeled heart failure with preserved ejection fraction, whereas ejection fractions of under 40% are labeled heart failure with reduced ejection fraction.

The guidelines recently are recognizing this middle range of ejection fractions between 40 and 50 that clinically behave more like reduced ejection fraction, but may have a little bit better prognosis. And then, finally, we recognize a category called heart failure with improved ejection fraction, patients who may have had a low ejection fraction historically and improved with medical

therapy. And so, those are really the four groups of heart failure, and they're all treated a little bit differently.

Kendall Williams, MD: So, you know, we call heart failure with reduced ejection fraction HFrEF, and then there's now heart failure with improved ejection fraction, as you mentioned, as well as heart failure with mildly reduced ejection fraction. Have we come up with a way to say that in a short way?

Stuart Prenner: Not that I'm aware of. I don't know about you, Dr. Goldberg.

Lee Goldberg: Yeah. They're saying HFmrEF sometimes for the mildly reduced ones. I don't know what we're going to do with improved ejection fraction, though.

Kendall Williams, MD: HFimpEF, something like that.

Lee Goldberg: That's right.

Stuart Prenner: It's a lot of acronyms.

Kendall Williams, MD: So, one of the first things I wanted to do is really drill down on the drugs. On this podcast, we really focus on being pragmatic and going over drugs and doses and so forth. But I want to spend a little bit of time on physiology because it's important to understand Entresto particularly, so I'd just go back to the physiology.

So, I want to take a moment and remind ourselves of physiology. When we were all in medical school, we learned about the RAAS system. Renin going to angiotensin I, angiotensin II, and aldosterone, and those having effects on the body in terms of the salt preservation and so forth and then angiotensin having vasoconstrictive effects. One of the things that comes up in heart failure is that system obviously has evolutionarily evolved to provide benefit to us, but it does seem to be the source of problems when we talk about chronic heart failure management. Lee, can you speak to that?

Lee Goldberg: Yeah, absolutely. So, when there is a low cardiac output and reduced blood flow, particularly to the kidneys, but even in other organs, this activates that renin-angiotensin system. And under normal circumstances, this would trigger to the body, "Oh, There's dehydration. Perhaps there's bleeding." And evolutionarily, the way to compensate for that would be to hold onto salt and water to increase blood pressure or vasoconstrict to preserve perfusion to the organs.

But in the heart failure state, what this does is actually creates really a positive feedback loop that leads to very negative consequences, meaning that the more vasoconstriction you get, the more work the heart has to do to get blood out into the body, the more salt and water retention there is, therefore leading to volume overload in the body. And you end up in a cycle where the heart is working harder and harder, gets stretched more and more, the shape of the heart changes, pulling the valve leaflets apart and people get mitral regurgitation, sometimes tricuspid regurgitation, and the heart really has to compensate for that. And so, we think that although in an acute setting, these systems are compensatory; in the chronic setting, they lead to really a lot of negative consequences and ultimately negative remodeling of the heart, negative modeling of the heart that causes it to change shape and get weaker over time. And we think this is why when a heart, say, is injured by a heart attack, someone may do well for a period of time afterwards, but then gradually over months to years, they develop new-onset heart failure, that is the culmination of months to years of this system being overly active and leading to this negative remodeling.

Kendall Williams, MD: So, there's a counterregulatory system that goes on here too. The natriuretic peptides are released in response to the dilation of the atria. And that becomes important as we start to think about Entresto and neprilysin inhibitors and so forth. Can you talk about that, Lee?

Lee Goldberg: Yeah. So, one of the things that we started with, and to go back a little bit in time, is that it was recognized that an ACE inhibitor could obviously inhibit the impact of the renin-angiotensin system and, at the same time, can upregulate some other hormones including bradykinin and a few other hormones. And so, the thought was that this could prevent remodeling and fibrosis of the heart. We subsequently showed that these medications improved outcomes, both morbidity and mortality, and prevented progression and, in some cases, actually reverse remodel the heart, so that you could get into that heart failure with improved ejection fraction.

We then studied angiotensin receptor blockers and found that they were similar to the impact of ACE inhibitors, although they don't have exactly the same impact in terms of raising other neurohormones. But the new kid on the block was a combination of an angiotensin receptor blocker and a neprilysin inhibitor. The compound that now is available clinically is sacubitril, which is the neprilysin inhibitor, and it's combined with valsartan, which is one of the angiotensin receptor blockers. And it turns out that neprilysin inhibitors inhibit an enzyme that break down several compounds including bradykinin and the natriuretic peptides. And so by inhibiting natriuretic peptides, we can actually promote salt and water excretion from the kidneys, so remove volume. In

addition, they have some vasodilatory properties, which is important. We think that bradykinin is important in terms of preventing fibrosis of the ventricle, as well as improving cardiac performance and preventing negative remodeling. But one of the bad side effects of neprilysin inhibitors is that it also inhibits the breakdown of angiotensin. And so, what happens is that you actually end up with a little bit of vasoconstriction because that compound also ends up circulating for a lot longer.

So, we found through clinical trials that if we combine an angiotensin receptor blocker, we block that receptor so that that angiotensin can't really bind to it. We can prevent the vasoconstriction, but then we can also simultaneously improve or raise the level of natriuretic peptides as well as other compounds like bradykinin and a few others that actually improve cardiac performance. And that combination of an angiotensin receptor blocker plus the sacubitril together for the first time actually had improved outcomes as compared to ACE inhibitors that had been really the mainstay of therapy for about 30 years. Suddenly, we had a compound that actually had better outcomes. And we think it's because it's the neprilysin inhibitor actually really increasing those other compounds in the bloodstream, that is the benefit.

Now, that also leads to some of the side effects. So, one of the risks of a neprilysin inhibitor like sacubitril is that because it raises bradykinin, it can increase the risk of angioedema. And we also know that ACE inhibitors also can increase the risk of angioedema. Both compounds increase the risk of angioedema about the same amount in clinical practice. But if you combine an ACE inhibitor with a neprilysin inhibitor, you can end up with a very high percentage of patients getting angioedema, almost 30% in one of the early clinical trials. So, that strategy was abandoned.

But for us as clinicians, the most important thing to note is that you can never mix an ACE inhibitor with sacubitril/valsartan because the risk of angioedema is very high. And so when we're using these compounds, we ask that the patient have about a 36-hour washout period if they have been on an ACE inhibitor before starting the sacubitril/valsartan. So in our office, we'll say, "Hold, say, your lisinopril tomorrow. And then, the following evening, the day after tomorrow, you would start with your first dose of sacubitril/valsartan, so as to allow for that washout period." That is not necessary if the patient's already on an angiotensin receptor blocker. The next dose, they can start the sacubitril/valsartan. So, knowing that physiology and that pharmacology kind of explains one of the weird potential side effects or safety issues of sacubitril/valsartan.

Kendall Williams, MD: I want to hover on the neprilysin inhibition a minute because I find this interesting. There was this drug, nesiritide, right, Lee? So, you know, nesiritide, it was a natriuretic peptide, is my understanding, had these beneficial effects of diuresis, vasodilation and so forth. And it had its moment in the sun if you remember. But then, it was removed from the market and has not been seen since. But that was the only other foray as I recall or understand into trying to raise natriuretic peptide levels specifically, right?

Lee Goldberg: No, that's true. But remember that, you know, that drug nesiritide was designed to be used really in acute heart failure, right? In someone that's coming in decompensated in order to try to unload them in a sense, and to help them to diurese acutely, and it did have some effect. But interestingly, when we really studied it in terms of longer term outcome, did it improve longer term outcome morbidity and mortality? We didn't see that in the followup trial. So in the acute trial, we saw some benefit. But in the chronic trial, we did not. So, it added significant cost and complexity to infuse this drug in the hospital, but it really didn't translate into better long-term outcomes.

Now, the difference is with sacubitril/valsartan, we're chronically increasing natriuretic peptides and bradykinin and other compounds, which nesiritide did not do those other compounds. And it seems that that chronic elevation at a modest level seems to really improve outcomes and lead to positive remodeling. So, it may be the time of exposure, it may also be the difference of being acutely decompensated versus chronic heart failure, but it seems like the chronic exposure is better, and it may have to do with the company that it keeps, whether or not the other neurohormones are also elevated that may lead to those improved outcomes.

Kendall Williams, MD: That's really useful and I wanted to help provide that context. Now, I actually want to go back and sort of take a march through these drug categories. So, let's start with ACE inhibitors, which you said should never be combined with in Entresto. Obviously, these were the first drugs that came on the market to impact the RAAS system, were remarkably effective over multiple trials. They became along with beta-blockers, we'll talk in a minute, the foundational elements of congestive heart failure care. Where are you at with ACE inhibitors? How are you using them now that you have these other tools as well?

Lee Goldberg: Stuart, do you want to take that?

Stuart Prenner: Yeah. So, I think, as you said, part of the historical landscape here is that we have a lot of history with this class of medications and, in

general, vasodilating medications of which the ACE inhibitors are one flavor, and they do so as you mentioned by blunting the renin-angiotensin system. And so, these really remain a cornerstone of our medical therapy. And actually, when patients present with acute heart failure, meaning in the hospital decompensated, we're often reaching for these types of medications first, meaning we're typically trying to undo all of the upregulation in the RAAS system first before tackling other pathways of therapy. And so, ACE inhibitors or angiotensin receptor blockers are really the first agents that we're often starting in acute heart failure to vasodilate these patients and to really start getting the hearts kind of back on a normal Starling curve.

In the chronic heart failure setting or in the ambulatory setting, ACE inhibitors and angiotensin receptor blockers, again, are our cornerstone of therapy and are really sort what we're reaching for in addition to beta-blockers when we're first managing patients. And in general, I tend to practice as clinical trials were designed and will first ensure that a patient can tolerate a modest dose of an ACE inhibitor before switching them to angiotensin inhibitor neprilysin inhibitor because that's how the clinical trials were designed. And in general, those are a little bit more potent. And so, to answer your question again, the ACE inhibitors really are a cornerstone of our medical therapy. We reach for them very early on in acute heart failure, but even in ambulatory newly diagnosed heart failure, we're also reaching for these agents very aggressively.

Kendall Williams, MD: I'm curious on two questions with ACE inhibitors. As you're actively diuresing someone who's in the hospital, do you hold them or do you continue them? That comes up a lot. And then, just a second question is what's your favorite ACE inhibitor? How do you use it? What's your goal doses?

Stuart Prenner: So, I can tackle that. In general, if someone's just coming in congested, we'll try to continue as much of their medical therapy as possible. In fact, there's good evidence that withdrawal of medical therapy particularly if it's not re-instituted before a patient's discharged is associated with worse outcomes, and there are reasons for that. But in general, we would continue ACE inhibitors while diuresing a patient. If a patient presents in shock or is very decompensated, we might consider reducing the dose of a beta-blocker, for example. But the vasodilatory properties of the ACE inhibitor are generally only going to be helpful.

And then as far as my favorite ACE inhibitor, it actually depends. In the chronic setting, I always prefer patients to be on something that's once a day. And so, I will generally reach for something like lisinopril. In the inpatient side, however,

patients can be a little bit more tenuous, I will reach for something a little bit shorter-acting like enalapril because it's twice a day. I don't know, Lee, if you have other thoughts.

Lee Goldberg: No, I agree with that. I actually practice the same way. You know, I use lisinopril. The advantage of lisinopril is that you have a dose as low as 2.5 milligrams. You can really use a tiny dose. The maximum dose I use is 40 milligrams. Many patients are on between 10 and 20 milligrams as the usual dose range. And similar to what Stu was mentioning, I will use enalapril in the hospital to allow titration, but I do prefer the once-a-day dosing, just to simplify things, of the lisinopril.

Kendall Williams, MD: One of the things I've seen the residents doing in the hospital, and I assume it's because you guys are teaching them to do it, is that they're starting the ARB instead of the ACE. They're starting valsartan more specifically with the idea that eventually they're going to transition them to Entresto. Is that something you're doing?

Lee Goldberg: So, I can take that one. And the answer is yes. And it ties back to what we talked about earlier, about the need for that washout period, that 36-hour kind of washout period. And a lot of us prefer to start the ARB now, especially if we think that this patient will be a candidate to switch to sacubitril/valsartan, and valsartan is actually the easiest thing to start, just because we know that they will have tolerated it, although any of the ARBs are acceptable. So, it doesn't have to be valsartan, but we'd like to see patients on a reasonable dose of valsartan, the equivalent of about 40 milligrams daily, prior to initiation of sacubitril/valsartan.

I will say that in my own experience, and we can see what Stu's experience has been, the sacubitril/valsartan is a little bit better at lowering blood pressure. And so, if someone has marginal blood pressure, we want to start with the lower dose, the 24/26 dose as opposed to the mid-range 49/51 dose. But if they're already tolerating a good dose of valsartan, that gives you a sense of where you can start the dosing, whether you would start the low or the medium dose.

And that's kind of how the labeling of the drug came out, that if you're already on an ACE or an ARB at moderate or high dose, you can start the mid dose. And if you're on low dose or no dose, then to start with the low dose. So, it's just easier logistically to have someone on an ARB and then just flip them to the sacubitril/valsartan.

Kendall Williams, MD: Any thoughts on that, Stu?

Stuart Prenner: I completely agree. That's how I practice. And I think the reason to test the water a little bit, as Lee was saying, and particularly with an ARB, is that then you're not committing the patient to being on nothing for that washout period. And the other is that even in the actual paradigm study, 20% of patients didn't tolerate kind of these run-in doses to allow them to go on to even the lowest dose of in Entresto. And we do see some patients like this when they first present in the hospital. And so, you do just want to test the water a little bit with one of these agents to get a sense of, firstly, what dose of Entresto you might use. And also, to Lee's point, they are somewhat more potent. And so, you just want to make sure they do tolerate some dose of ARB before you start them on a sacubitril/valsartan.

Kendall Williams, MD: And you're viewing sacubitril/valsartan as a replacement for ACE and ARBs, but also superior to ACE and ARBs?

Lee Goldberg: I would say that the data that we have from the sacubitril/valsartan trials that led to, first, the FDA registration and then, ultimately, additional trials that kind of got it into the guidelines showed that there was a superiority of this agent, especially for HFrEF, so for ejection fractions that are really under 50% that there was a morbidity and mortality benefit as compared to at least ACE inhibitors. Remember the clinical trial was done, enalapril versus sacubitril/valsartan in the original trial. And there was a significant benefit.

So, the guidelines are written that actually the ARNI as they refer to, an angiotensin receptor neprilysin inhibitor combo, that that is the preferred agent if possible. And there are times when patients can't tolerate it. If they have a history of angioedema to ACE, we tend not to put them on an ARNI, on the angiotensin receptor blocker neprilysin inhibitor, because we're concerned about the risk of subsequent angioedema. But if patients can tolerate it, they can get it. They can afford it, then that would be the first-line drug. And there's even now a move afoot and it's hinted at in the guidelines that it may be a first-line drug, meaning that someone comes in with new-onset heart failure, we may go ahead and just start the Entresto as they're coming through the door, as opposed to going through ACE or ARB. That's not exactly the way we're practicing. But certainly, the guidelines suggest that that may be the way to go just to expedite getting patients on the right drugs in the hospital and then discharging them on the right medications, so that you don't have to go through a conversion process subsequently.

Kendall Williams, MD: What are your experiences with the cost issues?

Stuart Prenner: It's a real concern. I think what is becoming a little more clear is that we're finding more and more patients are able through some mechanism to afford these drugs. There are still some where it's cost-prohibitive. But through various programs and vouchers and coupons and things like that, we're finding again in part because of the evidence and because, you know, we're now seven years into using this drug, that we're finding more patients are tolerating it. It's also something that we're looking into before we are getting ready to discharge patients. And so, if we're even thinking of starting it, we'll look into these issues ahead of time so that we don't set a patient up who's doing well on it to have trouble affording it down the line. But we are seeing improvements year by year noticeably.

Lee Goldberg: And I will say that by having this agent in the guidelines now, we really have evidence-based practice to help us with insurers. So, the barrier has less been about them not being covered at all as compared to having a prohibitively high copay. So, a slightly different problem for us, and we're having a lot less issues with prior authorization with the Entresto than we had in the past, now that it's in the guidelines and recommended almost first-line. We've seen that a lot of insurers have loosened up and have made it a lot easier for us logistically.

Kendall Williams, MD: So if someone has an EF less than 40%, your goal is to get them there. If they're in the 40% to 50% range, let's say they're doing well on their ACE or the ARB, do you feel the urgency to do it? Or how do you manage these? How do you manage sort of the subtlety, if you will?

Stuart Prenner: So, I just looked this up actually. I had a patient that kind of fell into this category. I think it is a gray area, right? Because the reality is there aren't a ton of clinical trials that looked at this population. They either looked at people who had frankly low EF or frankly normal EF. The gray area is a little bit less studied.

And so, I think to your point, it really depends on how the patient is feeling, meaning if they are NYHA functional class I, they're really not having symptoms and their ejection fraction is in the mid to high 40s on one or maybe two agents, I'm generally not in a hurry to transition these patients. And it's in part because, when the clinical studies were done, they really focused on symptomatic patients. And so, I'm not aware that there's evidence for asymptomatic patients with only mild reduced ejection fractions to transition them. I'm curious if Lee has a different approach, but that's how I practice. It's a symptom situation because they may be a little better unloaded on

sacubitril/valsartan. But if they're feeling well, I generally would not rush to switch them. Lee, what are your thoughts?

Lee Goldberg: Yeah. I mean, I can say that we have a little bit of data, although I'll admit freely that it's post hoc and a little bit extrapolated. But the PARAGON trial was a trial that was looking at heart failure with preserved ejection fraction and Entresto. And what was interesting was they included patients that had ejection fractions 40% or greater. And the trial overall was not positive. It was similar. Both arms behaved similarly to the ARB versus the Entresto in that particular trial. However, when they did subgroup analysis by ejection fraction, they found that patients that had ejection fractions 40% to 50%, really did see a signal of improvement. Now, again, that wasn't the primary endpoint, that was subgroup analyses. They did pre-specify those analyses. But again, it was a small group of these patients. However, as Stu mentioned, they were all symptomatic. So, the way that I practice is very similar to his. If the ejection fraction is less than 50%, but they are symptomatic, I do try to get them on the sacubitril/valsartan because of that subgroup analysis from PARAGON saying there was benefit there, as well as the fact that we believe that maybe that'll lead to more remodeling and improved outcomes over time. For those patients that are asymptomatic in that group and doing well with good blood pressure control on an ACE or an ARB, I actually leave them alone. I don't make that change because I don't know that we have data yet to show us that it really makes any difference.

Kendall Williams, MD: That's very helpful to both of you. Thank you. We face all of these practical problems in our areas in primary care as well as we're trying to think through all of this. So, the ACE and the ARBs and the ARNIs are sort of the workhorse and there's these other workforce of beta-blockers, which have not gone away, right? So, I think we're basically down to carvedilol and metoprolol succinate as the primary drugs. Anything to say about beta-blockers?

Lee Goldberg: I mean, I can start with this just because my career started as beta-blockers were being introduced and there were generations of physicians who were taught that beta-blockers would be dangerous in heart failure because the adrenergic system is kind of part of the compensatory mechanism. And it was true that if you gave high-dose beta-blockers to someone who had acute left ventricular dysfunction or decompensated heart failure, you could make them much worse, and so that was the observation. But we learned that the chronic stimulation of the adrenergic nervous system also leads to some of the same negative remodeling that we know from the angiotensin-renin system. And

there's even a little crosstalk between the systems where activation of renin-angiotensin tends to also activate adrenergic system and a little bit of vice versa.

And so, really in the late 1990s, mid-1990s, there were a series of small trials that were really a heresy at the time, right? That you would give beta-blockers in very low doses, first of metoprolol and then some other agents were done leading to the large scale trials that were done in the late 1990s. And there's actually three drugs. One is long-acting metoprolol succinate, one is Carvedilol, and then the third one is a drug called bisoprolol, which we don't use a lot in the US, but is commonly prescribed in Europe. And so, those are the three that are in the guidelines. And I will say that they significantly reduce morbidity and mortality. Mortality in the 30% range across all three agents, and that's on top of an ACE or an ARB. And so, they are really part of the cornerstone therapies that having patients on an ACE, ARB, ARNI plus a beta-blocker, is really the key therapy for all stages of heart failure and really for all heart failure with ejection fraction less than 50%. And so, we try to get both of those agents on almost no matter what. And there's just buckets of data on the reduction in morbidity and mortality. So, we want to emphasize that both agents are required in order to get patients to move forward, and they've really stood the test of time.

Kendall Williams, MD: And you said lisinopril 40 milligrams is your gold dose. How about for carvedilol and metoprolol succinate, Lee?

Lee Goldberg: So for carvedilol, we try and get patients to 25 milligrams twice daily as the target dose. That's where the clinical trials were done. We know that there's clinical benefit at a dose of 6.25 milligrams twice daily based on a clinical trial called MOCHA, which was a dose-ranging trial. So, we call that a threshold dose. If you can get patients to at least that dose, you know that there was morbidity and mortality benefit. And then, for patients that are greater than 85 kilos in the early carvedilol trials, you can even go to 50 milligrams twice daily. And I do have a handful of patients who really have difficulty controlling their heart rate or their blood pressure, and I have gone to 50 twice daily if they're heavier. But for the most part, I would say over 90% of my patients, my target is 25 milligrams twice daily.

For metoprolol, the clinical trials went to 200 milligrams once daily. I admit that I shoot for about a 100 milligrams, not twice daily, once daily, and I shoot for about 100 milligrams once daily as my max dose in my heart failure patients. I rarely get to a higher dose than that in the metoprolol patients. But the labeling and the guidelines say that you can go to 200 if you need to for heart rate control or for blood pressure control. And then occasionally for

antianginal or for antirrhythmic reasons, it's also good to go up on the beta-blocker dose.

Kendall Williams, MD: Stu, any thoughts to add there?

Stuart Prenner: Nope. I think Lee summarized it perfectly.

Kendall Williams, MD: So, the other drug in the RAAS system that we didn't talk about, or the other sort of drug class, is the aldosterone blockers, primarily Aldactone and eplerenone, which are additive to the ACE, ARB, ARNI combo. And I'm curious how you're using those and which ones are you using? Eplerenone wasn't available for a long time, but now is. So Stu, how are you using those?

Stuart Prenner: Yeah. So, in general, the way that I practice, I mean, again, the guidelines support the use of these medications very aggressively. But I'll generally lean on the initial RAAS blockers. We mentioned ACE inhibitors, ARBs, and the beta-blocker first. But the MRA should really come up quickly thereafter. There's a very strong evidence base both in nonischemic and ischemic diseases, both for spironolactone as well as a eplerenone. Just in terms of my own practice patterns, I will typically use spironolactone. That being said, one of the side effects of spironolactone is gynecomastia. And that is typically not seen as commonly with eplerenone. And so if patients do have that side effect, I will switch them.

The other thing we need to be careful of is that with each of these additional therapies in the RAAS system, you have incremental propensity for hyperkalemia. And so, you just need to be mindful of that. It's typically commonly seen if you're going to check labs. Within the first seven to 10 days and then again, within the first two to four weeks, you'll typically catch it. But it is important to know. So, yeah, MRAs are definitely important. The guidelines recognize them upfront in terms of medical therapy. And the nice thing in general is while they have some blood pressure action, typically we can get them onto patients, even if the blood pressure is somewhat marginal, and I'll often like to see that in the regimen for patients before aggressively titrating other agents to the max dose just because it does have a lot of benefit.

Kendall Williams, MD: Lee, anything to add there?

Lee Goldberg: Yeah. The only thing I would add is the safety reminder that, when we start these agents, just to make sure that we're monitoring serum potassium. They're potassium-sparing diuretics, they cause potassium level to

go up. Sometimes you can stop potassium supplementation that they might be on, because they may be also taking loop diuretics. So, we traditionally will check a serum potassium over five to seven days and make sure that it's stable. And sometimes, we'll check a couple if we see that it's going up to be sure that we're not causing hyperkalemia. There was a study after spironolactone was recommended for HFrEF after the RALES trial in Canada that they saw a lot of hyperkalemia in the emergency department and arrhythmias because it was being used kind of just ubiquitously without really good monitoring. And so, we took a lesson from that. And occasionally, we have to stop it for hyperkalemia because they're on other agents like ACE, ARB or ARNI that can also cause a little bit of hyperkalemia. So, it does take a little bit of monitoring when you start that agent.

Kendall Williams, MD: So, the new kid on the block are the SGLT2 inhibitors, which don't work by any means that we've mentioned to my knowledge. They work on the kidney to help dump glucose into the urine, which has made them effective anti-diabetic agents. What I guess has been surprising is that they seem to have benefits beyond that and particularly not only on the kidney itself, but also on the heart. And so, that's, I would say, the brand new stuff in CHF, right?

Stuart Prenner: The story of this drug class is also just worth telling. You know, this is a lesson learned from prior scenarios we found ourselves in where diabetic drugs that had good glucose improvement were actually associated with worse cardiovascular outcomes. And a lot of it had to do with worsening heart failure. And so, this was sort of a success story and that line of work in the sense that the signals in this drug class actually came from safety profile studies that not only showed the drug to be safe in terms of not causing worsening heart failure or incident heart failure, but actually to the contrary, preventing it in a high risk patient population.

And so, I think the story of this development of this drug class is actually very remarkable in the sense that it really was a referendum on other times where we didn't get it right. And so, the signals from these diabetic trials were very exciting, and it led to a series of studies in multiple heart failure populations, initially diabetic, and then both diabetic and non-diabetic, both in a reduced ejection fraction population, and then more recently in a preserved ejection fraction population.

And so, the obvious excitement here is the outcomes that we saw across all of these populations, but also the fact that these drugs do seem to be remarkably safe. There are clear signals of ketoacidosis that need to be monitored as well as propensity for genitourinary infections. But unlike a lot of the drugs that we've

spoken about where there are sort of concerns about fluctuations and hemodynamics or blood pressure, these drugs seem to really be remarkably tolerated to the point where we're really thinking about getting these ready for patients when they're heading for discharge. And so, Lee, I'll be curious to hear your thoughts as well. But I just wanted to highlight the story behind the development of the class effect in heart failure because it's really a lesson learned and it's quite remarkable.

Lee Goldberg: Yeah, I mean, I think for us in the cardiovascular world, now we have a new cardiovascular class of drugs, the SGLT2 inhibitors that we inherited from our endocrinology colleagues through that literal serendipity that a safety study became an efficacy study. And so, that's led to the development. Literally over six years now, we have two drugs completely approved, and then the guidelines and two or three more that are coming along.

I think that we were thinking about mechanism as we were talking about ACE, ARBs and beta-blockers, et cetera. We really don't know the mechanism here. But one thing that we have tested and have at least observed is that it doesn't seem to be associated with glucose effect because it works in diabetics and non-diabetics.

In non-diabetics, it does not influence blood sugar at all. And so, it doesn't seem to have that mechanism. And many of us thought that maybe it was the diuretic effect of these drugs, but it's actually independent of the diuretic effect. We've looked at patient weights and urine outputs and whatnot in clinical trials and haven't seen that that's the mechanism. And so now, the working mechanistic approach, which scientists here at Penn and others are looking at is, is there a metabolic effect of these drugs at the cellular level that are somehow making the myocytes more effective in utilizing glucose, which is the main fuel for the heart under normal conditions? And is that somehow changing things? And is this a totally different therapeutic target than any other agent that we've talked about? And so, there's some excitement in trying to understand the mechanism because there may be other agents or other drugs that may be able to target that or there may be some patients that benefit more from one drug or another. And if we can understand the mechanism, we may be able to tailor or personalize our therapies. Right now, we're applying, our therapies to every patient all the time. But we may be able to further modify that on mechanistic ways.

So in quite a surprising way now, we have a whole new class of drugs. One exciting thing is that there's recent clinical trials data that showed that these drugs lead to positive remodeling of the ventricle like we've seen with ACE, ARNIs and beta-blockers. And the magnitude of the effect is similar to like

adding a beta-blocker, so ejection fraction changes of 5% to 10%. On top of that, we're seeing additional improvements with the SGLT2 inhibitors. And so, we went from kind of being a little skeptical, I think, as cardiologists to being very aggressive and trying to get these agents on board and whoever can tolerate it.

The other side effect to think about in addition to the general infections and whatnot that had been problematic for this class is the possibility of euglycemic ketoacidosis or ketoacidosis in general. And we worry about that in patients with changing renal function or being NPO or being aggressively diuresed, for example, all things that we do to people in the hospital. And so, specific care needs to be taken in using these agents in the hospital or if patients have elective procedures, being sure to hold these drugs so that we don't run into trouble with the metabolic kind of ketoacidosis that can be seen with these agents.

I don't think we're seeing it as much in real clinical practice as we worry about it. That being said, we're rolling these drugs out to a huge number of patients and we're just learning about them. So, I do think we need to be particularly cautious about patients being hospitalized and being on these agents. And we have been holding them. There are now some clinical trials showing that they can be started and continued safely in the hospital, even during acute heart failure hospitalizations. I think we're still getting our arms around that to understand exactly who would be safe to continue them in.

Kendall Williams, MD: So, are you adding them now to anyone that you feel might benefit or that can get it approved and the insurance company will approve it? Or are you just rolling it out in that way?

Lee Goldberg: So, I would say yes. I'm curious, what Stu thinks. I have been. I think of all the drugs that we have ever been introduced in heart failure, I'm probably rolling this one out the most quickly. And that's because it's pretty well tolerated and sometimes we can even back off the other diuretics. And so, I have been doing that.

The main barrier has been the challenge with insurance and cost for a lot of our patients since this is a new indication for this drug. And so, I don't know that our insurers have kind of caught up with the science. Stu, what is your thought?

Stuart Prenner: Yeah, I completely agree. And like the story you told with sacubitril/valsartan across ejection fractions, we have that data now. We have data for the SGLT2s, literally across all ejection fractions both from the reduced studies and also from the two preserved ones. And so, I agree with you,

especially if someone's on diuretics. We'll often find ourselves cutting the dose of the loop diuretic by at least 50% when we start this, and that's only a starting point. So, that's one consideration. And then, the other, as Lee mentioned, is that they're really well tolerated in general with the caveats of the euglycemic DKA worries and periprocedural concerns. They're very well tolerated and don't, in general, require much monitoring after a little bit of chemistry the first week or two. So, I agree. I'm definitely rolling this out, I think, more briskly than I initially expected.

Kendall Williams, MD: So, you mentioned diuretics and, for years, this was basically what you did if somebody comes to the ED and they're overloaded. And so, you start diuretics and most of heart failure care was really about managing diuresis. But it's interesting because as the better we get with the other drugs, we're trying to get ourselves away from diuretics, right? Ultimately in some ways in the management of chronic heart failure, we want to get to the point where a patient doesn't need any diuretics. Is that right?

Lee Goldberg: Yeah. So, I can take that on. You know, there was data from our colleagues at Mayo Clinic that actually showed that the lower the dose of the diuretic, the better the outcomes. And there's some confounding there because patients with really bad heart failure do worse, they need more diuretics. And those that have renal insufficiency tend to do worse, but also need more diuretics. So, we always wonder a little bit if there's some confounding there. But we all know that the diuretics actually activate the adrenergic system, something that we're trying to block with our beta-blockers, and also tend to activate the renin-angiotensin system, which we're also trying to block. So, diuretics seem to be necessary to get rid of excess volume and sodium, but they have a dark side in that they activate some of the other systems that we know lead to worsening heart failure outcomes.

So, the goal in most heart failure programs, including ours, is to try to get patients to the lowest dose of chronic diuretic that's necessary and then, as needed, we can augment the dose if there's a situation where they have volume overload or they have an illness and they get decompensated, we can use the diuretics, kind of bump them up as needed. But the goal is to try to get them to the lowest dose possible. And even we manage a bunch of patients with relatively low ejection fractions who are on the other meds and don't need any standing diuretic at all and use some as needed PRN diuretic.

So, you're absolutely right, we've shifted the paradigm away from diuretics as being cornerstone and rather focus them on being symptomatic relief, but actually not as therapy. And that's why we always get anxious. A patient comes

in with new peripheral edema, say for example, and they get discharged from an emergency department or urgent care and someone gives them 40 of furosemide and no other workup. For a heart failure doc, that makes us super anxious because if the mechanism is heart failure, either preserved or reduced ejection fraction, you've now activated a bunch of hormonal pathways that may actually exacerbate or progress heart failure over time without any counterregulatory beta-blocker, ACE inhibitor, whatever on board. So, you're absolutely right. We want to try and minimize the diuretic as much as possible, but they are a necessary evil in our population.

Kendall Williams, MD: I am curious, because we have now three, I guess, major diuretics that we use, loop diuretics. There's furosemide, bumetanide and torsemide. I'm curious which one you tend to prefer.

Stuart Prenner: I can start. Generally, we'll start with furosemide. It's generally fillable in most pharmacies without too much difficulty. And I think it's really just been the workhorse for loop diuretics over the years.

One issue that will come up though is the bioavailability of these drugs and there's clear pharmacokinetic data that suggests that some of the other loop diuretics, meaning not furosemide, have better bioavailability, specifically bumetanide and torsemide, and it may not matter in a reasonably compensated heart failure patient, which you choose. But certainly as patients start developing cardiorenal physiology, and for patients that have more of a right-sided kind of congested liver and GI system, it can be hard to diuresis people with furosemide once they start getting overloaded. And so, as people's renal function deteriorates or they start developing right-sided heart failure, we often are finding ourselves transitioning to those other loop diuretics, specifically bumetanide or torsemide, because there is some better bioavailability.

Although interestingly, there was some discussion at the American Heart Association looking at some real world experiences with this where it didn't quite pan out that way, meaning there didn't seem to be much difference between all of these. But in general, many of us are finding ourselves starting with furosemide. And then, if the doses are getting sufficiently high or the patient is developing more of a gut edema phenotype, we're finding ourselves switching to those other loops. Lee, are you sort of similarly practicing?

Lee Goldberg: Yeah, absolutely. Sometimes it's also a psychological barrier. You know, patients 120 milligrams of furosemide sound like so much, so they'd rather take 4 milligrams of bumetanide, sometimes we do do that to make it easier to make it fewer pills, but I agree. My personal experience is that

torsemide does work better in right heart failure with bowel edema and gut edema because it's better absorbed. And theoretically, that's the case. But I agree with Stuart that actually the clinical trials have been kind of mediocre in saying that. But our clinical impression, or at least what we believe, even if it's not true scientifically, is that the torsemide works better in that setting.

And then, occasionally, we will combine a thiazide diuretic, like metolazone, as like a booster. And the reason that we do that pharmacologically is that the thiazide diuretics deliver a lot more urine to the proximal tubule of the kidney. The loop diuretics work at the loop of Henley further distal down. And so, what happens is that you deliver a lot more juice to the loop. And then, the loop diuretics will work much more efficiently. And so, we will combine a thiazide diuretic, a long-acting one like metolazone at low dose, 2.5 or 5 milligrams once daily, 30 minutes before the loop diuretic whatever one you're choosing as a booster dose. And that does tend to significantly increase urine output. Some patients are very sensitive to that, others less so. But that's one of the tricks that we use in order to use when we need to kind of get fluid off of someone who's getting into trouble, we'll use a little bit of metolazone. Sometimes people will use chlorthalidone for the same thing, either intravenously or orally.

One caveat is that when you combine the diuretics like that, that the risk of hypokalemia and other electrolyte abnormalities goes up dramatically. So, you really do have to monitor labs and also check in with the patient because they may have such a brief diuresis that several pounds come off quickly and you may not want to continue thiazide combined with loop diuretic for many days. You may want to just do it for a day or two and then reassess, and then maybe another day of the following week to get patients where they need to be.

For patients that are really engaged in managing their disease, some of them will use metolazone as needed. And if that you have a relationship with them and a sliding scale that makes sense, then we sometimes do that as well. And that has really been a trick in the heart failure program for years to keep patients out of the hospital and keep them compensated when their heart failure becomes much more brittle as their disease advances.

Kendall Williams, MD: So, this has been a great discussion of the major medications we use in heart failure. There's a lot more to talk about, including HFpEF where we need to drill down on that. And there's finally some real therapeutic options, and talk about other aspects of congestive heart failure care.

So, Stu and Lee, I'm going to bring you back for a part two, so we can get into all those details. Is that good?

Lee Goldberg: That would be great. Thank you so much.

Stuart Prenner: Looking forward to it.

Kendall Williams, MD: All right. So, thank you all for joining the Penn Primary Care Podcast. We'll see you next time for a part two on congestive heart failure.

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