Kendall Williams, MD: Welcome everyone to the Penn Primary Care podcast. I'm your host, Dr. Kendall Williams. So, we're back with part two of a discussion with Dr. Lee Goldberg and Dr. Stu Prenner about congestive heart failure. In the last podcast, we went over most of the drug classes that are used for congestive heart failure and updated some of the new changes in that whole armamentarium of what we can use.

Today, we wanted to talk primarily about heart failure with preserved ejection fraction and some of the changes there. But I also wanted to get back to a couple of subsidiary issues related to HFrEF or heart failure with reduced ejection fraction, as well as some new changes in the workup of congestive heart failure.

So, let's just jump into HFpEF. And Stu, I'm going to turn this over to you primarily, because I know this is your area of expertise. Can we just step back and talk about heart failure with preserved ejection fraction because the physiology here is really different from HFrEF, right?

Dr. Stuart Prenner: Absolutely. And I think it's good to start with a historical perspective here because it's definitely changed over time and the nomenclature of how we have referred to this condition has also changed over time. So, it's worth saying that historically, well before echo, we diagnosed congestive heart failure clinically at the bedside by examining patients, detecting signs and symptoms of volume overload, and then having some objective evidence that the heart was the cause of this, namely cardiomegaly on an x-ray. And so if you go back several decades, that's how we made the diagnosis generally of systolic heart failure.

But it became recognized that there were another group of patients that really behaved similarly in the sense that they developed signs and symptoms of heart failure, edema, dyspnea, volume overload that got better with diuretics. And yet, assessment of their ventricular function looked normal, meaning that their systolic, their squeezing function looked normal. And in general, these patients were thought to be a little bit older and to have thickened hearts or left ventricular hypertrophy. And so, this condition was described several decades ago, and ultimately took the name diastolic heart failure initially, thinking that, "Well, geez, if these patients don't have systolic heart failure, their ejection fractions are normal, then the problem by definition must be diastolic." And the disease entity took the term diastolic heart failure.

We've moved away from this over the last 15 years, and you referred to the condition by what we're currently describing it as, which is heart failure with

preserved ejection fraction. Nowhere have we commented on diastolic dysfunction being present. We've simply said that there are a whole boatload of patients, millions of them in fact, who have signs and symptoms of heart failure. But when you look at their hearts by echocardiography, their ventricular systolic function appears impaired, meaning their ejection fraction is at or above 50. And so, I think this historical landscape is important because it helps us to understand how we got here, but to also reflect upon the fact that heart failure really is a clinical diagnosis. And so, particularly when the ejection fraction is grossly preserved on an echo, it's really important to dig down into the symptoms the patient's having and to really look for signs and symptoms of heart failure in a patient who's coming to you with really unexplained shortness of breath.

And so, I think that historical landscape is important because while these patients were initially described as all having hypertension and having small hearts that were thick, that's not always what we see. And so, we have taken a much broader stance more recently and labeled this condition heart failure with preserved EF, recognizing that there are many reasons people come to have this condition, and it's not all simply that they have diastolic dysfunction. And so, I think I'll stop there as kind of an overview.

Kendall Williams, MD: So, I want to dig into that in terms of some of the echo reports we get back, Stu, because sometimes you get an echo report back and it'll say moderate diastolic dysfunction, mild diastolic dysfunction. How should we be thinking about that in relationship to HFpEF?

Dr. Stuart Prenner: So, it's a great question, and I think the first thing to do is to take a big step back and just offer a definition of what this is because it's really a clinical syndrome. It's a constellation of symptoms and kind of ruling out other things that ultimately leads us to this diagnosis. And so, there's a couple things to say.

Firstly, it's important when you're entertaining this diagnosis. Even if the ejection fraction is normal now, you want to go back and make sure that it has not been impaired previously. Because we now recognize a whole other disease called heart failure with improved EF, where people had previously low EF and it's now normal. So, part of what I tell residents and other trainees when we're talking about this is you got to do your homework. You have to go back and make sure you're not dealing with a previously low EF, because these are patients that have a whole different disease mechanism and benefit from all of the drugs we previously spoke about.

The other thing is you don't want to be dealing with valvular heart disease that's severe and be calling it HFpEF, right? If somebody has severe aortic stenosis or severe mitral regurgitation or even maybe two valvular problems that are moderate, that really should be separately dealt with before you label the patient as having heart failure with preserved EF.

And those are important things to keep in mind when we're working this up. And so again, ruling out recovered low EF and ruling out valvular heart disease are two very important things when you're thinking about a patient who is having signs and symptoms of heart failure, and the EF is "normal."

To get to your question though about the diastolic dysfunction, part of the challenge here is that based on the current guidelines, it isn't always easy to bin a patient as having significant diastolic dysfunction unless multiple parameters on the echo are abnormal. And so, it isn't unusual for patients to have indeterminate reporting of their diastolic dysfunction because they don't read the handbooks, and it turns out that patients may have a couple parameters that skew abnormally and others that don't. And so, I remind myself that even in the clinical studies that enroll patients with proven HFpEF, when we can talk about that via right heart cath, many of them have even just mild abnormalities in diastolic dysfunction or even normal diastolic dysfunction by echo. And that certainly does not exclude this condition. And so, it's very important that people are not dismissing a patient as having HFpEF simply because there's not severe derangements in diastolic dysfunction on the echo.

Kendall Williams, MD: So, that does beg the question of how do we know and who should we work up? Like patients come in with dyspnea, and we've all had these patients where they come in with dyspnea. We don't think it's the lungs, that's not a PE, their symptoms are sort of chronic. We're trying to work them up. Their EF is normal and maybe their BNP is up a little bit, but not significantly, and we're trying to sort that out. What are the things that might lead you to say, "Okay, I think they may have diastolic heart failure as a cause of their dyspnea, and we need to do further workup including maybe even a cath"?

Dr. Stuart Prenner: So, I'll take a quick stab at that, and then I want to hear what Dr. Goldberg's perspective is. But one is even if the EF is grossly normal, and even if there is not severe derangement in the diastolic assessment, typically most of these patients are going to have some enlargement of the left atrium because that's the chamber that's most affected when the pressure on the left side of the heart is high, which is generally required for this diagnosis. And so, I will quickly look to see whether the left atrium is even a little bit enlarged and

that already is raising my index of suspicion if someone is short of breath and we have ruled out the common other things like asthma, COPD, et cetera.

The other though is to think about the company that this diagnosis keeps. And we're a little bit reminded of this by the typical comorbidities that these patients have in clinical studies, but also by a really easy to calculate scoring system called the H2FPEF score. And it should sound a little bit like CHA2DS2-VASc. We're pretty simple in cardiology. We can only come up with so many ways of scoring things. And so, this computes very similarly to the CHA2DS2-VASc score that we use to decide on anticoagulation for AFib in the sense that you get various points when you're evaluating a patient who has unexplained shortness of breath. Based on a couple of things, most of which are comorbidities. So, you get points if they're over 60. You get a lot of points if they have AFib, because we think of that as being a disease of the left atrium. You get points for having a history of high blood pressure. And then, you get a couple points for some easy-to-calculate parameters on the echo.

And so, rather than focus exactly on the score cutoffs for normal and not normal, my point is that this scoring system is in part based on the typical comorbidities that people with these conditions have, which is they're typically over 60, and 99% of them have a history of hypertension, diabetes, or obesity. And so if you have a patient with those risk factors and they have unexplained shortness of breath, considering HFpEF is a very solid thing to do. Lee, what are your thoughts?

Dr. Lee Goldberg: I agree with that. I think that one of the things about being a great internal medicine doc is kind of thinking about all the possibilities or acknowledging or recognizing the patterns that things that come together. So, it's really important, as Stuart was mentioning, to kind of think about the comorbidities and then are there any other clues for any other disease state?

So, it may be true that they have HFpEF, but the underlying disease may actually be amyloid or the underlying disease may be uncontrolled hypertension. And so, I do think it's important for us to kind of think about, are there any other findings, any other clues, any other lab abnormalities that guide us to a diagnosis that not only explains the dyspnea, but really gets to the root cause of what's going on.

Kendall Williams, MD: So once you've put that clinical picture together, and I think, by the way, Stu, many of us were not familiar with that scoring system and that's very helpful. Obviously, you also have a test in a sense of just

diuresing somebody and seeing if they improve. To what degree do you use that when you're not sure?

Dr. Stuart Prenner: So, that's very helpful and I think it's just worth saying that that gets back to the original Framingham criteria. So back in the '70s before echo, when we were diagnosing heart failure, again, it was a clinical diagnosis. And one of the criteria was putting a patient who appeared to have volume overload on diuretics and seeing them lose weight. And so, I think that absolutely applies. So, I think that's sort of the poor man's test. And I think that that's very, very helpful because what you're basically saying is that the dyspnea is due to high filling pressures in the heart that you're improving with diuretics.

Some of the challenge though is particularly in earlier forms of the disease, I think the type that we wish we diagnosed more, but unfortunately don't. Some of these patients may not have high pressure in their heart at rest. The echo's going to look relatively normal, and that may not be a patient who's going to benefit from a trial of diuretics if they're telling you that their main symptom is exertional intolerance and they're not having clear volume overload, at least on exam.

So yes, the trial is helpful and I would say if it rules them in, then you're probably done. But I would also be prepared for an equally, if not more common scenario, where that doesn't move the needle because the patient isn't having a high wedge pressure at rest and you may need to dig deeper. But absolutely, I think that's a poor man's test. And it goes back to the Framingham criteria of how we diagnosed this back in the '70s.

Kendall Williams, MD: How does one get to the issue of exertional HFpEF, if you will?

Dr. Stuart Prenner: So, that's a tough question, and it's common, right? So, the earliest form of this disease is not one in which there's enough derangement where the echocardiogram is going to be striking. Generally, there will be something there, but not always. And often the NT-proBNP or the natriuretic peptide levels are normal.

Part of that, right, is that these are typically obese patients, and we know obesity skews the BNP low, but also the hearts are not stretched in the same way as our typical dilated patients. So, the wall stress is very low because the hearts are normal or thick and they're not dilated. And so, that signal that drives BNP secretion in our other heart failure population is often null here. And in fact, it's

been proven in like 30% of people who have an abnormal right heart cath, the BNP will be stone cold normal.

And so to tease out a disease that's predominantly one of exertion, what I say is you have to study the patient during exertion. And so, there are a couple ways to do this. One of which is to put them on a treadmill and do an echo, like a stress echo. But rather than look for systolic dysfunction like we would do if we're looking for ischemia, we actually are looking for diastolic abnormalities that are elicited during exercise. And there are good sort of guidelines to go off of.

I think practically that isn't the easiest test to do. And so oftentimes if we're unsure of the diagnosis, we will do the same provocative maneuver, except we'll do it during a right heart cath. And so, we'll do a full right heart cath and then we'll have the patient exercise. That's the easiest way to really and that's the gold standard way of proving this. Because at early stages, particularly if they're not on diuretics, it's a disease of exertional intolerance. And the only way to detect the abnormality is by invasively studying the patient during exercise. If you don't exercise them, you may miss this. And so, I think that's an important take-home point.

Kendall Williams, MD: I was going to jump into that, because I'd really like to see that study. But I think I'm going to leave it alone for an interest of time. I'd like to see how you do that. Let me move on. Stu, do you think there's anything more to say about just diagnosis and initial workup?

Dr. Stuart Prenner: So, I think the last comment I'll make, and then I think we'll move obviously to the new clinical trials, which were exciting, is that people need to have a very high index of suspicion for this. In a patient with the type of risk factors that I mentioned, high blood pressure, diabetes, and age, unexplained dyspnea has a reasonable likelihood of leading to this diagnosis, particularly if other things have been ruled out. And I can't stress enough that a normal BNP level does not rule this condition out, nor does a normal echo because again, it's earliest flavors, the constellation of problems that leads the echo to be abnormal has not yet set in. Yes, in more advanced diseases or things like amyloid, the echo is typically striking, but not always. And so, people need a very high index of suspicion for this disease and to go to MedCalc and calculate those points on the H2FPEF score, if you're sort of entertaining this and then if the score comes out indeterminate, you might want to work it up further.

And I think that would sort of be the parting message here, is that this is very common. And it's also concerning. The prognosis after a heart failure

hospitalization with this heart failure type is about the same as that of reduced EF. And so, this is an important disease to diagnose a patient with, so you can counsel them and ideally get them on some of the appropriate therapies we now have.

Kendall Williams, MD: So for years, I would give a CME lecture on heart failure to a primary care and hospitalist audience. And I did it on CHF and I would do HFpEF. And there was really just one slide for HFpEF, because I would talk about the CHARM trial, which had candesartan, which showed a little bit of potential benefit. But other than that, there was no treatment other than just controlling the blood pressure. But we've made a lot of progress since then especially more recently. So Stu, we have some new options now. Can you review those with us?

Dr. Stuart Prenner: I'm happy to and I think it'll be helpful to hear Lee's perspective on this class because it's broader than just the comments I'll make. But we were excited to have two clinical studies, DELIVER and EMPEROR-Preserved, which examined a different heart failure population than the prior clinical studies in low EF with the class of SGLT2 inhibitors.

Importantly, however, both of these clinical studies included patients with an ejection fraction all the way down to 40. And so, this is important because really by the guidelines, EFs of 40 to 50 are not HFpEF. That's really heart failure with mid-range. But needless to say, there was a good representation of patients at all spectrums of ejection fraction. So across both of these clinical studies, a third had EF 40 to 50, a third had EF 50 to 60, and a third had a higher EF. And then importantly, there had to be some other signal that the patient had heart failure, namely the BNP level had to be elevated and/or the patient had to have had a hospitalization for heart failure. So, they are looking at a particular type of patient population in this clinical study. So, we have two clinical studies that included a large proportion of patients with an ejection fraction over 50. And both of these clinical studies met their primary endpoint, which were in general combination endpoints of cardiovascular outcomes and all cause death.

And so, they were combined endpoints, but the clinical trials both showed benefit of SGLT2 inhibitors over placebo. What was interesting though was that the signals differed literally in the opposite direction in terms of who benefited the most. And Lee, keep me honest here, I believe in the EMPEROR study, what we saw was that patients with the highest ejection fraction, meaning over 60, did not benefit. Whereas those 50 to 60 benefited, but barely. And those 40 to 50 clearly benefited. But interestingly, we saw the exact opposite trend in

DELIVER, which was that people at the higher end of ejection fraction benefited the most.

Either way, the study was positive. But I do think mechanistically, it's interesting to think about who they included and who may or may not have benefited the most from the drug. So, I'll stop there. I'm curious, Lee, what your take on it is, because this wasn't without controversy, especially when we saw the trends pretty clearly going along with ejection fraction and what was your take on that, Lee?

Dr. Lee Goldberg: I will say that the SGLT2s were an exciting addition, I'll say, to the HFpEF armamentarium since it was a whole new class of drug that was being approved. But I agree with you in terms of how do we know which patients are going to benefit? And the trend at least has been looking at those patients with ejection fractions on the lower end of normal, 55 or less. And that's a similar story to what we got with the ARNIs and potentially even with the MRAs, with the mineralocorticoid antagonists.

And so, I think there is somewhat of a trend there. I think we're going to need a little bit more data on the SGLT2s to really break the tie here or to understand exactly which population they benefit for. But, overall, the trials were positive in patients with ejection fractions greater than 40%. And this was a major breakthrough to have two clinical trials that were positive. And so, we have a whole new class of drugs, not only helpful as we've heard previously about HFrEF, but now also those patients in the mid-range, and then at least in the lower end of the normal ejection fraction range for HFpEF.

So, that was an exciting breakthrough and something that we hadn't seen, you're right, in 25 or 30 years of clinical trials on HFpEF. We really had not had any medication move the needle very much. So, that was considered a big breakthrough in this disease state.

Kendall Williams, MD: So, we do say that no specific medication moves the needle, but what about blood pressure control generally across all classes of blood pressure control agents. Can they improve it over time?

Dr. Lee Goldberg: I'll jump in there and then Stu can add any other thoughts. We know that blood pressure control is absolutely critical in patients with HFpEF, the challenge has been understanding are there additional benefits of one agent over another. And that's where we really have gotten into trouble.

What we have learned most recently is that a couple of agents seem to have beneficial effects in addition to their blood pressure-lowering effects, and so therefore, probably should be on the top of the pile to use first. Although many of these patients may require multiple agents to get their blood pressure to the target, which now the guidelines suggest a target systolic blood pressure of less than 130 as the target for the heart failure population.

So, the angiotensin receptor neprilysin inhibitor, the sacubitril/valsartan that we've talked about, that was such a game changer in HFrEF, has also been studied extensively in HFpEF. And these class of drugs has an amazing impact on lowering blood pressure. That can be a disadvantage in some patient populations; but in this population, oftentimes is helpful.

And in the PARAGON trial, although overall the trial was negative, which was a little bit disappointing, this was looking at sacubitril/valsartan in patients with ejection fractions greater than 40%. When they looked at the whole population and cut it down into quartiles of ejection fraction, what they found is that, in the lower ejection fractions, ejection fractions say under 55% all the way down to an ejection fraction of 40%, there was a significant benefit in the ARNI group. And so based on that, the guidelines have kind of come out and said, "Okay, we have a level of evidence 2b kind of data that suggests that ARNIs may be the right choice to use for blood pressure control as well as to improve outcomes in the HFpEF population." Especially in those in the guidelines, it says ejection fractions under 65%, I think the clinical trials data may suggest the number was a little bit lower than that, but certainly on the lower end of normal. And then in the 40% to 50% range, the ARNIs are beneficial, which gives it an indication from the lowest ejection fractions all the way up to say 55% and, again, a drug that's great in controlling blood pressure.

Kendall Williams, MD: So, it's really in those people that are sort of in that middle range over 40% to 50%, the mildly reduced ejection fraction population. But as you said, Lee, just to summarize what you said, to go even up to the 55% range, there was benefit for Entresto (sacubitril/valsartan)

Dr. Lee Goldberg: That's correct. And then, there were two other agents that were called out in the guidelines for therapy. One was spironolactone, a mineralocorticoid antagonist. This was a little controversial. The clinical trial was called TOPCAT, was sponsored by the NIH, but was done internationally, including in Eastern Europe. And the trial overall was negative, which was pretty disappointing after lots of pilot studies showed a lot of positive signal at least. But when the subgroup analysis was done and they looked at the patients that were enrolled in the Republic of Georgia as well as in Russia, those patients

seemed to have very little benefit to spironolactone. But if you looked at the North American cohort, including the Canadian and North American sites, US sites, what you found was that there was a significant benefit to spironolactone in this patient population. And there's lots of theoretical reasons why that might be the case, including blood pressure control, electrolyte control and volume control, but maybe also antifibrotic effects and diastolic effects of the mineralocorticoid antagonist. And so, this drug has also been added to the armamentarium for HFpEF treatment.

And then lastly, the ARBs, you mentioned at the beginning about candesartan, also level of evidence 2b kind of a single clinical trial, but also an ARB. So in those patients that can't get an ARNI or have a side effect or had a history of angioedema, an ARB may be a reasonable alternative and that also falls into the guidelines.

So for blood pressure control, those are the drugs that are recommended upfront. But obviously then, these patients may need to go onto other classes of drugs like calcium channel blockers or even beta blockers. And obviously, if they have another indication like coronary disease or atrial fibrillation, et cetera, then selecting drugs that'll be beneficial for those agents and also lower blood pressure control makes a lot of sense. So, there's a little bit of art about how to stack these medicines based on the comorbidities and other cardiac conditions that some of these patients may have.

Kendall Williams, MD: But you would say, so as we prioritize these, the SGLT2 inhibitors should be given to everybody that you feel have HFpEF. And then if, as we noted, 40 to 55% range, they may benefit from Entresto. You're so much better at saying sacubitril/valsartan than me. So, I'm just going to go with the brand name. And then, additional blood pressure control and others, we can look at the mineralocorticoid receptor antagonists, Aldactone being the most common we use and/or an angiotensin receptor blocker like olmesartan, valsartan candesartan, I suppose, if it's still available. Does that summarize it right?

Dr. Lee Goldberg: I think so. I mean, I think one thing that I would add is that the mineralocorticoid antagonist, so in this case the spironolactone, Aldactone, or even eplerenone. The guidelines suggest that we should be using those also across all patient groups, similar to the ARNI in a sense, almost an overlap in terms of the benefit seems to get better as the ejection fraction gets lower. Stu, what do you think? How do you approach kind of stacking these various meds?

Dr. Stuart Prenner: So, I completely agree with you. I think a lot of HFpEF management is really balancing comorbidities with the drugs that you're going to use. And initially, the SGLT2 inhibitors were a good example because we didn't have the data just in HFpEF. So, we were using it in our diabetics.

But I agree with your points, Lee, and I think spironolactone can be a very helpful medication. Sometimes if patients are on loop diuretics, it could help keep the potassium up. But the other is the patient that, you know, has a significant hypertensive disease burden and for whom, despite multiple agents, the potassium is low. And so, one of the biggest red flags for me is someone whose potassium is low, despite already being on RAS blockade. That to me is always a signal that there's likely some degree of hyperaldosteronism, even if you can't prove it. So, they may not have kind of like hyperaldo as the cause of their high blood pressure, but it's an abnormal state to be in. And so, that's another disease situation where I rely on spironolactone if the patient's hypokalemic despite RAS blockade. I think that's another good reason to put spironolactone on. It's also nice if someone's on potassium supplements, for whatever the reason. It can kind of replace potassium supplement with something that's disease-modifying. So, that's kind of how I think about it. And I agree with you about kind of layering and tailoring the approach based on the patient.

The other thing that's just interesting to say out loud is in addition to there being clear differences across spectrums of ejection fraction, there also seems to be some gender interactions. And one of the signals from PARAGON that was interesting was while in general patients benefited at lower EFs in terms of sacubitril/valsartan compared to the ARB. It seemed that women benefited from sacubitril/valsartan almost no matter what the ejection fraction and all the way up to, I think, 65 or 70. And so, there are some gender differences with this disease that I think are still not completely understood and it gets, I think, to our discussion about the nuance in this condition and sort of tailoring the therapies a little bit to the patient, rather to some degree from what we do in HFrEF, where it's a little bit of a cookie cutter to some degree, because there's just such a strong evidence base for all of the drugs across all patients.

Kendall Williams, MD: So, I want to ask about lifestyle issues, because, Stu, you had mentioned that obesity was part of the comorbidities associated with HFpEF. And we could get to lifestyle issues in relation to HFrEF. But for specifically for HFpEF, how much is weight loss effective in improving the condition?

Dr. Stuart Prenner: So, it's a great question and I think Lee, more than anyone, can speak to this in REF and probably across all of our patient populations. I'll say briefly for PEF, it's clear that obesity is very much tied to this heart failure syndrome, in part because most of these patients are overweight and because the obesity causes changes at the cardiac level that the heart can't keep up with. And so, it's been shown with bariatric surgery and other methods of relatively rapid weight loss that a lot of the hemodynamic changes and even structural changes we see with all forms of heart failure, but particularly with HFpEF, can go away when people lose weight.

And so, this is the subject of a clinical trial that's ongoing using semaglutide for weight loss. And just in general, diet and exercise have been shown to improve functional capacity in HFpEF as measured by the VO2. The challenge is that it's not easy to get patients to do this. And so, I think part of it is counseling these patients and part of it may be pharmacologic.

I'm curious, Lee, what your thoughts are about this, particularly because, as we know, cardiac rehab, while approved for REF, is not approved for PEF, and this is something that comes up a lot. Lee, what are your thoughts?

Dr. Lee Goldberg: Well, I agree with you completely that we have so much anecdotal evidence that weight loss is beneficial, both just in reducing the workload that the heart has to do. But in addition to changing the metabolism, the endocrine state, the inflammatory state that's all associated with obesity, that weight loss is definitely going to be helpful here.

I think that we need to prove that in order to kind. the benefits of insurance to kind of align with what our patient's needs are. There are some trials now looking at the benefit of exercise in the HFpEF population in terms of trying to expand the benefit for cardiac rehab to higher ejection fractions. And so, we'll see how that pans out over time. And I think a lot of us are very interested in some of these newer GLP-1 agonist drugs that are being used for weight loss. They also have beneficial cardiovascular effects that might be independent of that, whether these drugs are going to have a major impact in the HFpEF population in particular because of the relative weight loss. So, I think more to come.

I do want to throw in a plug to think about also sleep apnea in this patient population, which unfortunately has been a little bit controversial because of clinical trials that have kind of ended up on all sides of the answer here. But we do know that particularly obstructive sleep apnea is associated with the development of atrial fibrillation, which is common in our HFpEF population.

Obviously, fatigue, worsening self-care, depression, et cetera. And so, thinking about, in our obese patients, also screening for sleep apnea, potentially helping them to be treated may also be kind of some secondary benefits in this population, including maybe helping them lose some weight.

Kendall Williams, MD: So, that is great information. I wanted to tackle, in the time we have remaining two specific questions. And it may seem like I'm bouncing around a little bit, but I think there's been some changes in these areas, that it would be valuable to address. So, the first, and maybe I'll throw this to you, Lee, when should we put in an AICD in patients? We all know the EF standards, but now that we have effective therapies that can raise the EF, how are you timing that in relation to those therapies?

Dr. Lee Goldberg: This is a great question and I think that it is somewhat of a moving target. I'll give you kind of the official guideline-directed guidance that we get, and then there's, I think, the clinical guidance that we have.

So for most patients, if you know they're coming to you with new-onset heart failure and they have not been treated with guideline-directed medical therapy, most of us want to try to get that therapy on board as quickly as possible and then reevaluate the ejection fraction.

The current guidance suggests that we should wait approximately 90 days or three months to see whether or not the ejection fraction is improving over time before committing a patient to an ICD. And most of us in the heart failure program practice that way and we kind of try to give at least a little bit of time. Where the art of medicine comes in is how long do you wait and how quickly can you get the medications on board? And this ties into something that's new in the guidelines this time around in May of 2022, would suggest that we're supposed to start all four classes for at least for HFrEF as close together as possible, kind of simultaneously before moving towards titrating all the meds to their maximally tolerated doses. And the theory is that you want to stack the benefits of all the classes early and start that positive remodeling effects as quickly as possible and then, fine tune the medical therapy over time.

So, the party line is you're supposed to wait 90 days. I think some of us do wait a little bit longer. If we start to see the ejection fraction significantly improving, but haven't hit the threshold, we may wait another month or two. On the other hand, patients that are high risk, so patients that are ischemics, patients that have a family history of sudden death or genetic myopathies that are associated with arrhythmia, those patients do need to come to ICD sooner. And I think, you know, if you don't see the improvement in ejection fraction quickly or there's

another risk factor, then an ICD is indicated. And if there's controversy about how safe it is to wait, we do have the wearable defibrillators. There's now two brands of wearable defibrillators that are available in the marketplace where the patient can wear a vest and be protected with an external monitor and defibrillator system until a decision is made, whether to move to an ICD internally and permanently or whether or not their ejection fraction has come up to the normal range or you've finished your risk stratification in terms of genetic testing, whatever else you need to do, that they're protected in that interim. And so, that's the alternative is to be able to use a wearable defibrillator to kind of get you there. So, we are still waiting the 90 days, although these meds are so powerful that sometimes we wait a little bit longer in order to make the decision around an ICD.

Kendall Williams, MD: And Lee, the EF number is still 35%, right?

Dr. Lee Goldberg: That's correct. Yeah. And then, the lower the EF, the higher the risk we think.

Kendall Williams, MD: So, the other question I have is related to the workup of congestive heart failure and, you know, I would always teach the medical students and the residents when we were managing a patient on our medicine service who had just been diagnosed with heart failure, that the first thing we need to do in addition to everything we talked about, getting them on the proper medications, is to not forget to work them up for ischemia. Ischemia remains the most common cause of heart failure with a reduced ejection fraction. And we would target to try and get an ischemia workup in place, whether it be through non-invasive imaging or even catheterization within a couple weeks. Because I was always worried that people would leave the hospital and never get that evaluation, show up two years later and not having had it.

Now, there's this new study that came out this past year, I believe it was the New England Journal of Medicine that looked at the value of opening up blood vessels in patients with reduced ejection fractions. And it did not appear to be as beneficial as we thought. Lee, can you speak to that?

Dr. Lee Goldberg: Yeah, I mean I think that this is kind of a theme that we've been seeing now over several clinical trials over time, and that is that just because there's a narrowing of a blood vessel, doesn't necessarily mean that we should intervene upon that vessel. And there are two schools of thought around why that might be the case.

One is that when you intervene on these blood vessels, what ends up happening is that you stir them up, right? You actually create an injury to the blood vessel by placing your stent, et cetera. And that can lead to complications and narrowing and further disease that otherwise would have been stabilized on its own. So, it would've been stabler to leave it alone.

The other issue is whether or not the myocardium distal to the blood vessel is alive or not, is it scarred or not, and how much additional benefit the patient's going to get from revascularization. And then, this is also, and this is kind of my own commentary, but this is also a testament to how good our statin therapy has become in terms of stabilizing coronary plaque in particular, but also carotid plaque and plaque elsewhere on the body. And that the number or the incidence of acute plaque ruptures leading to myocardial infarction has actually been going down as our guidelines got so much more generic and just said, "Start everybody on a high-dose statin," that is translating into a population benefit that we're seeing fewer acute MIs across populations of patients.

And so, I do think that there's some controversy now over whether or not it's beneficial to revascularize every blood vessel. And I think these clinical trials are kind of beginning to stack on that. And so even for patients that are having some angina, there's some controversy over whether medical therapy may be as good as, or even superior to the risk of having a coronary intervention done. And so, we have to really weigh those things pretty carefully.

And I'll defer to Stu as well to get his thought, I will say that there are scenarios where patients have a significant amount of hibernating myocardium that we detect on a nuclear scan or an MRI, or even a PET scan. And we recognize that restoring blood flow to those segments of the heart may actually improve cardiac function more than medical therapy and improve the ejection fraction and improve outcomes. So, there are scenarios where we would go after these lesions and it's a little bit more of a nuanced decision than an all or nothing, I would say. But in general, I think we're starting to become a little bit more conservative about just intervening because the disease is there and rather trying to put it into a much more nuanced clinical context. Stu, do you have any other thoughts about that?

Dr. Stuart Prenner: I think you summarized it really well, and I agree with you. I think the overall improvements over time, they speak a little bit to the benefits of statin therapy. The other, I think, is that they also speak to the benefits of now what is quadruple therapy. And so, a patient who may have needed revascularization for angina or other indications can oftentimes be improved significantly just by starting guideline-directed medical therapy. A lot

of which has improved over the last decade or two since we've really continued to think about ischemic heart disease. And so, I completely agree with you.

I think the reason it's still important to think about is because you will still have patients whose heart failure is predominantly driven by that and, despite medical therapy, they do still have symptoms. But the other is that there will be patients that have extensive proximal coronary disease that may be excluded from some of these clinical trials. And while those patients may not be common, they are not always included in these clinical studies. And so, I agree that the needle has shifted to stop stenting everybody, and I think with good heart failure therapy, that's probably likely to continue moving forward.

Kendall Williams, MD: So, it reminds me of the discussion regarding invasive versus conservative strategies for NSTEMI where it really came down to the risk, that the higher the risk for the patient, the more they tended to benefit from invasive strategies, and that seems to be similar here. But what's also true in that, I think, is that our invasive strategies got so much better than our medicines. But now, it may be the case that our medicines are actually improving so much that they're outpacing our invasive strategies. So, it's an interesting dynamic and it always reminds us that everything is dynamic in medicine.

Dr. Lee Goldberg: I think it also teaches us that sometimes we think we know the answer, and then it turns out that we don't. And that's why it's important to continue to do the clinical trials. And even the observational registry trials have been instructive in generating hypotheses that then we can go on and test.

Kendall Williams, MD: So, this has been a great discussion. I am sure we could do another part and maybe we can talk about that or bring you guys back at another time for more focused discussion. But this has really been very valuable. I often leave our guests an opportunity to just address any residual issues you want to put out to the primary care community. Stu, maybe we'll start with you just on HFpEF. And also, Lee, maybe you can also just tell us who's appropriate to refer down to your program as well.

Dr. Stuart Prenner: Both great questions, so I guess we can go in that order. So yeah, I think just as kind of my parting words, heart failure with preserved EF is on the rise, especially in community settings. More than half of heart failure is heart failure with preserved ejection fraction. And there's a reason for this. We're getting better at treating a lot of the things that lead to low EF heart failure. And so, what we're seeing in the community more and more is

preserved EF heart failure. And that's only going to stay especially as the population ages.

And so again, just reminding folks that if you have a patient with some of the risk factors that we mentioned, who has unexplained dyspnea, exertional intolerance and, you know, they didn't smoke and you don't have other thoughts to the explanation to really not give up on that line of thinking and to pursue it and to not rule out that type of heart failure just because the BNP is normal or just because the echo doesn't look very strikingly abnormal. MedCalc has a calculator, it's worth looking at. And again, just keeping a high index of suspicion for this diagnosis because it's common. And so, I think I will stop there.

Kendall Williams, MD: That's great, Stu. I've really learned that from your comments. It's really helpful. It's new information for me.

Dr. Lee Goldberg: I can comment a little bit on who to refer down. And I think, in general, patients who are not responding to the four-drug regimen despite kind of a good effort by the patient and I think a good effort by the clinician to kind of get them there. These are individuals who definitely would benefit from a trip down to see us in the heart failure program.

I think that there's an acronym called I NEED HELP, which identifies patients who are at very high risk and might need advanced therapies, or at least an advanced heart failure program. So, those are patients who've required intravenous inotropes, who have Advanced New York Heart Association class IIIB or IV or persistently elevated natriuretic peptides; if they have evidence of end-organ dysfunction, so worsening cardiac or liver dysfunction; ejection fractions less than 35%, new defibrillator shocks that they hadn't had in the past, more than one heart failure hospitalization in a year, worsening peripheral edema despite escalating diuretics, a low systolic blood pressure less than or equal to 90, or a heart rate that's consistently elevated. And then, lastly, they have become intolerant to a medicine, a guideline-directed medicine, that they had been tolerating in the past, and you've had to withdraw it because of renal insufficiency, or hypotension, or symptomatic dizziness or bradycardia, et cetera. Those are all the kind of high risk signs now that we look for. And that would be the group that should definitely be referred for evaluation in the heart failure center.

Kendall Williams, MD: Well, Lee, that's great. All of those sound like things that I would certainly think about sending them down to you. So with that, I want to thank Dr. Lee Goldberg and Dr. Stuart Prenner for this very

illuminating discussion on congestive heart failure. Again, hopefully, we'll have you guys back again. There's much more to discuss. For the audience, thank you again for joining us on the Penn Primary Care Podcast. See you next time.

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