PH Roundtable: Use of Off-Label PAH Therapies

Murali Chakinala, MD, Washington University, St Louis, Missouri led a discussion with Mardi Gomberg, MD, George Washington University Hospital, Washington, DC; Elizabeth Klings, MD, Boston University Chobanian & Abedisian, School of Medicine, Massachusetts; Josanna Rodriguez-Lopez, Massachusetts General Hospital, Boston; and Susie McDevitt, NP, University of Michigan Health System, Ann Arbor.

Murali Chakinala: Today's topic is off-label use of PAH medications. But first, it's important that our readers understand that off-label use of PAH medications should not be taken lightly, and their use in individual cases should only be undertaken after thorough evaluation and careful discussion of the potential risks and benefits with a knowledgeable prescriber.

I thought we'd start with a general background on what off-label really means.

Mardi, I'd like to throw the first couple of questions to you. Could you explain what "off-label" therapy really means? And how often does it happen in general practice, not just in PH? I think people would be surprised by how often we are using off-label therapy.

Mardi Gomberg: Thanks, Murali. I think off-label is, in the purest of senses, when you're using a medication for an indication that it was not initially approved for, or at a dose that it was not initially approved for, or at a frequency that it was not initially approved for. When we design clinical trials, we try to the best of our ability to use what we know of the pharmacology of the medication, and how long it lasts within the body and the pharmacokinetics to design a study that's going to get the most efficacy from that medication, if it is going to work.

What we've learned over time is that sometimes when we design a study, in practice, we don't use it based on how it's labeled, or how the clinical trial initially designed it to be used. That would be, I think, the most frequent time that we use things off-label, but when it comes to using it for a different indication, a lot of times there's overlap within disease processes, and we often don't have approved therapies for the other disease.

Within pulmonary hypertension, an example would be chronic thromboembolic pulmonary hypertension (CTEPH). Before we had riociguat approved for CTEPH, I think all of us here on this roundtable utilized all of our PAH therapies for these patients. Scientifically this made sense because we knew the pathophysiology was similar in the small vessels that weren't affected. Our patients did well, we had great results, but the treatment was technically off-label, and not for what the medication was originally approved.

As for how often do we use drugs off-label, my guess is that a lot of times it's "off-label" based on drug frequency of administration, especially in a rare disease. Having worked with PCORI, I know there's a lot of times when we approve a drug for once a month administration, but we could actually use it once every 2 months. Over time with patients providing input, and having the science to back it up, we often get the labels changed so that we can work within what's clinically indicated, and not just the specifications in the original label.

Murali: That's a great intro, Mardi.

I think it happens a lot more than we think. Liz, let's discuss the more extreme examples; that is, expanding the indication for a drug on an off-label basis. What are some of the things that go into the conversation you have with a patient in that situation?

Elizabeth Klings: Thank you for that question, Murali. I really think it depends on the disease process that you were using an off-label therapy for. What do I mean by that? I think that, as Mardi alluded to, there are within pulmonary hypertension a number of diseases which are quite rare, and very difficult to study in isolation without other forms of pulmonary hypertension. Yet, there may be benefit for using PAH therapy. Then there are other conditions where things may be more dicey.

I think when I talk to a patient who doesn't have maybe pure pulmonary arterial hypertension or fits into a patient group that would've been included in a clinical trial, I do explain to them that sometimes when we use these therapies, they may not be as effective for you specifically. It is also possible that they may cause other problems to occur, such as developing more issues with fluid overload, and congestive heart failure, and that sometimes we need to manage that as well as the therapy.

I try not to focus on the off-label usage, because I often will draw upon my own clinical experience with some of the rare disease-related cases of pulmonary hypertension, and what benefits that I've observed hemodynamically, as well as clinically, in my patients, and presented as part of that as well.

Murali: Josanna, Liz said something that I think is real important. Could you talk specifically about some of the toxicities of PAH medications that you most worry about when using drugs in unstudied populations? In general, is your approach to risk aversion and tolerability of these adverse effects different with off-label usage versus when you're using the drugs as they were studied and intended for?

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 DOI:10.21693/1933-088X-22.4.170

Josanna Rodriguez-Lopez: Thank you, Murali. That's a great question. I think it depends on what disease we're talking about. Is it a PAH patient that happens to have also heart failure, or some lung disease, or is it a completely off-label patient with mostly group 2 PH, and you're trying a drug? I think the conversation with the patient is this: "These medications may not have been as well studied in patients like you. We have to monitor very closely for side effects, and also because they haven't been studied as well in patients like you, we may not know if they're going to help, and we have to be really vigilant for the possibility that you could get worse on them, and we have to be able to identify that."

For instance, in a patient who happens to have also some heart failure, you really want to pay attention once you start a pulmonary vasodilator: are they gaining weight, are they getting more volume overloaded? Also discuss with the patient when to call you, what to look for. I would say, probably, you would be more likely to stop a medication early if you're seeing any signs of worsening, or bad outcomes, or side effects.

Murali: I totally agree. To me, the other one I worry about is when there is some underlying parenchymal lung disease and worsening oxygenation through worsened VQ mismatch.

Mardi: I just want to caution, I rarely use PAH therapies off-label. There are studies with PH in left heart disease have not been successful with PAH therapies, multiple times over and over. As a cardiologist, I don't see a lot of PH-ILD, but in the past when used, it was very rare that they had improvement with our agents. It's also really hard to get covered by insurance.

Another example is group 5 PH in patients with ESRD on hemodialysis. I do think sometimes, especially in these patients who really have pulmonary vascular disease, where we don't have any known therapies or trials and we want to get them to transplant, we use PAH therapies off-label. This use is only when their hemodynamics are significantly abnormal even after achieving euvolemia with dialysis. It is still a difficult process and not always successful, more often than not. Off-label use is not easy and requires personalized care.

Off-label also encompasses stuff like the case reports of imatinib early on, which was clearly off-label compassionate use, which is a very different off-label use. That then set the stage for us today, where we're looking at a new inflammatory pathway in PAH.

Murali: Mardi, I think those are great points. I think your admonishments are well received. I want to come back to that a little later when we go over some of the specific situations where we might try it, and you've done a great job already introducing it. Liz, did you want to say something else?

Liz: Yes, I agree with Mardi and want to clarify what I said earlier. When I talk about different disease states, I actually do not use these drugs routinely in my practice for left side of congestive heart failure no matter how much our cardiologists try to push me to use them, to be honest, because that never really goes well. The scenarios where I do use off-label therapy are in group 5 PH, and particularly in patients who have pure precapillary PH related to sarcoidosis, and in patients who have pure precapillary PH related to sickle cell disease.

In both scenarios, you can unmask left-sided heart failure, but in both scenarios, based on the case series that have been published as well as my own clinical experience, patients can get symptomatic improvement, hemodynamic improvement, and echocardiographic improvement. In both of these diseases, there is a very mixed population, and in many of our sarcoid patients, this is actually a form of PH-ILD and reacts differently to vasodilators than other forms of PH-ILD. What I mean by that, is this group of patients seem to be more responsive to vasodilating therapy. I often will use inhaled treprostinil as my first agent in patients with sarcoid and extensive ILD. Those are the 2 groups of patients where I do use off-label therapy.

Josanna: I'm going to agree with both of you. Obviously, I don't think anybody in this panel is here to try to promote use of off-label PAH therapy in group 2 PH. I think that part of the problem is how difficult it is with our classification system. And it's so hard to know, if this a real group 1 PAH patient or not, and is their heart failure not easily identified? In reality, patients don't read the textbook, and they have all sorts of comorbidities, so it can actually be quite challenging sometimes to even know, are you treating group 1 PAH, or is this more of a mixed picture? In those patients who have a lot of comorbidities, I definitely have the more thoughtful discussion about the risks of trying PH therapy.

Susie McDevitt: I'll add to that, Murali. Just from our center's perspective, I think if you look at clinical trial inclusion-exclusion criteria, and you look at the real patients we're taking care of every day, some could argue a lot of that is off-label use based on comorbidities and everything you guys are mentioning. For us, it's really about the hemodynamic profile, whether precapillary pulmonary hypertension is out of proportion, however we define it, and we don't have good criteria for any of the groups. Also looking at that with the right ventricle, and really trying to optimize all those underlying medical conditions first in a very systematic approach with very close follow-up with these patients.

We feel very strongly that these patients need transparency about the limited rationale or limited evidence we have. We do trial quite a bit. When you think about all the populations we don't have evidence for that we're probably all using the medication for, there's a lot in group 3, and group 5, and even some in group 2. I would say we do try to use the therapies, but we try to optimize everything. I'm sure you guys do as well.

Murali: You're all making some fantastic points, and I'm crossing off questions already because you're bringing them up in our conversation! You can already

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sense, even on our panel, there's some variability from practice to practice about the extent of off-label use of PAH medications. Some centers are more conservative, and some are a little more liberal. It may depend on the types of patients they're seeing. For example, Liz has a good number of sickle cell patients.

I think an underlying theme is that any time that off-label use is going to be considered in patients that don't fit into our silos of PH groups, they need a very thorough evaluation. We need to know everything about them, their hemodynamics, RV function, and comorbidities. And someone with an understanding of the pharmacology of these medications is carefully selecting the patients who might get a net benefit.

Sometimes that's a decision you can't make in one encounter. You have to follow these patients over months, and tweak things like diuretics, dialysis, immunosuppression, etc. We've tuned them up as much as possible, yet there is still significant pulmonary vascular disease. Maybe now we would consider off-label therapy.

Liz: I think the other big piece, and Josanna referred to this, and you just did as well, is the need to see people frequently. You can't just start these medications, and then have the patient come back in 3 to 6 months and expect everything to be fantastic. There is a need for a very specialized approach and individualized approach to the patient.

Murali: Maybe just one more general question before we might get into some specific clinical scenarios. Susie, maybe you can comment. There's the off-label piece of the story, but then there's also the unfortunate financial aspect to consider. A lot of times, off-label use of inexpensive or generic drugs is not a big deal. No one's going to get in your way. We know PAH medications are different. They require prior authorizations and are expensive. Could you discuss the extra work and potential nuances of prescribing off-label PAH in terms of coverage and assistance programs?

Susie: Sure. I think we would all agree that in our programs and all across the world, we're spending exorbitant amount of time on paperwork, prior authorizations, grants assistance, charitable grant assistance, etc. We've got to do something about this. The labor that is involved is amazing. Now we're talking about patients that don't fit exact criteria on the label for the medication. The workload is tremendous, we would agree.

We have just creatively come up with mechanisms and verbiage that we put in our medical documentation just basically stating this is significant precapillary pulmonary hypertension, out of proportion to underlying group 2, group 3 PH. We've been pretty successful with that. Every now and then, we will need to get a little more on the phone, or do the actual meetings with the insurance companies and the medical directors. We've been pretty successful with that. I don't know if you guys have found the same thing.

We recently had our first denial in the other direction. We had a denial for a mean pulmonary artery pressure of 24 with a PVR greater than 3, and they've completely denied medication because it's not the old definition of greater than 25. We'll see where this is all going to go in the future as more medications come out; it gets more complex as the costs go up. So I think it's just going to be more work. We have really learned to use this significant precapillary pulmonary hypertension out of proportion. What are the other programs doing?

Murali: Yes, I think that's a great point. The legwork that has to be done is definitely greater. Oftentimes these are appealed, and then unfortunately, sometimes some of the assistance programs, especially the drug company–sponsored programs aren't options, as people aren't eligible when it's off-label. They're not allowed to provide support in those situations. It can be tough to get a drug approved. Liz, you had a comment?

Liz: Yes, it's interesting. I told my nurse a couple weeks ago that it's like the "Secret Society of Pulmonary Hypertension Clinicians." A patient shows up from some outside facility, and my first question is, "Where are you getting your meds from?" Because half the time they're not, and nobody outside the PH world actually gets that, but I think that with the group 5 patients, if you submit the right heart cath data, they get approved.

I don't have to write any letters; showing significant precapillary PH gets it approved, even if I say it's pulmonary hypertension related to sarcoidosis. Where it doesn't is with inhaled treprostinil related to sarcoid. You have to say that's ILD-related. I would have to say it's gotten less challenging for the group 5 patients, but it can be worked on.

Murali: Great points! Maybe now in the remainder of our time, we can focus on some specific clinical scenarios we encounter. You guys have been touching on this already, but I'd like to delve into a few clinical scenarios that might trigger you to off-label use.

Josanna, I'll start with you. You work at a very busy and active CTEPH center. We only have 1 drug approved for CTEPH. We have 2 fantastic interventions that help the majority of patients. Can you talk about patients who either have persistent PH after interventions or inoperable CTEPH and you've already got them on Rio, but you're still not satisfied with their treatment response. We don't have any other on-label options at this point, but we do have some evidence from trials. How do you approach that patient, and how successful have you been in treating those CTEPH patients beyond riociguat?

Josanna: Yes, that's a great question. I think that, thankfully, as you said, we have a lot of options now as far as treating CTEPH, and hopefully getting people well enough that they don't need PH therapy, but there are people who will have residual disease after PTE that I may treat while I get them to BPA; or after all the interventions still have residual pulmonary vascular disease that's not treatable by any other interventions. I agree, we use Rio as

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our first-line therapy, but there will be patients where that's not enough. I have used macitentan. I feel like the (MERIT) study showed improvement. It didn't show any worrisome issues, and for the most part, we have been able to get that approved, although not for everyone. There are some insurance companies that will say, "It's not approved, we don't want to give it," but if you write an appeal letter and show the study, for the most part, I've been able to get people on it. It's not a huge portion of patients, but it can be quite helpful to have an additional second agent in patients. With those patients, really, at the end, we are now dealing with small vessel vasculopathy that's not a mechanical issue anymore. It's really very similar to PAH. It also makes theoretical and scientific sense to use these drugs in that scenario.

Liz: Prior to riociguat getting FDA-approved for treatment of CTEPH, as Josanna and Mardi alluded to, we were using every class of drugs to treat PAH for this population. I think that I do use macitentan based on the MERIT study as my second line agent, if riociguat is not enough.

I think that, in real life, our patients don't fall neatly into the groups. The WHO groups are becoming more outdated as we learn more about this disease. I would say, in the general CTEPH scenario, macitentan would be my second choice of drugs.

Mardi: I would say that the ones that I had 20 years ago, they were all on IV vasodilators because they were really sick, they weren't surgical candidates, and many did extremely well. I don't think riociguat is as potent as IV prostanoid and if you're failing riociguat, and you're a lung transplant candidate, then it should be lung transplant. I don't have a particular agent that I favor, because I look at the hemodynamics, and treat accordingly. I think it's great that we now have procedures for these patients that are effective.

I remember a study from UCSD from 2008 or 2009 when they looked at patients started on PAH therapies before they got their thrombectomies. They didn't do any better with the initiation of medications and it just delayed the surgery. Just to clarify if patients are surgical candidates that should be offered.

What's unfortunate now is it's harder to get approval for other agents to add to riociguat without the supporting clinical trials.

Josanna: You're right. If somebody presents an overt RV failure, you're probably going to reach for a parenteral agent.

Susie: I can also say BPA patients need to be optimized before BPA. They often need more therapy than just Rio.

Murali: I've also had some success getting parenteral treprostinil approved in CTEPH patients. There are a couple of reports that can be cited, mainly out of Vienna, including the more recent CTREPH trial. So at least there's a study that can be submitted to an insurance company. That's a lot of good advice on CTEPH.

Maybe we can spend a little bit of time on group 5. Mardi, let me go to you first. Group 5 is obviously a very heterogeneous group. Of course, the ticket that gets you into the door to that category is because we either don't know why pulmonary hypertension develops, or they have multiple mechanisms, sometimes in an individual patient, that leads them to developing PH.

Clearly, this harkens back to our earlier conversation that any group 5 patient you're going to treat needs a very thorough evaluation with all issues outlined. Talk a little bit about some of the group 5 patients that you might treat with PAH medications on an off-label basis. What are the key features that might sway you?

Mardi: I think I'll start on sarcoid. At the last PH World Symposium, there was discussion about which group should sarcoid patients sit in. I think sarcoid needs to be in every group: it's 1, 2, 3, 4, and 5. To stick it in 5 is part of the problem, because we all have had patients with a little bit of group 3 and a little bit of group 2, who have had a clot in the past, but they're really predominantly group 1 pulmonary vascular disease. I think it's appreciating that some of group 5 have a predominant vascular component, and those are the ones that need to be treated. Roxanna Sulica, I think, had the first case series, but there's been lots of data.

Trying to do a sarcoid trial has failed miserably because there is such a mix of patients and it's hard to get people in a study who aren't already on off-label PAH therapy. Again illustrating that group 5 is probably not the best way to group these patients, because it ends up confusing things, and making it harder to get therapies that may help them. I'm not sure that's going to get fixed anytime soon, but I think it affects us in the US more than Europe because of our approval processes. If you're in group 5, the answer becomes "no" instead of, if you're group 1 PAH with associated concomitant disease, "yes."

Stuff like all the hemoglobinopathies, I think that for the most part they are not severe pulmonary vascular disease, with perhaps mild pathology. I think there's always going to be a spectrum, a bell-shaped curve, where some people are going to be at the 95% end, and they do have pulmonary vascular disease, but most patients don't have significant disease.

I think ESRD really needs to be studied, because whether it's the high flow from the fistula or just chronic renal insufficiency, we do know chronic renal insufficiency is a bad prognostic indicator in PAH at presentation, during follow-up, and on admission to the hospital. We also know that patients with high flow over time, whether that's congenital heart disease, or portal pulmonary, some patients can develop vasculopathy in the lungs. We should be looking for things to treat them. It's a high-risk population; I treat them, the dialysis patients, when I'm trying to get them to kidney transplant. Our colleagues at UVA had a case series just showing that if you did dialysis 4 times a

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week, and really monitored fluid removal to a new dry weight verified by right heart catheterization hemodynamics, they were able to get a renal transplant. I think that that's what needs to be done more.

I think we probably should try to measure hemodynamics on dialysis sooner, and not wait till they're 10 years out because the left atrial compliance fails, and when left atrial compliance fails, then no matter what you do with your volume status, you can't fix the abnormality. I think that that's when I tend to use PAH medications in ESRD. But there's so much that we need to learn from that, because I do think that it really relates to what ends up leading to their mortality. The patients can't tolerate dialysis because their RV fails and they can't generate systemic pressures. We probably need to look at it like we did with scleroderma, where everybody got screening echoes and maybe a right heart cath every so often, but I think a lot of work needs to be done. That was a very long answer, but it's probably because group 5 is the one that needs the most work. So, it's not really crazy to think that group 5 should just go away, and we should just try to phenotype people better.

Murali: I think that you made a lot of great points about the ESRD patients, and we've also had some very nice results when some of these tough patients switch to nightly home hemodialysis, and you really get that fluid off and get the dry weight down. We've seen some remarkable improvements in their hemodynamics sometimes after just a few weeks. We empty the tank with all the other issues that could be contributing to PH and need to be addressed. There's such a high prevalence of sleep apnea in that population that often goes unrecognized because the only physicians they're seeing are their dialysis team, and they're overlooking it, even if they're not of the typical body habitus to have sleep apnea. I think doing all of that, ruling out CTEPH, evaluating the fistula, are essential things before we reach for a PAH drug to work on the pulmonary vasculature. Like you, it's the ones that I'm trying to get into transplant, or we're starting to see worrisome RV changes that are going to threaten their ability to be dialyzed. That's when we'll think about trying PAH medications, but it's a select group of patients. It's not a lot, yet there's such a large dialysis population out there. We have to funnel it down to those few cases.

Liz: I have a couple of comments. I agree with Mardi, that there is a lot of variation amongst group 5 diseases, and my approach to them. I actually will start with the end-stage renal disease. I would agree with both of you that really the only scenario where I would even consider PH therapy in this population is to try to get somebody to renal transplant.

From my experience and from working with our renal transplant group, this is predominantly postcapillary PH due to significant left heart disease. There is a very rare patient in that group that really should be considered for PH therapy.

I want to say something in contradiction to what Mardi said about the pulmonary hypertension of sickle cell disease. I think you will occasionally see isolated precapillary disease with a vasculopathy, in the context of so much postcapillary PH in our sickle cell population, very similar to what we see in sarcoidosis. We know this from limited autopsy studies that have been done, usually in 30 patients or less. They've looked at the lungs in these patients no matter how they die. They have medial hypertrophy of their vessels. They have plexiform lesions, and they have thrombosis. This is a PH that probably belongs in 4 of the 5 WHO groups. There's not significant interstitial lung disease in this population, although the term pulmonary fibrosis gets misused in these patients. There is also a significant proportion who have sleep-disordered breathing, including obstructive sleep apnea, from group 3 PH. In our patients who have significant precapillary pulmonary hypertension, I do treat them with meds. My go-to agents are combination therapy with an endothelial receptor antagonists, with macitentan as my agent of choice these days, combined with riociguat.

We recently completed a phase 2 safety trial of riociguat versus placebo in patients with sickle cell disease, the results of which are under review right now. This was actually not for pulmonary hypertension per se, but for abnormal echocardiography or systemic hypertension or proteinuria. The reason to do this was because of the issues of the Walk-PHaSST clinical trial of sildenafil in this population. Suffice to say that riociguat was safe in this randomized placebo-controlled trial of a hundred patients.

I have occasionally, over the years, needed to use intravenous therapy for hemoglobinapthy with severe precapillary PH in this population. One other thing you need to remember is that the chronic anemia of these patients leads them to have a baseline elevated cardiac output of 7 to 9 liters per minute. That goes back to right heart cath data published in the 1950s. This needs to be kept in mind that this is often a disease where the output is preserved, at least relatively, so the PVR elevations are actually often quite mild.

I agree with what was said about sarcoid, that there is a subgroup of the sarcoid population who have isolated pulmonary vascular disease, they don't have significant interstitial lung disease or significant left-sided heart disease, and that is a group that is most responsive to PAH therapy.

Murali: Those are great points, Liz, and I can't let you slip that in there without making a general comment. You mentioned the Walk-PHaSST trial. It's a perfect example of the cautions we have to apply when using off-label. We thought there was a biological basis for one of our therapies to benefit a group of patients, but we actually saw the increased adverse events. So that's why we have to study these patients whenever possible. And when the data is there, it has to help inform us which way to go. So thanks for bringing that up!

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Mardi: For sickle cell disease, the group at NIH had a lot of positive experience treating the PAH, for sure. But most of the sickle cell I see tends to be pulmonary venous hypertension, or high-output failure, and you don't know that until you thoroughly examine, and do the right testing, which I think Murali had mentioned earlier.

Liz: Definitely. I have people who have combined pre and post, for sure, and there's so much underrecognized diastolic dysfunction in this population.

Murali: In our remaining time, I'm going to dare and touch that "third rail" by bring up the group that we cringe at dealing with and that's the HFpEF-PH patients, the folks with combined pre- and postcapillary PH. Some of you have touched on this already, but, Susie, let me turn to you. You work at a center with a huge cardiology focus. Are there some patients who fit that HFpEF-PH definition that you are treating with off-label therapy? Who are they and what's your experience been? And let's assume they don't have a concomitant group 1 risk factor, like scleroderma with some diastolic dysfunction.

Susie: Yes, great question. This is probably one of the largest groups that we all see in our programs, and the largest groups that we have after their right heart cath. For us, it's a slippery slope, difficult and challenging. If it's true combined pre- and postcapillary, and that PVR is pretty elevated, that's when we would "dip our toe." If they come back with PVRs of 3 or 4, we may not dip our toe. At least now we have guideline-directed medical therapy, so we can be working on other things in the background, but I would say, it's really a tricky population.

We're probably case-by-case, for sure. If we've optimized the volume status as best as we can, and we still have that significantly elevated PVR and RV dysfunction on echo, then we would cautiously consider off-label therapy. We would start with a PDE5 inhibitor and they would have very close follow-up, watching for volume optimization. What's our success rate with that? I think they don't symptomatically subjectively feel a lot better in our experience, I don't know if you guys feel the same. We are looking forward to the new clinical trials coming out in this area because we feel like it's such an area that we need more data and more evidence, but we do dip our toe if that PVR is out of proportion, and we will trial, and just cautiously follow. I would say we have some patients who've had success and some subjective benefit, and some who've not.

Mardi: I would say if you have those patients, you should put them in the CADENCE trial of sotatercept or any of the other clinical trials in PH-left heart disease. (Note: I am the chair of the steering committee for CADENCE). Because we need to get the answers, right?

It's not an easy population because the patients often have so many different comorbidities. It's hard because we don't have therapies, and they have true elevation of pressures, whether if it's on exertion or even just at rest, and they are limited. Even when they're euvolemic, they're still limited. There's a definitely a gap in our knowledge of how to treat it. We haven't done a great job with our current existing therapies, and I agree with you. Some of it might be subjective improvements, which is good, but on the whole, I haven't seen dramatic improvements when I've done it in the past, so I try to stay away from it.

Murali: Susie, I loved your answer, and I also want to emphasize, at least we are making some progress with this patient population. I think a lot of our colleagues still take a nihilistic approach to the HFpEF population, in general. We have good data now with SGLT2 inhibitors, an ARNI, and emerging data with GLP-1 agonists. We need to be educating our colleagues, even the cardiologists, that these agents have become the standard of care, and they should be tried first before we start monkeying around with PDE5 inhibitors and ERAs, where there's even a chance they'll end up in the hospital due to medication-related fluid retention and volume overload.

Well, ladies, I want to thank you for an informative and spirited discussion, on a very difficult and complicated topic. I think you made some great points. There was a lot of consensus but with some variability in opinions because of the lack of data. Nevertheless, some general points and approaches are echoed by everybody. I really appreciate you taking time today to have this conversation!

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