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Panel Discussion: Controversies Arising from 2022 ERS/ESC Guideline Revisions

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Dr. McLaughlin:
So now we have some time for discussion. Ruben, thank you for joining us. Ruben, maybe you want to make some comments on some of your own thoughts on the guidelines?

Dr. Mylvaganam: Yeah, definitely. I guess I'll pose a question to both Mike and Val, and in sort of in relation to the guidelines and the PVR threshold. So far, no trials have included patients who've had PVR between 2 and 3, or anything sort of just north of 2 less than 5, really. Do you think clinical trials in the future are going to move in the direction where they're going to start to include patients that have a PVR north – or between 2 and 3? And if so, what should those trials look like? I do know of one trial that's starting to include patients with a PVR greater than 2.

Dr. McLaughlin:
I think that I think the entry criteria for the clinical trials will change, they will lower the threshold, maybe not in the phase 2's where PVR is the primary endpoint, because if you get too many people with a low PVR, you don't really have an opportunity to make a treatment effect. But I think for the phase 3's, where PVR is not the primary endpoint, that they'll change it. I still think there will be a very small number of patients with a PVR of less than 3. And it'll be difficult for us to really make any academic conclusions on those patients.

Dr. Cuttica:
I'll add to, or comment off of that or comment on that. Do we think, or do you think, Val and Reuben, do you think, the flaw in the guidelines, or if want to call it a flaw or the question in the guidelines, is it around that definition? Or is it that they didn't address how we should be treating patients with a PVR of 2 to 3? Right? Because as you think about guidelines, I think, for the group in general, I like the data that shows that the PVR is associated with an increased mortality in patients. I agree with you, with that population, it's probably all diastolic dysfunction, all COPD. But from a guideline standpoint, as we're trying to identify patients at risk for bad outcomes, would it make more sense to include the definition of a PVR greater than 2 Wood units? Because we're trying to identify and push people to identify patients earlier, but the guidelines fall short by not saying specifically, these are patients you probably shouldn't be treating, these are patients that maybe we should be optimizing lung disease and heart disease? And then make a statement to the effect of the treatment of patients is based on the classic definition of PH where the PVR is higher, where we truly think these patients have Group 1 PAH?

Dr. McLaughlin:
Yeah, I agree. And I think that maybe they didn't emphasize treatment of comorbidities. And I don't think they emphasize the limitations of that VA database that led to that. But I do think they have in the guidelines, they make it very clear that we have no data on treating patients with a PVR between 2 and 3, and more research needs to be done. I think in reality, in Group 1 PAH, at least in my practice, outside of the scleroderma patients, our scleroderma program very aggressively screens, we cath everybody with the positive DETECT

score. And we definitely find some patients with PVR is between 2 and 4 via that mechanism. But outside of that, I think it's pretty rare for us to get a true Group 1 patient with a PVR between 2 and 3.

Dr. Cuttica:
I agree.

Dr. Mylvaganam:
Yeah, I like the idea that they sort of based it a little bit on that VA data. I know they age adjusted and adjusted for some comorbidity. So it's nice to know that there is a high risk population of a PVR greater than 2 and it leads to these all-cause mortalities. I think what behooves us as clinicians and researchers in the space is just to study this group and sort of see how many of these patients who, if we do capture them with a PVR between 2 and 3, how many of them progress? What do they look like? Are they just your left-sided disease patient? Or your Group 3 patients? And would treating them at that had any sort of meaningful clinical impact? And I think all of us would suspect that at that low of a PVR, it's less likely to sort of make a true meaningful impact or maybe just sort of worsen their treatment burden.

Dr. Cuttica:
I think, again, defining what treatment means, right? I don't think necessarily the idea that, you know, maybe treating the patient with a PVR of 2 to 3 is really just aggressive diuresis, blood pressure control, comorbid conditions, and then that's it for those patients, right? Yeah.

Dr. McLaughlin:
Victor?

Dr. Moles:
So I have a couple of questions. One is related to the PVR threshold, which I fully agree with the panel, but is there any subgroup that you would consider maybe in special occasions using that lower threshold to treat maybe it's scleroderma population? Maybe it's the portal pulmonary hypertension patients will have such a worse kind of prognosis compared to the rest? And the other question is, we talked a lot about the European risk stratification model, but where do you put the REVEAL score and the REVEAL Lite score into all these?

Dr. McLaughlin:
Yeah, to answer your first question first, I think you hit it on the head. It's, for me, I am treating the scleroderma patients, so when our scleroderma program screens the patients with DETECT and we cath them, if their PVR is 2.5, I'm going ahead and treating them. I'm using monotherapy in them, but we know the scleroderma patients have a poor prognosis. You know, a single therapy in patients like that, you know, whether they would have stayed well for a number of years or not, I have many patients who've done well on single therapy for a long, long time. But let me ask you guys to answer that question before we go to the risk stratification.

Dr. Mylvaganam:
I've obviously not been in the practice nearly as long as you.

Dr. McLaughlin:
Hey, don't call me old.

Dr. Mylvaganam:
But I'll agree though that I think the two in my short tenure here that I've treated with a PVR north of 2, but less than 3 had been the scleroderma patient population, like you mentioned, Victor. So I think that population, I would think pretty heavily about treating for it because of their poor prognosis.

The portal pulmonary hypertension, I think that's the second population you mentioned. Maybe this is my bias, but I would say that if we think that they have portal pulmonary hypertension, they've been PVR between 2 and 3, I think I'm starting to push the transplant teams to think about we have them in a good space, we should think a little bit more about that because we know our PH therapy, while it's beneficial, it can lead to some more poor outcomes now with ascites and varices, and all that stuff.

Dr. Cuttica:
Yeah, I agree. The portal - I think I agree with what Ruben said, and Val said about the scleroderma population. I go back to the idea of maybe the EPI data that shows the PVR is elevated should be pushing us to say are there other populations that we should be more aggressively screening and studying to find out like scleroderma that came to? But the portal pulmonary patients, I think, are specifically pretty interesting question, right? As Ruben alluded to, I think those lower PVR patients, maybe they are people that we should be treating, but I'm sure, you know, we've all seen the patient that we know has portal pulmonary, or think has portal pulmonary, you put

them on pulmonary vasodilator therapy, and all of a sudden they transition into the high output liquid failure patient where they're getting more ascites, and they've got more edema and everything. So I like that idea of sort of watching them closely and maybe treating aggressively. But it's a, I think, a higher risk population than a scleroderma patient.

Dr. McLaughlin:
And then on to the REVEAL risk score. So this has been a subjective debate for a long time. And, you know, I think there are a couple points to be made. The full REVEAL score, I think, is a very accurate prognostic determinant. And it takes into account some of the non-modifiable risk factors that do influence prognosis. So such as etiology, like portal, like CTD, like heritable, things that, you know, other things you can't change such as age and, well, gender sort of, but it's - so it takes some of those into account. So it's good in terms of prognosis, but those aren't things that you can target with therapy, right? And so, REVEAL 2 Lite I think, is really this the 6 modifiable variables that you can target. And me - Tom, Victor, and I, we use both REVEAL Lite 2 and the 4 strata, we have a flow sheet, and it just gets those scores appended to the end of our note. And you know, I think the main point about re stratification is just do it, whether you want to use 4 strata, whether you want to use REVEAL Lite 2, whether you use both of them, you just do it, you need something objective. Now, it's not perfect. And you know, the cases that I'll present this afternoon are really meant to illustrate some of the limitations of risk stratification. But I think it's just really key to do it in everyone and then react to it and intensify therapy, if appropriate. What do you guys use?

Dr. Cuttica:
We use primarily REVEAL, because, so for those of you who maybe don't live in the world of pulmonary hypertension all the time, interested, right, there's a couple of different risk scoring systems that we use. And in the United States, there was the REVEAL registry to enroll from 2006-2007. Eventually the REVEAL risk score came out of that. But in the last couple of years, a bunch of publications out of Europe are different scoring systems that the Europeans use. And that's the difference between our guidelines here and why they talk about other risk scoring systems versus REVEAL. But we just, years ago when we were working within our system, we built the REVEAL risk score into our EPIC system. So we primarily use REVEAL and it's the complete REVEAL, not REVEAL Lite, that's just what's built into our system. But I agree, it's just more important, when we think about the treatment of PAH, whatever one you want to use, you just make sure you're using it, and you are risk stratifying your patients. And using that in your conversations with patients about how do we manage you? What's the best treatment for you?

Dr. McLaughlin:
Do you guys use BNP or NT-pro?

Dr. Cuttica:
We are BNP at Northwestern.

Dr. McLaughlin:
Okay.

Dr. Cuttica:
Downtown. Outside of downtown, they'll use NT-proBNP. So it's inconsistent within the Northwestern Healthcare System.

Dr. McLaughlin:
So that's one of the issues with REVEAL, right? Like the REVEAL risk score for biomarkers is really essentially built for BNP and the NT-pro, you just have the value in the very lowest group and the very highest group. And if your NT-pro is in between, you know, it doesn't really fall anywhere.

I think, so the advantages to REVEAL outside of, you know, that issue with NT-pro, I think it brings other things into consideration, right? The vital signs, the kidney function, you know, with only three variables in the 4 strata, like if you have a really horrible walk for another reason, like it really affects your score. And you know, there's other things to compensate for that in REVEAL. Tom, did you have a question?

Dr. Cascino:
I was just going ask the question to everyone. So we've talked about the hemodynamic definitions and they've changed, and the mean PA pressures changed, the PVR has changed. The one that hasn't changed is the wedge.

Dr. McLaughlin:
Oh, that's a great point.

Dr. Cascino:
Do you foresee changes to it? And if you do, how will you use it in your practice?

Dr. McLaughlin:
You know, that's a great point, Tom. And I should have brought that up. Because they lowered the main PA to 15. But like really is a wedge of - I mean, they lowered the mean PA to 20. But is a wedge of 15 really normal? What, like if my wedge was 15, I don't know if so and be very happy, right? Like, if you read Grossman's textbook of caths, like, Dan it's 12, right? Isn't it 12 and any cath textbook? Yeah. So a left heart filling pressure of 12 is really the upper limits of normal. So it's a little disingenuous to lower the mean PA, lower the PVR, and leave the wedge at 15. Right? Because you're really going to let the diastolic heart failure patients who've been moderately diuresed to kind of squeeze in there. I agree with you. I do not know of - well, I actually don't know if they're addressing this at the next World Symposium in that group. I hope they are. I should look at that outline and ask them to address it if they're not.

Dr. Mylvaganam:
I think along those lines, like whether or not additional maneuvers during cath would be included in the guidelines whether or not wedge should be sort of mandated in diagnostic right heart cath, or volume challenging for instance, and sort of unmask the diastolic dysfunction too. That's a good question.

Dr. McLaughlin:
Yep, please.

Dr. Raza:
Thanks, guys. So a question that I had is your incorporation of exercise cath and the management, then also early treatment, especially keeping I think with the theme of what we've been discussing recently with lower PVR and, you know, a lowering of mean PA pressure and really thinking about those scleroderma patients. So I think there was one I can at least recall off the top of my head, a study looking at like ambrisentan, I think from like over 10 years ago in exercise-induced PH patients, so that definition has certainly now changed, I think for the better. And so I feel like our practice at Northwestern, we've seen a lot of patients where they may have normal resting hemodynamics and then also multiple risk factors and older patient with like Group 2 as well as Group 1 risk factors. Unclear exactly what the pathophysiologic, you know, primary driver is based on non-invasive testing, so they'll undergo exercise right heart cath, and so one, is this really exercise-induced HFpEF? Or is it exercise-induced pulmonary vascular disease? So just curious to hear about others' practices? And then for those patients, particularly again, thinking of scleroderma, higher risk, are you starting to treat those patients when they have normal resting hemodynamics? And oftentimes, they'll still have a normal RV, I find, but then have exercise-induced, you know, pulmonary vascular disease.

Dr. Cuttica:
Are you treating the exercise-induced PH in scleroderma?

Dr. McLaughlin:
It's a great question. So Scott Visovatti, who is one of our partners who has moved on to that institution that shall not be named. In his K Award, he did exercise caths on scleroderma patients. Like we screened all these scleroderma patients, and if they had normal resting hemodynamics, he exercised them all. And almost all the time, their exercise PH was because their wedge pressure went up. So you know, common things happen commonly; diastolic heart failure is really, really common. And so it's very common to see that as the etiology.

If a patient with scleroderma that we exercise, so the rest of human dynamics are normal, the RV is normal, we're cathing them because they screened positive on DETECT or something like that, and we exercise them, and they have exercise pulmonary vascular disease, and their slope is high, their PA pressures go up but their wedge pressure doesn't, I may or may not treat them depending on how symptomatic they are. You know, if they're symptomatic, if you know, if they have exertional dyspnea and I don't have another reason for it, then I'll offer them treatment and follow them closely. If they're not symptomatic, we've just been following those patients. I don't know if that's right or wrong. That's just what we've been doing.

Dr. Cuttica:
So do you think then, based on the data with the prodigal son who's gone off elsewhere, do you think that especially high-risk patient population like scleroderma who is cathing, do you think those wedge elevations are accurate in that population? Do you think an elevated wedge in an otherwise normal person is a precursor to PAH? Or do you really think all of those scleroderma patients just have diastolic dysfunction and none of them would go on to develop PAH?

Dr. McLaughlin:
It's a good question. You never know for sure. But they are that population of, you know, older, primarily women, often with comorbidities, and you know, so I feel it's very likely that we're eliciting diastolic heart failure.

Dr. Cuttica:

Yeah. I mean, Yasmin and Ruben, you can comment too. I agree, I think that's a challenging population both to identify and get drug therapy for if we think they need to be treated. Although, you know, I do feel like especially in scleroderma, we see patients when they have established PAH over years, then eventually going on to develop what maybe looks more like they have left-sided heart disease as well, they get elevated wedges later on. Like the underlying cardiac pathology on these patients, I think, is interesting, right? And maybe early PAH has sort of a diastolic flare, and then some of those patients go on to develop PAH, and some of them go on to develop more cardiac disease.

Dr. McLaughlin:
So yeah. It's also the longer we keep people alive with PH therapies, the more likely they are to get other diseases. I mean, we've probably had more than a half dozen patients now with scleroderma that have been alive for decades, that go on to develop AS and you know, so yeah, so I think those things are common.

Dr. Mylvaganam:
I have one question. And I think it's unfair to try and answer this in 2 minutes, that's on the clock. With the addition of potentially new medications that are coming to market in 2024, with a disease-modifying drug like sotatercept, or potentially disease-modifying like sotatercept, how do you see drugs like that in the treatment algorithm, as Dr. Cuttica just presented on there? And this is for both of you too. Do you see it as a drug to be deployed in intermediate-risk patients? Do you see it in place of a prostanoid, or alongside prostanoid? How do you sort of see that fitting in, in a real-world landscape of treating patients with PAH?

Dr. McLaughlin:
You want to go first?

Dr. Cuttica:
No, I'd like you to go first.

Dr. McLaughlin:
So yeah, so there's a lot of buzz about sotatercept, which is an activin ligand trap basically, and intended to rebalance the pro-proliferative and anti-proliferative functions of the BMPR2 activin pathway. So we have to think first about the data that we have. And the data that we have about sotatercept is in a highly pretreated prevalent population. So the mean duration of disease in patients that were enrolled into the STELLAR trial was 9 years. You know, probably I think it was like, you know, 40% of them were on parenteral therapy, 60% of them were on triple therapy. So that's the data that we have. So we need to think about that. Now, it was, you know, very, very effective in that population. So that really does give you confidence the drug is doing something. If you can really make impact on top of a pretreated patient population like that, a 40-meter improvement in 6-minute hall walk and hit 8 of the 9 secondary endpoints, like really, really remarkable.

We do not have data at this time about using this earlier in the course of the disease. There's a trial going on, HYPERION, looking at adding it to patients who do not meet low-risk status within the first year of disease. And we do not have that much data in the really super sick patients. So there's a trial going on, ZENITH, about that.

When we think about the really super sick patients that, you know, you alluded to, like do you - what risk status do you use it in? And, you know, the one thing I would like to point out is that, while this drug had a remarkable effect on pulmonary artery pressure, a decrease in mean pulmonary pressure about 14, it really didn't affect cardiac output at all. So when you think about those really super sick patients, I don't think this is a replacement for prostacyclins. Right? Like we - people with cardiac index of 1.7, they need a parenteral prostacyclin. And so I think that part of your question is easy to answer.

Where I think it's likely to come in is no sooner than a third-line agent, I think we have such great data with upfront double combination therapy with ERA PDE5, those are relatively well tolerated, you know, probably less expensive than what this is going to be. So I think that's still going to be the first line and for patients who do not meet low risk, for patients who are intermediate risk, you know, not the super sickies that still need prostacyclins, I think it's likely to be the next agent that we go to after that.

Dr. Cuttica:
I agree. I think your question is going to be answered in the next 5 years. If and when it gets approved, it'll be in background therapy patients, and then clinical practice will guide what happens in the postmarketing studies and these clinical trials that are going on now to figure out where it fits into the guidelines.

Dr. Mylvaganam:
I can see clinically, patients struggling with the options that they may be alluded to on whether it's patient support groups or elsewhere, when they're faced with a provider who says it's parenteral prostanoid time, versus I have a drug I could take sub-q once every 3 weeks.

Dr. Cuttica:
That's another really interesting point, right? Because the buzz out there is this cures the disease. And there are patients that are already saying, 'Hey, I want to be on this drug because it's going to reverse it. You tell me when it's available, and I'm going on it.' And I think that's going to be a real problem.

Dr. McLaughlin:
Alright, good. Well, this has been a great discussion. I'm really excited to go on to the next session.

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