Conundrums and Controversies in PH-ILD: To Treat or Not to Treat—Identifying Optimal Treatment Candidates

This fall, Jeffrey Edelman, MD, Associate Professor of Medicine at the University of Washington and at the VA Medical Center in Seattle, Washington, gathered with Jean Elwing, MD, Professor of Medicine and the Director of the Pulmonary Hypertension Program at the University of Cincinnati; Anjali Vaidya, MD, Associate Professor of Medicine and Co-Director of the Pulmonary Hypertension, Right Heart Failure & CTEPH Program at Temple University in Philadelphia; and Steve Mathai, MD, Associate Professor of Medicine at Johns Hopkins School of Medicine and Co-Director of the Ann Dana Kusch Multidisciplinary Research Program for Pulmonary Hypertension and Interstitial Lung Disease, to discuss pulmonary hypertension (PH) in World Health Organization (WHO) Group 3 patients with interstitial lung disease (ILD).

Dr Edelman: Good morning. I'd like to start with discussing some general concepts, and how we approach these patients. Pulmonary hypertension is certainly common in patients with interstitial lung disease. There's been an increasing awareness of the prevalence of interstitial lung disease accompanied by increased identification of interstitial lung disease patients with associated pulmonary hypertension.

We have a burgeoning population of patients that we are seeing and it's important to discuss how we approach these patients in our clinics. It might be prudent to start with discussing the evaluation of these patients, and how it may be different than what we do with other PH patients. Are there different things that we should focus on in this population?

Dr Mathai: I think, in general, the approach is very similar to any patient in whom we suspect pulmonary hypertension. The recommended algorithm should be undertaken, including history physical examination, pulmonary function testing, imaging, echocardiography, etc. Determining whether or not a right heart catheterization is indicated I think is something that is important to consider as the evaluation progresses.

Some of the motivation and indication for right heart catheterization may vary based upon the individual patient who is in front of you. If the patient has severe interstitial lung disease and is really headed towards a lung transplant, catheterization may be absolutely indicated to understand whether or not pulmonary hypertension is complicating that patient's current situation and thus would increase the urgency for evaluation and potentially receiving a lung transplant.

Other clinical scenarios exist, perhaps someone at the extreme of age or with significant other comorbidities that preclude their candidacy for lung transplantation, a right heart catheterization may not be indicated because of the likelihood of other forms of pulmonary hypertension being present and/or limited utility of available therapies for pulmonary hypertension in that setting. I'm curious if others have a similar approach or if there are different approaches that Anjali or Jean might adopt.

Dr Elwing: I echo what you've just said, Steve. We take the approach, as you've mentioned, to go through the routine algorithm to work up a patient with pulmonary hypertension because we really want to know all the factors that might be contributing. The thing that's really changed is that, in the past, we when we diagnosed Group 3 disease, we would concentrate on symptom management and potentially discuss transplant evaluation. We would discuss PH and make the patient aware that we previously didn't have any approved therapies that were shown to benefit patients with hypoxic PH in large clinical trials, but now we can look at that differently.

As Steve has said, we focus on looking towards transplant, assessing goals of care, and then deciding if we need to go onto more invasive testing to prove the presence and severity of pulmonary hypertension. What about you, Anjali?

Dr Vaidya: Yes, I agree with all of that. Certainly, the thorough and comprehensive approach in the evaluation and diagnosis for all of the reasons that both of you just nicely described is very important.

I think, because we know these patients are what we would call "mixed physiology pulmonary hypertension" with underlying lung disease, my mind goes to the actual clinical phenotype of the patient—is it somebody with pulmonary heart disease Type 1, which is predominantly that of lung disease with a relatively mild phenotype of pulmonary vascular disease and right heart failure, or is it more of what we would call Type 2 pulmonary heart disease, where, yes, they have parenchymal lung disease but also a really strong phenotype of PH and right heart failure? I think we have to think about those patients very differently.

You're right. While we now have on-label treatment options that have opened up an opportunity for more discussion of treatment with our lung disease PH patients, I think, at least for the last 8 to 10 years, we've been having physiologic and phenotype-based discussions and categorizations of these patients to determine if we need to think about targeting the PH. We take into account, not just the severity of PH and right heart failure but their baseline oxygenation requirements, the severity of their [pulmonary function test] PFT and [computed tomography] CT scan abnormalities, and the risk of wors-

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ening oxygenation if we were to consider treating them. It's certainly another layer of complexity in the evaluation of these patients.

Dr Edelman: I think it's also important to consider some of the comorbidities that come along with these patients, particularly in the group of patients with idiopathic interstitial lung disease that tend to be older. We need to think about not only the severity of lung disease and the severity of hypoxia, but also other conditions such as sleep-disordered breathing.

Also, I always like to make sure that we've looked for chronic thromboembolic disease because that is an entity for which we may also have other treatment changes. Granted, these patients are less likely to be candidates for surgical treatment, but at least we can consider medical treatment and hopefully prevent disease progression and recurrence with reference to thromboembolic disease.

Dr Mathai: Just to add to that important discussion about comorbidities, I think coronary disease is also something that would be perhaps at a higher prevalence in the age group that might be affected by [idiopathic pulmonary fibrosis] IPF. There's some literature suggesting that there's at least an increased risk of coronary disease manifesting after the diagnosis of IPF. That's something that also should be considered, particularly given the potential complications of giving patients pulmonary vasodilators with coronary disease.

Dr Edelman: I fully agree. I think coronary disease can be quite sneaky in this population because the symptoms can certainly fly under the radar screen. Manifestations such as worsening dyspnea can be attributed to interstitial lung disease. Then, lo and behold, you find coronary disease perhaps in evaluation for transplant. When that's treated, some of those symptoms get better. Yes, I do think that coronary disease is certainly a common comorbidity and something that we need to be aware of.

Dr Elwing: I think we all are saying the very same thing. These patients deserve that full workup and really a global approach to their care because, oftentimes, they are a very different group of patients than our younger idiopathic patients who frequently have no other comorbidities. The only way to help these people feel better is really to not only address their pulmonary hypertension and ILD and assess what they want out of treatment, but also make sure we're not undertreating any other comorbidities. It seems we're all thinking about this patient population and approaching their care similarly.

Dr Vaidya: Jean, it's interesting how you mentioned how they're feeling and helping them feel better, which I think is an important point in this complicated population because sometimes I think, as the physician, we feel limited knowing that this patient has multiple contributions to their dyspnea, and it can feel very discouraging. We might treat one or another but overall might not improve their symptoms.

Sometimes that can feel limiting in what we should do or what we can do, and sometimes I have to remind myself that, if we choose the right patients, we may be able to at least minimize the comorbidity of the heart failure syndrome, which can help support that patient in the grand scheme of getting what they really need, which is often lung transplant, as Steve was saying.

Sometimes I have to remind myself and tell the patients, "Look, we might consider you for treatment, and while it might not help you be able to walk a mile around the track, it might stabilize you and get you out of heart failure, which will improve your nutrition, your renal function, and your overall wellness to be able to safely undergo lung transplant." I wonder if other people think about that in a similar way.

Dr Edelman: Certainly in the absence of other significant comorbidities, transplant remains a definitive therapy in this setting, particularly if they have ILD with significant pulmonary hypertension. I think that lung transplant is a very important part of the discussion and an important part of the goals of care. Several of the comments have touched on other issues such as symptom relief. I think it's important also to think about palliation and goals of care for patients who may not be able to get to transplant and who have significant progressive disease.

Dr Mathai: I think, with any chronic progressive disease, and in this scenario, we're actually dealing with 2 of them—pulmonary hypertension and interstitial lung disease—discussions about management of symptoms and goals of care are integral to overall patient management and satisfaction.

What is a goal for the patient in terms of interventions and whether the patient wants to consider additional therapy for either interstitial lung disease or pulmonary hypertension or both, or whether he or she would prefer more of a symptom-based approach with palliation? I think these are fundamental things to discuss with the patient to understand his or her perspective and to inform your treatment plan going forward. I think those are really important things, particularly since these diseases are progressive and portend a poor prognosis.

Dr Elwing: I agree 100% with that. I think sometimes, in this population, we are surprised by what people really want from our care. Patients with advanced lung disease and pulmonary hypertension may not anticipate that we are going to change things dramatically. They just want some relief of this daily dyspnea that is occurring with routine tasks like walking to the bathroom or the disappointment they have that they can't do certain things like going out shopping or spending time with family and friends.

Echoing what Steve just said, this patient population's goals may be very different than our idiopathic or pulmonary arterial hypertension patients. I think we have to ask detailed questions, understand what they want and what they are expecting out of what we can offer them so we can really modify our treatment plan to fit that.

Dr Vaidya: I agree with that as well. That's such an important discussion, not necessarily for hospice transitions, but to

really help with those goals of care conversations and to alleviate the suffering. It's a whole other level compared to, like you said, Jean, our idiopathic patients.

Dr Edelman: How liberally do you use pulmonary rehab in this population? I think pulmonary rehab can benefit some patients, but it can also be quite complicated for patients requiring high amounts of oxygen, not only complicated with reference to actually participating in rehab, but also the added care burden of having to go to pulmonary rehab. This may not be as much of an issue over the last year as a lot of our rehab programs have been inactive, but I'm wondering how people utilize pulmonary rehab in this population.

Dr Elwing: I've been taking a little bit different approach for these individuals that have significant ILD and more advanced pulmonary hypertension. If they are homebound when I meet them, I've been offering home physical therapy and then working up to outpatient physical therapy for core strengthening when they are ready.

The physical therapy teams I've been working with have been very helpful and are communicating when the patient is ready to progress to cardiopulmonary rehab. Then when the patient goes to cardiopulmonary rehab, I've been really trying to communicate clearly about saturation goals in addition to choosing exercises that they derive benefit from but don't cause as much hypoxia. It has been by experience that some types of exercise machines seem to be better tolerated for ILD-PH patients than others. I'm not sure if anyone else has had that experience, but that's been my approach for the PH-ILD patients with significant deconditioning.

Dr Vaidya: I haven't had that experience, but it sounds great, Jean.

Dr Mathai: Yes, I was about to say the same thing. It sounds like a really important protocol you have there. Starting with focused physical therapy and then moving towards pulmonary rehabilitation is something that I haven't done consistently without some obvious indication for physical therapy prior to pulmonary rehabilitation. I think that's a really great approach and something that I will adopt from your guidance, Jean.

Dr Elwing: Thank you. It's been working for some, so I'd love to hear your feedback if it works for you also.

Dr Vaidya: I think that's so smart because we tend to sometimes undervalue the degree of musculoskeletal deconditioning that happens with all of our patients that have such chronic cardiopulmonary disease, and so it can be very challenging for them to participate in rehab effectively. I think this is such a smart approach. It's a great idea.

Dr Edelman: I'd add that there is a nascent field in pulmonary rehab which is home-based pulmonary rehab where it's not necessarily that there's a therapist coming to the patient but that there's a video link, and the patient is doing their exercise at home under the supervision of a rehab therapist who may be remote. That may be a very good intermediate compromise that includes some of the ideas that Jean mentioned where the patient stays at home. They can exercise, they're supervised, and care can be efficiently administered via remote approach.

Dr Elwing: That is very interesting. I've never tried that. Has anyone else?

Dr Mathai: We've used it for our [chronic obstructive pulmonary disease] COPD patients who may be more familiar overall with pulmonary rehab. For many of our patients who have already completed pulmonary rehab to reengage them, particularly during the time of COVID, we've done that. I've not done it yet for any of my pulmonary hypertension patients, but we have discussed it. I don't think anyone's taken me up on it yet.

Dr Elwing: I'm going to check into it.

Dr Edelman: I think it's another potential tool that we may have going forward in treatment of these patients. We're about halfway through and it's a good point to shift gears and talk a little bit about drugs and pharmacotherapy and to talk about not only PH treatment but also to recognize that these patients have ILD and that treatment may also include use of antifibrotic drugs.

For patients who are candidates for the anti-fibrotic drugs and able to tolerate them, these should be considered as part of the approach to treatment. It's not PH directed, but certainly there's evidence that that treatment at least slows progression. Would everyone agree?

Dr Elwing: I actually have a question. I am wondering, when you are considering an antifibrotic therapy for your ILD-PH patients, do you initiate that before you initiate pulmonary vasodilator therapy, or do you start the pulmonary vasodilator therapy first?

Dr Mathai: Well, I think, in part, that would depend upon the individual patient and the relative contribution of parenchymal disease versus pulmonary vascular disease to the clinical picture. For example, in a patient with progressive interstitial disease with severe restrictive physiology and severe hypoxemia with mild pulmonary vascular disease, as determined by heart catheterization, I think I'd be more inclined to focus on the ILD. If the reverse were true, more significant contribution of PH relative to parenchymal disease, I might think about targeting the PH. I think, in general, we're talking about medications that have a lot of side effects as well, so tolerability becomes an issue. Quite frankly, I've not had many patients on the combination of the inhaled treprostinil and either of the antifibrotic medication[s]. I'm curious whether others have had issues with tolerability in combining these medications.

Dr Elwing: That is exactly why I asked the question and hoping to gain more insight in this challenging situation. It has been my experience that people do have difficulty tolerating both therapies, and like you had mentioned, trying to figure out which sequence to introduce therapy so that they can adjust to one medication before we add another. I very much like your approach of looking at the biggest driver of their symptoms

from their assessment and then target that first and then followed by targeting the other part of their disease process.

Dr Vaidya: I would agree with that approach as well because, very often, it's not going to be a mystery, which is the driving factor. Certainly, some patients have severe phenotypes of both PH and lung disease, but there are certainly many patients where it's clear they're suffering predominantly from heart failure from PH with their neck veins up to their ears, peripheral edema, and an echo-Doppler study with an [right ventricle] RV that's bigger than their [left ventricle] LV and evidence of a double-digit [pulmonary vascular resistance] PVR and low cardiac index.

I would argue in those patients, as Steve was suggesting, to opt for the PH medical therapy first, try to alleviate their degree of severe heart failure, then perhaps in short sequence, adding on the ILD therapy.

Dr Mathai: I think, in addition, we've been talking a lot about IPF, but other patient phenotypes may also dictate or at least contribute to our decision making regarding treatment of pulmonary vascular versus parenchymal disease. Those patients with connective tissue diseases, scleroderma, as an example, where the combination of pulmonary vascular disease and interstitial lung disease is very common might warrant targeting both the interstitial disease and pulmonary vascular disease.

Dr Vaidya: I agree. I think, those patients, that brings up an important distinction between classifying patients versus characterizing patients. Then I think it's much easier in that scenario because connective tissue disease patients are characterized and phenotyped in the same way that they're classified (as Group 1 [pulmonary arterial hypertension] PAH). We have a much lower threshold and a green light, so to speak, to go forward early with their PH medical therapy while treating their lung disease.

I would argue that there are some patients with WHO Group 3 that don't have connective tissue disease that, from a pure PH perspective, behave in the exact same way in terms of severity and acuity of PH and heart failure presentation. They may warrant a similar consideration for approach.

Dr Edelman: I think it's reassuring when you have an associated WHO Group 1 diagnosis such as scleroderma or [rheumatoid arthritis] RA to know that you're using treatments that have at least been studied and shown to be effective in those groups. I do tell people that even though they have a WHO Group 1 diagnosis but also have significant interstitial lung disease, their expectations for a significant response to therapy may be lower. The other thing I would add is that the lines get even more blurred when we start to think about where our knowledge has evolved with reference to the autoimmune conditions associated with ILD.

There are a lot of patients who don't fall under the typical autoimmune diagnoses that we think of in PH, but do have interstitial lung disease. I'm referring to the group of patients with anti-synthetase syndromes. I think we've seen a growth in that population, and I'm not sure where to classify that specific group of patients. I think it's probably good to have some discussions about the approach to the use of vasodilators in this population. I'd like to hear from the group. What your thoughts are on this topic?

Dr Vaidya: There was a really nice paper. I want to give credit to Rajeev and Rajan Saggar, who had published in *Thorax* about 7 years ago right on the topic. I found it helpful, or if anyone's interested, they talked about changes in hemodynamics and echo function in an advanced PH pulmonary fibrosis population where they used parenteral prostacyclin therapy.

It was a study of patients with relatively advanced lung disease. I think their percent predicted [forced vital capacity] FVC and [forced expiratory volume in 1 second] FEV1s were in the teens and 20s and diffusion capacity about 13, but what was really interesting was that they picked a population that had at baseline a phenotype of really significant PH. Their right atrial pressures were nearly 10, cardiac index was 2.3, and PVR, I think, was in the double digits. When treated with parenteral prostacyclin therapy, they suffered no change in oxygenation requirements or lung function on PFT.

This was over 12 weeks, with dramatic improvements in 6-minute walk distance, [brain natriuretic peptide], PVR, cardiac index. I just want to give them credit for looking at this very challenging population and describing a phenotype that might guide us in this discussion and how we approach patients. It directly applies to what we're talking about here. It's similar to what Marco Guazzi did years ago when he took a severe PH/right heart failure phenotype within the heart failure with preserved ejection fraction patient population and published on benefits with sildenafil use.

Dr Elwing: I personally find these patients extremely challenging because of the unpredictability of their response to therapies. I'm not sure if anyone else has had that experience, but because of that, I always am very cautious about what I talk to the patient about in terms of their expectations from therapy. I divide them out in terms of, do they have risk factors for Group 1 disease, or are they truly an interstitial lung disease patient or a combined emphysema fibrosis patient?

This information helps me choose best therapy options. For those that have ILD or combined emphysema and fibrosis as etiology of their pulmonary hypertension, I would take the approach of what we learned from the INCREASE trial that they may have benefit from inhaled prostacyclin therapy. In contrast, those that have the risk for Group 1 in addition to coexisting interstitial lung disease would be approached differently. The best example of this group would be our PH patients that are associated with connective tissue disease and also have some degree of ILD. I often open up many more options for PAH therapy to this subgroup of patients. I'm wondering if everyone else is having a similar approach or they're approaching it differently.

Dr Mathai: I agree with that approach, Jean, and it's similar to what I employ. I will try to temper expectations with patients, and in general, I'd say it's a rule of thirds: a third of the people may get better, a third of people will have no significant change, and a third of people may get worse. I'll tell patients that, "I don't know into which you're going to fall with a trial of therapy."

I also consistently use that term "trial of therapy" and tell patients we're going to reassess in 1 month and 3 months after you start therapy. This is to see if you're feeling better or having significant side effects that make it intolerable for you to continue on the therapy before deciding whether there's been a treatment response or not. I do think that tempering expectations is important because of the heterogeneity of the phenotypes of patients that we're seeing, if it's really hard to know exactly who is going to benefit and who isn't.

Dr Elwing: Despite being Food and Drug Administration (FDA) approved, payors may not be ready. That's the really challenging part for us because we have a therapy that we've shown to be effective in a randomized controlled trial. We can prescribe but not uncommonly having issues with cost. We are oftentimes utilizing assistance programs to help patients with expense of therapy.

Dr Mathai: Yes, that's been my experience. Although I've had some success recently with insurance approval.

Dr Elwing: That is wonderful news.

Dr Vaidya: I agree with the prior comments of really managing expectations of the patients if we do embark on treatment. I would only add that I think, if you take all patients with this combination of PH and ILD, there are certainly patients that I think we do know that they would have no chance of a meaningful symptomatic or clinical benefit with PH medical therapy based on the imbalance of lung disease versus PH. Then there's the opposite extreme of patients with severe PH and right heart failure versus more mild ILD, where we actually do know with certainty that they are likely to benefit. There certainly are some patients in that in-between where it is a bit uncertain, and setting those expectations is really key.

Dr Edelman: How important do people think that the inhaled route of therapy is? The rationale applied has been V̇Q̇ matching with the inhaled route because obviously the drug is being selectively delivered to presumably less affected areas.

Dr Mathai: I think that's a tough question to answer. As you point out, the theoretical advantage of an inhaled therapy would be targeting functioning lung units with therapies directed to the pulmonary vasculature, as opposed to targeting the lung as a whole, in which dilating the pulmonary vasculature in areas of the lung not participating in gas exchange might worsen systemic hypoxemia. I think that, while this mechanism is theoretically appealing, whether that happens in reality or not is a little bit challenging to determine.

There are older studies using multiple inert gas elimination or MIGET techniques in patient populations with underlying lung disease, both COPD complicated by pulmonary hypertension and interstitial lung disease without pulmonary hypertension, that demonstrate differences in ventilation-perfusion matching at rest and exercise when patients are exposed to oral pulmonary vasodilator therapy. This type of investigation would be interesting in our PH-ILD patients in particular to see if what we suspect is happening theoretically is happening in reality.

I think it's important to point out that, in the INCREASE study, there was no significant worsening of oxygenation, either at rest or at the end of the 6-minute walk test, which was the major safety concern about the study. I think there's some reassurances there, but the exact mechanisms that explain why inhaled therapy is potentially superior to other delivery mechanisms of pulmonary therapy remains uncertain.

Dr Edelman: The reason I brought that up was the recognition that treprostinil does have a relatively long half-life, and it is systemically absorbed. Granted, obviously, there will be preferential higher concentrations at the site of delivery, but there also will be a systemic effect of the drug. I would hope that maybe there is some future consideration to studying the oral route of delivery for treprostinil as well in this group because I am not sure how important the inhaled route would ultimately be for this drug. I think you outlined the uncertainties very nicely, Steve.

Dr Mathai: I think the other interesting finding from the INCREASE study was born out of the safety data looking at pulmonary function, in particular FVC, that demonstrated some possible improvement in FVC in patients receiving the study drug. This finding has prompted a larger prospective randomized study of inhaled treprostinil in isolated interstitial lung disease. I think that's an interesting observation, and it might explain some of the improvement in functional capacity as well if there was improvement not only in pulmonary hemodynamics but also in lung function.

Dr Elwing: I agree with that also. I thought that it was very reassuring to see that lung function did not decline with the inhaled therapy in this population with parenchymal lung disease. We've never studied inhaled prostacyclin in this patient population before in a randomized placebo-controlled trial. I was also happy to see that we're going to look at the potential of positive effect on lung function further with a randomized trial.

The other thing I thought was very interesting was an abstract that was presented at American Thoracic Society (ATS) by Dr Steve Nathan, looking at the worsening events in these patients that were treated with the inhaled treprostinil versus placebo. Dr Nathan presented a waterfall plot showing that patients who received therapy with inhaled treprostinil had a delay to the first event of worsening and the second event to worsening.

This information made me think hard about how we treat ILD-PH patients. This patient population frequently experiences exacerbations. They fre-

quently have worsening. We should not think about giving up on our treatment strategy with inhaled treprostinil when they do present with that episode of exacerbation because with this data, we learned that a large percentage of PH-ILD patients are going to have worsening events, but they are delayed in those treated with inhaled prostacyclin in the INCREASE trial. I don't know if anyone else found that interesting or that information helpful in their treatment.

Dr Vaidya: I think that's a great point, and it's very important not to react to those ILD decompensations in a way that makes us then withdraw or withhold some of the PH therapy that might have actually been helping them.

Steve had mentioned earlier about assessing oxygenation at rest, after the 6-minute walk. I think carefully assessing this, when we do choose to treat, when they presumably are not having an ILD exacerbation, is really helpful. It guides us in the future when they present with dyspnea and hypoxia not to jump to the conclusion that it's related to their PH medical therapy. This is another angle of thinking about it that can be helpful.

Dr Mathai: I guess I'll add to that and bring up another interesting result from the study, which I found important: the lack of response in patient-reported outcomes. Despite improvement in 6-minute walk distance, lack of worsening oxygenation, and improvement in the secondary analysis of time to clinical worsening, there was no improvement in symptoms as assessed by the St. George's respiratory questionnaire (SGRQ). I'm curious about the other panelists' impression of that and whether my bias that the SGRQ might not have been the best tool to assess the quality of life in a combined population such as this with PH and ILD is shared by the other panelists.

Dr Vaidya: One of the possible contributions that is worth noting is that the patient population in INCREASE was a somewhat modest phenotype of PH compared with what we've all been talking about and are used to seeing. Their average PVR was only 6 Wood units, which is of course abnormal but not as severe as is commonly seen in clinical practice and some of the other published data in this area.

You would potentially expect to see and have the patients report a more dramatic subjective improvement when they're going into treatment with a worsening PH hemodynamic profile. That may have been part of it. It was a positive study and certainly met its primary endpoint, but they may have had a greater opportunity for symptom and other clinical improvement with a more severe hemodynamic abnormality going into the study.

Dr Elwing: I think it also circles back to us talking through our goals for these therapies with each patient. Quality of life impact measured by SGRQ wasn't a positive finding in the study; however, as Steve mentioned, this may not have been the optimal questionnaire for this patient group. Maybe something more targeted towards this type of patient would have been more helpful. Hopefully, when we study more patients with PH-ILD in the future, we will assess with additional quality of life questionnaires to help us better understand this complex patient population.

Dr Edelman: I think, going forward, it will also be interesting to see if we can parse out which groups of patients have a greater degree of response to treatment overall because there certainly were some signals in INCREASE that there was a variation in response based on different patient groups.

Dr Elwing: Group 3 pulmonary hypertension is a heterogeneous patient population. We have a lot more to learn from this group. Over time, we may learn that there would be benefit from taking a different approach to the various subsets of PH-ILD patients. For example, we may find our IPF-PH patients, combined emphysema fibrosis patients, and CT-ILD patients benefit from different management. Additional study is needed, but I was happy to see we at least saw a signal in the positive direction for this group in the recently published INCREASE trial.

Dr Edelman: I think we can perhaps summarize by saying that this is a heterogeneous group. I think we've also discussed taking a very broad and global approach to the evaluation of these patients with careful attention to addressing and identifying comorbidities, thinking about goals and expectations of care, and now understanding that we do have at least one PH treatment option that may modify disease course and progression and lead to improvement in 6-minute walk and perhaps even lung function. I want to thank everyone for a very thoughtful discussion.