Gaps in PH Guidelines

Guest Editor Robert Schilz, DO, PhD, assembled a group of veteran clinicians to discuss the implications of guidelines that have emerged based on new etiologic, diagnostic, and pharmacotherapeutic evidence combined with experience. Joining the discussion were Robert Bourge, MD, Senior Vice Chair, University of Alabama at Birmingham Department of Medicine, Assistant Vice President, Physician Integration and Regulatory Affairs, UAB Hospital, and Head, UAB Pulmonary Vascular Disease Program; Charles Burger, MD, Professor of Medicine, Mayo Clinic College of Medicine, and Medical Director, PH Clinic, Mayo Clinic Jacksonville; Richard Channick, MD, Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School; and Srinivas Murali, MD, System Director, Division of Cardiovascular Medicine, Medical Director, Cardiovascular Institute, Allegheny Health Network, and Assistant Professor, Temple University School of Medicine. Following is an edited transcript of their lively discussion.

Dr Schilz: We're looking at the approach to medical therapy in pulmonary arterial hypertension (PAH) and navigating the space between evidence and experience. We've assembled tonight what I can best gather is somewhere in excess of 100 years of experience in treating PAH to further discuss the theme of this two-part issue, "Navigating the gaps between knowledge and experience in the treatment of PAH."

As a way of getting started, I would like to cover the following topics during our discussion tonight. Number one, goals of therapy and how they impact both initial choices of therapy and escalations. Number two then, the discussion of the gaps which to some degree are covered in the text.. And, number three then, the opinions of the discussants on key elements that are lacking in evidence and how we best navigate those. As a way of getting started, I'll mention the articles: there is a column suggesting difficulties in the adoption and writing of guidelines; an assessment by Hap Farber of trying to understand what we know, what we don't know, and what we wish we did; a discussion of calcium channel blockers including when a drug works, it works; when it doesn't, it doesn't; issues of whether monotherapy is obsolete in our current guidelines; and the assessment and selection of infusion therapy patients, as well as how to position new drugs.

I'd like to start by parsing everyone's personal perspectives of where they feel gaps in guidelines particularly exist and in which parts of your practice really drawing on experience seems to be the most necessary. So Charlie, I know we've been discussing this a bit, so maybe we can get your thoughts up front.

Dr Burger: I just want to start with a disclaimer that I don't represent the majority of that 100 years of experience you mentioned so I'll let the others weigh in on what percentage they represent. I'm very excited to participate in the roundtable because we face every day, as do all of the participants, challenges of decision-making in the treatment of PAH. We have always worried a bit about our ability to translate published guidelines, particularly to educate and assist younger providers who are getting into the space of pulmonary vascular disease and providing care for these very complex patients. One challenge, of course, is that the guidelines assume equal access and tolerability, which certainly may not be true for any one individual situation, starting of course from insurance coverage, restricted formularies, and particularly for those patients who have more meager socioeconomic means. Lessening of support structures for payment of medications, as has recently evolved with Caring Voices' narrowing their coverage down to one drug, is an example; as well as the varying examples of side effect profiles. In addition, we cannot assume equivalent efficacy and tolerability of any one drug within a class. The most reproducible of these examples would be the hepatotoxicity with bosentan as compared to limited hepatotoxicity with the later generation ambrisentan and macitentan. So I'm excited to participate in this roundtable discussion and am very much looking forward to the opinions of how to address these gaps going forward.

Dr Schilz: Srinavas and Bob, you are among the original prostacyclin investigators, participating in the pivotal trials that really started our modern era of drug therapy. Certainly there's been a tremendous evolution since that time. In your perspective, Srinivas, certainly drawing on this kind of experience starting with infusion therapy as we all did in the '90s, and now having-double-digit drugs for treatment, what kinds of challenges do you now face? In the grand scheme of things, guidelines clearly identify a calcium channel blocker, which is the rare bird, and they clearly identify infusion therapy for very sick patients, but that is a large gap in between. How do we navigate that these days?

Dr Murali: Thank you, Bob, for asking me to be part of this roundtable, being part of this group of internationally renowned experts in the field. The question you ask is a good one. I think as the condition and the knowledge have evolved over the past two decades and new therapeutic targets have become recognized and tested and trialed-- we now have, as you mentioned, double-digit numbers of choices the ability to treat these patients has actually become more complex. When we were treating pulmonary arterial hypertension in the mid-'90s, there was only one approved drug. And even though it was an infusion parenteral drug with all the

complexities that come with administering a continuous infusion agent, it was somewhat straightforward because that was the only choice available. So you made the diagnosis and you moved on. Obviously, some evidence-based clinical trials have allowed us to come up with algorithms and pathways of how to navigate through the decision-making process. Just having a lot of treatment choices doesn't automatically make the management simpler. And as we move along this discussion, we'll be able to highlight some of the gaps that the addition of these therapies has actually created in the care of these patients.

Dr Schilz: Absolutely. Bob, certainly representing a little bit more distal geography, I appreciate you joining us today. And I can remember being on conference calls with you for many, many years. Your perspective of the evolution of therapy now, going toward three decades?

Dr Bourge: Now it's past three decades actually. I'm 31 percent of the 100 years now. (laughter). I got started in the medical therapy because we were the first heart/lung program in the Southeast. And with the opening of that program, all of a sudden I had a slew of referrals for heart/lung transplant, which was thought to be the best therapy back then. And most of them died before I could get a heart/lung block. That's why I got involved in the original epoprostenol study; I put nine patients in that study. By the way, two of them are still alive, doing quite well, which is remarkable.

Dr Schilz: And Bob, to come back to that, because I think that there are very few patients that we shake hands with two, almost three, decades later, but I agree with you, I still follow a few people that were placed on prostacyclin therapy in the mid-'90s.

Dr Bourge: Yep. I treated over 100 patients with epoprostenol before it was approved. And back then, the pharma company would give us the drug and that was about it. I raised money from wealthy patients to pay for the placement of the Hickman catheter; got doctors to do it for free. Patients spent five days in the clinic, learning how to mix and give themselves the drug. And if they couldn't do it, they couldn't get the drug. I had no choices; I had no choice but to do that. Then after 11 years of doing it by myself, I became division director and hired more people. There's still five of us in our group and I'm actually recruiting two people,

With that being said, I agree with Srinavas, in that when you only have one choice, you use that one choice. And now that we have more choices, what we've done as a group is gradually develop guidelines that we all follow. It's very important when you have a group of physicians caring for a large group of patients that we stay on the same page. I can go through my approach, if you want. But basically, it's a simplified version of the current guidelines because I think they're a little too complex. Basically, it's we don't do vasodilator studies anymore. We've had deaths with vasodilator studies. And as there's no approved drug and we don't find that they last that long, I only have one patient that lasted longer than three years on an oral calcium channel blockers in all these years, and that's thousands of patients. So we don't do them anymore, especially since we have cheaper alternatives.

Dr Schilz: Bob, that's a great point. Certainly, it remains in the guidelines. But the numbers of patients who truly benefit from calcium channel blocker therapy are quite small, indeed. And again, as you point out, performing the trials is not without morbidity and mortality. I think that understanding that these are rare patients and either the drug works or it doesn't is an important part of experience and may not be well reflected in guidelines. That's a great point. I was a little more fortunate up north; I have about four people over the last 22 years that are like that. But they're indeed an exceedingly rare bunch. And I think you brought up another really good point because I think that everyone has a way to simplify and marry their experience with the available literature. So could I ask you to hold that thought a little bit and we'll come back and explore its perspective. I think intrinsic in most approaches is both assessing risk and also setting goals. and having, as you say, a common theme to approaching patients who aren't calcium channel blocker responders or infusion candidates. So l would like to come back to that playbook and examine your perspectives a bit if we have time.

Rich, you're on the phone as well, and I appreciate your input in the article in this issue about monotherapy. Certainly the concepts of monotherapy are still in guidelines--not dead; however, increasing pressure is there with combination therapy. You, too, grew up in an era where we were giving exclusively infusion therapy. Your perspective of evolution over the years?

Dr Channick: I think that the gaps, if you will, in the guidelines are focusing on treatment strategies. I think one of the big problems is we don't have head-to-head comparisons with the different drugs; so everyone has their preferences, etc. What probably we can agree on is developing treatment strategy. And one of those is, do we start one drug, do we start two drugs, do we start three drugs? When do we start IV therapy ? Do we do vasodilator testing? So those are sort of broad strategies. I think the guidelines do focus on that and that's probably more helpful for less experienced people to think that way than to go through, "do you use sildenafil or tadalafil or… whatnot." And so the monotherapy thing is interesting because I think clearly the guidelines are going to evolve more aggressively toward upfront combination therapy. Does that mean that monotherapy has no role in any patient? I don't believe that necessarily and I don't think – I don't know--if my colleagues agree but, one size doesn't fit all.

I have a patient who has mild pulmonary hypertension, early class 2 patient; PA mean of 28; a young woman. Am I going to start her on three drugs up front? No, I'm going to start her on one drug and I'm going to assess how she does. And I'm going to have a goal and that may be a hemodynamic goal, an echo goal. But that's a patient that I've seen very often will do very well on a single drug for many years. You always

want to have the option of adding another therapy and we do, as long as you're following the patient. And as I tell young doctors and patients, I don't care so much what drug you start first, it's how you follow the patients and make the changes in the treatment over time and being very aggressive in that respect. So that's sort of more of a, I guess you'd say, a strategy. Of course, there are other patients who clearly we throw the kitchen sink at up front. And that is a judgment based on experience. Do you think this patient is sick enough to need two, three drugs, IV therapy, etc., versus sequential therapy and watching them closely? And that's where I think the experience comes in.

Dr Schilz: Well, Rich, you brought up about three great points. And I wonder if we could explore them quickly before we get back to looking at strategies and integrating experience and evidence-based medicine. Number one, how many of us sitting around the table have patients that have been on single, non-infusion, oral monotherapy for greater than five years and are class 1's and 2's, normal or mild RVs and essentially with great pulmonary pressures, and at what many would consider aggressive goals for therapy? I know I have a few and they clearly exist. Rich, you already alluded to the fact that you have some.

Dr Bourge: I have some, but it is rare.

Dr Schilz: And Srinavas, do you as well have any of these folks that have done extraordinarily well on a single oral monotherapy for many years?

Dr Murali: Yes, a few certainly. I think they have done very well. They got monotherapy in the early 2000's, maybe 10, 12, 14 years ago, because only one or two older drugs were available at that time. And they have surprisingly done well. We continually evaluate them and, using all the known adverse risk factors, they seem to continue to fall in the good risk category and have done pretty well.

Dr Schilz: And so from your perspective, and again... 5, 10, 15, 20 years from now, I guess pick an arbitrary one, understanding pharmacogenomics or some other factors that make these patients most likely to respond to a single drug or anything else might be the key to ultimate understanding. But in the meantime, drawing from experience, you brought up a point that most of the folks that have done very, very well--and this was echoed by Rich Channick--that these folks tended to fall in the lower risk category. Again, not people that were functional class 3. Not patients with severe or moderate to severe RV dysfunction, high right atrial pressures, and so forth. Is that everyone's general perspective on this rare patient?

Dr Bourge: I agree. We occasionally have, for some reason, a patient who doesn't have collagen vascular disease. Sometimes it's a patient who has a family history. And they will come into our clinic with mild symptoms or it was picked up on an echo and it turned out to be real, that they had a PA pressure mean, a little elevated if you will, say 28, 29. And our goal in therapy is no sign of overt right heart failure, which means a normal jugular venous pressure, normal RVEF, a 6-minute walk test greater than 300 meters, and class 2 or better symptoms. And a normal cardiac index. On occasion, we will get a patient like that and usually now we would put them on a PDE-5. I tend to use a once-a-day one, unless I'm forced by an insurance company to use a different one. And that is happening more and more. And some of those patients do quite well and I've had some last years, literally, on just a PDE-5. I will say that the last time I looked at it was about a year ago, 85% of our patients are on two or more drugs. Very few are on less. And some of those that are on less because they either didn't want anything else or didn't tolerate anything else.

Dr Channick: I think I agree with that. I wasn't trying to imply that these people won't end up on more than one drug. But I think that the initial strategy of starting one drug in these lower risk patients still has a role. Clearly, the vast majority of our patients, as well, will end up on more than one drug at a year or more. But if you look at the trials-- so I'm thinking of the macitentan trial where a third of patients or two-thirds were on background therapy with sildenafil mostly-- the placebo curve in that trial, the people who just stayed on the single drug, 35% or so had an event, but 65% didn't, up to two years. So the likelihood is even in that study that patients are going to be relatively stable on background therapy. Now, in this study, macitentan clearly decreased that likelihood of an event. That was significant, even in background therapy. So again, that would support sort of that sequential approach that patients have been on sildenafil or whatever drug and they still have some symptoms, to consider the second drug or the additional drug. That's one strategy.

Dr Burger: It would seem to me that the points of emphasis are proper patient selection-- however you would define that: mild disease, less risk of progression, perhaps. Knowing the reality of it, we often start one drug for a variety of reasons--whether it's insurance coverage; whether it's a period of time to determine tolerability--as all of these medications have side effects, and as you look at the trials of adding drugs, the percentage of side effects clearly increase with numbers of drugs. And then thirdly, very close follow up, with clear goals of therapy, such that you're not putting them in peril by potentially going too slowly or not evaluating the proper goal of therapy. I think if you stay within those guidelines with experience and judgment you can certainly do this. There will be a sub-segment that will do fine on a single drug for some indefinite period of time; I think that's a reality.

Dr Schilz: Yes, Charlie, I think what I'd like to do is come back to that concept of following people closely, looking at goals and so forth. I think that Rich, everyone here, has unearthed also a very interesting patient that really wasn't represented in the vast majority of either combination trials or the sequential add on trials. We know those trials historically have mean pulmonary pressures that are right around 50, with predominance of functional class 3

patients. And really, patients who have been hemodynamically identified with resting PAs, in the low 30s and so forth have not been extensively studied. But, I'm hearing everyone saying that, "This might be exactly the patient in whom I would consider initial oral monotherapy and then follow up longitudinally," and in their experience may do well. So I think that this represents a class that we're starting to see more of, perhaps because of increased screening, increased awareness, and so forth. But also one that is poorly represented in trials and represents a great deal of experience in decision making, since we don't have any trials addressing this patient population. Fair statement?

Dr Bourge: I think it's fair. Years ago, I started asking family members who had the possibility of genetic predisposition, if you will. I offered to screen the family members, children, and often the mother of a patient, a middle-aged patient. In fact, that's actually what got me started in PH. I had a young lady who came in with it. Listed her for transplant. Six weeks later, she passed away waiting. This was before epoprostenol. I subsequently diagnosed her mother with it a year later. Using this strategy, we're going to find some early patients who have minimal or no symptoms I still treat with at least a PDE-5. These patients really are class 1 or class 2, if you will. Fortunately, most of those have stabilized. I've rarely had them progress.

Dr Schilz: So I think this is our first point of looking at and exploring monotherapy in the very-well patient. Certainly intrinsic in this discussion was the discussion of risk. And, certainly the concept of assessing risk was introduced in the mid- to later-2000's in most guidelines as a very important part of the treatment strategy--more specifically suggesting that treatment strategies may be different in low-risk versus high-risk patients. We also have, however, stratification by functional class, which just as a point of discussion, I would say doesn't always represent or, in my opinion, isn't always equal to risk, especially in the large class of WHO Class 3 patients. It seems like everyone considers the concept of risk in their decision about therapies, so I'd like to talk about that a little bit, as well as the potential disconnect between risk and functional class. To start the discussion, I think we're acknowledging the fact that some people appear sicker, some people more "well," and that we approach treatment choices differently in these groups of patients. Srinavas, I know that you talked about risk. How do you think about risk in relation to functional class and what factors do you put into that equation?

Dr Murali: Yeah, that's a great question. Being a heart failure cardiologist-- and I think Bob can attest to this-- we had always recognized that pulmonary hypertension patients decline and perhaps die from progressive right-sided heart failure. Certainly, that has proven to be the case in pulmonary arterial hypertension. And so really, the risk of any given patient at any given time, if you fundamentally look at it, is directly a correlate of how the right ventricle is performing. Everything else is ancillary, subjective, and perhaps not very reliable. And the reliability of all these other ancillary findings lessens as the patient's disease progresses. So, for example, WHO functional class is a good example. The reliability of the functional class becomes less as the patient advances within the class 3 space. So early class 3 to late class 3 is really a subjective distinction. We often see patients move in that space, from one end to the other, without having any other corroborative, objective supporting data. This can be very challenging. The same thing can be said about the 6-minute walk test, although this is certainly a proven important metric and a reliable one. For example, in an elderly patient or a patient that has other comorbidities, such as osteoarthritis or other physical limitation, the reliability of this measure becomes very challenging when you are trying to correlate this to disease severity and/or patient risk. And so, right ventricular assessment is central to risk assessment in a PH patient. I think that we have gotten increasingly better at right ventricular assessment, though we still don't have easy and perfect tools, we certainly have far better tools and far better instruments for right ventricular assessment today compared to 10 years ago. For us to really be on top of risk assessment in a patient with pulmonary hypertension, we must be able to measure right ventricular response to pulmonary hypertension in a very reliable and reproducible manner.

Dr Schilz: So Srinavas, for you, the right ventricle is really the key. And really walk distance, other kinds of parameters,t to some degree pale. You don't discard them and certainly declines in 6-minute walk have recently been shown to be more important. I think all of us would agree that no matter where you start, if you're declining because of your disease process, that's bad and that represents a risk. Charlie and Rich, from the pulmonary perspective, right ventricle, what do you think about it, as far as its role in this, in your algorithm for risk assessment?

Dr Burger: I would agree with Dr. Murali's comments. I would put it in the context that in my particular practice, we have dedicated echo techs and cardiologists interested in the right ventricle, with focused assessments as it would relate to not only the degree of elevation of pressures but what's going on with right ventricular contractility and a variety of different ways to assess that, both subjectively and objectively. So it's with dedicated resources, with commitment and expertise in that area, that I've been fortunate to have the reliable echocardiography assessments of right ventricular size and performance such as TAPSE, RIMP, and strain. The second comment I would have is I personally look at the echo images with the cardiologist and not just rely on an interpretation that might come out of the busy echo lab. And then thirdly, it's still within the context of seeing the patient, talking to the patient, understanding what are the components that might contribute to that functional class assessment. We also add in BNP, heart rate response at the end of the walk versus heart rate recovery at one minute. So it's a constellation of assessments, all coming back to Dr. Murali's comment, is what's the compensatory status of the RV at the

time, does it remain coupled or are there signs of decoupling? But it's not a single measure. It's a composite.

Dr Channick: I certainly don't disagree with the comments. I guess I would take a little bit-- just for the point of discussion--different view and say that there are objective parameters and there are subjective. You can dichotomize it. How the patient feels and functions are important; in fact, they're the most important to the FDA, which is why they use that term "feels, functions, survives" for drug approvals. But in practice, it's not always that simple. And, we've all seen patients, typically men--that's a joke--that say, "Oh, I feel great, doc," and you look at them as their wife is shaking her head to indicate the patient is basically in horrible shape, but says they feel fine. If you didn't know anything about that patient, you'd say he's probably a class 1 patient, because he's got no complaints. So that's an extreme example, but I think you can only take a subjective so far. I think we need objective confirmation. I mean, I still like hemodynamics, even though drugs aren't approved based on that. I still think that invasive hemodynamic values really do tell me a lot about how sick this patient is and how I risk assess.

Dr Bourge: I agree with you, Rich. In fact, if you look at the things I mentioned early on where we strive to get our patients, they are really surrogates for right ventricular function. Some of them are direct measurements in terms of cardiac output, but I think the 6-minute walk test, jugular venous distention, all these things are affected most by the cardiac output or cardiac index, much more than the pulmonary pressure. That's why I tell patients to forget about your pulmonary pressure.

Dr Channick: Exactly.

Dr. Bourge: The first thing we're going to see that gets better is your cardiac index, because how much blood your heart is pumping is going to get better. And one thing I would love to know--and maybe somebody on this phone call can tell me-- is why do some patients that we're treating continue to spiral down and their RV function gets worse even though we're treating them appropriately. I've never heard an adequate explanation of that. Very frustrating. Those are the ones we list for transplant and transplant.

Dr Schilz: Bob, that is a great point and certainly the increasing focus of research in recent years. To summarize this part of the discussion, all of us, number one, don't trust words on pieces of paper. Even the pulmonary specialists among us read our own echos and assess RV function as an important part of our risk assessment. Rich brings up an important concept of subjective vs objective measures of function and potentially misleading subjective patient reports and suggests the additional importance and correlation of hemodynamics in an overall strategy for evaluation.

Although we cannot discuss all of the subtleties of evaluation, I did want to point out the occasional disconnect between walk distance and RV performance and hemodynamics; the patient walking 500+ meters with a moderate to severely dilated RV and significantly abnormal hemodynamics. These are less frequent but represent patients who are still at great risk and in my experience will deteriorate sooner rather than later. For the most part, however, I must say the patients that are long-term survivors, decades, appear to be people who have had robust responses, normal or near normal RVs, very good hemodynamics which start approaching normal or achieving normal, sometimes assessed with exercise. They have no RV failure, and unless they have orthopedic limitations, in general have very good and maintained walk distances. Has that been your experience in the long-term survivors among the panel?

Dr Bourge: In general I agree with you. We also obviously have to take into account other reasons why people can't walk far, like orthopedic reasons. But assuming there's not one, I agree with you.

Dr Schilz: So I wondered if we could, realizing that we're still trying to look at the overall strategy, examine for a bit in our remaining time, goals of therapy. We know that goals have been outlined in various fashions in various guidelines over the years. And currently, I think there's a continued discussion, certainly at the World Symposium, the last World Symposium, consistently evaluating goals. I think Rich pointed out earlier, that we should continue to aggressively look to see that we are achieving goals or improving patients. And number three, picking more aggressive goals as a standard rather than an exception. So Bob, I think you were talking a bit about your strategy and part of your goals was restoring near-normal functional class. Could you tell us a little bit about that?

Dr Bourge: Well, balancing side effects obviously is important in our center. I learned that from epoprostenol, when it's all we had. We had to balance effect versus the side effects of the drug. In order to achieve this balance, we add drugs or increase dosing until patients have as little symptoms as we can get, with no sign of right ventricular dysfunction. We try to go for early class 2 symptoms: a 6-minute walk test of greater than 300 meters, JVD less than 10, 11 cm of water. We advance therapy until the cardiac index is normal if we can get there and have no signs of overt right heart failure, meaning the right atrium is not enlarging, etc., etc.

Now, to do that, we have to also not only take into account the side effects but patients' wishes. Fortunately, today we have other ways to give prostanoids, other than IV, because many patients don't want IV. We're soon going to have an implanted pump which really markedly changes the outlook of giving prostanoids. One patient I mentioned earlier-- I have two--but one of the ones that was in the original epoprostenol study, now has the implanted pump. She's class 1. She sees me every 6 to 8 weeks to refill her pump and she takes two pills every morning. And she has no symptoms whatsoever. And this is a lady who was near death, because she was randomized to placebo in the original Flolan study. Fortunately, she got it, in the open label phase, just after we entered that phase and she did better over the years.

So again, our goal is quite simple. We divide the patients into the less sick and the more sick. Gestalt is a big part of that. If they're the more sick, they're going to start out with a prostanoid and we're going to rapidly add a PDE-5 and then usually, unless there's a reason not to, endothelium antagonist. Patients that we start out with a prostanoid, once they've gotten better, we may be able to wean the prostanoid down onto some oral prostanoid or one of the other newer drugs, if you will. So we try to improve their quality of life from the disease and not make their quality of life bad from the therapies. That's my quote to our group. Improve the quality of life from the disease but don't make it worse because of the therapies you're giving. That was the reason I pushed for actually 14 years to do this implanted pump study, so we'd be able to give IV, without people dangling from a Hickman or a Groshong. This patient I just described considered it her Christmas present. She got the pump on December 4th, the first year of the study. It changed her life totally.

Dr Schilz: Very good. Rich, you had said before that you can start therapy in many ways but when you look at any patient, ideally what is your goal which you would like to attain, both ideally and practically, to optimize their long-term survival and well-being? Ideally when you evaluate a new patient, what do you want them to look like in 6, 12, 18 months?

Dr Channick: It's a combination. You want the quality of life to be good. So again, it depends, I think Bob said that initially, it depends on what they want. If for example, it's an older person who just wants to be able to do light housework and isn't going to be running or doing any great exertion then, that's your goal, or to stay out of the hospital. If it's a young person, the bar may be set higher-- and it's set higher not just from how you make them feel, but even hemodynamically. I mean, when I have a young idiopathic PAH patient, a young woman, my goal is virtually normal echo and normal hemodynamics. And we're very aggressive. If I re-cath them and we still see p-amine that's mildly elevated and a PVR that's not quite normal, the patient may feel fine but I'm thinking, "You're 30 years old. We want you to go to 80. So, we're going to add madications; we're going to be very aggressive." Even if the person were 70, I might look at that cath and say, "Geez, that's awesome," or that echo. So it really does depend on the patient substrate and who you're dealing with, as to how high a bar you set.

Dr Schilz: Right. Rich, I think just from a practical standpoint-- just to chime in on this topic as other than the moderator--I think to simplify things, I agree with your statement across the board, but also I'd start with the tenet of wanting to turn people normal or nearly normal, unless I have a compelling reason not to do so or I run out of medication. I think that, again to be provocative in the discussion, I completely agree with all the modifiers that everyone has said. Patient perspective, drug tolerance, acceptable goals, acceptable longevity, and so forth. But I think I start with a very high goal, which I think is becoming increasingly advocated in guidelines. And I think that this drives my decisions. Rich, as you point out, just feeling good or walking 600 meters is maybe not good enough if your RV is moderately dilated and your mean PAs are still 60. I still do have those patients every once in a while. For me, assessing and setting goals very high is more my standard and only backing away from those goals with compelling reasons to do so. Srinavas, Charlie, your perspectives on goals and how you think about goals in the context of therapeutic choices and treatment escalation?

Dr Murali: So, Bob, as everyone knows, the diseases have significant heterogeneity. And because of that, I think the goals have to be individualized. You have to really tailor your goals to the patient, as some of you have already commented. If the desire is to improve survival, obviously getting the patient or having an aggressive goal to get the patient completely asymptomatic and restoration of good or normal right ventricular function will achieve that endpoint. So you have to discuss the goals. You have to tailor the goals to the patient and be aggressive about pursuing those goals. Which then means that you often--and this is what is interesting about pulmonary hypertension-- to achieve goals, you often have to make decisions related to escalation of therapy before the patient may actually complain of worsening symptoms. So if serial assessment shows that perhaps the right ventricular size is getting bigger or if strain imaging shows deterioration (there's some wonderful recent data from Europe on the prognostic value of that) even in the absence of a decline in symptoms, I may consider escalation of therapy. Whatever method you use, if you recognize a change in risk based on any of these parameters, that shouldn't stop you from being aggressive and escalating therapy, so that you can continue to strive to achieve the goals you set for the patient.

Dr Bourge: Well put.

Dr Schilz: I think, you bring up a the important concept of anticipating problems, that is, deterioration. Many times, we see patients who have been started on therapies that have been ineffective or minimally effective and kept on those therapies until they have declined a great deal. This in my mind is a failure of follow up and treatment strategy when the patient's goals were higher. I agree with you; in my practice, I escalate therapy based on failure to move toward goals, not decline. Unless of course the patient is on maximal therapy with initial reasonable goals and only has transplant left as a therapeutic option. That may be the only patient where I would escalate therapy--transplantation--primarily in response to a decline. It sounds like what you're saying is if you wait until people are measurably, demonstrably in greater right heart failure with poor exercise tolerance, that that's just not acceptable for you. Furthermore, that trying to anticipate decline by looking at subtle changes, monitoring right ventricular performance, and anticipating problems is critical. Rich, I believe you referred to that, as well, as you mentioned you want to make sure that you continue to move toward goals, without letting patients

either languish or fail to advance. Rich and Charlie, your strategies on advancing therapies and looking at goals in the context of both adding on therapies and in response to what triggers?

Dr Burger: I think it's obviously reflective of a push in medicine to more objectively rely on methods by which you can make shared decisions. And, being in this space, I think we've all evolved to having that forthright discussion early on, as to what the specific goals of the patient are. And it's evolved from "do you want a pump or a pill?" No, that's not the question. The question is, "what do you want to achieve?" And as has been described, depending on the circumstances of that particular individual patient, then you make decisions regarding therapy to achieve those goals. It may be that it's very aggressive to get normalization of right ventricular function to maximize the ability to survive, even with some significant burden of side effects or complexities of drug delivery versus just being able to do a certain amount of activity. Conversely, there may be a patient not so concerned about longevity and would prefer to have minimal side effects, minimal medications, minimal interventions, minimal risk of therapy. So it's teasing out those details in an individual situation that guides my decisions regarding escalation, not only in terms of numbers of medications, but types of medications.

Dr Schilz: Rich, your perspective?

Dr Channick: Very similar approach to Charlie's. But I think it goes beyond that because we have these emerging data from long-term morbidity and mortality studies. These studies suggest that the purpose of multiple therapies isn't just to improve patients, but to prevent worsening. And so to that end, I sit with a patient and go through the data from all these long-term studies that we're now doing, saying, "Look, , you're feeling good now. You're a class 2. You're walking a lot but we have evidence that by adding another drug or another two drugs your likelihood in the future of getting worse is maybe cut in half." That's a little bit harder for them to accept because they're feeling pretty good. But, data are data, and reduction of hospitalization risk, reduction of need for parenteral therapy, avoiding transplantation--I'm often presenting that sort of a strategy for why we may want to be more aggressive.

Dr Schilz: Rich, it seems like you've incorporated both the data and also your experience for patients to continue to do well over the time. It's a fair statement?

Dr Channick: Yeah.

Dr Schilz: Very good. Well, the hour is late. What I'd like to do is go around the room and close out with final comments on some of the challenges and the difficulties that you see in the patients that get referred when experience and guidelines don't always meet. So I'll give you a bit of a time to think about that, while I summarize some of our discussions.

I think we've identified the fact that guidelines do not take always take into account the complexity of patient presentation. They may not take into account the multiple factors that may represent risk, as well as the heterogeneity of single functional classes. Practical assessment of patient may reveal incredible gaps between reported symptoms, hemodynamics, and performance, which are often very indicative of risk.

Number two, application of aggressive monitoring and aggressive re-evaluation of people as they're moving toward goals has been echoed by all. This evaluation needs to take into account a number of different factors, including individual preference. And lastly, understanding that all drugs, both with regard to efficacies and side effects, are different and that the ability to make people better may be affected by those choices. So in final comment and final closing, Charlie, your perspective?

Dr Burger: First, I just want to thank you for facilitating what's been quite an illustrative discussion, in my opinion. Clearly, there are lots of available resources to support good treatment decisions, such as current publications, guidelines, and experience in this field. But yet, a whole lot more to learn. I would just encourage folks to take advantage of this particular issue of *Advances*, as it addresses a variety of relevant topics. And to continue participation in other forums, such as that that's provided by the PHA, where a difficult case are discussed, and allows a variety of different experts to weigh in on different approaches, not only the diagnosis and treatment. So, more to learn and I've been honored to participate in the roundtable and certainly have benefitted from the discussion.

Dr Schilz: Charlie, thank you. Srinavas, your perspectives on integrating guidelines, goals, and your lessons learned over the years?

Dr Murali: I also thank you, Bob, for arranging this very, very interesting discussion. When you think of guidelines, I think it's important to recognize that guidelines are recommendations. They are recommendations that allow you to decide on a direction of therapy. And that's what they are. The guidelines are developed based on evidence in the literature and evidence in the literature comes from clinical trials which have specific inclusion/exclusion criteria and statistical analysis. Whatever it is, I think guidelines are just recommendations. So you have to take it in that context when you apply them. Since you're dealing with a very heterogeneous disease, you have to articulate goals of therapy and tailor those recommendations to each patient individually to get the best clinical outcome. Because of that, I think guidelines are not a cookbook recipe that applies to everybody. And the outcomes may not be as predicted by the guidelines in every patient. These are some of the gaps that we encounter, not just in this field, but in any field when you translate guidelines into clinical practice. But as the guidelines become more mature, as more robust data become available and some of these gaps will narrow, and perhaps then the translation of guidelines to clinical practice can be absolute. In pulmonary hypertension, we are not there yet.

Dr Schilz: Very good. Rich, your closing perspectives?

Dr Channick: Thanks, Bob. Great discussion. I would echo what I think the others are saying and maybe it does have to do with our advanced experience levels or age, you might say, the 100 years. If guidelines were perfect, you wouldn't need physicians, right? I mean, you could just go down the recipe and say, "This is what I do, number 1, number 2, number 3." I don't think we're there nor I don't think we'll ever be there. I think in complex diseases like pulmonary hypertension there's too much heterogeneity; there are too many nuances, so that a set of written guidelines can't manage patients. It can bring up very broad ideas about treatment strategies based on very well done clinical trials, but I don't think it is nor will ever be a substitute for clinical judgment and experience. So I guess that's job security. (laughter)

Dr Schilz: Well put. Speaking then from job security, Bob, as was pointed out earlier, you have some of the longest job security among us. I thank you for joining us in this discussion. Your closing perspectives?

Dr Bourge: Well, let me thank you, too, like the others. I'll say having participated in lots of calls like this, Bob, you did the best job of anyone I've ever been on, in terms of moderating and getting people focused. You did a great job. What I like to say in terms of following the guidelines, and this is actually what I say to a lot of medical directors of insurance companies, guidelines are recommendations, they're not, and I underline, not rules. In other words, they're suggestions on how to do it, based on what we know so far and they're continuously changing. I can remember the days when we didn't have any guidelines because there was no therapy, other than hopefully getting a heart-lung block for a patient who was likely to die before they got that transplant. So we've come a long way.

Dr Schilz: I truly appreciate everyone's input to this very important discussion of not-so-straightforward topics and what I think of as necessary exercises in navigating the space between evidence and experience.