Reflections on PHA's International Conference

The Pulmonary Hypertension Association's 10th International Conference occurred June 17 through 19, 2016 in Dallas, Texas. 1,028 patients and caregivers attended the 3-day meeting, and 447 healthcare professionals participated in scientific sessions, abstract presentations, and research opportunities in addition to speaking at patient- and family-focused programs. *Advances* Guest Editor and Conference Scientific Chair Tim Lahm, MD, along with David Badesch, MD, Professor of Medicine and Clinical Director, Pulmonary Hypertension Center, University of Colorado Health Sciences Center; Kara Goss, MD, Assistant Professor of Medicine, Division of Pulmonary and Critical Care, Department of Medicine, University of Wisconsin School of Medicine and Public Health; Eric Austin, MD, MS, Assistant Professor of Pediatrics and Director, Vanderbilt Pediatric Pulmonary Hypertension Program, Vanderbilt University School of Medicine; and Karen Fagan, MD, Professor of Internal Medicine and Pharmacology, Chief of Pulmonology and Critical Care, Director, Pulmonary Hypertension Center, University of South Alabama Health System, shared their observations regarding the Conference during a call transcribed here.

Dr Lahm: Thank you for taking the time to talk about the 2016 Scientific Sessions and the Conference. My goal for today is to review the meeting with you and to see what everybody's thoughts are. As you all know, this year's conference marked a remarkable milestone as it celebrated the 25th anniversary of the Pulmonary Hypertension Association. Since several of you have been coming to the conference for a long time, as a first question, I wanted to find out from the group how the conference has changed over the years. So maybe Dave, you can get started on that?

Dr Badesch: The first conference, as many of you probably know, was held in Stone Mountain, Georgia. It was a small meeting, and involved what has become the Scientific Leadership Council, as well as some patients and their families. I believe Bruce Brundage played an important role in leading the organization at that time. It's grown enormously over the years. That was now almost 25 years ago, and the conferences have occurred every two years. It has become, I think, the premier international meeting for pulmonary hypertension patients, caregivers, nurses, physicians, and other professionals. It's always been an exciting meeting for me, and it just becomes more so over time. The organization now has thousands of members worldwide. And the meeting is typically attended by somewhere between 1,400 and 1,800 participants. The scientific sessions were a relatively later development, and have been an important addition. It's a full day conference, in advance of the patient-led and professional-led sessions that occur over the weekend.

Dr Lahm: Thanks, Dave. Eric, what are your thoughts?

Dr Austin: You know, I thought the same. This was my fifth conference, and we have witnessed a tremendous growth in the interaction and the opportunity to interface with people of all walks of life relative to pulmonary hypertension, similar to what Dave just mentioned. A particularly exciting change for me is the development of the scientific sessions, which has become an important calendar piece for the PH clinician and scientist to get an understanding of a broad view of what's going on in the field. The scientific sessions this year certainly lived up to this expectation. I was very impressed and thought it worth the time and effort it took to attend; it has maintained an important presence despite a large slate of conference opportunities in our field. The other thing that I would highlight that was exciting to me is the growth of the research room, which was created by Dr. Greg Elliott in collaboration with the PHA years ago. It has really grown and developed due to tremendous investment of time and energy by the PHA staff, patients, families, and the investigators who participate. We are seeing more and more studies each year that derive at least in part from interactions established in the research room.

Dr Fagan: This was my eighth conference and I concur with Dave and Eric. As Eric mentioned, the growth of the scientific sessions has been an additional way to unite clinicians and researchers in our common cause and, especially for the scientists who work mostly in a laboratory, bring them together with the patients.

Dr Badesch: The other thing that's evolved over the course of the conference is the international involvement; it has increased dramatically. There are now patients, family members, and providers that attend the conference from around the world. And that's certainly a development that's occurred over the last 10 to 15 years or so.

Dr Lahm: Thanks; these are great points. I can certainly echo that there's a lot of positive energy at the conference, no matter where you go. And the research room is a truly unique component of the conference. I participated in a project there two years ago, and I was just amazed by how much is going on there and how motivated the patients are in participating. They are literally lining up in order to participate with as many projects as possible. So it's truly remarkable. Kara, I wanted to ask you about your impressions, since this was only the second time for you that you visited the conference. And I know the first time you went, you were very involved with the research room and didn't have the opportunity to explore other parts of the conference in great detail. So what about this year? How did you experience the conference, as somebody that is relatively new to the PH com-

munity? How does it compare to other meetings that you attended in the past?

Dr Goss: I think the PHA conference is a really unique venue for a number of reasons, and I realized that when I was there for the first time in 2014. As you mentioned, I was predominantly in the research room and conducting a survey of pulmonary hypertension patients. We had over 50 patients respond to our survey, and the number of patients who showed up and were willing and eager to participate in a number of different types of research projects was really impressive. To have that sort of collection of patients in one place for quick and relatively easy sampling is really a testament to what's been done over the years with the research room. But the thing that really struck me both times that I attended the conference is really how multidisciplinary it is. You know, we have patients, caregivers, providers of all levels-- whether it be respiratory, nursing, nurse practitioners, physicians--and it's really the only conference that I've been to that I think is that integrated from a standpoint of the number of different faces of the care of pulmonary hypertension that are present and dialoguing together at one point. So that I think is one of the really unique features of the conference. As you mentioned, I did attend the scientific sessions in 2016. And I would agree and echo with what's already been said, that it is a very nice overview of the big picture--global aspect and global science--that's happening with regard to pulmonary hypertension and pulmonary hypertension research. I know each of us has our own focus within a piece of that, and so it's nice to come together as a group and a community to think about how we can approach the broader picture.

Dr Lahm: Super. Well, thank you all; these are all great points. The scientific sessions this year focused on global aspects of PH and the progress we have made over the last 25 years, and I wanted to circle back to that part. Dave, you gave a fascinating talk that focused on what we have learned from the modern worldwide registries. Can you talk about some of the more surprising findings that came out of the registries when you put the data together?

Dr Badesch: It's interesting, Tim. Looking back at the initial registry, conducted by the NIH in the mid-1980s, a female-to-male predominance of about 1.8:1 was noted. And I think that's led to a lot of interest over the years in why the disease is more common among women than men. The REVEAL Registry was completed five or six years ago now here in the United States, so it's a much more recent registry than the NIH registry, and showed a female to male predominance of about 4:1. So the female prevalence in the disease appears to have increased over time, at least here in the United States. That's very interesting. And I know that it's the basis for a lot of ongoing research in the field. Eric Austin can certainly comment on this. The female-to-male predominance may be an important clue in terms of understanding the disease, and perhaps trigger factors and second hits and things. I'd be interested in Eric's thoughts on that in a moment. But another thing that became apparent in comparing the registries is that we really don't have a good handle on the role of anticoagulation in the treatment of these patients. The REVEAL Registry kind of suggested one thing with respect to the effect of anticoagulant therapy, while the COMPERA Registry might suggest something else. I think this just once again points to how registries can raise questions but not always answer them definitively. A trial is needed in that area to sort out the potential role of anticoagulant therapy in pulmonary hypertension and the patient populations that might benefit the most from it. I think it's also interesting, when one looks at registries from around the world, that perhaps the disease differs just a little bit across different geographic regions. I would say that perhaps one of the most important things I noted as I was putting this talk together is that access to therapy varies a lot around the world. I learned this personally from some involvement in South Africa. We certainly have our own issues with respect to access to therapy here in the United States, but the challenges that we face are nothing compared to what lesser developed parts of the world face in terms of accessing these expensive therapies. I think we've made considerable progress in treating the disease, and that becomes apparent from these longer-term registries. Survival appears to be improving over time, from a median survival of perhaps 2.8 years to something more like 7 years or greater now. And our ability to predict survival is improving as we develop better predictive models, with the REVEAL Risk Score being just one of those. There are certainly other predictive models, from the French Registry and others, that help us to counsel patients and to perhaps better time the need for things like transplant.

Dr Lahm: Those are a lot of really interesting and pertinent points. And all the points that you raised clearly underline how powerful registries can be and how much we can learn if we really pay close attention to the patients that we see and if we combine all our observations across the country and across the world. Eric, since Dave mentioned the female-to-male predominance, and since this is one of your areas of interest, can you share with us where we currently are in this field? Have we figured out why there is a female-to-male predominance?

Dr Austin: As you each know well, the registries have taught us so much about the skewed profile of sex in pulmonary hypertension. And it does appear to be rather consistently seen across the board, with a few exceptions, within Group 1 pulmonary hypertension. Epidemiologic information has really opened the door to a lot of interest in the field and scientifically to pursue the sex discrepancy issue. What is exciting to me is that there's a real surge right now of information coming out in the basic science and in the translational fields from many labs in North America and beyond providing a surge of understanding around the molecular reasons that may be different according to sex. But we've also opened up many questions, and those include what is the nature of the detrimental and potentially beneficial effects of sex hormones that contribute to pulmonary vascular

disease, both development and adaptation. It may also be different for different groups of PH, so understanding this is going to be incredibly important as we move forward. From a translational and a human subject focus level, there is very interesting work coming out from multiple groups looking at the way the right ventricle adapts to stress and whether sex and/or sex hormones contribute to this. Novel studies using both PH, non-PH cohorts has improved our understanding of how the heart functions and handles stress according to sex that may have relevance to the individual with PH. And finally, led by translational and the clinical work by Dr. Steve Kawut and colleagues, we now have a clinical trial, sponsored by the National Institutes of Health, that looked at aromatase inhibition, which modifies estradiol levels, in men and postmenopausal women, with a suggestion that at least manipulation of that pathway is safe and worth further study. So the registries have highlighted the inequities by sex, and stimulated further science that is now extending back to human populations into the trial setting. Hopefully, we can help people with PH and also make absolutely certain that sex hormone modification is not detrimental long-term, which needs to be determined.

Dr Lahm: Thanks, Eric. That was a wonderful summary and a great example of how we can leverage the power of registries. Along those lines, Kara, can you talk a little bit about your research, which also started with some astute clinical observations? Can you also emphasize how you used the research room to help address your hypotheses?

Dr Goss: Sure, one of my interests has been in early risk factors for the development of adult-onset pulmonary hypertension. This actually stemmed from meeting a patient in clinical practice and identifying her as a newly-diagnosed patient with significant RV dysfunction and pulmonary arterial hypertension. Interestingly, we identified in talking to her that she had a history of prematurity, and so this really prompted new questions about whether premature birth or early-life exposures or risk factors could be a risk for the onset and presentation of adult pulmonary hypertension. With that question in mind, we began to study an animal model and conducted a survey. The survey was completed in part through the PHA's 2014 conference's research room, and we're now analyzing that data. Certainly, the availability of the scientific community and the research room through the PHA was able to make that possible. To be able to take a clinically-driven question and apply it to a population of patients with pulmonary hypertension is a testament to the PHA community, and if you're working in isolation, there's really not a great option without the help of a group like PHA.

Dr Lahm: Very exciting! I think this is also a good example of how research questions and research findings can influence the design of registries. I talked to Steve Kawut about this a few days ago, because I was wondering if they asked for prematurity or early life events as risk factors for PH development in the PHAR registry. And interestingly, this is not something that is being captured in that registry. But with more and more data coming out that early life events may be an important modulator of PH development later in life, maybe this is something that could be captured in the future in the framework of a registry. So this is a terrific example of how things can go either way--either from the registries into the basic science and/or translational world, or the other way around.

Dr Goss: There is a Swedish registry of pulmonary hypertension patients that looked specifically at history of premature birth and the incidence of pulmonary hypertension in that group versus those who were born at term and suggested that it is a significant risk factor. But I think because it's such a longitudinal study, it takes a large registry and some recognition of what these potential risk factors may be--whether it be prematurity or early life respiratory illnesses, or something else-- it really takes asking a lot of people these sorts of questions to be able to drill down to lead the next line of research on the early risk factors.

Dr Fagan: These examples really speak to the need for the scientific sessions to get the clinicians and basic science and population scientists together to share important observations that lead us to asking better questions to understand *who* gets the disease and leading our scientists to figure out *why* they get the disease.

Dr Austin: You know, the PHA has done such a good job of highlighting this concept of the zebra and finding the individual who is at risk, and making sure that we're PH-focused and aware in our lives, that I'm really excited about these susceptible populations like Kara's work and others' looking at the premature associated lung disease, and those individuals with Down syndrome or those individuals with congenital heart diseases, and the like. It's really exciting that I believe there's a broader understanding of the risk posed to individuals who have certain underlying conditions. I'm really hopeful that that's going to lead to connections with registries, connections with new opportunities, and maybe one day preventive therapies, whether we use our standard therapies as prevention or new novel therapies. So kudos to the PHA for really improving awareness and helping contribute to this.

Dr Lahm: That's a really important point. Since we just talked about prematurity and early life events, I will use this as a segue to talk about pediatric aspects of PH. I know that there was a lot of interest in this area at previous conferences, and previous attendees identified this as an area that they wanted to learn more about. And given this interest as well as the impressive recent activity in this field, we really wanted to cover this area at the scientific sessions with update on pediatric PH. Eric, I thought you gave an amazing talk about the recent developments in the pediatric PH world. Will you highlight one or two findings from your presentation?

Dr Austin: Oh, absolutely, I'd be happy to. I was honored to discuss work that

has been conducted by so many people—this is a really exciting time for pediatric pulmonary hypertension. There has been an increasing recognition in our pediatric clinical field that there are characteristics of pediatric pulmonary vascular disease, and in particular pulmonary hypertensive vascular disease, that are not well represented on traditional World Symposium Classification schemes and that are not as actively represented in clinical trials to date. As a result, there has been a real focus in the pediatric pulmonary vascular disease community to try to highlight the similarities and differences between pediatric and adult pulmonary hypertension. A number of international collaborations are ongoing which we took the opportunity to highlight because of the international focus of the scientific sessions. Some of those include the Pulmonary Vascular Research Institute, in particular the Pediatric Task Force of the PVRI, which has been instrumental in helping to develop a new paradigm for thinking about pulmonary hypertensive vascular disease that I'll talk about in a moment. Additionally, the European Pediatric Pulmonary Vascular Disease Network has really pulled together and made important contributions to clinical and research understandings in the last several years. Here in North America, there's a Pediatric Pulmonary Hypertension Network (PPHNet), made up of ten centers that are actively working together to conduct research to better understand pulmonary hypertension in children. And, there is an international collaboration between Europe and North America that's tracking outcomes in pediatric pulmonary hypertension, the TOPP Registry collaboration. These collaborations, as well as the effort now by the PHCC program to pull together accredited adult and pediatric centers, provide tremendous opportunity to both gather information about children and focus on about how we can treat them better. One exciting example is the development of the PVRI Classification of Pediatric Pulmonary Hypertensive Vascular disease, which highlights some complexities which are unique to the pediatric population. For example, in pediatrics there is a heavy influence of developmental and growth abnormalities that occur pre- and post utero. There are pathologic insults to the growing lung, as well, that contribute to pulmonary hypertension in pediatrics. We have a burden of chromosomal and genetic syndromes that may be larger than seen in the adult clinics, as well as a similar array of individuals who have more traditional pulmonary arterial hypertensive disease such as idiopathic and congenital heart disease-associated PAH. So PVRI has provided an interesting advance forward for our field, to think about how would we classify our children so that in the next set of registries, and in the next set of clinical trials, and in the next set of studies, we can better phenotype people, so that when we go to move to precision medicine, we have an understanding using the broader population. In addition, a recent series of clinical guidelines have highlighted this classification scheme, and used it as a framework to think about diagnosis and management of PH In pediatrics. For those interested, if they have not already, I'd refer them to look at the American Heart Association (AHA) / American Thoracic Society (ATS) Joint Guidelines for Pediatric Pulmonary Hypertensive Vascular Disease and a parallel set of guidelines that came from the European group (The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and of the European Respiratory Society (ERS), both published in late 2015, which provide a set of independent child-focused guidelines for pulmonary hypertension. And so those are some of the areas in which we tried to focus in our discussion at scientific sessions in 2016.

Dr Lahm: Wow, I am really impressed all this progress. For sure, there is a lot of impressive and terrific development happening in the pediatric pulmonary hypertension world. I will take that as an opportunity to steer the discussion toward treatment and drug therapy for PAH. There was an outstanding talk by Dr Vallerie McLaughlin on drug therapy, in which she highlighted the role and history of prostacyclin treatment for PAH. As all of you know, intravenous epoprostenol has now been FDA approved for 20 years, and obviously, this has revolutionized PAH treatment. So I was wondering if all of you can maybe comment on what your thoughts are on the next big thing that will revolutionize PAH treatment. Is there a new epoprostenol on the horizon? Or is combination therapy going to be the next big thing? Are there any other new developments?

Dr Badesch: I think I see three or four major areas of development for treatment going forward. And I think you've mentioned one--how to best combine the therapies that are currently available, so studies of combination therapy. I think the second area of development is going to be novel therapies, therapies with new mechanisms of action and different approaches to the disease, whether it be anti-proliferative approaches or immunomodulatory approaches, or some combination of those things. The third area of growth and development I think might be studying how best to treat pulmonary hypertension that occurs in expanded patient populations. I think we've done a good job of enhancing therapeutic options for patients with Group 1 PAH. But we haven't done so well in addressing pulmonary hypertension that accompanies other heart and lung diseases. So studying those expanded patient populations I think is important and our ability to target therapies. I think the ultimate goal would be the ability to target or more appropriately select therapies for certain patients. So those are areas of future development that I think are on the horizon.

Dr Goss: I'd second you with a comment about the expanded population for patients with pulmonary hypertension outside of PAH. I think that at least half of patients we have referred to PH clinic are non-group 1 pulmonary hypertension patients, many with significant pulmonary vascular disease and significant RV dysfunction. Those patients are incredibly challenging to know how to treat because the trials are really lacking. There's certainly evidence of harm with some of our current therapies. A number of trials really aren't as well designed as we would like to see to specifically target

the patients who would be most likely to benefit; i.e., those with higher pulmonary vascular resistance, heavier burden of vascular disease, or RV dysfunction. So I completely agree that that is something that needs to be addressed in the next several years to help us clinically know how to treat these patients. The two other things that I would mention are, number one, targeted therapies for RV dysfunction and RV failure. Perhaps that's the target for some of these group 2 or group 3 patients that we've been missing. But there currently aren't any specific therapies that would target the dysfunctional RV. We think of it as a muscle and an afterload problem, but there may be specific therapies that would further enhance the RV's ability to withstand a higher afterload and improve patient outcomes. The second thing that I would mention as a new area-- and this kind of relates to what Eric was mentioning about pediatric pulmonary hypertension-- is a target for the developing pulmonary vasculature. If you could really help support a developing or growing pulmonary vasculature early on, you may mitigate some of the risk for patients who then, as they begin to age and begin to have vascular dropout, are more susceptible and more likely to develop pulmonary hypertension long-term. So particularly if we know who those high-risk patients are and can help them develop a normal vascular surface area early on in life, we may significantly decrease their risk for disease long-term.

Dr Austin: I think that was really well said. When you think about what would revolutionize – it would be novel therapies that are going to work toward reducing the underlying pathophysiology that is occurring. For example, reduce the intimal proliferation, medial hypertrophy, and adventitial expansion, all of which may be helped by our current vasodilatory-directed therapy but may not be profoundly helped. I agree that overall, we are in an exciting time. The pediatric group has been fortunate to really follow in the footsteps largely of the ongoing adult pursuit of care and care combination approaches; for example, the AMBITION trial was an important study for all of us which has both influenced practice and clinical trial considerations moving forward. I believe that the pediatric community coming together to try and perform clinical trials that are either sponsored or not sponsored by industry is going to be revolutionary in the pediatric world and I hope soon to expand.

Dr Lahm: I completely agree. There are so many exciting developments. We have – rightfully so - focused a lot on the pulmonary vasculature in PAH, and that is clearly an area where exciting developments are going on with new therapies. But clearly, there are other areas that are worth addressing, such as the RV and the pulmonary vasculature in non-PAH PH. One of the things that will be interesting to see is whether PAH therapies will be able to help alleviate non-PAH PH or if we will need a separate set of therapies and approaches. Another of the things that may help us here--and that has been raised by several of you--is the issue of targeted therapy or personalized therapy. Martin Wilkins gave a really nice and thought-provoking talk on that topic. He promoted a way of thinking that really focuses on targeted and personalized therapy. I was wondering if everybody thinks that this is the future of PH therapy? Is it going to be similar to the oncology approach where patients are assessed for underlying genetic or genomic mutations and therapies are then directed toward the affected pathway?

Dr Austin: Boy, I sure hope so. I think, as Kara mentioned, one of the things that is so challenging with pulmonary hypertension is that many of these people have other illnesses, as well, or other diseases. But, it is important for clinical trials to have a tight phenotype, which sometimes hurts generalizability. For example, for those patients with mixed left-sided dysfunction and pre-capillary pulmonary vascular disease, it can be challenging to apply existing clinical trial data that is focused on a more-clear cut phenotype (e.g., Group 1 PH). That is just one example of the manner in which it would be exciting to really focus our therapies, as Martin Wilkins highlighted, at a personal level. What is so challenging about that is first coming up with enough individuals with a spectrum of disease that's similar, yet sub-phenotyped, that we can understand how to then take it to the personal level. That is going to be an important and exciting advance.

Dr Lahm: Yes, I completely agree. And your group has done some beautiful work in this area, looking at genetic differences and similarities in pre- and post-capillary PAH. Dave, you as a pioneer in the field of PAH and PH treatment, do you anticipate a strong role for personalized medicine in this area in the future?

Dr Badesch: Oh, absolutely. You know, I'm excited to think about where we'll be in 10 or 15 years, Tim. Right now it's such a shotgun approach. I think as basic scientists, including yourself, Eric, and others, learn more about the pathogenesis of the disease, we're going to be able to target the underlying mechanisms. I think we're going to learn how to better profile patients, both phenotypically and genotypically, and that will help us to target our therapies on an individualized basis. And I think, I'm hoping at least, that in ten years, we'll be looking back on what we're doing now as being rather crude. It would be terrific to enhance long-term efficacy and avoid off-target toxicities, addressing the proliferative and immune components of the disease that have been somewhat neglected to date. So I'm excited about the future.

Dr Fagan: The hope and promise of personalized medicine for the future of PH treatment will be a milestone achievement for sure. It is both far away and nearby in terms of achieving this goal and the International Conference, research room, and scientific sessions are all going to play an important role in facilitating these discoveries.

Dr Lahm: For the last few minutes that we have, I wanted to talk about some of the abstracts and the science that was presented from young investigators. We had more than 80 abstract submissions

this year, both from the basic science as well as from the clinical science side. I am interested in everybody's thoughts on what you heard at the meeting that you felt was particularly promising or exciting to you. And if there were any exciting new things that you learned?

Dr Fagan: I enjoyed walking amongst the abstracts to see the work and hopefully meet the persons who did the work. As a fellow and junior faculty these types of sessions were really important to helping my career but also in making me feel part of the PH professional community. Those interactions have resulted in collaborative relationships as well professional and personal friendships. Specifically, attending the International Conference and Scientific Sessions helped me develop my relationship with the PHA. I love that we continue to prioritize the poster sessions so that others con hopefully develop these same relationships and commitment to PH.

Dr Austin: You know, I think the use of systems biology is upon us and provides great opportunity to expand knowledge. I was excited by the combination of different aspects of -omic therapy—the concept that there are people who are now understanding how to take multiple layers of data, genetics, RNA-seek or expression data, proteomic data, maybe metabolomics, and also clinical variability, lay them together, and then demonstrate associations with whatever outcome is of interest at the time, be it PVR, be it clinical outcomes, survival, etc.

Dr Lahm: I have to say, I really enjoyed the oral abstracts. I thought those were really exciting and really novel. And they – actually, I think all or most of them-- have now been published in high impact journals, so that was great. I especially enjoyed the one about the prolyl hydroxylasein PAH pathogenesis. There was a teriffic abstract on TGF-beta 1 and 3 subtype inhibition with a TGF-beta trap. And then some really teriffic from your group, Eric, looking at RV lipotoxicity.

Dr Austin: The role of the RV in PH is clearly so important, but not my personal area of research expertise. Evan Brittain and Anna Hemnes and others here at Vanderbilt and certainly beyond have made compelling findings regarding impact of RV changes on pathogenesis and adaptation to PH.

Dr Lahm: That impressed me a lot. Yeah, so I think with that, we have covered a lot of ground in the last 45 minutes. And as Dave alluded to, I think we can all agree that there have been great developments, that the future is bright and, if we have this conversation again in 25 years or so, we probably will be able to review a lot of cool, novel, and cutting edge developments that will have occurred by then. So I would like to thank all of you for taking the time to join us on this call. I really enjoyed hearing all your terrific thoughts. Thanks again.