Roundtable Discussion of the Impact of the 4th World Symposium on Pulmonary Hypertension


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A discussion among attendees of the 4th World Symposium on Pulmonary Hypertension took place to share "an insider's look" into the current and future research and treatment implications in pulmonary hypertension. Myung H. Park, MD, guest editor of this issue of Advances in Pulmonary Hypertension*, Assistant Professor of Medicine and Director, Pulmonary Vascular Diseases Program, Division of Cardiology, University of Maryland School of Medicine, Baltimore, moderated the discussion. Participants included Robyn Barst, MD, Professor Emerita, Columbia University, New York; Marc Humbert, MD, PhD, Universite Paris-Sud, French Referal Center for Pulmonary Hypertension, Hopital Antoine-Beclere, Assistance Publique Hopitaux de Paris, Clamart, France; Ivan Robbins, MD, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; and Lewis J. Rubin, MD, Clinical Professor, Department of Medicine, University of California, San Diego.*

Dr Park: Thank you all for participating in what I hope will be a stimulating and insightful discussion from the 4th World Symposium on Pulmonary Hypertension at Dana Point. The meeting was composed of 11 scientific working groups reviewing and discussing the most current research and information on pulmonary hypertension (PH). The goals of this discussion are to: (1) gain your perspectives as the key contributors of this meeting; "an insiders' look," if you will; (2) learn your thoughts on the progress that has been made in pulmonary arterial hypertension (PAH), specifically focusing on the past 5 years since the Venice symposium; and (3) to gain some insight into the future and the challenges that lie ahead of us. So to start the discussion, can you share your thoughts on our current state of knowledge on the genetics of PH? I know this was the main focus on several different parts of the published reports—understandably so given the tremendous amount of research that has been accomplished in this field. What are the current recommendations regarding the screening process? Specifically, who would you recommend this to and when would such a screen be appropriate? And from a clinical view point, how does one follow these patients once they're identified? Dr Rubin, maybe you can start the discussion?

Dr Rubin: You know, I think maybe Ivan would be the best one to talk about the genetics.

Dr Robbins: Okay, I'll say a few words. The classification was changed to reflect our updated understanding of the genetics of PAH and in the Dana Point classification, there's a new category of heritable disease. This includes the families that have a known mutation as well as patients who were previously felt to be idiopathic, but then were found to have a mutation. And at that point their disease becomes a heritable disease. Then, of course, there are well-described families in whom we have not been able to identify a mutation. With regard to following patients with heritable disease, there are some recommendations for serial echocardiograms in family members at risk, although there are no good data supporting this recommendation We've tried to look for some biomarkers and haven't been successful.

Dr Barst: I think at this point we do not have specific recommendations based on a consensus. And the recommendations really reflect the clinical investigator and clinician. But the one point I'd like to stress strongly is that I do believe there is a very strong consensus from the PAH community that genetic testing should not be done without prior and ongoing genetic counseling. And I think that really is something that's very, very important to recommend, that first degree relatives don't just go obtain genetic studies without really going through counseling with the genetic counselor who has the experience working with a PH center.

Dr Park: So if you're counseling or discussing this with a patient of yours, what specific advice would you give them as to who this is most appropriate for and where they would go to get this kind of specialized genetic screening?

Dr Barst: There are at least several PAH physicians who have had a focus on the genetics of PH including Vanderbilt, Columbia, and Utah, as well as several other

centers. I think it's valuable if there is a family followed by another center for that investigator to contact one of the larger centers that specifically has genetic counseling. I think all of these centers have lay information that we've always had available for our patients and families. That's certainly a starting point. It doesn't mean that the patient or his or her family needs to go to one of those centers, but I think it's something that can be discussed. As we've all seen, there is enormous guilt on both sides of the family. There's guilt if you've given the gene to one of your children and you don't have the disease, and there's just as much guilt if you marry someone who has the gene and now your child has the disease and you shouldn't have married someone with the gene. So it's really very, very complicated. And it does a disservice to patients just to have genetic testing. Now the one instance when I think it is very valuable is if we have a family where we have identified a mutation and there is a woman who is of childbearing age and the issue comes up with regard to potential for pregnancy. Certainly if she has genetic testing and does not have the mutation and it's been well demonstrated in her family that the disease is associated with the mutation, to me that's a valuable use for genetic testing. I'm quite comfortable in that instance saying to this young woman that I believe she can go ahead and plan a family.

"I do believe there is a very strong consensus from the PAH community that genetic testing should not be done without prior and ongoing genetic counseling."–*Dr Barst*

Dr Park: Certainly for family planning, this would be a very important discussion to have with the PH specialist. If I may move on to the next topic, the other very comprehensive portion of the report covers our current knowledge on the pathogenesis and molecular biology of PH. Can you share your thoughts as to what are the new key pathways that have been identified during the past 5 years? And which of those pathways do you think holds the most promise in being translated into potential new therapies within the next 5 years?

Dr Rubin: I think we need to recognize that while we have made advances in our understanding of the pathogenesis of this disease, our understanding remains quite incomplete. There are a lot of abnormalities that have been identified. Which of these is important or central or even contributory to the pathogenesis remains to be determined. One of the ways I think we find this out is with clinical trials that use treatments that target those diseases, those mechanisms. And they help clarify for us the relative contribution, the relative importance of those pathways. Certainly there is a great deal of interest in tyrosine kinase inhibitors. You know growth factor pathway contributions; I think there's interest, great interest, in that. There is VIP, vasoactive intestinal peptide. There is interest in that, and a clinical trial is underway that will help, I think, to clarify that potential role. But we have a lot of potential pathways and we still don't have a full understanding of the disease mechanism. We'll need to prioritize for clinical trials which of those pathways have the strongest rationale and the best evidence to go after at this point because our opportunities to study patients in clinical trials are somewhat limited.

Dr Park: Thank you, Dr Rubin. Certainly a number of interesting potential targets for new therapies exist. Dr Humbert, any additional thoughts?

Dr Humbert: The first thing we can say is that we still have no cure for the disease, but we understand better how to use the treatments targeting endothelial cell dysfunction. We still have a lot of work to select novel pathways which should be targeted in priority. It is widely accepted currently that growth factors such as PDGF or VEGF may be of interest, and we will soon test growth factor inhibitors, which may have a positive action on pulmonary artery remodeling. In addition, genetics may help us identifying additional pathways of interest within the transforming growth factor superfamilly. However, despite the fact that we understand more and more the complex pathways involved in heritable and idiopathic PAH, we still don't know really what should be the target to select in order to prevent or to reverse pulmonary vascular remodeling. Maybe we should emphasize the fact that pulmonary vascular remodeling is extreme in PAH and, when the patients are symptomatic, the vessels are really markedly remodeled. Maybe we should have better tools to identify as early as possible remodeling in patients with predisposing conditions such as systemic sclerosis or genetic risk factors in order to intervene earlier. But this is still science fiction. We don't have any clue to say that early intervention will translate into reversal of the condition.

Dr Barst: I think Marc brings up something that's very valuable in that it's a potential prospective study or trial that could be considered. I'm not saying that this is being done or should be, but it's an area where perhaps we really could investigate, prospectively, patients that are at increased risk to develop the phenotype, that is obligate carriers in families in whom we have demonstrated a mutation. If we identify a cohort of carriers who, in fact, are truly asymptomatic with normal oxygen consumption and normal ventilatory efficiency and normal hemodynamics at rest and with exercise, could we consider a randomized clinical trial evaluating the safety and efficacy of a given PAH therapy in a cohort of asymptomatic obligate carriers? However, it would have to be quite a long study. This is certainly something very premature, but it's a possible avenue to allow us to explore whether we could prevent the development of PAH. So I think what Marc brings up is very, very valuable. What do we know about early treatment? We do know that at least now we have data from a 6-month randomized controlled trial with only functional class II patients that demonstrated that early intervention seems to be clinically significant from a hemodynamic standpoint and with respect to morbidity and mortality, defined time to clinical worsening. The question I'm intrigued by that Marc brought up: is there some way that we could absolutely prevent the disease from starting?

Dr Robbins: We've talked about a prevention study in familial disease. I know you have considered that as well, Robyn. The problem is the numbers of patients you're going to need and the fact that only 20% of obligate carriers are going to get the disease on average.

Dr Barst: Absolutely. It's a consideration. This would have to be an international study.

Dr Robbins: Right, and over many years.

Dr Barst: Is there some other way from a novel investigative stand-

point where we could see if we can prevent the disease, which is something we all would be most interested in.

Dr Robbins: Well, the scleroderma population may be another group that can be studied prospectively.

Dr Rubin: Right. And that study is actually going to be done, I think, where an at-risk population, scleroderma, with early evidence of disease like exercise abnormalities or no evidence of pulmonary vascular disease will have intervention and look at that vs placebo and the time course of disease development. That also suffers from requiring large numbers because even an at-risk population of scleroderma patients has relatively low incidence of disease development. And Marc and his colleagues, I think, have provided important data in that regard. It also means following patients for long periods of time. But I think it's an at-risk population that's probably larger than the genetic population.

Dr Park: I think that provides an excellent segue. One of the topics that received a lot of attention throughout the World Symposium was the importance of early and accurate diagnosis of PH. Certainly, with the increasing number of approved therapies and studies demonstrating that early initiation of treatment is beneficial, the challenge facing us is how can we better diagnose this disease early in the hopes of having a bigger impact? There has also been a lot of discussion on the rationale, usefulness, and possible pathologic mechanism in performing exercise right heart catheterization. And perhaps this may be a way of identifying PAH in the early stage. So in this regard, can the panel comment on the rationale and the science behind taking this portion out of the current definition of PAH? And is the concept of exercise-induced PAH still felt to be clinically important?

"We have a lot of potential pathways and we still don't have a full under-standing of the disease mechanism. We'll need to prioritize for clinical trials which of those pathways have the strongest rationale and the best evidence to go after."–*Dr Rubin*

Dr Barst: I think it's important to realize that when we make recommendations and we want to publish consensus guidelines we want these to be applicable to physicians worldwide. We're not making these recommendations or guidelines for PAH centers. In my opinion, the reason for removing the exercise portion of the definition is not that I don't believe there is exercise-induced PAH. But if the exercise study is not done in a lab that is well-equipped with experience in performing exercise studies in PH patients, there may be difficulty in obtaining left-sided filling pressures at the time of exercise. My concern was that we may be diagnosing patients who have predominantly left ventricular diastolic dysfunction because an inaccurate or an unobtainable wedge pressure or LVED pressure is not being obtained at the same time that the pulmonary pressure is being obtained with exercise. This does not mean that the condition doesn't exist. But the concern is to falsely make the diagnosis of PAH when in fact the diagnosis is left ventricular diastolic dysfunction or another disorder which should be treated entirely differently than PAH. If I could take a second to mention another point that I thought you were going to bring up: that's how critical it is for clinicians to not merely depend upon Doppler-defined PH with suspecting PH because an increased tricuspid velocity regurgitant jet is measured. Without doing confirmatory right heart catheterization we may be significantly overestimating the number of patients that have PH. I think we're doing these patients a terrible disservice to say we believe you have PH; we will initiate this therapy without having a confirmatory right heart catheterization as part of the appropriate work up before we initiate therapy.

Dr Park: Definitely. I believe we all acknowledge the importance of recognizing the usefulness and the pitfalls of Doppler echocardiography, a subject which was very well discussed in the diagnostic portion of the World Symposium reports. And the important message that diagnosis requires right heart catheterization prior to initiation of treatment was indeed stressed, a critical message which hopefully will reach all physicians who see and treat patients with PAH.

Dr Rubin: Yes, I would just follow up on what Robyn said regarding exercise. I think the message is in part that it needs to be done correctly. But it's also not just to diagnose PAH. If you can diagnose and unmask diastolic dysfunction of the left heart with exercise causing PH, that's very useful as well. So exercise testing can be provocative in terms of PH in general. And the important challenge for the physician is, number 1, to reliably perform the test following appropriate standards and quality; and, number 2, to utilize the information to make the correct diagnosis and establish the etiology.

Dr Humbert: It's indeed very important. Lewis, you just mentioned the Itinérair-Sclerodema study, an incidence study following more than 300 scleroderma patients during 3 years. We performed a screening with Doppler echocardiography for PH in this population and identified 16 patients with PH and no pulmonary fibrosis. Of note, half of the screened patients had PAH and half had left diastolic dysfunction with postcapillary PH. So indeed, echocardiogram was of major interest, but, as you all said, right heart catheterization allowed to properly define who had PAH and who had diastolic left heart dysfunction. Echo is a great tool to screen for patients at risk of PH, but one should not stop investigating patients at this stage. Patients at risk of PAH should have right heart catheterization before being considered for PAH treatment.

Dr Park: With those wonderful comments, I'm going to open up the Pandora's box of a topic that appears in every major discussion, which is this class of "out of proportion" PH. One of the most novel sections that came out of this meeting was the one devoted to the non-PAH PH, where there is a formalized discussion and proposed recommendations for working up these patients that we see every day in clinical practice. These include patients with left-sided heart disorders and pulmonary disease. I guess my question is: given our current state of knowledge, is there enough evidence that some of these patients may benefit from treatment, thus there may be a rational basis in select patient populations to consider studying them in a systematic way? Do you foresee such a trial in our future in the next 5 years?

Dr Rubin: There's certainly a rationale to study them in the real world. I think there is experience in treating them. But, of course, in the real world that experience will be mixed. It is certainly a group that in its sheer size, I think, overshadows the other condi-

tions that we see, the true PAH. So there need to be good studies for those patients. And there have been a few small studies. There is a big ongoing study now looking at phosphodiesterase inhibitors in PH due to diastolic dysfunction. I think there is certainly a rationale for studying the many overlapping conditions or mixed conditions.

Dr Robbins: Lew, I think one of the big issues, and I don't know what the entry criteria were for that study, but is that you have strict entry criteria. In other words, these patients with diastolic dysfunction or left heart dysfunction, are they optimally diuresed? Are they optimally afterload reduced? That seems to be a very difficult thing to sort out. I'm interested to know the criteria they're using in this study.

Dr Rubin: I don't know that, per se. But I do know that at least part of the criteria were to optimally diurese them. As far as afterload reduction, I'm not sure what optimal afterload reduction for diastolic dysfunction is. I wish I did know, but I certainly agree that optimal diuresis is a critical element and I believe that's part of the criteria for the ongoing study.

"Certainly, with the increasing number of approved therapies and studies demonstrating that early initiation of treatment is beneficial, the challenge facing us is how can we better diagnose this disease early in the hopes of having a bigger impact?" *–Dr Park*

Dr Park: What I believe we are seeing in the community is a sense of understanding that we already have the evidence of efficacy regarding a certain class of drug in the non-PAH PH patient population. With this line of practice, there is significant potential to do harm, not only from the possible side effects, but also that other, more traditional therapies get overlooked. What would you all consider are best ways to get the right messages out in the community? And to educate our peers?

Dr Rubin: I think we do advocate for education. Those of us on the phone and many of our colleagues spend a good deal of our time and energy lecturing, writing, and encouraging referral to physicians with expertise. Certainly at the patient level there are national and international associations that serve as a resource for education information. The real challenge, I think, is you know we could spend our entire lives lecturing and writing, but if the physicians don't attend or read then they will not gain that knowledge.

Dr Park: That is so true. Dr Barst, any other thoughts regarding the non-PAH PH patient population?

Dr Barst: No. I think what's been said was covered well. However, I'd like to make one comment going back to what we were talking about with regard to exercise to emphasize its importance. It's imperative that if the clinician has any concern of LV diastolic dysfunction in the differential diagnosis, and he is not performing the cardiac catheterization personally, he must speak with the physician who is doing the procedure. More often than not, these patients undergo catheterization after an overnight fast. If it is not performed early in the day, the patient may be somewhat dry with a wedge pressure that's recorded at 15 mm Hg or thereabout. However, if we were to do provocative testing to rule out LV diastolic dysfunction, we may immediately see an abrupt increase in the wedge pressure that would confirm the diagnosis of LV diastolic dysfunction. It's very unfortunate for a patient to have a procedure and at the end of the procedure for the clinician to be left with an inconclusive "I don't know if you have LV diastolic dysfunction or not until we re-evaluate you."

Dr Humbert: Maybe one comment about COPD and chronic respiratory disease. In this rather large population of patients, it is appropriate just to emphasize again that echocardiography is not easy and most of the patients with PH have difficult echocardiograms. When there is a question about possible severe PH in these populations. It's recommended to perform once again a right heart catheterization. The word "disproportionate" is difficult to define but when the patient has a mean PAP above 35 to 40 mm Hg they usually correspond to a very unusual population even though they have significant COPD. So in COPD, first echocardiography might be difficult to interpret. And second, severe PH is rather rare and when present it should be considered as unusual and investigated because many of these patients have another cause of PH such as chronic thromboembolic PH or left heart disease. So these patients are difficult to study and when one investigates them, all possible causes of PH should be considered, even in the setting of established COPD.

Dr Robbins: The other thing, Marc, is that some of these patients have been referred to our center when an echocardiogram was obtained in the hospital during an acute exacerbation when they're much more hypoxic. As we all know hypoxia is a very potent stimulus for increasing pulmonary vascular pressure. So I think I agree with you there are a lot of caveats in trying to study and treat these patients.

Dr Humbert: You're right. You're right. COPD patients with exacerbations should be stable when investigated. If we consider treating these patients with PAH therapy, there is room for studies. For the moment there is no approval in this population.

Dr Rubin: And certainly the patients with lung fibrosis who develop quite severe PH. It's a substantial contributor to both morbidity and mortality. You need to focus some attention, I think, on that population.

Dr Park: Again, thank you for leading the discussion with another natural segue. In comparing the most recent treatment guideline from this World Symposium to the previous one, what would you consider to be the most significant changes? And now I am asking to gain an insider's point of view: what were some of the contentious points during discussion and what were some of the topics that needed to be ironed out? May I start with you, Dr Barst?

Dr Barst: Sure. I think one of the significant changes between these evidence-based treatment guidelines and those we published from the Venice 2003 meeting are that in 2003 we speculated that combination therapy could be safe and increase efficacy in treating patients who had an inadequate response to PAH disease-specific targeted monotherapy. But we didn't have the data at that time to support our hypothesis. However, over the

past 5 years there have been at least several studies supporting the use of combining at least 2 of the 3 approved classes of drugs to increase efficacy in an apparent safe manner. The largest of these studies was the PACES-1 study (Simonneau et al, 2009; *Annals of Internal Medicine*) in which we evaluated the addition of sildenafil or placebo to patients who were on a chronic stable dose of intravenous epoprostenol therapy. And in addition to seeing improved exercise capacity in the sildenafil-treated patients, although it wasn't one of the prespecified end points, it was quite interesting to note that there were only 7 deaths in the study and they were all in the placebo group. These data demonstrate that combining a prostacyclin analog, which in this case was epoprostenol, with a PDE-5 inhibitor, which in this case was sildenafil, is safe and can increase efficacy in patients who remain limited on monotherapy alone. There have been at least several other combination studies and perhaps Lew might want to comment on those. We now have strong data to demonstrate that we should consider combining drugs. It's particularly important—since all the drugs have side effects and many of the drugs are extremely costly—that we know the advantages and disadvantages of monotherapy vs various combinations. And unfortunately why one patient may respond favorably to a given combination and another patient who appears virtually identical to the first patient does not respond remains unclear. This is an area of intense research.

"Although we have combination therapy data now, what we still need—the one combination that we don't have—is with combination oral therapies."
– Dr Robbins

Dr Rubin: I would certainly agree with that. I think the other key additions to the algorithm are new drugs. They're all in the same families, the same classes of drugs as previous algorithms, but there are some new additions to the algorithm in each of the 3 major pathways. There is also emerging evidence supporting combination therapy, although still a great deal is unknown as far as what the optimal end points are in clinical trials, particularly for combination therapy. Which combinations are particularly robust in terms of efficacy? Which pathways are more important to target for which patients? More severe? Less severe? And then whether starting with a combination vs an add-on design or add-on approach is superior to starting with a single agent? So there are a lot of questions still unaddressed that will be addressed, I think, going forward. We'll also have new insights and information on drugs that target novel pathways. I think that will be a major advance going forward as well. Of course, there were other additions to the algorithm including rehabilitation and exercise as things that were encouraged. From a patient standpoint, that's very important. One of the common questions I get asked is, is it bad for me? Is it harmful for me to be physically active? And I think we have fairly compelling evidence now that quite the opposite is the case.

Dr Robbins: Although we have combination therapy data now, what we still need—the one combination that we don't have—is with combination oral therapies. There are studies ongoing to look at this, but clearly that's something that many physicians in the community do use, combining a PDE-5 inhibitor and an ERA. And as yet, you know we don't have conclusive data on that.

Dr Humbert: I agree that all these combination therapies are extremely interesting and, in fact, we are becoming more and more ambitious which is good news. I think another very important addition in the recent guidelines, and we mentioned it a few minutes ago, is early treatment. We now recommend treating symptomatic PAH as soon as it's class II, which was not the case a few years ago. Everybody thought this was important but now we have strong data in favor of early treatment. And regarding combination, we just mentioned that maybe one day the first-line combination will be of interest. We really need to be more and more ambitious toward this population and we need to use as well as possible all the drugs we have in order to produce better data to support the new treatment strategies. In addition, we hope we'll have new targets to identify and to treat in the next few years.

Dr Park: As the medical therapies advance, do you foresee a greater or lesser role for some of the surgical therapeutic options for our patients? There's been a lot of discussion regarding how to best utilize some of the surgical options in PH, such as atrial septostomy and lung transplantation. How do we apply these therapeutic modalities at the most appropriate time to obtain the most benefit?

Dr Humbert: Regarding transplantation, this is a very important tool for PH treatment. We need to identify as early as possible the best candidates for lung transplantation because there is still a shortage of lung donors. And obviously there is some subset of the disease like pulmonary veno-occlusive disease that is responding poorly to all available therapies right now. There are also are those patients who are refractory to first-line treatment and second-line combinations. I think the most important nonmedical approach for these patients is, of course, lung transplantation. In the future we need to better identify early those patients who have a poor prognosis and who should be listed on the transplant list before being unstable.

Dr Park: Thank you and, as a closing topic, I would like to ask from the panel, some thoughts regarding future considerations. So looking ahead and putting ourselves in the next 5 years to the 5th World Symposium, what do you foresee as possible changes that we can look forward to and the controversies that lie ahead? And some of the big hurdles that you all envision we have to overcome?

Dr Barst: I think what we should anticipate will be derived from the scientific advancements that Lew and Marc discussed earlier, particularly looking at growth factors and the role of inappropriate programmed cell death. At the same time I would like to caution that if phase II studies demonstrate proof of concept with a given novel compound such as a tyrosine kinase inhibitor, it is premature for a clinician to look at proof of concept data and treat PAH patients off label. It's exceedingly important, since all of these drugs have significant adverse events. These drugs may have cardiotoxicity and should not be used until we have truly demonstrated with pivotal trials that are well designed and well carried out that a drug is safe and efficacious in the patient population that we are treating. We recently prematurely terminated a clinical study in PH patients with sickle cell disease due to safety concerns. The study and the patient group is not what is relevant to this discussion but what is relevant is that a drug was being eval-

uated that was thought to be safe and efficacious but the trial was stopped by the data safety monitoring board. I would just like to caution physicians not to look at small series of open, uncontrolled data and decide to treat a patient with a drug before it has undergone rigorous study.

Dr Park: That is definitely very sound advice for all of us. It is so enticing to think that you know that if you can only add this 1 drug, your patient will get better. Of course, we don't have enough evidence to say this and this does not always turn out to be true.

Dr Robbins: There remain challenges here that have been challenges throughout our attempts to treat this disease, One major issue is that PAH is a rare disease. The patients are limited, and I think the pool of patients to be used in studies is getting fewer and fewer, and the studies likely getting diluted out with more and more marginal candidates. So it's really becoming difficult to get patients to test these drugs with. In addition, we don't have a good animal model to even look at the pathogenesis and, as we alluded to earlier on, we see these patients when they all have end-stage disease. All of the pathological changes that we see are end stage. So we don't know what the early changes are in this disease. We also don't know whether the mediator abnormalities that have been reported are the cause or the effect of this disease. So I think those challenges to improving treatment remain. Despite these limitation, as we've also talked about, there will be new classes of drugs out there, that will target different abnormalities. And hopefully investigators will think a little more outside the box to target more novel pathways. So that's where I see it in the next 5 years.

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Dr Rubin: I agree with that. I think in the next 5 years we'll certainly get more interesting information on basic pathobiology of the lung vasculature and I think the challenge then will be separating the wheat from the chaff and deciding which are not important and which are upstream and which are downstream mechanistically or just unrelated. As far as therapy goes, I think our big challenge will be to triage, to prioritize the treatments and the studies to provide the strongest quality data that will be clinically meaningful. Because we need to study a homogeneous population and, as Ivan mentioned, I think it has become a bit heterogeneous as trials have been broadened to include countries and centers where there is less experience with the disease and with performance of clinical trials. That has the potential to undermine the validity and the meaningfulness of those studies. So we need collectively, I think, to prioritize and we need to collaborate with industry and with government sponsors to do the studies that are the most important to address the most important questions for us and for our patients and find ways to accomplish that while still meeting their objectives.

Dr Park: A Herculean task for sure. Dr Humbert, any final thoughts?

Dr Humbert: I think it's clear that we have to be both original and creative but not take too many risks. For example, when we target growth factor and angiogenesis we don't really know if angiogenesis is harmful or protective or both. We don't really know the targets we should prioritize and there are many targets and many combinations of targets. We don't really know the side effect profile of the novel agents we will use in a population with a cardiovascular condition. So I really agree with all the panel that we have to first identify the best targets based on good quality preclinical and early stage studies and then we have to agree on the targets/pathways and drugs which seem to be the best. But this is challenging because there are currently many, many agents, many pathways, and we really need to be well organized and identify the priorities.

Dr Park: Well thank you all so much for taking the time to participate in this roundtable. I think our readers will truly gain some wonderful insights from this discussion. Hopefully we can look forward to more stimulating and challenging topics from the next World Symposium! ■