Prognostic Indicators for Pulmonary Hypertension

Dr Burger: The articles that are in this issue range from biomarkers to right ventricular imaging to risk scoring. That is quite a breadth of topics. It allows this particular discussion to touch on some of the gaps in those areas and, of course, provide expert opinion regarding where we are as of 2015 with our ability to prognosticate with PAH. I'll start the discussion by throwing out a question to the panel, beyond the obvious utility, the ability to prognosticate with our patients, what above and beyond is so important about our ability to determine prognosis in a more refined way? Ioana, what do you think?

Dr Preston: It's a very interesting question and complex, both question and probably answers. So Charlie, pulmonary hypertension is such a complex disorder. It involves malfunction not only of the pulmonary vasculature, but the right heart, also the left heart. And it ends up being a truly systemic disease that affects the entire body. So taking up very fine details of the severity of the disease is not easy. And that entails understanding not only the pathophysiology but also ultimately how long our patients will survive, how well will they survive, their quality of life. And how can we adapt our therapies that we have available to improve several aspects of their disease and their life.

Dr Burger: Do others have comments?

Dr Benza: Yeah, I have probably a few things that I try to keep in mind. And what I try to teach is the reason why risk prognostication should be done with some frequency in patients with this disease. And most importantly, it's to diagnose the rapid progressors, particularly those who are newly diagnosed or have been recently discharged from the hospital. Because if you look at the attrition rates with pulmonary hypertension, these are the patients who will survive the least and the ones who you need to be on top of, in order to amplify their therapy, to improve their long-term outcomes. And I think identifying these rapid progressors is incredibly important in the community setting and among less experienced practitioners. And risk prognostication allows some equalization of the playing field in those less experienced settings, so that these appropriately ill patients can be identified and have their therapy changed accordingly. I think risk prognostication also provides a basis for the institution and timing of types of therapies, based on needs and risks, so the sickest patients get the IV prostacyclins and the least sick patients perhaps get the oral analogs. I think it provides an opportunity to enhance consistency among therapies, so that everyone who is class 4 gets an IV prostacyclin, such that these patients are treated more according to guideline therapies. And obviously also, risk prognostication is essential for the appropriate timing for lung transplantation, which we all know is really the only cure for this disease. Many of our colleagues who do lung transplantation fret when we send them patients who are too advanced in their illnesses, such that their life expectancy is disproportionately judged by at least in the U.S. by the LAS score. But I think risk prognostication for those four reasons is essential for our patients.

Dr Burger: Certainly, this issue contains a very well done review on biomarkers, serum biomarkers. What does the panel feel is the current state of affairs with serum biomarkers and how they should be used in the practice and their potential role in more complex scores, which we'll get to as well, as we evaluate our patients?

Dr Preston: I think biomarkers are a very useful tool for any disease. Now, in pulmonary hypertension, although different groups have looked at several biomarkers to try to identify patients at risk for progression or patients who have severe disease, so far in clinical practice, we currently use brain natriuretic peptide or its precursor, anti-pro BNP. I think at least in my practice, it is a useful marker to pick up subtle changes in volume status, subtle changes in disease progression, maybe before it's completely overt and clinically obvious. So that's, I think, the main markers, serologic markers, that we can use currently.

Dr Benza: I think our issue with biomarkers in the current state of treatments is that the studies that have analyzed these biomarkers have been usually single center or several center studies and so their utility I think is limited in scope because of the small populations they’ve been studied in. And
really, the only biomarkers that have been studied with any significant degree of patient population is that natriuretic peptides, as Ioana just mentioned. And here, they do hold fairly substantial weight and risk prognostication. But I think what the important thing to remember is that biomarkers in and of itself may be important, but they're much more important when they are utilized in the context of multiple other risk factors or prognosticators, so that you don't hang your hat on just one thing and they're used more to paint the entire picture and to paint the entire picture.

**Dr Preston:** I agree.

**Dr Burger:** Before we get to putting various components together, I would ask if Jonathan might address something that Ioana alluded to. And that is, what exactly does a rising BNP mean? And so from a practical perspective when you’re seeing a patient in a clinical who has doubled their BNP, how do you sort through volume retention versus RV dysfunction?

**Dr Rich:** Well, I think that’s a great question about how to best utilize BNP levels in clinical practice. We know that the presence of an elevated BNP or NT-pro BNP is an ominous prognostic marker. And I also agree with one of the previous comments that BNP levels, when used in conjunction with other known prognostic factors in PAH, is ultimately going to be even more powerful. But your question is a really important one as it contributes to the conversation about how to know when to pull the trigger on more intensive therapies and leads us to ask some intriguing questions. For instance, are there ways to utilize biomarkers such that changes in BNP could be used to reliably predict response to therapies? A lot of this work is being done in the left heart failure arena. In PAH, can you rely on the finding of serial improvements in BNP to suggest that that particular patient is favorably responding and is likely to continue to respond to current therapy? Conversely, to your question Charlie, can you reliably consider a rising BNP as a marker that specifically the status of the RV is getting worse? Personally, if my patient had a doubling of his/her BNP level, this would worry me that it is a reflection of worsening RV wall stress and in PAH, it is all about the RV. But is that rise in BNP alone sufficient by itself to warrant a closer investigation into whether we need to start to make changes to therapies or perhaps as you indicated, may it in some instances simply be a reflection of a little extra fluid retention, a change in renal function, etc and not necessarily indicative of a marked change in RV function? So I think that the particular role of BNP, not just the actual elevation of BNP, but the changing and dynamic nature of BNP, can be leveraged in both prognosticating and clinical decision making, perhaps as part of a larger panel with other emerging biomarkers, whether it be high sensitivity troponin or some of the newer ones that are emerging, like ST2 and so forth. The utility of having a panel of markers to use is likely to be additive in value to BNP alone when trying to make clinical decisions. But for now, I will simply conclude that in both left and right heart failure, a rising BNP is something I don’t like to see. And an improving BNP, of course I’m happy with. But the ultimate question remains, can we utilize biomarkers in a more refined way to really guide both decision making and prognostication?

**Dr Burger:** Ray, obviously you’ve done tremendous work in working with the REVEAL registry database to develop the REVEAL risk score. And that’s discussed in this issue in the manuscript by Dr. Agarwal as a validated methodology for prognostication. What would you advise the practitioners as to the role of calculating the score during outpatient visits for patients under treatment for PAH?

**Dr Benza:** Yeah, I think the REVEAL calculator, just like in any other individual markers that we’re talking about, are tools that you fill your tool belt with. It just happens to be one of the biggest hammers in your tool belt. And I don’t think the REVEAL calculator is meant to be used on every touch point with the patient. But certainly, with some degree of frequency throughout the course of a patient’s disease, the score can be used several times per year to make sure you’re on track with that patient. And I think the recent literature that we publish with the serial use of the score suggests that not only are changes in the score important in predicting outcome but use of the absolute score serially is equally as important. So both the delta change and the repeat absolute score seem to be very important. And we have capitalized on this and we’ve incorporated the calculator into our daily practice at our center. And I think it has resulted in a significant improvement, both in identifying patients that need more aggressive therapy and has improved our long-term outcome, at least within our own practice. So I advocate the regular use of it, again not every single time someone comes to clinic, but certainly they can give you an idea how people respond to many of the things that we do routinely on a clinical visit for a PAH patient are vital parts of the calculator, assessing their functional class, you know, assessing them for volume, doing their BNP levels, doing your 6 minute walk test. And so you can use the calculator roughly in those situations to guide you, but periodic use of the calculator throughout a patient’s course I think is very valuable in identifying people who are moving in the wrong direction and those who you can pull back by appropriately amplifying their therapeutics.

**Dr Preston:** So Ray, not all the parameters, the 19 parameters in the REVEAL score, are newly recorded within a visit. How do you take into account missing parameters?

**Dr Benza:** So in the construction and initial calibration of the calculator, we took into account that all tests weren’t going to be done at any particular interval. And the original algorithm accounts for missing-ness of data. And some of that is accounted in by the correction factor that you note that you have to use when you use the actual raw calculator. So it does account for missing
But at least on a yearly basis, we use this to guide whether we have appropriately managed that patient over the course of the year. In the newly diagnosed or recently decompensated patients, we use the calculator probably a little bit more frequently than yearly. And we found that to be a useful way to utilize it.

Dr Burger: Ray, on a practical note, since the patients obviously, and to their credit, are very focused on their disease and sophisticated in their understanding of what we’re measuring, so they will ask about their 6 minute walk distance or their BNP. And as you would calculate this score, do you share the actual number with the patients or how do you handle the potential challenge of the patient perseverating, if you will, on their calculated score during their visit?

Dr Benza: Well, I think that we actually do review the scores with the patients in detail. And we show them the Kaplan-Meier curves that the scores actually reflect. And I think most patients, most of my patients are intensely interested in how their scores – what their scores are and how they change with time. And often at the end of their risk stratification visits, they will ask what their REVEAL score is, because they know the relevance to their one year survival of this. I don’t think any of the patients have come to a point where they’ve actually perseverated and worried about it, but I think it allows them to put their next year in perspective and tells them whether there’s going to be a lot of work that needs to be done this year or this is going to be a good year for me and I can relax a little bit. And so I think it just helps a lot of our patients put their disease into good perspective and allow them to view their next year within the context of what is either a good comfort zone or not a good comfort zone.

Dr Burger: So taking the REVEAL risk score in light of Ioana’s comments about how some of the factors aren’t measured at each visit, specifically the hemodynamics and perhaps the diffusing capacity, are you envisioning continued refinement of risk scoring, perhaps with combination of contemporaneous RV assessment by imaging?

Dr Benza: Oh, absolutely. And that’s just a fantastic question. The calculator was never meant to be the standalone, unalterable tool. And as new clinical tools evolve, the calculator will obviously need to be refreshed, refurbished, with the older factors relooked at, to determine if they hold the same relevance as they did in the past, when these newer tools were not available. And obviously, the biggest addition to the calculator, in my opinion, not only has to include the serial changes in score which give prognostic information, but estimates of – better estimates of right ventricular imaging. You know, in the original evolution of the calculator, many of the qualitative estimates of right ventricular function were significant on a univariate level. But because of the way the registry recorded these data they were very qualitative and so they fell out in a multivariable analysis. But as we get better imaging tools that are more objective, I think these are certainly going to be a great addition to the calculator that can be utilized to quantitate overall risk in conjunction with some of the other stuff that likely will maintain significance. In addition, I think one of the other biggest additions to the calculator that needs to be done is the addition of incremental risk when a decompensation occurs, because as we know and as was beautifully illustrated in some of the literature that came out of REVEAL is that when a patient has a decompensation, that their likelihood of having a mortal or a morbid event in the next six months is extremely high after that event. And so I think that’s an element of risk that certainly needs to be used in conjunction with the score. And in our own group, when we utilize the score, we usually use a three-tier system. So we have the score. And then we try to add to that and put into context their right ventricular imaging. And also whether or not they had or had not had a decompensation. And using that kind of three-tiered decision tree – the score, the imaging, yes or no recent decompensation event – I think those patients’ total risk is depicted more clearly, using a combination of those elements.

Dr Burger: Well, Jonathan and Ioana, how often do you image the RV in your patients that you’re seeing in clinic? And are your decisions swayed by their functional class and their six-minute walk? Or is it something you do routinely?

Dr Rich: Well, I can tell you what I do. And I tend to be pretty aggressive up front in the evaluation and management of the newly diagnosed PAH patient. I think what we don’t necessarily have data for is if we can make patients rapidly better, i.e. as indicated by a significantly improved REVEAL score or by using other markers or indicators of clinical improvement; is that going to project a better long-term outcome than if we take a more “reactive” approach and simply respond to say a worsening in the REVEAL score or other markers, and only then do we layer on or escalate therapies. I tend to be a bit biased in saying, let’s try to make the patient as well as you can, as soon as you can, and be more proactive rather than reactive. And so, I try to utilize everything – with
hemodynamics, a low cardiac output in a young patient who tries to convince me that he’s a functional Class II but his numbers look terrible and his RV looks terrible, I’m really worried about that patient and I would have a very low threshold of going straight to an IV prostacyclin to try to get that patient and their RV function as stable as possible. So early on, I think the invasive hemodynamics, coupled with a careful physical examination, imaging, and functional capacity should all be used together to formulate an initial treatment plan. But then moving forward, it’s impractical to be taking patients back to the cath lab on a frequent, regular basis. And so I usually will use simple measures such as how the patient is feeling, are there objective changes in functional capacity, is RV function looking a bit better on echo, which, as Ray pointed out, we’re getting better at in terms of trying to quantify that but it’s still somewhat qualitative and subjective. And then circling back to biomarkers, are we seeing improvements in BNP levels and things like that. You know, if a PH patient told me that it wasn’t long ago that he was playing softball and running the bases and now he can’t do it, I keep pushing the envelope until he tells me he’s getting close to being able to do that again. Even if in some cases it is impractical, I always try to get patients back to as close to their previous baseline as possible, so I might be more aggressive than some. I think it would be nice in some ways actually if we can use calculators such as the REVEAL score and other markers to not only prognosticate whether the patient is more likely to have a difficult year, which is really important like Ray was talking about, but also should we be recalculating these types of scores again really quickly after initiating the initial therapy and if they do not achieve a significant improvement in that score, would that predict the need to escalate more quickly. Because I think we need to be a little more aggressive in most scenarios to try to keep the patient out of trouble rather than waiting until we need to try to get them out of trouble. As Ray said, once they’re decompensated and coming into the hospital, they’re usually in pretty bad shape.

**Dr Burger:** So what does the panel feel the role of exercise is in this whole business of trying to more accurately assess where patients are in their clinical course? Particularly those who fall into the less severe end, if you will, spectrum of functional Class III, where they’re starting to manage their activities of daily living, but, still have exercise limitation with heavy exertion. They’ve made some progress perhaps with some of these other markers that we talked about. But, of course, their symptoms are with exercise and measuring something with exercise might be useful, such as end tidal CO2.

**Dr Preston:** That’s a good question because typical symptoms for our patients are when they exert themselves. But the markers that bear prognostic value that are derived from the cardiopulmonary exercise test are those that show really bad disease. So by the time they hit those markers, their clinical picture is, I think in my opinion, more obvious, obvious enough that the disease is severe. And we don’t know yet if by improving these markers and to what level that translates into better survival. Nevertheless, in my practice, I use maximal testing, exercise testing, in those young patients in whom, like Jonathan was describing, they seem to underreport their symptoms and they seem to have kind of like a good functional capacity, even though they have severe disease, to better analyze their limitation and their severity of the disease. So younger people, I do exercise them, yes. And it’s just a piece of the puzzle to better understand and determine what’s their disease process.

**Dr Benza:** I guess I use cardiopulmonary exercise testing in people who are reaching their upper limits of clinical predictability in the 6 minute walk test, which is what I use routinely. So if I have a patient who’s still not doing what they think they should be doing but their walks are consistently greater than 400 meters, those people I typically will put on an exercise treadmill and do metabolic testing on them, to see where their perceived dyspnea is coming from, whether is it really an impaired cardiac reserve or impaired ventilatory reserve. And that’s where I’ve found it to be most useful.

**Dr Burger:** Ray, I’ll ask you, because you have recently published in *Advances* a review of ambulatory hemodynamic monitoring. Where do you think the role of ambulatory monitoring devices, CardioMEMS is one example, and the parameters that they would measure are in prognostication and assessment that patients particularly as the conversations always seem to loop back to, are we being aggressive enough with our treatment strategies?

**Dr Benza:** Yeah. Well, I guess this is just as food for thought. I mean, given the rapid and progressive nature of this disease, as I mentioned earlier, I think we continually need to reassess risks, particularly in those who are newly diagnosed and recently decompensated, because they’re the ones who have the most risks. But if you think about it, we’re really limited in our risk prognostication by the number of touch points that we have with our patients. Our patients don’t live with us. We don’t see them every day. So the only time we can risk prognosticate is when they come to clinic or, by chance if we call them on the telephone, are able to assess some sort of factors of their daily disease state from that telephone call. So there’s limitations in touch points that we have, particularly in these people who are at higher risk, I think this really shows us the limitations in our ability to risk prognosticate on a rapid basis, to make sure that these people who are at the highest risk are being treated as aggressively as we want. And as Jonathan mentioned earlier, since hemodynamics really best reflect the status of the disease, the question that’s then begged is, could daily assessments lead to better outcomes, by serving as an early warning signal to identifying decompensation and to augment therapy. I think that’s where the utility of these indwelling hemodynamic monitors will likely be best utilized, at least in the beginning, is to tele-video this group of patients that we
Dr Rich: Ray, what device are you using in those ten patients?

Dr Benza: So the contract that we have with the NHLBI is with the usage of the CardioMEMS device.

Dr Rich: That’s fascinating, because obviously those of us who also take care of patients with left heart failure, for which it is currently approved, I think we can all appreciate at least the theoretical if not practical value of something like CardioMEMS because we know that PA pressures are going to change frequently, and that’s usually a direct reflection of the left-sided filling pressures and LV function. But in pulmonary arterial hypertension, it always made me wonder if there could truly be a significant utility in the CardioMEMS device itself, since we think, generally speaking in PAH, that PA pressures, until the disease state gets to a very end stage, probably don’t change much or at least my perception is they don’t change significantly when we bring them back to the cath lab. And the clinical trials seem to support this notion where even after about 12-16 weeks of therapy, the mean change in PA pressure is perhaps around single digits of pressures. Thus, it would almost make me think, what if we could come up with a right atrial pressure monitoring device, similarly to what we have currently with some experimental devices in the left atrium, and perhaps that would actually in some ways be a better marker of fluctuation in patient status. But perhaps the study you are doing with CardioMEMS, which sounds fascinating, will teach us something that we don’t know.

Dr Benza: You bring up a very valuable point. I think this is something that is underappreciated by many of us, in that the right heart catheterization I think lulls us into a false sense of security with some of these patients, because the procedure in part is really artifactual or artificial, in that the patients when we perform these is in supine position and is resting, in the resting state. So what we’ve been able to appreciate with these indwelling devices is that pressures dramatically change with the ambulatory environment, such that when we check ambulatory pressures using this device, there is a significant difference from what we see at rest. And in some patients, that can be the trick in making them feel better, in that we are not or do not have a good sense of whether controlling ambulatory pressures can help these people reduce their morbidity and mortality events that occur throughout their years of observation. And so I think exercise hemodynamics that we get with the use of this device, that you can glean from this device, really open up a whole new avenue of exploration for possible treatment titrations for these people. You know, controlling pressures at rest and with exercise are two totally different things. The other interesting thing with this device is that although not FDA-approved at this point, and we are utilizing this through some algorithms that we have helped develop, is that you can very nicely detect cardiac output with this device, such that you have pressures and outputs and therefore, you can determine resistances and by virtue of knowing that just imagine the other things you can check compliance, that you have pressures in output, RV power. You can do RV stroke work index. So all the parameters that we know are useful when we have a Swan in and we’re managing hemodynamics in the unit, you can get now on an ongoing basis. And so although you don’t have the right atrial pressure, you have strong surrogates of right ventricular function by virtue of knowing the pressure and the outputs. And so these additional things that we are working on and showing that you can do on a long-term basis I think will prove to be very interesting in the future. And obviously, these are not the things that had been reported prior in the literature that you can do with this device but it makes perfect intuitive sense that you can do this. You know, the similar things that we did with the Chronicle device that we utilized a number of years ago, which did give us estimates of right ventricular contractility. So these are very interesting new derivations that you can use, just by virtue of knowing simple pressures and outputs.

Dr Burger: I think this has been a wonderful discussion and particularly enlightening for me personally. I would have the panel, if they’re comfortable, take sort of one final question as we wrap up. And that is, beyond what we discussed, is there anything that you focused on or have seen in the literature and/or participating in study that you would call a novel prognostic indicator?

Dr Ioana: I’d like to mention that hopefully in the near future, we’ll have some biomarkers of inflammation or oxidative stress that we can measure as a whole, the disease process. There’s also some new research on micro-RNAs in
their blood level. And maybe they will become a marker in the future.

**Dr Benza:** One of the things that I’m particularly interested in and trying to do some work in is the predictability of genomics and genetics in determining outcome in patients with this disease state. And I think there is going to be some data that’s going to be coming out shortly, hopefully, that will help better identify patients who are at high risk of decompensation or worsening prognosis based on their genetic fingerprints. So I think genetic fingerprints are going to be very helpful I think in the future in pre-identifying people who may have a more aggressive course.

**Dr Burger:** Well, with that, I would like to thank the panel for their very insightful comments. This has been a wide-ranging discussion of an area that’s dynamic and critically important to our practice and certainly ripe for new discovery and new refinement of our current ways of evaluating prognosis and response to treatment.