0129 PH Webcourse Transcript

Slide 1 – Title Slide

Bradley A. Maron, MD: Welcome to this activity titled, “Diagnosis and Management of Pulmonary Hypertension: The State of the Science.” This educational activity is provided by the Potomac Center for Medical Education and supported by independent educational grants from Actellion Pharmaceuticals US Incorporated and Bayer US.

Slide 2 - Faculty

My name is Bradley Maron. I’m an Associate Professor of Medicine at Harvard Medical School and Associate Physician in the division of Cardiovascular Medicine at Brigham Women’s Hospital and co-Director of the Pulmonary Vascular Disease Center at the Boston Veterans Affairs healthcare system. I’m joined by my colleague and good friend, Dr. John Ryan, who is an Associate Professor and Director of the Dyspnea and Pulmonary Hypertension Centers. He’s also the Director of the Cardiovascular Medicine Unit all at the University of Utah.

Slide 3 – Disclosures

The faculty and non-faculty disclosures are listed here. We will take a few minutes to give you the opportunity to review these.

Slide 4 – Educational Objectives

At the conclusion of this activity, participants should demonstrate the ability to first conduct prompt diagnostic evaluation of patients suspected of having pulmonary hypertension, which we may abbreviate throughout this conversation as PH, toward
arranging for prompt diagnosis. Secondly, participants should be able to describe the clinical properties of specific advanced drug therapies and explain the rationale for early treatment initiation by specialty centers to achieve the best clinical outcome for patients.

Slide 5 - Definitions of Pulmonary Hypertension (PH) and Pulmonary Arterial Hypertension (PAH)

I’d like to begin the talk with a brief review of the definitions of pulmonary hypertension and how this differs from pulmonary arterial hypertension.

Slide 6 – PH Has a Diverse Pathobiology

First, it’s important to recognize that PH has a diverse and heterogeneous path of biology, and it is in part for this reason that the World Health Organization first described five different categories of patients according to specific features of their individual grouping pathobiology.

Slide 7 – Hemodynamic Definition of PH/PAH

I would also like to point out that the hemodynamic definition of PH and PAH are both different, but also ultimately are required to make an appropriate diagnosis. On the one hand, PH describes an elevation in the mean pulmonary arterial pressure diagnosed by invasive right heart catheterization performed on a patient supine while at rest. The current standard or traditional standard for defining PH using this criterion was 25 millimeters of mercury or greater. We’ll get back to that in just a moment. On the other hand, pulmonary arterial hypertension, abbreviated as PAH, includes patients who have PH defined by an elevated mean pulmonary artery pressure, but also requires two additional hemodynamic values for diagnosis. First, the pulmonary capillary wedge pressure, which assesses the left-sided heart filling pressures must be equal to or less
than 15 millimeters of mercury. The pulmonary vascular resistance, which is dependent on the mean pulmonary artery pressure, the pulmonary capillary wedge pressure, as well as the cardiac output must be greater than three Wood Units. Over the past 10 years, there has been interest in understanding whether the spectrum of risk related to mean pulmonary artery pressure should be reconsidered. Data from catheterization registries and smaller clinical studies suggest that patients may be at higher clinical risk when mean pulmonary artery pressure is higher than around 19 to 20 millimeters of mercury. Exactly the role of this revised definition and how patients are diagnosed and certainly, whether or not this should be used in any decision-making relative to treatment remains both controversial and a moving target.

John, any thoughts on this particular issue, which is both very recent and in some circles, somewhat controversial?

**John J. Ryan, MD:** Yeah, thanks for bringing that up. I have no doubt that people who have a mean PA pressure of 20 have a higher mortality than someone who has a mean peer pressure of 14 or 15, which is essentially 14 or 15 being normal. However, how to intervene on people who have a mean PA pressure of 20 is unclear. In that regard, I think we need to figure out, for example, if starting PH therapies, when people have a mean PA pressure of 20, is that valuable or is it a matter of these people have higher risks for developing disease further on and need to be followed more regularly.
Bradley A. Maron, MD: Thank you for that important perspective. In any case, it is important to remember that in practice, right heart catheterization remains the gold standard for diagnosis and in turn, as will be discussed a little later, non-invasive assessments, which are estimations of pulmonary pressure, although have bio-echocardiography, although have an important role in the evaluation of patients are not sufficient to clench the diagnosis of pulmonary hypertension.

Slide 8 - Classification of PH

The classification of PH is oftentimes a point where people become confused, they may find this area particularly difficult to follow. I can understand that, but what we’re going to do now is demystify what is otherwise a complicated system to some and break it down into its simplest and most informative parts. Patients with World Health Organization Group 1 PH are those who are also diagnosed with pulmonary arterial hypertension, which as we’ll discuss, is an uncommon disease characterized by effacement of the normal architecture of distal pulmonary arterials and is due to interplay between genetic and molecular factors. Much more commonly encountered in clinical practice is PH in a setting of pulmonary venous hypertension, which can be due to any abnormality on the left heart. That includes a left ventricular impaired diastolic relaxation, left ventricular impaired systolic function, any form of mitral valve disease, and other assorted abnormalities, which ultimately cause an increase in left atrial pressure.

WHO Group 3, pulmonary hypertension, is associated with parenchymal lung disease, sleep disorder, breathing, or other hypoxic disorders. Like Group 2, pulmonary
hypertension is far more commonly encountered in routine clinical practice compared to PAH or Group 1 pulmonary hypertension.

Group 4 PH is an important subgroup because it is potentially curable by surgery and this form of PH is due to in-situ thrombotic remodeling of distal pulmonary arterials, which most commonly occur as a consequence of an initial luminal pulmonary embolism.

Group 5 is a grab bag of other important, but less frequently encountered causes of PH, which include sarcoidosis, sickle cell disease, and other disorders of the hematologic system, such as patients who develop PH following splenectomy.

Slide 9 - Pulmonary Hypertension Nomenclature
A detailed table providing subgroups within each of these five major PH groupings is provided here. I think there are some important individual subtypes that are notable and require particular discussion.

Slide 10 – Updated Clinical Classification of PH
First, if we focus on PAH, we can see that there are three principal causes of PAH that are encountered most commonly in the absence of another clinical disorder. First, unfortunately, most cases remain idiopathic. I should say most cases in the United States and in developed countries remain idiopathic without a clear-cut ideology. There are a variety of familial or heritable forms of pulmonary arterial hypertension, most classically described, for example, in the context of a BMPR2 mutation, described originally by Vanderbilt University. As a third form of pulmonary arterial hypertension,
which is increasing in prevalence, are drug and toxin-associated disease and that includes in the former era diet pills in the form of fen-phen. Then more recently, we are seeing an increase in methamphetamine-related cases. Other forms of pulmonary arterial hypertension include those that occur in the setting of other specific risk factors, particularly, connective tissue disease, including systemic sclerosis, but also among patients with HIV infection, those with liver cirrhosis, those with uncorrected congenital heart shunts. More commonly worldwide in third-world countries includes infectious forms of pulmonary arterial hypertension, such as schistosomiasis. Other specific forms of pulmonary hypertension are provided here for left heart disease, for parenchymal lung disease, and for Groups 4 and 5 respectively.

Slide 11 - PAH: A Group of Diseases

I think it is fair to say that PAH is really a group of diseases that are defined by a similar pathology and a similar clinical syndrome, which often involve a number of marquee symptoms, which I’ll review in just a moment. We are recognizing increasingly that insulin resistance is part of the pulmonary vascular pathobiology in PAH. Of course, it’s also critical to recognize that patients with PAH have abnormalities in the absence of another cardiac or respiratory cause.

Slide 12 – Pulmonary Arterial Hypertension: Symptoms

Diagnosing PAH can be somewhat difficult, since the two most common symptoms are quite non-specific. Most often, patients will present with a precipitous change in their respiratory pattern, including shortness of breath and the sensation of dyspnea. This, of course, is difficult to distinguish from other more common causes of these symptoms,
such as coronary heart disease, smoking-related lung disease, and others. Indeed, the time to diagnosis of PAH is delayed.

**Slide 13 – Time From First Symptom to Diagnosis of Primary PH**

This figure here shows that on average, patients are diagnosed at least two years after the onset of vascular changes or even the onset of symptoms have been identified.

**Slide 14 - Is There a Reason to Suspect PAH?**

This is important for the practitioner, since it remains a priority for greater awareness of PAH as a potential cause of symptoms in patients presenting even with these general and non-specific complaints. A high index of clinical suspicion is warranted in those for whom no other risk factors can be identified in the setting of exertional dyspnea or shortness of breath. This table shows reasons to suspect PAH divided according to history, exam findings, and other related signs. Starting with history, as we mentioned, dyspnea is common. Other non-specific symptoms are also reported commonly including fatigue. Chest pain can result from ischemia of the right ventricle in the setting of very high pulmonary artery pressure and syncope and dizziness are very concerning symptoms that should be considered more urgently. Physical exam findings are consistent with the changes to right heart function, including accentuated P2 component of the second heart sound, a right ventricular lift, or heave in the setting of an RV S3 or S4 heart sound are observed in patients with moderate severe pulmonary hypertension and changes to normal tricuspid valvular function can be appreciated by identifying a tricuspid valve, regurgitant murmur, usually a low-pitched systolic sound in the right lower sternal border.
Other examination findings that are suggestive of right heart disease in the setting of pulmonary hypertension include elevated jugular venous distension with an increased a wave and v wave, hepatojugular reflux on compression of the right upper quadrant, a pulsatile liver, and other signs, such as increased lower extremity swelling, which may be also observed in patients with moderate to severe disease.

**Slide 15 - Patient Presentation: Nonspecific Symptoms**

As mentioned previously, early detection is important in part because our current approach is associated with delayed diagnosis. Even in contemporary clinical trial registries, such as that from the REVEAL study, the median time from symptom onset to diagnosis by a trained clinician is greater than one year.

**Slide 16 - Is It Left Heart Disease?**

One of the great challenges, particularly, for cardiologists in practice is delineating PAH, or pre-capillary pulmonary arterial hypertension from patients who present with PH in the setting of left heart disease. There are some clues that can be gleaned from patient presentation, including symptoms history and some findings on electrocardiography and echocardiography, none of these are a stalwart for excluding left heart disease or including left heart disease, but they can point you in one direction or another. For example, patients with left-sided heart failure are more likely to develop paroxysmal nocturnal dyspnea. They are more likely to have risk factors associated with heart failure and preserved ejection fraction or coronary heart disease. These include diabetes, systemic hypertension, central obesity, and other components to the metabolic syndrome.
The electrocardiogram in the absence of right access deviation or right ventricular hypertrophy can be informative and certainly, echocardiographic features suggesting remodeling of the left heart such as left atrial enlargement, particularly, over 4.4 centimeters measures in the parasternal long axis, evidence of intraventricular septal thickening can collectively point clinicians towards a left-sided ideology to pulmonary hypertension.

Slide 17 – Is it PAH?
As mentioned previously, findings suggestive of right heart failure can also be useful, and therefore, a detailed examination is particularly important when trying to decipher if patients are presenting with left-sided symptoms, right-sided symptoms, or combined symptoms the latter of which would, by definition, include some component of left heart disease.

Slide 18 – PAH Risk Factors
On the other hand, PAH risk factors have also been described. For example, patients who have a family history of pulmonary arterial hypertension may harbor BMPR2 mutations or another form of hereditary PAH. Patients with systemic sclerosis and other connective tissue diseases should be considered carefully for PAH. As mentioned previously, patients should also be evaluated carefully for congenital heart disease, which may present even at late ages despite the belief that most congenital heart diseases are detected early in life.

Patients with a strong alcohol use history or other toxin exposures that may affect portal circulation can also be at increased risk for PAH. As we mentioned previously in the
discussion, environmental or drug-related risk factors, particularly, methamphetamines in the current era should also be considered as risk factors for developing PAH.

**Slide 19 - Prognosis**

Despite progress in the identification, care, and management of patients with PAH, prognosis remains unfavorable and is particularly poor in untreated patients related to the effect of pulmonary hypertension on right ventricular structure and function. Ultimately, untreated or inadequately treated pulmonary hypertension results in right-sided heart failure or cor pulmonale and early mortality.

**Slide 20 – PAH: Hemodynamics over Time**

This figure shows the relationship between time on the X-axis and different hemodynamic measurements on the Y-axis. In specific, we can see that in the magenta color is the change in pulmonary vascular resistance over time. In the red color is change in pulmonary artery pressure over time. In the light blue arrow is change in cardiac output over time. Essentially, what we see here is that with progressive disease corresponding with differences in symptom burden and heart failure status, there is a progressive increase in mean pulmonary artery pressure up until the time there is a drop in cardiac output due to the effects of increased afterload on right ventricular function. At end stage disease, pulmonary pressure can actually be only mildly or modestly increased compared to a time point earlier in that patient’s trajectory where pulmonary artery pressure was higher, owing to a compensated right ventricle that could maintain cardiac output. Since pulmonary vascular resistance increases inversely with a drop in cardiac output, the pulmonary vascular resistance is a telltale sign for
end-stage pulmonary arterial hypertension since this value remains elevated, even at end-stage disease or in the setting of cor pulmonale.

**Slide 21 – Updates in PAH: Epidemiology and Pathophysiology**

It is important to remember that PAH, although requires a particular evaluation and makes patients eligible for a specific form of treatment, remains uncommon compared to other forms of pulmonary hypertension. This figure here shows a relative prevalence between patients who have PH with heart failure from left-sided disease compared to those who have true idiopathic pulmonary arterial hypertension. We are recognizing that in clinical practice, finding patients who have a pure form of either of these disorders is even less common than patients who present with high left-sided heart pressures, but also have an increase in the pulmonary vascular resistance and an increase in the pulmonary artery pressure. Those patients are identified increasingly, classified as having both pre and post-capillary pulmonary hypertension corresponding to an elevated pulmonary artery pressure and elevated wedge pressure and an increase in the pulmonary vascular resistance.

PH patients in the current era have enjoyed an improvement in survival compared to the original description from the NIH registry in the mid-1980s. Comparatively speaking, we can see here that survival is improved in PAH relative to heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Despite these gains, as you can see, there remains a 40 percent mortality rate three years following diagnosis. There’s still work to be done.

**Slide 22 – Survival in PAH: Etiology Matters**
Furthermore, in this regard, survival differs by PAH subtype. Among the highest risk form of this disease are patients with HIV, followed by patients with collagen vascular or connective tissue disease. Those with idiopathic PAH or portal pulmonary hypertension appear to be more treatment-responsive and congenital heart disease patients following surgical correction of intracardiac shunt oftentimes will go on to live with a reasonable quality of life and even near-normal longevity.

**Slide 23 – PAH is Diagnosis of Exclusion**

**Bradley A. Maron, MD:** It’s important to remember that PAH is a diagnosis of exclusion and should only be considered after a standard of care evaluation has been pursued to address the possibility of more commonly encountered diseases.

**Slide 24 – PAH Diagnosis: Algorithm**

This shows the diagnostic algorithm for PAH in which patients present with symptoms or clinical features and most commonly in echocardiogram suggestive of pulmonary hypertension. The focus should be on left heart disease and lung disease, which can be considered in clinical practice based on risk factors, electrocardiographic findings, pulmonary function test results, chest X-ray data. Often, findings on a high-resolution computed tomographic study of the chest as well as other diagnostic tests.

**Slide 25 – PAH Diagnosis: Cardiac Catheterization**

To pursue a diagnosis of pulmonary hypertension, as we discussed in the beginning of the presentation, it requires a right heart catheterization. Patients who have an increase in the wedge pressure or who do not have pulmonary hypertension, based on the pulmonary artery pressure, should not be treated with medications designed to improve outcome in patients with PAH, or pulmonary arterial hypertension. It is reasonable,
however, to optimize therapy for the underlying cause of pulmonary hypertension in those patients, and in the setting of right ventricular enlargement or systolic dysfunction, to refer those patients to a coronary specialty center.

Among those who do have the hemodynamic criteria for PAH and have no other risk factor for pulmonary hypertension, additional diagnostic evaluation is warranted to confirm the diagnosis of PAH or diagnose thromboembolic pulmonary hypertension, as well as pulmonary venous diseases, which can also present in a similar way. At the time of cardiac catheterization, we often review the safety with patients. Overall, this is a very safe procedure associated with extremely low rate of mortality. Complications can include infection or bleeding at the site of the venous access, but overall, it's tolerated quite well. A complete study for pulmonary hypertension is one that includes oxyhemoglobin saturation measurements in various vascular compartments, including the superior vena cava, the inferior vena cava, the pulmonary artery, as well as the wedge position, if it can be done safely. The pulmonary artery wedge pressure itself should be the average of three measurements and calculated based on levels at end-expiration.

It’s important to remember that in patients with chronic obstructive pulmonary disease and other respiratory diseases, there can be quite a bit of undulation in the pulmonary artery wedge tracing, which can, in turn, affect diagnosis if not measured at end-expiration. A left heart catheterization performed at the time of right heart catheterization is reasonable in patients who have multiple coronary artery disease risk factors or who
have a clinical presentation suggestive of ischemic heart disease, and in patients with severe pulmonary hypertension for whom elevated PA pressure can potentially cause compression of the left main coronary artery. Pulmonary venous disease, specifically pulmonary veno-occlusive disease be suspected in patients with subpleural thickening in this septal lines observed on CAT scan, which also accompanies central lobular opacities, mediastinal lymphadenopathy, which in turn, can correspond to severely remodeled and sclerotic pulmonary veins.

There is no gold standard way to diagnose pulmonary veno-occlusive disease based on right heart catheterization, although in the setting of combined cardiac catheterization with right and left measurements, there can be a difference in the pulmonary artery wedge pressure and left and ventricular end-diastolic pressure, which is suggestive of pulmonary venous disease in the absence of disorders of the mitral valve.

Slide 26 – PAH Diagnosis

Cardiac output is best assessed directly, either with a metabolic cart or using a Douglas bag and owing to wide variability in results when using thermodilution or estimated Fick. Both are recommended in the absence of directly measuring cardiac output from either the Douglas bag or the metabolic cart. If only one method is available, the preference is thermodilution.

Vasoreactivity testing is indicated in patients with idiopathic PAH, hereditary or familial forms of PAH, as well as drug or toxin-induced PAH. This can be accomplished by the administration of inhaled nitric oxide at 20 parts per million for five minutes or
intravenous epoprostenol using published protocols and much less commonly, intravenous adenosine. The purpose of vasoreactivity testing is to inform calcium channel blocker therapy, which can be very effective in patients who have a positive vasoreactivity test. Increasing data also support the role of vasoreactivity testing for prognostic purposes. Overall, consensus on a positive test is lacking, but generally speaking, a drop in the mean pulmonary artery pressure by greater than 10 millimeters of mercury to a final level of less than 40 in a setting of an increase or unchanged cardiac output is used in clinical practice to define a positive test.

Slide 27 – ACCF/AHA 2009 Consensus: Evaluation of PH

This figure shows how key tests can be performed which steer suspicion for or against pulmonary arterial hypertension. Essentially, summarize some of the information we’ve just discussed, but using a different format. Key tests beyond the history in physical examination include echocardiography, nuclear ventilation perfusion scanning to assess for chronic pulmonary embolism, pulmonary function testing to assess for parenchymal lung disease, serologic markers of connective tissue disease, and then functional test including six-minute walk distance, cardiopulmonary exercise testing, which can very important for re-stratifying, prognosticating, and for determining treatment selection or escalation.

Slide 28 - Importance of Prompt Initial Diagnosis and Referral of Suspected PH to Specialist

Prompt diagnosis is important and referral to a PAH center is emerging as one key step that can be taken to improve outcome.
Slide 29 - Delay in Diagnosis

Data from PAH registries suggest that functional class of diagnosis also indicates a delay in diagnosis. PAH is more common in women, although men appear to do less well clinically and have higher rates of hard endpoints. PAH spans a broad age range, even though most patients are diagnosed late in the disease. Importantly, despite increasing awareness, PAH and its presenting symptoms, there remains a delay in diagnosis in clinical practice, which is common.

Slide 30 - Echocardiography

Echocardiography is often utilized as the screening test of choice, owing to its noninvasive characteristics and wide availability. Doppler echocardiography can estimate the systolic pulmonary artery pressure, but other information can be gathered, which is also important in understanding the chances of a patient having PAH, including right atrial and right ventricular dimensions right ventricular and left ventricular systolic function, the presence of valvular abnormalities, intracardiac shunts. If present, a pericardial effusion can be important for prognosis since this finding is a particularly worrisome echocardiographic feature in patients with PAH.

Slide 31 – Echocardiography

This is from two-dimensional echocardiography, focusing on the right heart. The triangular structure representing the right ventricle is enlarged relative to the left ventricle. The right atrium dominates the image. This illustrates the anatomical effect of increased pulmonary artery pressure on the normal cardiac chamber size and orientation on both the right and left side. On the right is a short access view of the interventricular septum, acquired at end-diastole. You can see that the interventricular...
septum is flattened, suggesting at least volume overload and possibly the presence of pressure overload in the right heart.

Slide 32 – Inaccurate Doppler Estimations of PAP

It’s important to recognize that echocardiography is a noninvasive estimation of pulmonary artery pressure, and can be limited in its accuracy by poor acoustic windows, improper alignment of the Doppler signal, the absence of tricuspid regurgitation, and from time to time, misinterpretation of tricuspid valve closure as indicative of the jet itself.

Slide 33 – Accuracy of PH Diagnosis by Echocardiography

These data show here the accuracy of PH diagnosis relative to the gold standard of right heart catheterization. The presence of pulmonary hypertension echocardiography is more likely to underestimate estimated pulmonary artery pressure. Data from community populations in which the two studies are performed at the same time or temporarily close to one another, they correlate only modestly.

Slide 34 – Overestimation of PH by Doppler

Overestimation of pulmonary hypertension by Doppler is also common and can be seen here by incomplete tricuspid valve jet signal, which can lead to bias in how the jet length is measured.

Slide 35 – Underestimation of PH by Doppler

On the other hand, underestimation of pulmonary hypertension by Doppler can occur by similar mechanism in which the jet is incomplete and cursor placement to determine the pulmonary artery pressure is inaccurate.

Slide 36 – Cardiac Catheterization to Assess Severity and Prognosis of PAH
The indications for cardiac catheterization that we reviewed previously, but it is nonetheless important to reiterate that there are alternative indications, which may be useful in the assessment of patients at risk for pulmonary hypertension, particularly, to assess for intracardiac shunt to get an accurate measurement of left heart pressure and for the purposes of establishing PH severity and prognosis.

**Slide 37 – Need for Specialty Centers of Excellence**

Patients should be referred to specialty centers of excellence when severe pulmonary hypertension is a consideration in a patient. If access to rapid and sophisticated differential diagnosis is needed through PH protocol, transthoracic echocardiography in patients for whom a detailed right heart catheterization study is needed, if vasoreactivity is indicated, and for other specialized diagnostic maneuvers. All treatment for PAH should at least initiate at a center of excellence before consideration to co-managing with a patient’s local providers is reasonable.

**Slide 38 – Goals of Collaborative Care**

The goals of a collaborative care plan include a strong relationship between local practitioners and PH specialists in which evidence-based medicine is the principal guide for determining the best diagnosis and treatment plan.

**Slide 39 – Collaborative Care With PH Centers**

Collaborative care can be particularly useful for interval changes and fluid management, subtle dose adjustments, which are best managed in combination with a specialist. Referral is better served in patients for whom advanced PAH therapeutics including surgical approaches may be under consideration, in those for whom transplant evaluation is needed, or in patients for whom a clinical trial enrollment is reasonable.
Slide 40 - Ongoing Collaborative Care With PH Centers

It is important to recognize that managing PAH patients expands well beyond the use of PAH drugs. This includes emotional support, education, and identifying all resources that may be useful to maintain an adequate quality of life despite the high burden of this disease on activities of daily living.

With that, I'll hand over the conversation to my colleague, Dr. Ryan, who will start the discussion on treatment in calcium channel blockers.

Slide 41 - Calcium Channel Blockers

John J. Ryan, MD: Thank you, Brad. Calcium channel blockers are vasodilators, and they're suitable for people with pulmonary arterial hypertension who are responsive to vasodilator challenges.

Slide 42 – Algorithm for Assessment of Vasoreactivity in Patients with PAH

There’s a lot of uncertainty about what vasodilator challenge means and what vasoreactivity testing means. This algorithm puts it in context. The goal of vasoreactivity testing is just to determine if they can be treated with calcium channel blockers or if the patients need to be treated with other therapies. Some people have described it as treatable versus untreatable, but that’s not the case. It’s to determine if they can be treated with calcium channel blockers, if they’re a responder. As Brad initially referenced, use nitric oxide, prostacyclin, or adenosine if they’re non-responders, consider other therapies.

Slide 43 – PAH Therapy
The general treatment for pulmonary arterial hypertension revolves around diuretics for managing fluid retention, right heart failure, as Brad mentioned, oxygen. Low oxygen levels contribute to hypoxic pulmonary vasoconstriction, which can contribute to higher PA pressures. Oxygen is an integral part of this. There is some evidence suggesting the use of digoxin in the setting of right heart failure.

Some evidence showing favor anticoagulation, some against, and then the vasodilator therapy has reformed the backbone of pulmonary arterial hypertension therapy. Also likely, have an antiproliferative effect. Atrial septostomy has been proposed as the treatment for pulmonary arterial hypertension as refractory to treatment and lung transplant, obviously as the only definitive treatment for pulmonary arterial hypertension currently.

**Slide 44 – Effects of Anticoagulation on Survival in Primary PH**

Pulmonary arterial hypertension anticoagulation, a lot of it is based on older literature, non-randomized data, but patients were treated with warfarin or not treated with warfarin. As you can see from the survival graph, the people who were treated with warfarin had an improved survival compared to those who were not treated with warfarin.

**Slide 45 – PAH Specific Therapy – Vasodilators**

However, the backbone of treating pulmonary arterial hypertension is using PAH-specific therapies, I'll refer to as pulmonary vasodilators. The calcium channel blockers are a key component to this and those who are deemed to be reactive or vasoreactive.
Then there are four broad groups: prostacyclins, endothelin receptor antagonist, phosphodiesterase 5 inhibitors, and soluble guanylate cyclase stimulators.

Slide 46 – Definition of a Ca Channel Blocker (CCB) Responder

Those who are calcium channel blocker responders, again, it comes down to a hemodynamic definition. The number is small, approximately 5 to 10 percent of all the patients with pulmonary arterial hypertension. It is important to follow these people closely to determine that the calcium channel blockers are indeed being effective and indeed are safe. The definition is based on post-op analysis of registry data showing that the following three hemodynamic parameters are indicative of long-term clinical response to calcium channel blockers. Those are a decrease in mean PA pressure by more than 10 millimeters of mercury to an absolute mean PA pressure of less than 40 millimeters of mercury with an increase or preservation of cardiac output. This is in response to nitric oxide, adenosine, or prostacyclins have noted not in response to nitroglycerin. Also note is that the cardiac output cannot decrease because if the cardiac output decreases, then mean PA pressure will also decrease slightly.

Slide 47 – Effect of High-Dose CCBs on Survival in PPH

In those who do respond to calcium channel blockers, as you can see from this graph from more than 20 years ago, the calcium channel blockers in those responders had a very good prognosis.

Slide 48 – Initial Therapy

Ultimately, in order to start your therapy, you really have to be comfortable that you’re making the right decision. First of all, you’re comfortable that the patient truly has pulmonary arterial hypertension, and not another more common form, as Brad laid out,
pulmonary venous hypertension, left-side heart disease, hypoxic lung disease, etcetera. You also need to get a sense of the severity of the disease, what the patient’s preferences are, and then you try and weigh the data in an evidence-based fashion and compare clinical trials, and examine the object of characteristics and outcomes of those clinical trials.

**Slide 49 – PAH Diagnosis**

Because of these challenges in making sure you’re making the right decision on the initial therapy, there are some risk stratification tools that can guide you to determine just how sick this patient is. Two that are used broadly right now is the REVEAL PH risk score, which incorporates the subgroups, the functional class, the vital sign, the walk distance, and the other hemodynamic, and noninvasive testing. Then there’s also what was published in European Respiratory Society, European Society of Cardiology, Pulmonary Hypertension Guidelines from 2015, where people are placed into low risk, intermediate risk, and high risk with the treatments, recommendations differing depending on if the patients are low risk, intermediate risk, or high risk. These are the things, such as clinical science of right heart failure, other symptoms, some noninvasive testing, and invasive hemodynamics.

**Slide 50 - Prostanoids**

The first group we’re going to talk about are the prostanoids. These have vasodilator effect and likely have some antiproliferative effects as well, mainly impacting the pulmonary arteries and the muscle cell, hyperproliferation, that results in narrowing the pulmonary vasculature. The medicines that are available currently are epoprostenol,
treprostinil, then there’s iloprost, which is an inhaled form, and then there is selexipag, which is in oral form and strictly speaking, is prostanoid agonist.

**Slide 51 – Prostacyclins**

Prostacyclins themselves can be delivered intravenously with epoprostenol and treprostinil. They can be delivered subcutaneously with treprostinil. They can be delivered inhaled with iloprost and also a form of treprostinil. Oral preparations are available, beraprost, which is not available in the United States and treprostinil, which is, and then as I mentioned, the prostanoid agonist, selexipag.

**Slide 52 – Survival Among Patients With IPAH**

The landmark clinical trial demonstrating the efficacy of epoprostenol was published in the mid-90s and showed that in people with idiopathic pulmonary arterial hypertension, epoprostenol was associated with an improved survival and a decreased mortality compared to conventional therapy.

**Slide 53 – Required Supplies for Epo Administration**

However, there’s a lot that goes into treating people with epoprostenol. Not only do you have to have the epoprostenol, they also have to have a diluent in each two pumps. You need medication cassettes. You need training. You need some dexterity, some needles and a strong support system.

**Slide 54 – Usage and Limitations of SC Treprostinil**

Subcutaneous treprostinil, many consider equivalent to epoprostenol, but with the subcutaneous, there’s an ambulatory pump that’s designed for these infusions. You insert the catheter. The patient or the care provider or the family member inserts the catheter themselves, and it’s more stable at your room temperature. Again, however, it
still requires a capable patient, good family support, and the side pain is the main problem, it’s affecting the 85 percent of people. Different treatments that are available for this includes ice, heat, lidocaine patches, gabapentin, etcetera, PLO gel.

Slide 55 – Treprostinil IV: 6MWD (TRUST)

Ultimately, treprostinil has been shown, when given in IV form, to improve six-minute walk distance as represented by this graph with the yellow being the treatment with the treprostinil over time.

Slide 56 – Prostanoid Side Effects

The side effects of prostacyclins are not insignificant. They vary according to drug and route of delivery, where they include flushing, headache, jaw pain, commonly dizziness, cough in the inhaled form, as well as most particularly delivery side complications in particular with the subcutaneous form.

Slide 57 – Treprostinil Usage

The inhaled treprostinil use the daily ampoule provides a full-day supply of the medication. It takes about two to three minutes to treat. You do this four times a day. You can choose different dosages, depending on what the range is. The device is easy to transport, and you clean it once a day as well. It’s got a rechargeable long-life battery that last seven to 10 days.

Slide 58 – TRIUMPH-Inhaled Treprostinil

The clinical trial data of inhaled treprostinil is the TRIUMPH trial, which showed an improvement in six-minute walk distance over the 12 weeks of the treatment, again, administered via an inhaler four times a day.

Slide 59 – Oral Treprostinil Sodium
Oral treprostinil is also currently available. Intention to treat analysis showed improvement in the six-minute walk test also.

**Slide 60 – Selexipag**

Selexipag, although grouped among the prostanoids, is an orally selective prostacyclin receptor agonist and had been studied in a large clinical trial and showed that there was an improved outcome composite endpoint in selexipag versus placebo in people with pulmonary arterial hypertension. It’s a twice-a-day medicine and with uptitration of doses over the course of treatment.

**Slide 61 – Endothelin Receptor Antagonists**

Endothelin receptor antagonist, there are three available: bosentan, ambrisentan, and macitentan.

**Slide 62 – Endothelin Receptor Antagonists (ERAs)**

There are nonselective endothelin receptor antagonist, which block endothelin receptor A and B. Those are bosentan and macitentan, and then the selective, which simply block endothelin receptor A, the one currently available in the United States, is ambrisentan.

**Slide 63 – Bosentan Trials: 351 and BREATHE-1**

The bosentan trials demonstrate its clinical efficacy in terms of a change in six-minute walk distance.

**Slide 64 – Ambrisentan in PAH: 6MWD (ARIES)**

Similarly, the ambrisentan trial, ARIES-1 and ARIES-2 demonstrated improvement in six-minute walk distance in people with pulmonary arterial hypertension.

**Slide 65 – Macitentan: Composite Endpoint (SERAPHIN)**
Macitentan clinical trial used the composite endpoint and with the primary endpoint being transitioned to prostacyclins, worsening of pulmonary arterial hypertension, lung transplantation, atrial septostomy, or death. Doses are the 10-milligram dose of macitentan, showed that there was an improvement. There was a decrease in the number of these events and the patients randomized to macitentan, and the combined endpoint of the two, to pulmonary arterial hypertension or hospitalization was also improved.

**Slide 66 - Endothelin Receptor Antagonists: Side Effects**

There are side effects with endothelin receptor antagonists as well. Some of them are similar to the side effects of prostacyclins, mainly nasal congestion, but some of them are unique. Abnormal hepatic function requires monthly LFT monitoring for bosentan. Also, anemia requires quarterly CBC. Lower extremity edema can be noted with these agents requiring addressing the diuretics, and these medicines are teratogenic, and do require dual contraceptive methods, prior to prescribing in females who are of reproductive capacity.

**Slide 67 – Phosphodiesterase-5 (PDE-5) Inhibitors**

There are two currently available phosphodiesterase 5 inhibitors in North America. Those are sildenafil and tadalafil. These are orally available agents.

**Slide 68 – Phosphodiesterase-5 Inhibitors (PDE-5): Oral Agents**

Sildenafil is a three-times-a-day medicine. Approved dose is 20 milligrams, three times a day. Tadalafil is a once-a-day medicine with a dose of 40 milligrams. There are no known interactions with other PH medicines or warfarin. Headache is oftentimes best treated with Tylenol. There can be some GI distress with these medicines.
Slide 69 – SUPER-1: Sildenafil in PAH

Sildenafil has been studied in the SUPER trial, shown to improve six-minute walk test.

Slide 70 – Tadalafil

Similarly, the tadalafil was studied and also shown to have an improvement in six-minute walk test when compared to placebo.

Slide 71 - PDE-5 Side Effects

The main side effects of phosphodiesterase 5 inhibitors are nosebleed, headache, dyspepsia, flushing, diarrhea, and visual changes, and have note, there are contraindications with the use of nitrates due to concerns for systemic hypotension.

Slide 72 – Soluble Guanylate Cyclase Stimulator

There’s only one available soluble guanylate cyclase stimulator currently in North America, and that is riociguat, which

Slide 73 – Riociguat in PAH: 6-minute Walk Distance (PATENT-1)

in the PATENT-1 trial, was shown to improve six-minute walk distance.

Slide 74 – Soluble Guanylate Cyclase Stimulator Side Effects

Side effects are similar to the other groups that we’ve mentioned: headache, dizziness, some GI upset, gastroesophageal reflux, and constipation. Also contraindication with the use of nitrates. Also contraindication with the use of PDE5 inhibitors, and there are contradictions in pregnancy.

Slide 75 – Combination Treatments

Typically, most patients with pulmonary arterial hypertension are now treated with combination therapies. This can either be done sequentially, one after the other or they can be done upfront.
Slide 76 – Initial Use: Ambrisentan plus Tadalafil in PAH

The main trial which shows upfront combination therapy is the AMBITION trial, which shows ambrisentan plus tadalafil in pulmonary arterial hypertension, showing that combined therapy decreased the clinical endpoints.

Slide 77 - Best suited for patients affiliated with PH Centers of Excellence

Patients with pulmonary arterial hypertension and also opting for upfront combination therapy or even combination therapy in general, through all the purposes, these are best suited for patients affiliated with pulmonary hypertension centers of excellence.

Slide 78 – Timing of Referral to a PH Center

The timing of the referral to a pulmonary hypertension center of excellence can depend on the local physician’s level of comfort. It can occur at multiple junctures. People who run pulmonary hypertension centers are very comfortable in getting referrals, and are very welcoming of referrals at any time. They can be at the very beginning after the initial screening echo, which is common with our centers. It can be after some testing. It can be after the right heart catheterization. It can be after treatment, or it can either be when the provider has decided that they’re escalating the treatment. Ultimately, these patients can be referred on at any time.

Slide 79 – Thank you

I want to thank you all for joining us today. To receive credit for viewing this program, you must complete the post-test and evaluation. This only takes a few minutes. Your feedback is very important to help us gauge the impact of the CME activity. Your responses also guide us in developing future educational programs targeted to your specific interest and addressing the clinical challenges you experience. Thank you once
again. This has been a real treat for me and for Dr. Maron to present this to you all. Best of luck with your treatment of pulmonary hypertension.