[MUSIC PLAYING]

MARK GLADWIN: I do want to say that I attended this last year. This is my first year as the chair of medicine here. And I really enjoy this course. I'll be here all day. If anybody has any feedback or ideas, I'm happy to talk to everybody. In starting, what I've done over my career is because I've run a big research operation in pulmonary vascular disease and sickle cell, I've really focused my clinical knowledge and clinical practice around critical care and pulmonary vascular disease. But in taking this job, I suddenly had to go to resident report, an intern report. The first case in resident report was chikungunya which I had not heard of before. So I immediately was very embarrassed and signed up for this course. So I'm absolutely delighted by the content. And I will be learning with all of you. So without further ado, I'll start.

So Mike and Terry and the organizers asked me to talk about the clinical presentation, the initial screening, the clinical workup and risk stratification of pulmonary hypertension. This is rapidly becoming a complex field, as you know, with almost 14 FDA approved medications. So I'll try to simplify and decipher it for you. Many of you are very experienced in the workup and management of these patients. So what I'm going to talk about are these bullets. How does pulmonary arterial hypertension present? And how do we diagnose this in the clinic? The echo shows an elevated pulmonary pressure. Do I have to do a right heart catheterization? How do I choose my initial therapy which, despite the broad number of drugs, you'll see is actually, I think, simplifying a bit. And how do I adjust therapy in my patients?

And at the same time, I'll talk about some pearls. So I'll bring up over and over that since we're in election times right now and the Clintons are coming back, you'll remember from Bill Clinton's election, "It's the economy, stupid." They had sort of a laser focus on the economy. "It's the economy, stupid." When it comes to pulmonary hypertension, I say, "It's the cardiac output, stupid." And I'll keep coming back to that, that we think about pressure, it's high pressure. But what really determines whether you need to do anything, what determines symptoms, what determines risk of death, and what all the drugs are approved for is maintaining right ventricular cardiac output. So I'll come back to that in terms of screening, risk factors, and how to guide our therapy.

So this was a patient. And I see a lot of patients that have sickle cell, so say pulmonary hypertension. But this could be any form of pulmonary hypertension. This was actually an 18-year-old that was referred to us for consideration of a lung transplant. But he had severe dyspnea, syncopal events, cyanotic lips, and peripheral edema. Pretty classic findings of pump failure and cor pulmonale. He had homozygous sickle cell disease. He had rare painful crisis. So he sort of wasn't the typical patient that you think about with crisis all the time. He'd been on transfusions since he was 11 because of stroke. And his lab showed what you'd expect, some inflammation, transfused hemoglobin. Most of his hemoglobin in his blood was hemoglobin A because he was heavily transfused. And because you'll see a severe pulmonary hypertension, we looked for secondary causes. Autoimmune disease, HIV, hepatitis, all of these tests were negative.

Now I'm just showing you the case because he illustrates some classic findings of severe pulmonary arterial hypertension that I think you need to know about. One is this is the CAT scan. Now hopefully this projects. And one thing you'll note is there is an area of greater attenuation, kind of whiter area and darker area. And as I scroll down, you'll see these areas of dark and light, dark and light, almost a mosaic pattern. And typically we look at something like this, and we say, this is ground-glass here, GGO, opacities. Now, ground-glass means there's water, blood, or pus in those alveoli, right?

But this is the little clinical pearl. With severe pulmonary arterial hypertension or with chronic thromboembolic pulmonary hypertension, you have the opposite. The abnormal lung is actually the dark lung. And what's happening is you're blocking blood flow either because chronic clots are blocking blood flow or because narrowing of the pulmonary vessels is blocking blood flow. So all of the blood flow is being redirected to the whiter area so there's a higher blood volume, which absorbs X-rays. So what this is called is a mosaic perfusion pattern. It's actually quite common in patients with severe pulmonary arterial hypertension. So during an inspiratory CT, you see a mosaic perfusion pattern. And this is just as you can see that. And I'll show you another example later.

Second thing is he had an echo. And I'm going to go over this in a minute. But his tricuspid regurgitant jet velocity was very high, 6 meters per second. And up here you can see his right ventricle's big, his right atrium's big. So immediately he has this mosaic perfusion pattern and a very fast tricuspid regurgitant jet velocity-- and I'll come back later to what that is. And this is his echo of his heart. This is actually his left ventricle. This is the right ventricle, right atrium. Notice that the right atrium's enormous. The left atrium's almost completely collapsed. His right ventricle's enormous. There is a D-shaped left ventricle with diastolic collapse. You can see that-- how can that left heart fill with blood when even during diastole, it's almost completely collapsing? So evidence of very severe right ventricular failure.

He had a right-heart cath. His right atrial pressure was 40. Normally it should be zero to five. His right ventricular pressure, 144 over 9, so a super systolic right ventricular pressure. His pulmonary pressure, 147 over 49. Pulmonary mean, 82. Should be less than 25, really should be less than 20. A wedge pressure that's high. And this is just to show you the wedge pressure. Sometimes with very severe right ventricular failure with pressure of that septum into the left ventricle, your left ventricular filling pressures can be falsely elevated. He is a young man so he'd manage to continue to preserve his cardiac output. Transpulmonary gradient, very high. Cardiac index still holding at 2.6.

So what are we talking about? We're talking about a disease that's restricted to the arterioles of the pulmonary vasculature. And if you look at these arteries, instead of being a nice open blood vessel in the pulmonary artery, we see this intimal hypertrophy, the complete occlusion of the intima. Here you can see the smooth muscle is proliferated and thick. There's intimal hypertrophy and obliteration of the lumen of the blood vessel. And over time, you can develop little bypass. These are called plexogenic lesions, where you start to bypass blood through new kind of holes in the pulmonary artery or around the outside of the pulmonary artery. It's almost like a cancerous lesion of that pulmonary vessel that's occluding blood flow.

And this is how pulmonary arterial hypertension progressives. Remember, it's a disease of the small blood vessels going from the right ventricle through the pulmonary artery into those pulmonary arterioles. So it's narrowing before the capillaries that perfuse our lungs. And so these blood vessels-- normally we've got our endothelial cell lining, you've got the smooth muscle cell lining. And the first thing that happens is you develop endothelial dysfunction, meaning your endothelium is not working. And you get a dysregulation of vasodilators. You can see there's vasodilators, nitric oxide and prostacyclin that open up the blood vessel. And then there's vasoconstrictors like thromboxane and endothelin-1. And you start to shift that balance. Too much endothelin-1, too much thromboxane, not enough nitric oxide and prostacyclin so the blood vessels become reactive and vasoconstrictive. That then starts to drive hypertrophy. The smooth muscle starts to hypertrophy. It drives inflammation. You get inflammatory cells coming in. And over time, you develop that lesion that I just showed you. And you can see on the end how it looked just like that lesion with these new vessels forming on the outside, and that's called a plexiform lesion, or a plexogenic vasculopathy.

So what happens is as these vessels narrow-- so this is a right heart catheter, as you know. The PA catheter goes through the right atrium through the right ventricle into the main pulmonary artery where you can measure that high pressure in the pulmonary artery. And this balloon tip catheter will go out and wedge in the periphery. And once it wedges, the tip of that catheter has a pressure transducer, and the reflected pressure backwards from the left atrium can be detected to estimate your left atrial pressure. And as you can imagine, that pulmonary pressure's really high. There's then a block or a dam at the pulmonary arterial. So once you wedge, your left-sided pressures are low or normal. So there's a sudden drop. There's a big transpulmonary gradient. And those wedge pressures should be normal.

So in pulmonary hypertension, you can see now this dilated right ventricle. What you see is the pulmonary pressures, the mean pressure should be less than 25. If your mean pressure is over 25, that defines pulmonary hypertension. Now if your wedge pressure is less than 15, it defines pulmonary arterial hypertension because the hypertension is occurring because of the arterioles. The left-sided pressures are normal. The pulmonary pressures are high. So your mean pressure is over 25, and your wedge pressure's less than 15. And that is the definition of pulmonary arterial hypertension.

So what are you looking at in clinic when you see a patient that has pulmonary hypertension? Well, first of all, you're going to have symptoms. Classic symptoms would be evidence of right heart failure, and you know that's very nonspecific. The other classic symptom-- remember it's the cardiac output that's driving this-- so you're short of breath, and you're short of breath with exercise. The presenting symptom, the most common, is shortness of breath, dyspnea on exertion. And it depends on what your patient's like. If you have a 30-year-old marathon runner or iron woman, they may present earlier with disease because they're going to start noticing they're dropping their times. They're getting dyspneic at their level of exertion. So sometimes we'll see people quite early who exercise in the modern era. But dyspnea on exertion. Once it's more severe, cor pulmonale right heart failure and syncopal events. All of them driven by a problem with cardiac output.

So you'd do an exam looking for signs of right heart failure cor pulmonale, loud P2, peripheral edema, jugular distension, hepatojugular reflux. Clear lungs usually because, remember, the blockage was before the capillaries so you don't get pulmonary edema. You'd get a chest X-ray and an EKG. Now if it's advanced, this is what the chest X-ray looks like. Clear lung fields-- remember, everything's in the arterioles. You're sparing those lungs, nice clear lungs. But you could see very large pulmonary arteries. And this is the aortic arch, the AP window with a big large pulmonary artery. Now something like sarcoid would be lumpy and bumpy. With pulmonary hypertension, you get a nice, smooth, large PA and a normal LV size, the LV's normal. And again, the pulmonary artery large on this side. It's got to be pretty advanced for you to see enlarged pulmonary arteries like on this X-ray. I'm sorry. I got to go back here. I left my little trigger. Can we go back one?

You'll get an EKG. Again, with severe disease, you have a classic EKG for a dilated RV. So first of all, on lead one, you have evidence of a right axis shift. So you've got your R and then big S in lead one. You have P pulmonale, a very tall P wave in lead two and a very significant biphasic P wave in V1. And again, I have all these slides for you. You have tall R waves in the anterior precordial leads because you have RVH. The RV's big. And you have repolarization abnormalities here in your right-sided precordium. And that's sort of the classic EKG for right ventricular hypertrophy. On echo, you see signs of right heart failure-- and I'll come back to that-- a dilated RV, flattening and bowing of that septum into the LV during diastole and a big right atrium. You have a big tricuspid regurgitant jet velocity. I'll come back to that. And you have pulmonary hypertension on right-heart cath.

So how do we work this up? Well first of all, your history and your physical exam, your chest X-ray, your EKG might be suggesting to you that there's RVH, that there's some heart failure, some right heart failure. And you have an index of suspicion. You might have some diseases that are typically associated with the development of pulmonary hypertension like scleroderma, HIV infection, liver failure. You get an echo-- and this is the most important thing-- and you're going to be looking not only at your estimated pulmonary pressures but signs of right heart failure.

At this point before moving on for a workup, many of us think then about symptoms, jumping to symptoms, looking at BNP, looking at exercise. And the reason is is the patient you're going to treat, the patient you're really going to aggressively workup are the ones that have signs of pulmonary hypertension with symptom limitation, a high BNP, a low walk. So oftentimes if you have borderline evidence of pulmonary hypertension, we risk-stratify based on walk and BNP. But if it looks like you have signs of RV failure, if your pulmonary pressures are high, you would then start thinking about secondary causes of pulmonary hypertension. A VQ scan, do they have chronic thromboembolic pulmonary hypertension? Pulse oximetry, do they have sleep apnea? Serologic testing, do they have HIV? Do they have autoimmune disease? Do they have scleroderma? And again, thinking about a right-heart cath.

So in addition to diagnosis, which we're using echo and screening tests for, many of these tests also give us prognostic information. They're going to tilt us towards thinking, I need to be more aggressive with this workup. I need to do more fancy tests. I need to think about treating the patient. And one of these tests is the brain natriuretic peptide which we think about for left heart failure. You're thinking about it for heart failure. But it turns out the right ventricle under pressure overload also releases BNP. And essentially, this is a preprohormone. When the cardiomyositis is subjected to wall stress, it releases this prepro BNP which is cleaved to a proBNP, and there's an end terminal fragment. You can either measure the BNP molecule or the end terminal proBNP molecule. There are two tests. They tell you the same thing. And this is actually a hormone. It drives vasodilation and natriuresis so it's actually a nice compensatory response to pressure overload. The heart makes a hormone that tries to get rid of its fluid. But this molecule, if it's high in the setting of a normal left ventricle, it suggests that you have pulmonary hypertension. And also, if it's high, it suggests there's a little bit of a worse prognosis because the RV is actually failing.

The most important test is the echo. And I tell people that you do need to memorize a few things about the echo even as a general practitioner, even as a specialist not focused on cardiology. And I think we're at a time in history where you have to memorize what the tricuspid regurgitant jet velocity is. And the reason is that this is the heart. Here's the left ventricle. Here's the right ventricle. And when the right ventricle squeezes-- remember, it's squeezing against a high pressure when someone has pulmonary hypertension-- there's some leakage backwards against the tricuspid valve. 87% of you in this room have a leaky tricuspid valve. Remember, this is a floppy valve on the right side of the heart. And there's always leak. And when that right ventricle squeezes, there is some backflow across that tricuspid valve into the atrium. And it's easy to measure the velocity of that backflow. And you can quantify that velocity, and it's called the tricuspid regurgitant jet velocity.

Because the velocity is always proportional to the change in pressure, the higher the pressure, the higher the velocity. You can convert that to a pressure estimate. And the equation is called four-velocity squared. And this is showing that Doppler envelope. And you can get that peak TR jet velocity-- it's reported in almost all echoes within the UPMC system-- and you can calculate four times the velocity squared. So this is 4 meters per second. So it'd be 4 times 4 times 4 is 64. Then you add an estimate of the right atrial pressure to that. When you do that, you can get that systolic pressure estimate. And I'll just tell you that a value less than 2.5 meters per second is completely normal. A value over 3 meters per second is when we think about working this up because that would be 3 times 3 times 4 or a systolic pressure of 36. We think about working up over 3 meters per second. And it has a reasonable sensitivity and specificity.

A second value that people are measuring is how well does the right ventricle pump. And there's something called the TAPSE. And that's the tricuspid annular plane systolic excursion, a big mouthy thing. But the right ventricle is a half moon sitting next to your left ventricle. And when it constricts, it does this, it shrinks on its short axis. And this is the tricuspid annular plane. And during systole, it moves a lot. If your right ventricle works well, it moves a lot. So there's a big systolic excursion. And a value over 1.6 centimeters is normal. If you have pulmonary hypertension, it dilates and doesn't move. If you have a big PE, it dilates and doesn't move. So that TAPSE, turns out it really predicts mortality. Remember, "it's the cardiac output, stupid." I'm not calling you guys stupid. I'm just referring to the Clinton campaign. If you have a low TAPSE, you have a worse survival. So that's another assessment. The great thing about echo is you can measure the pressures-- are they high or low-- and you can assess the function of your right ventricle which determines how sick you are, how aggressive you have to be.

So do you need a right-heart cath? First of all, accuracy. I told you how great the echo is for prognostication and for measuring pressures. But it's still not super accurate. The r value here for the estimated pulmonary artery systolic pressure, using that TR jet velocity, only has an r value of about 0.5 to 0.77 depending on the study. It's worse if you're obese, thick chest. So it's going to suggest that you have pulmonary hypertension, but it's not going to be completely accurate. So you might need a right-heart cath to determine the accuracy.

You have to get a right-heart cath to define the diagnosis. Is it pulmonary hypertension from left heart disease? Or is it pulmonary arterial hypertension because of the arterioles? And here's the key. For both types of pulmonary hypertension, your PA pressure is over 25 on your right-heart cath. But to call it pulmonary arterial hypertension, you have to have a low left ventricular filling pressure, a low wedge pressure less than 15. And you also want to see a high pulmonary vascular resistance. So right here is the definition of pulmonary arterial hypertension. And you'll notice the only way you get a wedge pressure is with the right-heart cath. So to really define what you have, you need a right-heart cath. Now does it matter? It does matter because all the drugs I'm going to tell you about, they were tested in people with a low wedge pressure. Many of the drugs, like the endothelin receptor blockers, were actually first developed for left heart failure and they worsened survival. So they work for pulmonary arterial hypertension, but they don't work if your wedge pressure's high.

Lastly, it tells you prognostic information. When you get a right-heart cath, how bad your cardiac output is-- if you have a low cardiac output less than 2 liters per minute, your prospective median survival is only 40 months. If your mean right atrial pressure's high, that's a bad sign. Remember, low cardiac output, high right atrial pressure means your pump isn't working. If you do a right-heart cath and the pump function's not working, you have a bad prognosis. And finally, you can do provocative maneuvers, like test the responsive to vasodilators.

So what's the cons? Well, it's invasive. You've got to put your patient through an invasive cath. But it's very safe, 0.06% fatality. It's probably one of the safest studies. It does have limited reimbursement. That's not a problem here. We have a lot of people very eager to do these tests, and you can get them done very quickly. Just as an example, between 2005 and 2015 at Presby alone, we did 20,000 right-heart caths. And we have very active right-heart cath in all of our hospital systems. And the right-heart cath typically doesn't use contrast, by the way, so you could get the study without contrast.

So what's the major reason to do it? Here's the major reason. If you see a patient with pulmonary hypertension, if they have pulmonary hypertension, really less than 10% of them are going to have pulmonary arterial hypertension. Almost all of them are going to have pulmonary hypertension caused by left heart disease. And almost all of them are going to have HFpEF, heart failure with preserved ejection factor. This is now epidemic, as you know. As you guys are doing a better and better job controlling coronary artery disease with statins and aggressive interventions, we're seeing less systolic heart disease. But as we're aging and we're developing more obesity and metabolic syndrome-- also more common in women-- we're seeing more HFpEF. And with HFpEF, the pulmonary pressures rise like all forms of left heart failure. So many of our patients that we think have pulmonary hypertension have HFpEF. The only way to figure this out is with the right-heart cath. They're going to have a normal LV ejection fraction. But during right-heart cath, you're going to find high filling pressures. The drugs I'm going to tell you about are not indicated for HFpEF. So this is an important reason you need a right-heart cath. Probably the most important reason.

So should I cath? You think about the prior probability of pulmonary hypertension. And this is just-- you can refer to this-- these are the classifications of pulmonary hypertension. So group one is the classic pulmonary arterial hypertension that you're going to treat with these drugs. And while idiopathic, you're not going to be able to predict, or even hereditable. There's other drugs like the diet drugs. It can be associated with scleroderma, congenital heart disease, portal hypertension, HIV. So you can think about how likely it is that they might have this. But then do they have left heart disease? It can be associated with hypoxemia from lung diseases like COPD or IPF, and then due to chronic thromboembolic disease. And finally this 5th group is miscellaneous.

So how likely is the patient to have PAH based on other diseases that are associated with PH? And what about alternative explanations? If they have severe lung fibrosis, if they have COPD, they're very likely to have group three disease. So that can guide you a little bit on how important it is to get a right-heart cath. And how concerning is the echo? Again, any sign of right heart failure, dilated RV-- dilated RV D-shaped left ventricle because that septum is being pushed in there-- dilated RV, right heart failure, you're going to think you need this cath. So again to summarize, what's the prior probability, likely alternative explanation, how concerning's the echo, symptoms. In other words, of course, be a doctor. And I would err on the side of doing a cath. It's very safe. Err on the side of doing a right-heart cath.

So how do I choose initial therapy? As a scientist, I had to freak you out with one complex slide. This is the world we're in now of pulmonary arterial hypertension therapy. It's actually an incredible example of science meeting the bedside very rapidly. There was a Nobel Prize awarded for the NO pathway, Nobel Prize awarded for the prostacyclin pathway. And right on the tail of these Nobel Prizes, drugs hit the clinic. It's really impressive. And that speed from discovery to drug development, as you know and you'll hear in the next two days, is quite impressive.

But if you think about it, there are three major pathways that control blood vessel dilation. There is an enzyme in our endothelium, nitric oxide synthase, that converts arginine to citrulline and makes nitric oxide. That nitric oxide binds to guanylate cyclase to make cyclin GNP and promotes dilation. Well we've targeted each step of this so we can give arginine. It's not FDA approved, but people give it oftentimes as a naturopathic drug. Most importantly, we have a drug, sildenafil, tadalafil, the PDE5 inhibitors that are used for erectile dysfunction. They've been FDA approved now for pulmonary arterial hypertension. They block the enzyme that degrades cyclic GMP. So essentially they're promoting eno cyclic GMP signalling. A new drug's just been FDA approved, riociguat. It's a small molecule that directly activates this SGC. And you can imagine you never want to use riociguat with Viagra together-- I can imagine that being a board question-- because what you'd do is you'd activate this enzyme, you'd make a ton of cyclic GMP, then you'd block the enzyme that degrades the cyclic GMP. So you'd get severe vasodilation and hypotension. So you never want to use sildenafil with a nitroglycerin molecule that's making NO. And you never want to use sildenafil or Viagra with riociguat, this new pulmonary hypertension drug.

Prostacyclins, the enzyme cyclooxygenase makes prostaglandin. Well look, there's three drugs that are FDA approved and four in Europe that are prostanoids. You can give epoprostenol or Flolan IV. You can give oral, inhaled or subcutaneous treprostinil. All three formulations are now FDA approved. You can give inhaled iloprost. Pretty much we're giving IV Flolan for severe patients. And we're giving inhaled treprostinil for mild patients, and oral treprostinil for mild patients, and subcutaneous or IV treprostinil for more severe patients. And then the endothelin receptor. Endothelin-1, by the way, is phenocopied by a snake venom. One of the most potent snake venoms is a phenocopy of the endothelin-1 peptide-- it's about 11 amino acid peptide-- one of the most potent vasoconstrictors known to man. And so the snake bites you and it vasoconstricts your blood vessels and kills the animal with hypertension and ischemia of the tissues. Well we make endothelin and it binds to two receptors that cause vasoconstriction. And there's now two FDA approved drugs that block those receptors called the endothelin receptor antagonist.

So you got all these drugs. What do we do with them? Well, first of all, you're going to treat your patients with non-pH targeted drugs. Oxygen, diuretics are very important to control your right atrial pressure and your edema and your symptoms. We're moving away from anti-coagulation. The studies are not panning out there. We're not using calcium channel blockers hardly at all. So our drugs, prostacyclins, endothelin receptor antagonists, PDE5 inhibitors, and the newly approved soluble guanylate cyclase stimulator riociguat. And then investigational drugs that are coming. And I'll only briefly mention that.

So how are you going to choose your initial drugs? Well you're going to look at your risk, severity of disease, if you've got right heart failure, if you've got pump failure. If your wedge pressure's low, you're going to be more aggressive about treating. If they're really sick, if they've had syncope, if they've got a really low cardiac output, if they've got any forward pump failure, you might be way more aggressive and move faster to IV therapy. So you're going to assess risk. Things like coverage status, patient availability, patient support, patient preference, side effect profiles are all going to modulate your treatment options. In general, you're going to want to assess risk to guide how aggressive you are with therapy.

And once again, it's the cardiac output. Most determinants of risk are based on evidence of heart failure and cardiac output, right ventricular cardiac output, what is the evidence of right heart failure. Progression being rapid, that's high risk. World Health Organization class, if you're class III or IV, it's higher risk. Remember, a class III would be you're short of breath just doing things at home like vacuuming, carrying your child, washing dishes, showering, brushing your teeth. If you're IV, that means you're short of breath at rest. You're just short of breath all the time. That's going to be a high risk thing. Six minute walk distance, if you're less than 300 meters in six minutes, that's bad. Why? Because your cardiac output's low. BNP high, bad. Why? Cardiac output's low. Echo findings of things like RV dysfunction, pericardial effusion. You get a pericardial effusion if you have right heart failure because you can't drain the pericardium into that right heart. Hemodynamics, the hemodynamic risk factors are not pulmonary pressure. It's right atrial pressure and cardiac output. Again, the low cardiac output's bad.

So if you're higher risk, you think about testing. And let's ignore this oral calcium channel blocker because we don't hardly ever do it anymore. We're looking in the cath lab and we're assessing risk. And if you're higher risk-- if you're lower risk, you're going to go to an oral therapy or an inhaled therapy. If you're higher risk, you might go more quickly to IV therapy, IV prostacyclin or IV treprostinil. And I'd be thinking a higher risk of really referring early and fast.

And consider combination therapy. Now here's where things are changing very rapidly. And I'd say they've already changed. The biggest update in the last year is that we're now going right up front to combination therapy. And here's the concept. And I think the answer, I'll just tell you, is yes. The current approach is that we do sequential combination therapy for deterioration or failed to improve. So you might start them on an oral endothelin receptor blocker, then you might add a PDE5 inhibitor, and then you might go to inhaled prostacyclin or IV prostacyclin. That's the way we were doing it. Some people started with a PDE5 inhibitor, and some people started with an ERA. It didn't matter. Based on patient symptoms and response, you'd be on one or the other and then you'd add them. And then you eventually go to a prostanoid. Now we start with these because these are pills. Prostanoids you need to give them inhaled, subcu, making a little higher threshold for our patients. But where we are now is combining them. Let's add them together right up front.

And the pivotable study is this study in the New England Journal called the AMBITION trial. The initial use of ambrisentan, which is a dual endothelin AB receptor blocker, plus tadafil, a long-acting phosphodiesterase-5 inhibitor like a long-acting Viagra, and we used them together. And a lot of patients were enrolled here in Pittsburgh, and here's what they saw. They looked at time to an event, hospitalization or death, and highly significant-- what's great about this study is two companies partnered together, and everybody got a drug. You either got ambrisentan alone, tadalafil alone, or both together. And we really didn't know the answer to this question. And what the result was just dramatic. Look at this Kaplan-Meier. This is 100% of people have not been hospitalized or died, and this over here is 60% hospitalized or died.

And you can see with combination therapy, there is a highly significant separation. People did better. The side effect profiles were similar. It was fine to get both drugs. Based on this, if you know you have pulmonary hypertension, you've confirmed it by right-heart cath, you have symptoms, I personally, as long as they tolerate it, would put them on ambrisentan plus tadalafil. And the companies are now working on packaging like the HIV drugs. Eventually they're going to work on one pill instead of having to take two pills. And these are all the studies now that are either completed or ongoing looking at combination therapy. And I just highlight that almost all of these studies, when they do them, show that improvement. If you add a drug or you start with two drugs, it works. So combining these pills seems to be safe and effective.

Now what's coming? You're going to hear about a lot of drugs in the news, a lot of things going on. I just showed you this incredible signaling pathway where converging around things like mTOR, All of these are cancer pathways that drive proliferation and cell growth. You don't need to know this. You don't need to remember this. But I'm just going to point out that these pathways are now being targeted in pulmonary hypertension with chemotherapy drugs. For example, there was this incredible study in Nature Medicine where they targeted transcription factor FOX01. FOX01's central to driving malignant proliferation. And it's targeted by Taxol which we use for breast cancer and many cancers. And this was a very nice study where they showed that if you treated people here with abraxane, which is a form of Taxol, you could improve that TAPSE, that squeeze of the right ventricle. You could reduce right ventricular hypertrophy in an animal model. And they're now studying Taxol for patients with pulmonary hypertension.

So what I've shown you is as this disease progresses and this blood vessel narrows to a plexogenic lesion and that right ventricle dilates, you go from this presymptomatic [INAUDIBLE] exertion to symptomatic decompensating to decompensated. And that pulmonary vascular resistance is rising and that pulmonary pressure rises. But you decompensate when your cardiac output drops. And that's when you get your bad symptoms.

So lastly, I'll just end with this case, just so you don't forget this other common, increasingly common form of pulmonary hypertension. And this is group 4 chronic thromboembolic pulmonary hypertension. This is a football coach I saw with-- he coached his son's football games. He's running up the sidelines. And he said, "Running up and down the sidelines, I noticed I was more and more short of breath." And we did his echo-- big right ventricle, big right atrium, big tricuspid regurgitant jet velocity, barely had a TAPSE, tricuspid annular plane systolic excursion. Big tricuspid regurgitant jet velocity, in this case, more than 4 meters per second four-velocity squared. Had his CAT scan, mosaic perfusion pattern. This is as good as you'll see it. Very common in patients with chronic thromboembolic pulmonary hypertension. But notice it's all black at the top of his lung. There's no blood flow at the top of that lung. Nice mosaic perfusion pattern. Did a VQ scan which is the test. Normal ventilation. But look at the perfusion. Again, no blood flow at the top of that lung. Looks like moth-eaten, big segmental defects. When you see multiple segmental defects with pulmonary hypertension, it's chronic thromboembolic pulmonary hypertension. We do an angiogram. He's got like a bonsai tree, pruning of the vessels. And I'm just showing you, look how there's no blood flow to the-- some areas have blood flow, some areas don't. And that's what creates that mosaic perfusion pattern.