BELINDA RIVERA-LEBRON: We're very glad to be here talk about PE and our approach that involves multiple disciplines in the treatment of not just acute PE but chronic PE as well. So as you know, PE is a very serious problem. It's very common in the United States. And just last year-- this is a quote from the CDC-- close to a million cases of both PEs and DVTs.

Out of that, almost 250,000 of them get admitted to the hospital. And out of that, maybe 100 to 200,000 of them die from a PE-related cause. Out of those who survive, 50% of them will have some kind of sequelae. Whether it is chronic pain from a DVT or chronic shortness of breath or any exercise limitation from a PE. And they could end up developing something called chronic thromboembolic pulmonary hypertension, which is an elevated blood pressure in the pulmonary artery, caused by chronic blood clots. So in up to about 4% of these patients.

VTE is still increasing. So it's still on the rise, as you can see from this slide. And in all sorts of flavors. So PE, DVT, and the combined, both entities in the same person, are still on the rise. And it is the third most common cardiovascular cause of death. So it's important to talk about and especially recognize early. So it follows MI and stroke and incidence of cardiovascular death.

--as you know, and I think that the PE has a natural history, it has a different spectrum. It has different ways of how to develop and progress. Most patients, however, have a complete resolution. About 90% of them. They come to the hospital, they get treated, and they get resolved. So that's a good majority of them and that's great.

However, there's up to about 30% that could recur in the first, after 10 years. And this could be even on anti-coagulation appropriately. So it's very important to know that the risk, it still on goes, even as far as 10 years down, as far as we know. And probably, it continues for life. And some of them are going to go for partial recovery. And then, again, some of them are going to go into developing CTPH, or the chronic thromboelmbolic pulmonary hypertension. As you can see here, the difference between an acute clot and a chronic clot, it's very different. The acute clot is very frail, very loose, and sort of easily ruptured. As opposed to a chronic clot, which is mostly a fibrotic tissue clot and it's very rubbery and kind of debilitating.

So the American classifications for PE, which is the most common one and the oldest one, tells us that PEs are classified in three different levels. So a low risk, an intermediate or submassive, which is one of the common names, or high risk or massive. So low risk are people who have a normal blood pressure, who have no RV strain or any dysfunction in the RV and have normal biomarkers. And by that, I mean a troponin and a BNP.

The submassives are people who are still normal tensive, but then are now starting to show signs of RV strain. And that could be either on a C.T. scan or an echocardiogram. And then therefore, it started developing or could start developing biomarkers that are positive, like the BNP and the troponin.

The high-risks, of the massives, are people who are now hemodynamically unstable. And that's defined by systolic blood pressure of less than 90 for over 15 minutes, who are in shock or requiring a vasopressor, or have a cardiac arrest due to a PE. Now the Europeans did an updated guidelines signed 2014. This is more recent than the American one. And as you can see here, it's a little bit more complex. So they not only just did the definitions, but they also included in the definitions what kind of risk assessment does each patient need to know which category or classification of PE they're going to have.

And the other thing-- is there a pointer here? No pointer? But the other thing that you can see here is the inter and on-- in the intermediate category, they actually subdivided the intermediate category in high intermediate, and low intermediates. And as you could see, that is primarily the main difference here when you're classifying patients. And in the high intermediate, you could see that both RV strain and cardio biomarkers are going to be affected, as opposed to intermediate low, which one of them is going to be affected. So the patient could have either the RV dysfunction and/or the biomarkers that are going to be elevated.

And the reason why they did that is because it changes their mortality. I'll show you that in this slide. But first, I'd like you to know that luckily, most of the patients have low risk. So over 50% of them are going to have low risk. And the minority of the patients are going to have a high risk. So 5% of the patients are going to have a massive PE.

However, there's still a good amount of patients in that submassive or intermediate category, and that could be up to 40%. So that's a very significant amount of patients that have a PE that are still going to have some kind of RV strain. And that is important to recognize, because the mortality jumps are quite some from having a low risk, which you have a excellent prognosis of less than 1% mortality, to in an intermediate low category, you have a 5% mortality. And then once your two parameters are abnormal, meaning the RV strain and the biomarkers are positive, this jumps from 5% to 15%. So that is not an insignificant jump here. And then as you know, the mortality for massives or high risk is quite high.

So our integrated approach to know what exactly do we need to order in patients to know what category do they fall into involves the PSI score-- which we'll go over in the next slide, but it's the PE score index. Imaging, that includes cardiac imaging, like echocardiogram and the CT scan. And the biomarkers, like I mentioned, the troponin and the BNP. So this is the PSI score, the P severity index. And like many other calculators, it comes in the original one, which is a lot more involved and a little bit more complex.

And then a simplified version. I like to use the simplified version because it actually is a lot quicker to do and you could memorize it. But if you don't have it memorized, this is on your Med calcs or you can Google it and it will come very easily. So this will basically entail all the different parameters that we know that will put you at a higher risk of not doing while in the hospital, such as older age, having a presence of cancer, or a cardiac or pulmonary chronic co-morbidity, having a heart rate of over 110, a blood pressure of less than 100, or oxygen saturation of being less than 90%. And this includes someone who is over 90% but that requires oxygen supplementation.

So the calculation is basically very simple. So you could either have a score of zero or a score of one or more. OK? And if you have a score of zero, your 30-day mortality risk is very low. It's 1% you'd do well. Basically, you're a low-risk patient. However if you have a point or more, that already increases your 30-day mortality to about 10%.

So in the imaging section, we use echocardiogram very frequently. And for the most part, we use the RV to LV diameter ratio or presence of RV dysfunction. And here are how sensitive and specific it is. So you know, this is probably highly sensitive but not as specific. But more importantly, it doesn't tell that if you have presence of RV to LV diameter ratio that is increased, your mortality is increased. And worse outcomes could happen. So, for example, you could have a higher risk of going on a ventilator or requiring a vasopressor, or actually decompensating to the point that you have a cardiac arrest.

For a C.T. scan, same parameter in terms of RV to LV diameter, as you can see here. The sensitivity is a little bit higher, but the specificity is actually lower. But it will tell us the same thing. Basically if you have it present, then it increases your mortality risk. One point that I really like to make is that when the radiologist will call the thrombus load into a massive amount, that is not a synonym for a massive PE. So the fact that the thrombus load could be larger, for example, someone that could have a saddle PE, that does not mean that the patient's going to have, necessarily, RV strain. And that does not mean that the patient has a massive PE. And that is a very important distinction, because they also do use this radiologic term when they were in there reading the C.T. scans.

For the last couple of years since the PE started, and mostly after Doctor Toma spearheaded this, now as part of our standard PE rule-outs, all the CTAs will have a mention of presence of RV strains or absence of RV strain in every CT scan in the Presbyterian Shadyside system. These are the biomarkers, the troponin and BMP. And as you can see here, I think that where I find it helpful is on the negative predictive value. If it's not present, then you can kind of safely sort of rule out that it's not there.

And that's pretty much the extent of how I take it. But I think that this is a very important slide. So you can see here that if we just use the PSI score, it'll give you a 10%, like we mentioned earlier. But when you keep adding parameters on top of that, like the cardiac biomarkers, and especially then if you also add presence of DVT in the same patient, you could see that the 30-day complication rate can increase to almost 25%. So it actually is very helpful. And it will pay off if you order them, because then that way, you will be correctly restratifying the patient into the different categories of low, intermediate, and high risk.

So I would say that this is increasing by the minute. All the options that we have now are definitely a lot more than they were 10 years ago. And so we have just plain old anticoagulation, we have thrombolytics, so whether it is in systemic form or catheter-directed form. And sometimes we use the ultrasound-assisted echos to that. Then there's the mechanical actual extraction of the clot, whether you can fragment it and aspirate it. Or also use some medications at the same time or going to the OR for open embolectomy.

And the reality is there are so many options, it's sometimes hard to know which is the one that applies best for my patient. So that is why we've created and sort of came together in this acute PE team or PERT team, so PE Response Team. And I think that this is how we're moving into a lot of different diseases, not just for PE.

But specifically, what we really want is we just have the expertise to be able to improve patient care. And that's our main goal. So what we do is we facilitate multidisciplinary consultation, and quickly. We also provide follow-up for patients for acute PE, to know what exactly happened to that RV strain. Did that resolve? Does this person need to be screened for presence of CTEPH in the future? We meet regularly to discuss cases in our ongoing research.

We have a registry to keep track of what we do internally, so that we could not just publish it but probably contribute to what helps different patients. And we have ongoing clinical trials, which Catelyn will talk about. Not just right now interventional, but also we're going to hopefully do some medical trials too. And we're part of the consortium. So there's a national PERT consortium of different hospitals that have a PE team and a way to approach this disease.

So you can see here that these are all the different players in our PE team. And so it goes from medical, then interventionalists, and then surgery. We also have hematology, definitely, for most important for the currents and the chronic follow-ups. And then we have early involvement with the emergency room participating as well.

So prior to having a PE team, this is actually what happened. You had someone with a PE and you didn't really know who to call. So maybe the referring hospital directly called the surgery team or maybe they called medicine or they sent the patient to the ED. And then from here, you know-- so it was very confusing and complicated on how to get to the right person that could help this patient.

And now with our new model, once you diagnose or suspect a PE, all you need to do is consult the PE team. And then we have a virtual meeting. And this is either in person or by phone. And then we involve all the people who are key players in making decisions. So that could just be, maybe, the pulmonary doctor with the interventionalist. Or it could also involve the surgery team. And it will always involve the primary team. So whether that patient's in the ICU or in a floor, we definitely would want your input, so that you know your patient best.

And then, we quickly implement the plan. Whether that is to start TPA right away or go to the OR or to the Cath lab. So how you actually get to us is you can either contact us through the operator or through Med Call. And just ask for the PE consult on call. Or you can go to Medtrack and then type in PE team. And as you can see here, then you'll have the option of just clicking here and paging the person directly.

So this is our algorithm. And this is an ongoing and ever-changing algorithm. And as more data comes on, more literature comes out, then this is adjusted. And I think that just to quickly go over the algorithm here. So if you have a pressure of less than 90, then you're automatically going into the high risk or massive category. And then what we do then is take into account what's the bleeding risk of the patient. So if the patient has a low bleeding risk, then we go with probably systemic thrombolysis. If the patient has a moderate bleeding risk, it's a catheter-directed approach for the most part. And if it's high, then we could do either a actual thrombectomy, which could be in an open surgical way or a mechanical and more interventional approach. Or just leave the patient on anticoagulation alone.

Another thing that we offer-- not often, but when it's absolutely necessary-- is if you have someone who's in ongoing cardiac arrest, then that person is not really going to survive when you push 50 milligrams of DPA during the arrest, right? So this person needs to go on ecmo and stabilize the cardiovascular system. So then, you can then implement whatever final treatment the patient will require in any of the forms that will come in here.

Then this is going to the other side, where you say the patient is hemodynamically stable. Then we go into taking into account if there is a strain and a CT scan or echocardiogram and if the biomarkers are elevated. If none of them are elevated and there's no strain, then they go into a low-risk category and start anticoagulation. But if there are abnormal, any of them, then they're automatically in the intermediate or submassive category. And then we go on into subdividing that again as per the European classification, if they had both the biomarkers and the strain or if they just have one of each.

So if they have both, we go again into calculating what their bleeding risk is. And then, we can offer either catheter-directed approach or anticoagulation or maybe a catheter intervention to take out the clot. And this is only a recommendation and it's only meant to be as a guideline. This is not an absolute and it doesn't mean that if you consult us, we're going to be pushing for any intervention whatsoever. So what we want to have is just a mere strict algorithm so that we have an idea of we're to go with each call. But it's meant to be individualized for each patient.

So there are new CHEST guidelines on anticoagulation that came out February of this year. In one of the very important recommendations that was a new recommendation is that for all VTEs that have patients with PEs and DVTs that don't have active cancer, that don't have malignancy, the first line of anticoagulation is not vitamin K antagonists. It used to be. It's actually a NOAC. So one of the new oral anticoagulation agents that I put in here. So it's either dabigatran, rivaroxaban, apixaban, or edoxiban.

And I put in some of the asterisks for the ones that require bridging with either heparin or Lovenox. And the reason why they made this strong recommendation is because when they pulled all those major randomized controlled trials that each of the drugs had, there is a significantly reduced risk of bleeding with the use of the NOACs. I think that because we are in the hospital, we tend to see more of the people who had the complications, right? So in the hospital setting, we see the people who bleed. But in reality is that for the comers, for everyone who's gone into one of these therapies, they actually tend to not have a complication as opposed to Coumadin.

One important thing to mention is that the only agent that has a reversal in the market is the dabigatran. There is another agent called Dexanil, which will be applying for the other three drugs, that is supposed to be presented to the FDA, but it hasn't been approved yet. So it is something that is expected to be in the market and approved in the next year. Now the recommendation for patients with some kind of VTE with cancer did not change, and that is lovinox as the first line.

This is another change, which is for patients who have provoked event, they get to be treated for three months. It used to be six to nine months and it was a little bit more of a range. So now this is a strict three month treatment for the anticoagulation. However this is another major change. If you have an unprovoked event, you get to be treated indefinitely. So that means that you are treated until the risk of bleeding exceeds the risk of clotting. So if you have an event, then in a few years down the road have some issues with GI bleeding, that's the moment to stop the medication.

Another change that the guidelines mention is what exactly do we need to do with a subsegmental PE? It's a question that we've had for years. What do we do about it? Do we need to pay attention to it or not? Sometimes a lot of patients get some screening scans for other reasons and then you found out, incidentally, that they have this small, tiny, distal PE. What to do about it?

So you don't need anticoagulation if it's only a single PE and subsegmental. If it's a low risk for recurrence, meaning that you don't have any active, ongoing risk factors like an active malignancy, for example. If you don't have a DVT on Dopplers and if you don't have symptoms, or if the symptoms could be explained by any other finding on the CAT scan.

And this did not change, which is the very strong recommendation on not using any IVC filters unless you can not tolerate anticoagulation. So out-of-hospital PE treatment was another thing that was discussed in the guidelines. And as you can see here, anyone who's low risk, who's kind of stable, doesn't have any complications, has a history of being compliant and coming back to appointments, and feels well enough to be treated with a simplified PSI score of 0 is a candidate to be treated as an outpatient. And that means that they could either get a shot of Lovenox in the emergency room or even the first dose of NOAC in the emergency room, and then given the script so that they could just fill it out and then see their doctor in the next week or two.

So how about systemic thrombolysis? Let's go over the literature of the systemic thrombolysis in high-risk or massive PE patients. So this is one of the initial meta analysis, included 11 randomized controlled trials that compare lysis versus heparin. And in all comers with any PE, there was a trend toward improvement in mortality, but it was not significant. However when they stratified it by massive, they did see that there was a decrease in their mortality and that was significant.

This is a more recent study that included a lot more patients that were hemodynamically unstable. And by that, they defined that by either being in shock or on a vasopressor or being on the ventilator. So we know that this is not necessarily the definition that we go by, but it's close enough and I think it's worth mentioning.

So in this study, they saw a pretty significant decreased reduction in their mortality when you had systemic thrombolytics. So how about systemic thrombolytics in the intermediate or submassive PE patient? So this trial that came out in 2014, called a patho trial, most of you know that, most of you are familiar with it. It randomized patients to either thrombolysis and heparin or just heparin alone. It included over 1,000 patients that had submassice PE defined by dysfunction, either on a CT scan or an echo, and having a myocardial injury by having an elevated troponin. So if we were to just try to classify this, I would say that these were the intermediate high sort of category patients. Their end points were an either all-cost mortality or hemodynamic collapse in the first seven days after a diagnosis. And that included either CPR or hypertension, or requiring a vasopressor.

So this was the results in the trial. So as you can see here, they had a very significant decrease in their mortality when they used the lytics. However when the data was looked at, when you looked at the data a little closely, you can see here that for death from all cause, there's really no difference in the two groups. However, the driver for the odds ratio was really the hemodynamic decompensation. So a very significant increase, 5% versus 1%. And that was mostly driven by some of these things. Either requiring an intervention or requiring to go on an open label thrombolytic. So this was the driver for the primary outcome.

And then when they looked at what were the bleeding risks, there was a five times higher bleeding risk, a 12 times higher stroke , risk which included hemorrhagic strokes. And this bleeding risk was a lot higher when you divided and looked at the patients that were over 75. So really all in all when we take a look at this trial, what we say is and what we can take out of it is lytics really worked, but at a very high cost. So I don't think that this definitely didn't make the guidelines. And the guidelines say that if you have a submassive patient, you should not be using systemic thrombolytics, ballistics because the bleeding risk is definitely a lot higher than what the benefit that you might get from hemodynamic compensation.

So how about low dose thrombolytics? There have been smaller studies that were pulled together in this meta analysis that looked at either 50 milligrams versus 100 milligrams of systemic TPA. No change and no improvement in the at all-costs mortality or recurrent PE. However there is definitely less bleeding when using lower dose.

So again just to reiterate, systemic thrombolysis in the most recent guidelines, it will say yes to use it with hypotension. So for masses. Yes, you use it when you have deteriorated, even after starting any kind of a anticoagluation. And in patients without hypotension that have severe symptoms or marked cardiopulmonary impairment, may benefit from lytics. So this is a very sort of wishy-washy, I would say, kind of statement. And I am not sure what kind of patient would fit this criteria because it's so loosely mentioned.

So that's why here, we only use systemic thrombolysis in patients who have a clear, massive, or high-risk PE. So how about catheter directed interventions or catheter=directed thrombolytics, especially in the intermediate risk patients. So I would say sit tight for that, because Catelyn will talk about that.

And we're now going to move on to talk about life after a PE. So what happens aftee a PE? So a lot of patients, as you can see, have different complications. And that includes anything from trouble breathing, decreased exercise tolerance, having chronic perfusion defects or chronic blood clots. And then, definitely, true exercise limitations. And again, something called CTEPH, chronic thromboembolic pulmonary hypertension.

So the natural history of the clots, it's very rare. It's very odd, I would say, because it's something that you think that everyone that has a PE, again, it will go away. However when we do VQ scans as an outpatient, we see that about 66% of the patients are going to have an abnormal VQ scan, meaning they're going to have some kind of perfusion abnormality at three months out. And still 12 months out, there's still a good amount a third of the patients are going to have that abnormal finding.

And what we know is that having a VQ scan normality or having a perfusion defect means that you're going to be more short of breath, that you're not going to be able to walk as far, and that your pressures estimated on an echo are going to be higher. So these are patients that we need to not just screen for, but we have to actually serially follow them, because what we don't know is what is the incidence of developing CTEPH with having some of these chronic blood clots.

And what we know is that the risk factors for having incomplete resolutions are, so this is where size matters. So before, size didn't really matter in terms of saddle and all those things. Here, definitely, it does matter. So the larger the clot, the more likely you have that it will not completely [INAUDIBLE], and the longer the time between your first symptoms and your treatment and the older age. So those three things definitely will put you at a higher risk of developing a chronic blood clot.

But then not everyone that develops a chronic blood clot has chronic thromboembolic pulmonary hypertension. And we'll go over what exactly the criteria is in the diagnosis. But again, this is pulmonary hypertension caused by chronic blood clots. And by chronic, we mean after three months from your acute event. We mentioned earlier there were about 4% of the patients that develop acute PE that go on to developing CTEPH. So that's still about 20,000 patients a year if we go by the 900,000 originally diagnosed with the VTE. So it's a very significant patient amount.

And one interesting factor is that a lot of these patients do not have that initial acute PE or acute DVT that is clearly identified. So about a quarter of them to almost 40% of them could have CTEOH without even ever having an acute event, so what we call the silent PE. So what we know is that from this recently published trial called inform trial that was based on retrospectively going through the claims of each patient, 87% of the patients that have an acute PE will have a complaint to their doctor about a PE related symptom. Whether it is shortness of breath, lightheadedness, chest pain, edema. But then only 61% of them had a diagnostic test to actually confirm any of these findings.

So I think that this is telling us that we need to have a higher surveillance for these patients. And to be able to follow them and ask them for the symptoms but then also act upon them. So whether that patient will need any of the specific testing to diagnose pulmonary hypertension. So in general for the screening of CYEPH, we start with an echo, like with any other pulmonary hypertension. And when pressures are elevated there or there's changes in the RV that are suggestive of it, then we go on to ordering a VQ scan. And note here how a CTA is not included in the screening, because VQ scans have a higher sensitivity and actual specificity to identifying a chronic blood clot, more so than the CT scan.

And the reason that is is because CTAs might not show those distal, smaller, chronic occlusions. And also, the VQ scan will allow you to recognize not just like where the clot is, but if they have a perfusion defect associated with it. OK? Then if those are abnormal, then we move on to a diagnostic right heart cath to confirm that the pressures are elevated. And then we obtain, now, we obtain a CTA and or a PA gram, to know where those clots are and if they are a surgical candidate.

And the reason why we obviously are interested in it, it's because if we left a CTEPH untreated, this five-year survival is very high. So the higher your pressure, the worse your survival. But even with a modestly-elevated mean pulmonary artery pressure of over 40, the survival is 30%, which is quite low. So the preferred treatment is actually surgery. So it's called pulmonary thromboendarterectomy. And this can be curative. So 70% of patients that go through a PTE that have their clot removed could actually be cured. And then after that, they don't need to be on any pulmonary vasodilators. And they don't have any pulmonary hypertension.

So there is definitely a surgical selection process to it that will be based on not just where the clot is or are, but the co-morbidities that the patient might have and how high the hemodynamics of the patient is. So it's quite an involved surgery that I won't go through, but it does involve circulatory arrest and their prolonged period of time.

So what if you can't go through surgery? Then medical treatment would be the next step. There is a drug approved about a year, two years ago now, called riociguat, the brand name is Adempis. And it's the only pulmonary hypertension drug that it's approved for CTEPH. It is sort of like a cousin of a PDE5. It's similar to sildenafil or tadalafil. But it's actually a stimulator of cyclic GMP, as opposed to an inhibitor.

And the indications are for either patients who are nonoperable or who have residual pH after they had surgery. And the approval was based on an improve in their six minute walk test by 39 meters and decreased BP PVR by 2.8. In addition to that, you're always going to be on anticoagulation, So once you're diagnosed with chronic blood clots or CTEPH, you're just going to stay on anticoagulation.

But one important point is refer early. This is not a moment to try drugs to see if you're going to do well, because surgery definitely works better than just medical approach. And we'll talk about these emerging catheter-based interventions right now. So my take home points are that PE, really third most common cardiovascular cause of death, with high mortality, especially in massives and submassives.

Systemic thrombolysis is reserved for massives, because they have a higher increased risk of bleeding, especially intracranial bleeds. The first line of anticoagulation for all PEs in general or DVTs are NOACs, and that's a new guideline. PEs can be associated with not just acute, but also long-term negative cardiovascular outcomes, including CTEPH. And we have both a PE, acute team, and a chronic team that is a multi-disciplinary, that we're happy to help for any questions that you might have.