BELINDA RIVERA-LEBRON, MD: So we're going to talk today about acute and chronic pulmonary thromboembolis. I specialize UPMC in pulmonary hypertension and PE's. OK so PE is a very serious problem, it's super common, almost a million cases both comprising PE's and DVT's in the United States every year. And this keeps rising. About 150,000 to 250,000 of those are going to be admitted to your hospital and you're going to be seeing them. And a lot of them are still going to die of a PE.

So you could see here, almost 200,000 are going to die each year from a PE related cause. And 50% of the survivors are going to have some kind of chronic complication related to the PE. Whether it is chronic pain from their DVT, shortness of breath, exercise intolerance. So most likely you're going to be encountered with one of these patients at some point.

And insignificantly, about 4% of those who survive or could develop something called chronic thromboembolic pulmonary hypertension, or CTEPH, which is elevated blood pressure in the pulmonary artery. And that is related to chronic blood clots from not going away.

So it is the third most common cardiovascular cause of death, following MI and stroke. And I think that most of us, or at least even myself, we think about acute PE as something that we see here, kind of like this friable blood clot that occludes the pulmonary arteries. Most of them actually fully and completely go away. So about 90% of patients are going to have a blood clot go away.

Now very significantly, 30% of those could have a recurrence in the first 10 years. And then this is even patients who are appropriately uncoagulated for the amount of time that they should be uncoagulated, they still could have a high risk of recurrence. And then again, about 4% of those could develop chronic thromboembolic pulmonary hypertension.

So two major classification systems are the American and the European. So we'll go over the American first. So lower risk PE's are patients who have normal blood pressure, who have no RV, right ventricle dysfunction, who are going to have normal biomarkers, and by that I mean troponin and a BNP.

The submassives, also known as intermediate risk, patients are going to be still normal tensive, but now we're going to show signs of RV dysfunction. And that could either be by having dilation on their CT scan, or echocardiogram, or biomarkers that are elevated. Again, the troponin and the BNP.

The massives, or the high risks, are patients who are now having hemodynamic instability. And by that, it is defined by a systolic blood pressure of less than 90 for over 15 minutes, who are in shock by requiring a vasopressor or actually go through CPR and have a cardiac arrest. The Europeans saw interest in the-- they went ahead and did something a little extra here. So you could see here that the major category stayed the same. The high, intermediate, and low category stayed the same. However, one big change was that in the intermediate category, they subdivided that between intermediate highs and intermediate lows.

And I'll point out the differences in a second. And then in addition to adding this subdivision what also they did was that they included different risk factors here for each of the categories. So you could see here that for the high risk, high is the only one that's going to have shock or hypotension out of all these. Four the PESI score, which we'll go over in the next slide, now the high and our intermediates are going to have a positive PESI score. And again, we'll go over this in the next couple of slides.

And then important to point out is that here in the intermediate category, the intermediate high are those who are going to have both changes in the imaging, whether it is a CT scan or an echocardiogram, and are going to have the cardiac enzymes that are going to be elevated, being again, the troponin and the BNP. The difference between the high and the low is that in the intermediate low, just one of them is going to be positive. And that is important because we see here that the prevalence of the low risk is a lot higher than the prevalence of the high risk. So that's great.

However, mortality actually funnels down in the opposite way. So for a low risk PE that is treated with anticoagulation within a reasonable amount of time, there is very low mortality, less than 1%. Most people will survive that acute and insult. Then for the intermediate risk, then you're going to have a jump from 5% for the intermediate low risk, to 15% to the intermediate high risk. And this is the reason why the European classification had that distinction between those two categories.

And now the high risk has a over 30% mortality. We all know that. We fear this in patients coming into our ICU. Sometimes there's not a lot to be done. And we'll go over what our options are in a little bit.

So what do we do to actually be able to prognosticate who's going to do well and who's going to do poorly? So these are the three parameters that I encourage you to use. So one it's going to be the PESI score we'll go over in the next slide. Secondly the imaging, so abnormalities in the RV, in the echocardiogram, and or the CT scan. And again, the biomarkers.

So go ahead and send those. Because if you don't send them, you don't know if they're going to be abnormal. So PESI score, it's a calculator. It's a calculator that encounters here. Most of the risk factors that we know are risk factors for PE's such as age, sex, having cancer or chronic heart or lung disease, having a heart rate of over 110, having hypertension, tachypnea, altered mental status, or desaturations.

So they put them all together in here and came up with a calculator. And like a lot of the calculators held there, there is a more comprehensive one and there's a simplified one. So the simplified one here is the one on the far right. And that's the one that I normally use. Because it's a lot easier to remember.

You can Google this, and it will come up very quickly if you put in PESI calculator. It's also on those metcalcs apps. So it's very easy to find.

And the important thing about this is that if you don't have any of this risk factors in the simplified one, your 30-day mortality risk is going to be 1%. However, if you have a single one of these factors or more, automatically that will give you approximately a 10% risk of dying in the next 30 days. So it jumps pretty significantly if you will, just from having any of these risk factors present.

So looking at the imaging, just first looking at the echo, then we'll look at the CT scan. So we looked at the RV to LV diameter ratio being over 0.9 or more, meaning that the RV then is now becoming larger than the LV. And you could see here the parameters, the sensitivity, and specificity. So they're not the best.

So quite sensitive, but not as specific, which means that other things that are ongoing at the same time could give you a RV to LV diameter ratio of over 0.1. For example, you have someone coming in critically ill, maybe with a pneumonia or acute respiratory failure. That also might give you a increased RV size. However, when it's pressing and it's due to a PE, it increases significantly your mortality. So you could see here 7% increased risk of dying.

And more importantly, it will increase your outcomes of doing poorly. So for example of recurring CPR, going on a vasopressor, or regarding thrombolysis for example. On a CT scan using the same parameter-- so you could see here comparing the right side on the left side on your CT scan-- sensitivity and specificity are-- probably the sensitivity is better, but the specificity is worse. Again still increases your P related mortality or chances of not doing well. And something that I really like to stress out is that the thrombus load, so meaning a super large clot or a saddle PE for example, is not related and it's not associated with mortality.

So you could have a young person who has very good cardiopulmonary reserve coming in with a saddle PE, that person could just have a low risk PE. However on the opposite end, you could have someone who already has chronic COPD or is a smoker or chronic heart disease of any kind, and might have a smaller clot burden who now is having signs of RV dysfunction under echo or CT scan. So the size, not necessarily again related to if you're going to have a low, intermediate, or a high risk PE.

And more importantly, and why we use this approach of combining all of these parameters is that when you add one on top of the other, you go from a 30-day complication of about 10%, to if all our press and plus you have a DVT on an ultrasound of your legs, it could be a quarter. So that is very important. And so you know, this is the patient that you probably need to follow more closely, maybe in a higher surveillance unit like an ICU or a step down. But certainly this is not someone that you want to discharge very quickly. You want to make sure that they are well observed.

So here are the alternatives. And there are a lot more coming. And I think that in the last few years, there's been tons more added to this list. So you can have anywhere from [INAUDIBLE] coagulation with an IVC filter, perhaps from balletic therapy, which that comes in either systemic or IV form, or catheter directed.

That technique can be added to an ultrasound assisted catheter directed technique. And then on the other hand, we have more like a mechanical option. So that is either surgically removing the clot or via catheter, actually breaking off that clot and then removing it.

So with these many options I think that it becomes even harder and harder to make decisions on which therapy to pick for your patient. And at UPMC we take a multidisciplinary approach by having an acute PE team. And this is actually something that most big academic centers are doing around the United States now, where we see that this discipline just really transpires across disciplines. So not just pulmonary, not just internal medicine, not just vascular surgery or cardiology. And it's really good when all of us come together to come up to make decisions on a patient.

So basically, we're just a group of people who have interest in PE and try to improve patient care. We try to facilitate rapid consultation. We follow patients in clinic. We meet regularly to discuss cases, facilitate research in clinical trials or some patients into our registry. And we belong to a larger national PERT which PE response team consortium, so that we can stay up to date in what others are doing as well.

So this is who is included in our center and our team. So you could see it. It goes across multiple disciplines, and it includes everything and anything from when the patient gets into the hospital to the emergency department to cardiothoracic surgery. And it's definitely been really great working with different disciplines and learning from each other in how to treat this disease.

So now going over through the new guidelines. So there were new guidelines that came out the chest this year in February. And the first thing that changed was that for all VTE's, so everyone who has a blood clot of any kind, PE's or DVT's, the first line of therapy are now NOACs. So those are the new oral anticoagulation agents. And these are the four different types.

So there is the dabigatran, rivaroxaban, apixaban, and edoxaban. And this decision was basically made because when they pulled together all those super huge trials for each of the drugs that came out, then they decided that the analysis was that there was a significantly decrease in not just like the major bleeding, but also the minor bleeding, and the fatal hemorrhages, which include brain bleeds. I put an asterisk here on dabigatran and edoxaban because those are the two that require bridging. So that means that for 48 hours the patient needs to be either on heparin drip or lovenox to be then transitioned to this agent.

The other two, rivaroxaban and apixaban do not require bridging. There is only one reversal agent in the market, and it only is for dabigatran. It's called praxbind. There is another reversal agent that will be for the other three drugs that it's called andexanet alpha, but it's still waiting for FDA approval. So probably I would say by next year, this is something that's going to be out in the market.

And I think that that's one of the major points of contention as you will for clinicians to start prescribing this drug is what do we do if they have a major bleed? And I think that as these sort of reversal agents come in the market, people are going to more comfortable prescribing them.

Now this stayed the same. So the guidelines say if you have a blood clot, but you have a malignancy, the first line of therapy is still going to be low molecular weight heparin lovenox. Other things that changed were-- and this is a very significant point-- if you have provoked clot, you'd need to be treated for three months and three months only. It used to be six to nine months and then get a D-dimer and whatnot. So now it's only three months.

And the other thing that changed was that if you have an unprovoked clot, you are going to get treated indefinitely. so indefinitely does not mean lifelong. Indefinitely means you're going to get treated until your risk of bleeding is higher than the risk of clotting. So Mrs. Smith goes on one of these agents. And then three, four, five years down the road she then finds out that she's having a ulcer in her stomach, and it's bleeding from that. So maybe that's the time to take a step back and take her off the anticoagulation agent.

No IVC filter unless unable to tolerate anticoagulation. And that stayed the same. So that was not a change. These two special scenarios were also included in the guidelines. So out of the hospital and subsegmental PE's, what to do about those two.

So who can actually leave from the hospital emergency room after they get diagnosed from a PE? So whoever has a low risk PE who is clinically stable, has good cardiopulmonary reserve, who has no contraindications, so no active bleeding or recent bleeding, has good renal or liver function, has good platelets, doesn't have a severe anemia, is known to be compliant. This is a person that's going to be coming back to your clinic and will be compliant with therapy. The patient him or herself actually feels good and doesn't feel like they need to be admitted to the hospital, and have a very low PESI score or a simplified PESI score of 0.

So you need to meet all of these criteria for you to be able to be discharged from the hospital straight out of the emergency room, or even from clinic, if it's something that you diagnose when you're in clinic. But it is important because it's a major health care cost. And if you can avoid it for the patient by just targeting them on a NOAC, then they can literally just leave from the emergency room.

Another point is the subsegmental PE's. I know we do see that quite a bit. You get a CT scan for something else, and then boom. There is like this small PE. What to do about it?

So you do not need to treat this PE if there is a single PE on a patient who has low risk of recurrence. So that means this is not someone who has active malignancy, or who has ongoing risk factors that will increase the risk of having another PE. If you do lower extremity dopplers and they don't have a DVT, and they're asymptomatic, this is someone that does not need to have that small subsegmental PE treated.

So now going over into the more advanced therapeutic options, starting off with the systemic thrombolysis. So this is the data on systemic thrombolysis in high risk or massive PE's. So this was a meta analysis that included an 11 randomized controlled trials that comparing systemic lysis versus heparin. And in all commerce, you can see here that there is a trend towards reduction.

However it was not a significant trend. However, when they looked at the massive PE's, they were able to show that there was a significant decreased risk of mortality. And it's not insignificant. It's by a lot.

And there was another trial. There was a cohort study that included a lot of patients that were all hemodynamically unstable, and by that they defined hemodynamically unstable by either requiring a vasopressor or being on a ventilator. So not quite the definition of a massive PE, but at least is helpful enough to know that the person is sick. And it also showed that there was a decrease in mortality from 47% to about 15%. So again, significant mortality decrease.

Now what about systemic thrombolysis for intermediate risk or sub massive PE's. So this used to be quite common probably about 5, 10 years ago, up until this trial came out. So this is the petho trial that came out of 2014. It was a randomized trial that did both lysis heparin versus placebo heparin. So lysis versus heparin if you will.

Included about 1,000 patients that had submassive PE. By that, they defined by having RV dysfunction and having an elevated biomarker. And their endpoint was really all cause mortality or hemodynamic decompensation within seven days of you enrolling in the trial.

And by that, they meant either requiring CPR or becoming hypotensive and needing a pressor or having end organ hypoperfusion signs. And this is the primary outcome of this trial. So very surprisingly, actually thrombolysis was superior in this population.

Now when you look at the data at this table very carefully and a little bit more closely, you see here that the deaths from any cause in both groups are exactly the same. So one had six, one had nine. So it was not a significant change. However, when you looked at that patients who had hemodynamically compensation, that was where the driver of this primary outcome is.

So pretty significantly decrease from 1% to 5%. So this was really the driver of this primary outcome. A lot of patients required thrombolysis in that placebo group.

And then on that next table, this is where they reported the secondary endpoints, such as bleeding. So look at this. Five times higher your risk of bleeding. 12 times higher risks of stroke. And this is a lot even higher when your patients are over 75.

So what do we come out of this? How What's the conclusion that the community got from this trial is thrombolysis really works, but at a cost. So there's going to be a decrease in hemodynamic decompensation, but then that patient might have a stroke. So thrombolysis is not recommended in anyone who does not have a massive PE. Only patients have massive or high risk PE are candidates for a thrombolysis.

So no thrombolysis for patients with submassive PE. And how about low dose? So instead of 100 milligrams, let's just get 50. Let's give 25. Let's just give a percentage of it.

And actually, when they pulled the meta analysis of five different studies, it looks like no difference in mortality. It does have less bleeding in the use of that when comparing it to a full dose. But then again, what's the point if you're not really going to have the mortality benefit, you're not going to have the benefit. So then these are the official guideline recommendations for systemic thrombolysis. They'll say PE with hypertension.

So meaning massives or high risks. PE with deterioration after starting an anticoagulation. So even if you already started your patient on heparin lovenox or that NOAC, whatever therapy you decided to start, and they have clinical deterioration, you still can use thrombolysis as a rescue drug, if they are sort of looking like they're going to compensate, but have yet not developed hypotension.

And then this is a very interesting point here that they made. They said PE without hypertension with severe symptoms or marred cardiopulmonary impairment. So I really don't know what this means, because it's kind of vague and it's not necessarily kind of like a slam dunk. But they said that that person, sure may benefit from lytics.

So how about catheter direct? So this is kind of like something new that's been more talked about in the last couple of years. So giving a smaller amount of thrombotic specifically through a catheter. And that the lytics will go at the sight of where the clot is. So it's basically putting in a swan, and giving a little bit of lytics through the swan.

You put in two different catheters. So because if you have a clot in the right and a clot on the left, then you're going to put in two catheters. So it's a special catheter, not necessarily the same as a swan. But you get the idea. So this is what it looks like here.

And this company made this catheter called an EKOS catheter. And that catheter has ultrasound capabilities. And so you can give the drug and the ultrasound actually directs the drug to where the clot is. So that's what the invitro sort of properties of the catheter is. So then they sponsored this clinical trial on patients that had some massive PE, smaller trial of say, 59 patients, and their primary outcome was that the RV to the LV diameter changed in 24 hours.

And these were the results which were quite impressive. So in here you see that this is the RV to LV ratio of 1.2. And it decreased to normal in 24 hours in the group that had the catheter direct at lysis, compared to no change at all in just using heparin. However, when they repeated the echocardiogram in 90 days, you see that they stayed the same, but this actually catched up. So that means that anticoagulation works, it's just going to take time.

So I think that this technique has a time and a place specifically for patients that don't have time. So you need to identify who is that patient who is a higher risk who might not do well and will not be able to survive 90 days just on anticoagulation that needs that extra therapeutic option.

So this is a trial that actually compared multi-center different places that use catheter-based intervention. And you can see that there were patients that had massive and submassive classification. And their primary outcome was whether or not they had success in terms of stabilization of their hemodynamics and actually improvement and reversal of that strain on the RV. And also if they survived from diagnosis to discharge.

And you could see here by using catheter interventions, a lot of them had clinical success. So 24 out of 28, 71 out of 73. When they measured, hemodynamics were lower. In majority of the patients are going to have RV strain.

And actually the minority of them had major complications like bleeding, no patients had intracranial bleeds, and most patients that had some bleeding had a little bit of site bleeding, mostly at the area where the catheter was placed in. So pretty safe, but we still don't know if this is something that will actually impact mortality.

This is a retrospective trial that used a national inpatient sample, a very recent data that was pulled and included a lot of patients, over 100,000 patients. And it sort of separated who actually had thrombolysis. And not a lot of them had. So only about less than 2%. But then out of those, then they subdivided that between systemic and catheter directed.

And they actually were able to find that there was a decrease in hospital mortality when you use catheter directed versus systemic. And this is mostly again related to bleeding complications. Similar length stay, however a much higher hospitalization costs. Very expectantly with new techniques and catheters and procedures like this one is.

Other things are catheter-based embolectomy. So what are these? So not giving any medication, but actually just going in with a catheter to remove the blood clot. And these are two different kinds. So this is an AngioVac system, which has a lot of suction power.

It's a pretty large catheter. And this one over here is a much smaller newer catheter that has some kind of stents in between so that you could sort of capture the clot in between those stents and then suction it out from the pulmonary artery. This is one of the cases that we did.

So you could see how the clot sort of comes in little pieces. This technique of catheter embolectomies can actually be used with TPA, if you so desire. Or it could be just used by itself.

Surgical embolectomy is certainly an option. And especially patients that are massive that for example, just came out of the OR or had a major procedures have very high risk of bleeding that will not be able to tolerate any kind of lytics. Mortality rate is not as high as it used to be, so about less than 5%. And having systemic thrombolysis certainly will increase the risk of bleeding, but it's not going to be a contradiction to getting surgery.

Other things to think about are RV assist devices, mostly ECMO. This can be used if a patient for example, has a massive PE and is not responding to systemic thrombolysis or if someone actually has arrest from a PE, you could put them on ECMO and that sort of will free time for you. And then you just can decide whatever you want to do later on, if you want to give systemic lytics or do catheter directed techniques.

So moving on from acute to chronic, again, a lot of patients that have PE's are going to have complications from a PE, whether it is persistent blood clots or cardiopulmonary limitations or post-PE syndrome mostly related to pain. And then CTEPH, which we'll go over in more detail.

But this is very interesting. So when patients get repeated testing after they had their acute blood clot, about 66% of them are going to have a perfusion defect on a VQ scan three months out. And about 30% are going to have perfusion defects a year out. So this really means that there's not that complete resolution that we kind of hope for. And especially those patients are going to have perfusion defects are going to be more short of breath, are not going to be able to walk this far, and are going to have signs of stress on an echo.

And these patients specially are going to have a higher risk of developing CTEPH, especially patients that have large clots. So this is where size matters. So if we're acute, not so much, but for chronic certainly. Patients who have a long, long duration between symptoms and coming into the hospital to starting on anticoagulation your patient that maybe been short of breath for two to three weeks and just ignored, ignored, ignored, and then suddenly has this his big, big plot, and the older the age.

So these three risk factors are going to put you at a higher risk of developing CTEPH. So important to diagnose after three months from your acute blood clot. We talked about how 4% of the patients who have an acute PE could end up developing CTEPH. So about 20,000 patients a year, if we go by the estimate of that initial 900,000 a year of VTE's. And this is another very interesting factor.

Some patients that have CTEPH have never been diagnosed with an acute blood clot. So 25% to 40% of the patients could have CTEPH just without having a history of having that blood clot. And I think that's very interesting.

So when we look at the follow up for patients from PE's, we see that this from the informed trial that came out maybe in the summer of this year, we see that about 87% of patients who had PE's are going to come to their primary care doctor or to their doctors with some pH related symptom, whether it is lightheadedness, presynchope, syncope, shortness of breath, chest pain, swelling in their legs. But only 61% are going to have a follow up testing that is related to the symptom. So most of the time, or I would say in 40% of the time, these symptoms are going to be ignored. And these are the tests that have been ordered, so not a lot of EQ scans.

Some people got echoes. Some people got repeat CT scans. And this is the true order of work up that you need to diagnose CTEPH. So for screening, like with any other type of pulmonary hypertension echocardiogram is usually the main test that it's ordered, and it's usually the first test that is ordered, then you're going to see signs of elevated RV systolic pressure. Either your RV might start to be dilated, or already show signs of dysfunction.

And then the other important test to get is a VQ scan. We talked about VQ scans by showing perfusion defects. And really, perfusion defects shown on a VQ scan are much more sensitive and specific for chronic blood clots than what a CTA can actually be. And is a very important point, because CTA is not part of the screening of CTEF or CT scans. VQ scans are the ones who'll tell you if those defects are going to be clinically important in that patient.

Now then after you go through the screening, then for diagnosis, like with any other type of pulmonary hypertension, you order a right heart catheterization. And I will tell my patients this is non-negotiable. You get this. No, no, no questions about it.

And then we then decide are you a surgical option? Are you a surgical candidate? Is surgery an option for you? And this is when anatomy takes place and a CTA or a PA angiogram might be necessary to decide where are those blood clots? Are they proximal or are they distal?

If they're proximal, they're more easily reachable by a surgeon. If they're distal, it's going to be harder for them to get it out. So you might not be a candidate for example. Comorbidities, do you have severe liver disease? Are you morbidly obese?

You have severe COPD? Other things like that make you a less desirable candidate. And we really do this is because the mortality is really high if you leave it untreated.

Here is the preferred treatment that I mentioned. So it will be pulmonary thromboendarterectomy. Under So it's removing the blood clot and the lining of the blood vessel. If you cannot get surgery, then medicine is an option. A new medicine that came out on the market in 2014 called Riociguat, but also lifelong anticoagulation for sure.

So again, this is something that will be with you forever. And newer techniques that we're doing are balloon angioplasty of that pulmonary artery to try to displace the blood clots to the side.

So really, just to summarize, PE is the third most common cardiovascular cause of death in the United States. Has a very high mortality in massives, but also significantly so in submassives. Systemic thrombolysis is reserved for only massive PE because of its risk of bleeding and intracranial hemorrhage.

Catheter directed techniques are good to decrease a clot burn in acutely, and might help in massives and submassives. And there are still complications that could develop like CTEPH. And thank you.