

**AHA COVID-19 Clinical Guidance Series**  
**Thrombosis**

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Speaker 1:

Welcome and thank you for joining us for this podcast brought to you by the American Heart Association. This podcast is part of a series focused on sharing information with healthcare providers who are caring for patients during the COVID-19 pandemic.

Dr. Hamburg:

Hi, this is Naomi Hamburg and I'm a cardiologist and vascular medicine specialist at Boston University. And this is your power bite about our discussion of thrombosis in COVID-19. The coagulopathy of COVID-19 is really interesting and it appears to be thromboinflammatory that may lead to higher rates of venous thromboembolism (VTE). And so it's really important to understand how we may prevent venous thromboembolism in patients with COVID-19. We're going to talk about the best way to diagnose these patients, because there are a lot of unique difficulties in terms of infection control and taking care of patients who are ill and patients who are prone in the intensive care unit. We're going to emphasize that treatment of VTE really should be the same as what you've learned about in other settings with some particular nuances to taking care of patients with COVID-19.

Dr. Hamburg:

It appears that arterial thrombosis also occurs in COVID-19, but less commonly than venous thrombosis. And we really need more research in this area to understand how the coagulopathy that's being seen in patients with COVID-19 might contribute to the progression of disease. And there are therapeutic trials that are being started to see whether treatment of the coagulopathy might be an important way to prevent disease progression.

Dr. Hamburg:

I am Naomi Hamburg and I have the honor of serving as the Chair of the Peripheral Vascular Disease Council at the American Heart Association. I run a translational vascular biology program, and we're really interested in understanding how it is that blood vessel function becomes abnormal and how to protect our blood vessels to reduce heart and vascular events. I'm joined today by Dr. Mary Cushman, who is from the University of Vermont Medical Center, where she is a hematologist and directs their

thrombosis and hemostasis program. She's a professor of medicine at the University of Vermont Lerner College of Medicine, and as a widely cited epidemiologist, studying risk factors and causes of venous and arterial thrombosis and reasons for racial disparity, which has been very important factor during this pandemic.

Dr. Hamburg:

So Mary, talk to us about what is the coagulopathy that we're hearing about and COVID-19.

Dr. Cushman:

Thank you so much, Naomi, the coagulopathy in COVID-19 is different than what we are used to seeing in other infections. It's not a classical disseminated intravascular coagulation (DIC) and it's characterized most consistently by elevation of D-dimer and elevation of pro-inflammatory mediators like C-reactive protein and ferritin. It appears from early studies during this pandemic, that abnormalities of these biomarkers predict higher mortality among inpatients with COVID-19. And in order to provide a framework for understanding this coagulopathy better, we have proposed that patients progress through three stages of increasing severity of the coagulopathy.

Dr. Cushman:

Ultimately the ongoing thrombo-inflammatory process, or stage three, ultimately this thrombo-inflammatory process can lead to a cytokine storm and can entail microvascular thrombosis and fibrin deposition in the lungs that contributes to the progressive respiratory failure seen in the sickest patients. It might even be that there's insight to macrothrombosis also forming in the lung, this mimics pulmonary embolism (PE). So it's quite a different thing than we're used to seeing. And the rapid recognition of it seems to be important in identifying patients at greatest risk of progressive disease.

Dr. Cushman:

Naomi, what is the risk of VTE with COVID-19? So deep vein thrombosis, pulmonary embolism, common complication of hospitalization in general, but what's the risk related to COVID-19?

Dr. Hamburg:

Yeah. So all of us who are taking care of these patients have definitely seen patients with pulmonary embolism and venous thrombosis. And the real question is how common is it and how common is it in different groups of patients? And one of the big challenges in this disease is that there's a lot of interest in getting information rapidly since we're taking care of something that's new, that we're taking care of patients who are very sick and it's hard to face the uncertainty of the lack of knowledge. But at the same time, we really want to balance this with getting high quality information, even as it comes out rapidly. So I would say the best information that we have about how common venous thromboembolism is in patients with COVID-19 is probably from the intensive care unit (ICU). And it seems from more recent studies, both from the United States and from Europe, that the rate may be relatively high, up to 20 to 30%.

Dr. Hamburg:

And most of these studies it's really based on clinical, some clinical suspicion of having VTE. And so it may be that there's some undiagnosed patients, although it's probably the ones who we diagnose that are most relevant, because they need treatment. In other settings, we have less information. So in patients who are in the general hospitalized patients, but not in the ICU, that's probably lower, less than

10%. And then there's a lot of interest in understanding whether it might be going on at home or after hospital discharge. And even though I have definitely had patients who've come back with pulmonary embolism after discharge, what the true incidence of this is less clear. So thinking about once we know this is happening, is there any way where that we know that we might be able to prevent venous thromboembolism in these patients who are in the hospital with COVID-19?

Dr. Cushman:

Yeah, so there are several guidance documents coming out on this topic and most of them suggest that the best approach is to use standard guideline -based prevention like we use in other medical inpatients. And so that would consist in the United States of enoxparin, 40 milligrams daily, or heparin 5,000 units twice a day (BID) or three times a day (TID). There are a number of different trials ongoing that are testing different strategies for thrombo-prophylaxis that include higher or intermediate doses of anticoagulation compared to the standard low dose anticoagulation. At the same time, as trials are happening, institutional protocols are rapidly appearing and these are not all based on established guidelines. They're based on people's desire to try to do the best thing for their patients and often times people think that the best thing is more. And so some institutional protocols are rising up that suggests even full dose anticoagulation for most patients.

Dr. Cushman:

And these are really not strategies that can be advocated at this time. I like to kind of pay attention to what experts say in general and the NIH, National Heart, Lung and Blood Institute just released a guideline on May 12th on prevention and treatment of VTE. So referring to documents like that, I think is the best strategy to making decisions for your own patients. And in the meantime, like everything, when we don't know the right answer, enroll your patient on a clinical trial, if you can get access to that.

Dr. Cushman:

So Naomi, we know the rate is, may be higher than other acute infections for VTE, and we know there's a lot of interest in prophylaxis and studying the best way. But what about diagnosis and treatment? What are some of the challenges you see in that regard in your practice or are you seeing literature and studies on so far?

Dr. Hamburg:

Yeah, so I think, well, one of the things that I've repeatedly told my fellows during this whole pandemic is, you still want to remember all the medicine that you knew up until this point. So one question is, how would you have done this before? And don't forget about that. And then the question is, are there any specific changes that we're going to do for this new illness for COVID-19? And one of the key challenges for diagnosis is literally twofold here. One is that there's a risk of infection of the people who are doing the testing. So how to manage the people who work in your vascular laboratory or the clinicians who may be doing the actual testing of the patients. And the other is, how to get tests on patients who are critically ill and maybe on unstable to do particular kinds of tests or maybe prone, in a prone position, and therefore harder to do ultrasound tests.

Dr. Hamburg:

So just clearly, I mean our main stage tests in this disease are going to be duplex ultrasound, looking for venous thrombosis in the limbs and generally CT scan to look for pulmonary embolism as well as echocardiogram to look at the right ventricle. So as an overall guiding principle, I would say you want to

focus on doing the testing that's going to be necessary in order to alter patient care and how can you do that with minimal risk of exposure to the people who are doing the tasks. And so one option is to do point of care ultrasound, which can be very useful, both for looking at, for lower extremity deep vein thrombosis, as well as for looking at the right ventricle as long as you have people, either clinicians or I vascular ultrasound technicians (techs) or echocardiographers who are trained at doing this.

Dr. Hamburg:

And then if it really is going to change what you do, that we still are having our vascular techs do tests in these patients and it's been a key part of their management. At this point, there's no clear indication for screening patients for venous thrombosis in the limbs, that is in patients who you don't have any clinical suspicion. Although there are clearly some places that they're using ultrasound as part of their physical examination. And if that's what you're doing, it may make sense. The guidelines currently that you just referred to do not suggest a routine screening for patients.

Dr. Hamburg:

And then the other issue is what about empiric therapy? So I said, it may be very hard if someone's particularly ill, in advanced stages of ARDS, to get diagnostic testing. And there are a number of different societies that are suggesting the possibility of doing empiric therapy with anticoagulation if you have suspicion for venous thrombotic event or pulmonary embolism causing a clinical deterioration. A patient that may be reasonable to anticoagulate without definitive testing first, and then doing testing when it's right from the patient.

Dr. Hamburg:

In terms of the treatment from anticoagulation, it's really going to generally follow the principles for DVT and PE and other illnesses. With one suggestion, there is some guidance towards using low molecular weight heparin or fondaparinux instead of unfractionated heparin, just because of the number of times that you may have to reenter their room to do blood testing for unfractionated heparin. But if that's the only choice that's best for your patient, you can still certainly use unfractionated heparin. And then a lot of questions come up about advanced therapies in these patients, partly because they are sick or deteriorating. We have had cases of using thrombolytic therapy, again, for a clinical indication if there is some suggestion or diagnosis that this comes from pulmonary embolism.

Dr. Hamburg:

We have a pretty high threshold for using catheter-based therapies or inferior vena cava (IVC) filters, just because of the amount of exposure that's going to happen to a large number of people who are doing the procedure and because you do have alternatives with thrombolytic therapy that may be safer for the whole care team. A number of questions have come up about some special circumstances, like what happens to patients that continue to develop clots even on current, on recommended therapy. And so there's been some discussion about whether or not you would want to use higher dose anticoagulation, in these patients, but really I would emphasize that there's no clear evidence about this and it really should probably be part of a trial. And you're going to have to think about what's best in terms of the risk benefit for your patients.

Dr. Hamburg:

And then I think a really interesting question is about what about when the patients leave the hospital. Again, there's not clear evidence that it's going to be different for COVID-19. There have been some trials looking at whether using prophylactic therapy after patients leave the hospital, just to clarify, these are in-patients who have not been diagnosed with VTE, that they would maybe benefit from ongoing prophylaxis. And I think all the suggestions from the various societies and from the NIH would be to follow your other guidelines for patients that could benefit, acutely ill medical patients who could benefit from ongoing prophylaxis when they leave the hospital and depending on the setting and their mobility when they leave. So it's not clear that it should be different for COVID-19. And in terms of continuing anticoagulation and how long, I think this is an evolving field, but at the moment, these patients are going to be treated like other patients who develop provoked deep vein thrombosis (DVT) in the hospital.

Dr. Hamburg:

And again, this of course is a field that's in some evolution in and of itself. And you really want to look at what are their underlying risk factors and what you think their risk is for having another clot when you think about how long ultimately are going to leave them on therapeutic anticoagulation.

Dr. Hamburg:

So we've talked a lot about specifics about venous thromboembolism and pulmonary embolism, but I think it's really interesting to think about some of the issues you raised in the beginning, Mary, about does this coagulopathy that we're seeing in patients with COVID-19 having an effect on other aspects of their COVID disease and what are their thoughts about that?

Dr. Cushman:

Yeah, thank you for that great review of diagnosis and treatment. I think I agree spot on with everything you said. So, as I mentioned before, it's believed that this coagulopathy can contribute to thrombo-inflammation in the lungs with micro thrombi or macro thrombi, and that people with coagulopathy have a worst prognosis. So it raises the question of whether treating the coagulopathy itself might improve outcomes. And there are several rationales that support the idea that anticoagulation could reduce disease progression from the infection apart from impacts on macro thrombosis. And an example of this comes from older literature, humans and animal models of acute lung injury that described benefits of anticoagulation. From the finding that heparin may bind directly to the SARS CoV-2 spike protein, interfering with viral attachment and entry into cells. And also that we know heparins have anti-inflammatory effects in acutely ill medical patients, including those with COVID-19.

Dr. Cushman:

There was a retrospective study that suggested among patients with severe COVID-19, they had lower risk of death if they were treated with heparin prophylaxis and that that impact was most prominent when the D-dimer was most elevated. So elevated D-dimer may be a marker for people who could derive benefit from even lower dose heparin prophylaxis in terms of mortality risk. So for these reasons we are seeking funding, and launching a trial at the same time as we're seeking funding, urgent times call for action. So we are launching and seeking funding for a multicenter randomized controlled trial called the Rapid COVID COAG Trial, which will test the hypothesis in ward patients with COVID-19 and elevated D-dimer that full intensity anticoagulation with heparin or low molecular weight heparin compared to the standard of care DVT prophylaxis will prevent progressive disease. And by that, I mean transfer to the ICU, use of mechanical ventilation or death over the next month.

Dr. Cushman:

And so there are a variety of trials similar to this with slightly different designs that are also starting. Some are including only ICU patients. Some are testing lower dose anticoagulant approaches, but I think in the end, all of these trials when taken together and hopefully in short time, will give us an answer as to whether there's this possibility of manipulating the coagulation system to improve the outcomes of patients. And I feel really intensely that any trial that's happening in this disease is going to need to address the subgroups of patients who tend to have worse outcomes. So as an example, African-Americans appear to have higher COVID-related mortality than Caucasian Americans. And we don't know really why this is the case. Do they get infected more or do they have a more serious version of the infection? We know that African-Americans have more adverse levels of several of the thrombo-inflammatory biomarkers that we were discussing, but we don't know if their coagulopathy is worse when they get sick with this infection.

Dr. Cushman:

So in our clinical trial, and I hope in any clinical trial that's being done, investigators should be aiming to determine whether the treatment or interventions, whether it's anticoagulation or hydroxychloroquine, or antiviral therapies, whether they differ in terms of their efficacy based on race ethnicity. So we're hoping to address that question in our study and also to include biomarker measurements in our participants so we can tease out the pathophysiology what's going on here. So of course, venous thrombosis is the most likely kind of thrombosis in people who have infections, but I wondered you're a cardiologist and arterial thrombosis is a type of thrombosis that of course kills more people worldwide than venous thrombosis. Can you speak to anything that we're learning on the rates of arterial thrombosis and the nature of it in COVID-19 infection?

Dr. Hamburg:

Yeah, so I would say compared to even venous thrombosis, we have more of a positive information in this area, but there have been some reports about arterial thrombosis in inpatients who are quite sick with COVID-19. And in particular, there was a report out of Italy describing about 20 patients with acute limb ischemia, that is ischemia happening in the legs that may lead to needing to have amputations. And the question is, is this specific to COVID-19 or is it related to the underlying disease of the patients? Some of these patients had factors we know are associated with the development of acute limb ischemia, like prior revascularization or atrial fibrillation. So it may be that this, what happens to them because they're severely ill otherwise. And so what I would say is we need to be attentive to looking at the limbs in patients with COVID-19, thinking about their underlying risk factors, making sure that we are checking pulses and this seems obvious, but again, these patients, they're getting more limited contact between their physician providers and even trying to limit potentially that time that nurses are there. So I would emphasize that this is going to be an important part of your perhaps limited, but comprehensive physical exam in these patients to make sure that we don't miss limb ischemia.

Dr. Hamburg:

And at the same time, I would caution against saying that this is just a reason to anticoagulate with therapeutic anticoagulation, as opposed to prophylactic anticoagulation, everybody with COVID-19 because we really need to know better whether the incidence is truly higher in patients with this disease compared to other comparably ill patients with underlying cardiovascular disease who are in the ICU. And then it's important to remember that, again, because it is a lot of patients with underlying cardiovascular illness who are getting sicker with COVID-19 that many of them may be on

anticoagulation at baseline, for example, for atrial fibrillation. And the recommendation is that unless there's clearly some bleeding complication, you would continue patients who have an indication for anticoagulation on their full dose anticoagulation throughout the course of their treatment for COVID-19 and similarly would continue patients on their other cardiovascular preventative therapies and treatments like ACE inhibitors, unless there was some contraindication that arose such as bleeding or development of hypotension that might make you need to alter their other medical therapies. But it's important to continue all of their usual preventive therapies, if possible, throughout their treatment for COVID-19.

Dr. Cushman:

This has been an amazing conversation. We've covered a lot of ground. And as we start to wrap up, I just thought I would summarize some of the large points that were made. I think that it's important in patients who are hospitalized with COVID-19 to think about how you want to prevent venous thromboembolism. And essentially this should involve using standard measures based on guidelines as they evolve, that you should have a high clinical suspicion for VTE, if patients exhibit illness progression, or symptoms of this, that we need more research on the epidemiology and risk factors for thrombosis in COVID-19 patients. And that the preference would be to enroll hospitalized patients on clinical trials if possible and to develop protocols outside of that, that are based on established guidelines.

Dr. Cushman:

So the preference would be to enroll hospitalized patients on clinical trials whenever possible for thrombosis prevention efforts and in the absence of that, developing institutional protocols based on guidelines, such as the recently published National Heart, Lung and Blood Institute (NHLBI) guideline is advised. And finally, I think, especially for our ambulatory patients who have infection and patients admitted to the hospital, staying on their chronic meds, if they have cardiovascular conditions like a history of thrombosis, stroke, or heart disease, peripheral artery disease appears to be critically important.

Dr. Hamburg:

So thank you. That was a wonderful conversation. And I'm really excited about your research study and all of the research studies that have been happening so rapidly in this field to be able to bring the evidence base that we need to be able to take care of our patients with COVID-19 in the best way possible. I want to thank all of the listeners to this program for your attention, and also for everything that you're doing, creating science for COVID-19 and taking care of patients with this disease. And I encourage you to return to the American Heart Association Professional Heart Daily, to listen to the other podcasts that are in this series and include related topics like stroke, pulmonary hypertension, treatment of patients with diabetes and with concurrent cardiovascular disease, all related to the management of COVID-19 to really get rapid scientific information during this disruptive and also I think moving forward time in healthcare delivery.

Speaker 1:

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