COVID-19 Infection and Vaccination: Understanding the Prothrombotic Risk

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Dr. Bell: Like to welcome our listeners and viewers again to another of our Interviews with the Expert sessions. I'm delighted to have with us today Dr. Damon Houghton who's one of our vascular medicine specialists within our Department of Cardiovascular Medicine who's really an expert in anticoagulation and thrombosis and is heavily involved with research in this area. Today, we've asked him to come and talk to us about COVID-19 infections and vaccinations and understanding what the prothrombotic risk is. So, really a warm welcome, Damon.

Dr. Houghton: Thank you very much. I appreciate the opportunity to talk about this.

Dr. Bell: Yeah, and obviously it's been something that it's been with us now for the last three years or so. So with that in mind, what have we learned about the risk of thrombosis associated with COVID-19 infection?

Dr. Houghton: Well, I think it's a great question. I think it's really important as we kind of conceptualized what's happened over the past few years. I think as the pandemic started, we were pretty overwhelmed by this concept of thrombosis from the initial reports that were coming out in other countries kind of before the big waves hit us in the United States. And really some of those studies were showing really high thrombotic rates, some of 'em up to 60, 70% of of patients having thrombosis. And this really set the stage for a lot of concern about thrombotic events in COVID-19-infected patients. In retrospect, I think we've learned a lot from those initial reports. I think many of those initial reports really had somewhat of a selection bias in terms of who was in those studies. Many of these were ICU patients. They were in some ways the sickest of the sick patients. Many of these studies included screening ultrasounds. Some classified minor thrombotic events such as superficial thrombophlebitis into their definitions. And many of these came from places in the world where anticoagulation prophylaxis really wasn't a mainstay of hospitalized treatment regimens. And so I think in looking at some of the initial literature and where we've come, it's important to go back and reconsider this concept of really how prothrombotic COVID-19 infection is with some of the data that's come out more recently. As the pandemic was starting, Dr. Chaudhary and I published an article with our initial case series review at Mayo Clinic. And this was published in Mayo Clinic Proceedings. And what we looked at is the first 100 patients who were hospitalized with COVID-19 infection in our hospitals. And quite controversial and very interestingly, we found a venous thromboembolic rate of only 2.9%. And so that was in stark contrast to much of what had been published in the previous literature in very high-risk situations in other countries. And so that was a big component of how we ended up approaching venous thromboembolism and prophylaxis here at Mayo to start with. 'Cause we had some good insights into what we were seeing initially. Subsequently, there's been a lot of additional research in this area. And I think when we look at larger studies and we look at studies that include both inpatients and outpatients, we really see a very different picture of thrombotic rates. Clearly, COVID-19 is associated with an elevated thrombotic risk. And we've seen this over and over again. The question is how high is that risk and is that risk higher in specific populations in a way that we can use that clinically? And

ultimately this is what we've found. Dr. Pasha and I published another paper in Thrombosis Research looking at over 50,000 patients with COVID-19 infections. And this topic looked at inpatients and outpatients. And interestingly, we found a rate of VTE about 0.67% in the 90 days after COVID infections. So quite low, especially when you consider some of those initial higher thrombotic rates. This rate has also been confirmed in a number of other studies. There's a study published in Clinical Infectious Disease. This was a population study out of Denmark. It showed a 0.4% risk at 30 days of venous thromboembolism. There was a Kaiser Permanente study published in JAMA Internal Medicine that had a 0.8% risk of venous thromboembolism. So, what we know is that there are very high-risk patients, but if you look at the thrombotic risk in general for all of the patients who are infected, this thrombotic risk is really much more reasonable and not as severe as many of us had assumed when we were getting initial reports from other countries.

Dr. Bell: So, that's really interesting. In fact, just stop you there for a moment. I mean, those numbers really, I mean, really less than 1% is really what you're saying with more recent studies. So, I appreciate you putting that whole thing into really a historical context there. But those low numbers, does that reflect a population that has been vaccinated? I mean, early on, we didn't really know how to treat COVID-19. And so again.

Dr. Houghton: Great question.

Dr. Bell: And then the second thing would be, many of these patients were arriving in hospital and then treated with antivirals. So, has that impacted that number? Maybe you can just sort of.

Dr. Houghton: Yeah, great questions. Absolutely. So, most of the data that I mentioned there was very early on in the pandemic. Our particular data was quite early, prior to most vaccinations. So, these were really rates of kind of the the first and second waves of the pandemic when there was little or no vaccination in the population. As it relates to COVID-19 kind of other treatments, I think that's actually a particularly fascinating area. When you look at a number of the other treatments that are out there. Remdesivir, for example, dexamethasone, other immune modulators that have been used, there really was not a significant difference of thrombosis reduction in those trials. So despite some of them being positive in showing that there was a mortality benefit from using 'em, they actually did not seem to reduce the venous thromboembolic rates, which I found quite interesting and a little bit unexplained. But those drugs didn't seem to have a huge thrombotic risk reduction.

Dr. Bell: And so far you've been talking about VT, venous thrombosis. Arterial thrombosis, has that been associated with COVID infections at all?

Dr. Houghton: It has been, and there's certainly been numerous case reports. I think that the data from an epidemiologic standpoint is probably more difficult here. And I think that's largely related to the type and variety of thrombotic events that we see in our clinical practice. And in many ways we saw atypical thromboembolic events in our COVID-19 patients. For example, large arterial aortic thrombosis and some embolization in the lower extremities associated with those. And so I think that's been a little bit more difficult for us to capture in our research topics. But, yes, absolutely, we have seen increased arterial events as well.

Dr. Bell: And so recognizing then these very low rates of thrombosis in the real world and when you've analyzed these very large patient populations, is there still a role for hospitalized patients for prophylactic anticoagulation that may be beyond what we typically might do for a hospitalized patient with a non-COVID illness?

Dr. Houghton: Yes, absolutely. So while the overall risks are quite low, we definitely know that there are populations of patients who are at much higher risk. Increasing age, for example, is a significant risk factor for venous thromboembolism. Hospitalization is a significant risk factor. And rates in the hospitalized patients are of course much higher than those in the outpatient setting. And so right from the beginning of the pandemic with these reports, we knew that prophylactic anticoagulation was important to continue. And for the most part, that was the practice here in the United States with hospitalized patients in general. So, that wasn't too different. But what we did start investigating, and numerous randomized control trials were launched in this setting. We start to ask the question whether we should be doing more than standard dose prophylactic anticoagulation. And so this really took the form of two different positions, with some folks saying we should increase to perhaps intermediate dose anticoagulation or intermediate prophylactic anticoagulation. And another group kind of hypothesized that maybe we needed to go all the way to therapeutic anticoagulation. And so the clinical trials that were designed in this space really kind of went to those two strategies to try to reduce thrombotic rates. The other thing which I think is pretty interesting is that the initial hypotheses here were not only that we could reduce thromboembolic rates, we actually thought that we could significantly affect and improve mortality with anticoagulation. And some of the hypotheses there were related to this concept of microvascular thrombosis with the thought and the assumption that much of the the comorbidity and mortality was associated with this hypercoagulable state in a way that was causing organ damage and contributing to lung disease and hypoxia and, ultimately, mortality. So, the hypotheses and outcomes of these trials were really designed to largely show a survival advantage and look for a mortality improvement with these anticoagulation regimens, in addition to the reduction in venous thromboembolic and arterial thrombotic outcomes. So, a few different trials were launched, and we ended up getting some data initially in the spring of 2021. And this was some first data from the INSPIRATION trial. And this was a trial that looked at that hypothesis of intermediate dose anticoagulation compared to standard prophylactic dose anticoagulation. And ultimately this was a negative trial. There was not any significant improvement in survival and there wasn't a clear reduction in venous thromboembolism related to the higher intermediate dose anticoagulation. A few other studies have examined this as well. There was a study by Dr. Perepu and colleagues also in a randomized control trial, again not able to demonstrate an improval in survival. A very recent study, there was an anti-COVID study that was recently published. Similar results actually, but did show a slight reduction in the venous thromboembolic and arterial thrombotic risk reduction. So, maybe there's a little bit of role in terms of thrombosis prevention, but we're clearly not seeing a survival advantage based on giving these intermediate doses. We then got additional data from some of the other randomized control trials that were looking at therapeutic anticoagulation. And there were a lot of trials in this space. The first trial was a trial called the ACTION trial. This was a trial that tried to incorporate rivaroxaban into the dosing regimen if patients were stable enough for it as the therapeutic option. Ultimately, this trial was negative as well. There was not any survival advantage with the use of therapeutic anticoagulation with a component of rivaroxaban compared to the standard prophylactic anticoagulation. So, this wasn't

the end though. There was a few other trials that came out. There was the RAPID trial, what we called the multi-platform trials, and then the HEP-COVID trial. All of which were answering similar questions with regards to therapeutic anticoagulation and slicing the populations in a slightly different way. What we ultimately found, in large part through the multi-platform trials, is that there probably was some benefit in terms of mortality improvement and reduction of end organ damage by using therapeutic anticoagulation. But it was a very limited subset of the population of COVID-19 patients who were hospitalized. And so what we ended up finding and was confirmed in these trials is that the sickest of the sick, those folks in the ICU really were not demonstrating any significant benefit to therapeutic anticoagulation. And in fact we may have been harming them with elevated bleeding risk in doing so. The area that was the most beneficial were those patients who were hospitalized and were mildly hypoxic. These folks who were on nasal cannula oxygen and had an elevated D-dimer. This sort of sweet spot. You had to be just sick enough but not too sick to potentially benefit from therapeutic anticoagulation throughout the hospitalization. And so this is really where kind of guidelines ultimately went is that we should be selecting a subgroup of hospitalized patients. Those who are at lower bleeding risk, those who are hypoxic but not too hypoxic. And we think that the elevated D-dimer in that hospitalized setting adds to that risk stratification. And so that's where these guidelines have gone for the moment.

Dr. Bell: I mean just very briefly, how would you treat those patients? What would be your anticoagulant regimen?

Dr. Houghton: Absolutely. So, most of the studies that were positive here used kind of a combination of heparin or Lovenox. There's been kind of the historical perspective of maybe these heparinoid medications have some antithrombotic effects. And the fact that the ACTION trial that used rivaroxaban was negative also lended towards kind of that interpretation of these positive results. But heparin and Lovenox were the mainstays of anticoagulation in these trials.

Dr. Bell: And the patient who's been hospitalized but is not in the ICU environment. Maybe they've got some coexistent disease. Prophylactic anticoagulation for them? Beyond what we might normally do for a hospitalized patient?

Dr. Houghton: So, a hospitalized patient who is not on oxygen?

Dr. Bell: Correct.

Dr. Houghton: So, this is a little bit interesting as well 'cause obviously at our hospital we would screen for COVID patients. And many times we would pick up positive patients who who weren't particularly symptomatic, weren't on oxygen, perhaps were in the hospital for some other reason. And so, correct, the recommendation would be in those folks if prophylactic anticoagulation was appropriate given their clinical circumstances, certainly add that on. But this recommendation wouldn't apply to those without some hypoxia associated with their condition.

Dr. Bell: Well, unfortunately, we're running out of time, but I do think that we should just maybe very briefly in a minute or so just address the other really interesting observation, and obviously worrying. I guess it was about two years ago now when recognized that there may be some

patients who had a vaccine-induced thrombotic, the vaccine-induced immune thrombocytopenia which was seen with the adenoviral vector vaccines. Obviously very, very rare. I mean, is this something that we're still gonna see in the future? Typically, the vaccinations now are going to be with mRNA vaccines. So, have you seen a case of that either recently or previously, and what's the current status of that? And I don't think we have time to go into all of the understanding of the pathophysiology of that. It's very, very interesting, obviously. If you can just, in a sort of a nutshell, just tell us what is the status of this vaccine immuno-mediated thrombocytopenia.

Dr. Houghton: Absolutely, yeah. So to my knowledge, I'm not aware of a case at Mayo Clinic. And as you mentioned, this is an extremely rare side effect that we've seen with the adenoviral-based vaccines. In the United States, the Janssen or Johnson & Johnson vaccine, and in Europe the AstraZeneca vaccine. AstraZeneca vaccine might have a slightly higher risk than the Janssen vaccine. There have been some studies now that have put this risk into perspective. And really as you mentioned, it is quite rare. About 3.8 per million vaccinated patients. And so this is a very rare, but obviously very concerning syndrome that's occurred after this. I think we've understood a lot more in terms of the pathophysiology. Dr. Anand Padmanabhan, and in particular here at Mayo Clinic is a hematologist who's done a lot of research in this area to help advance our understanding. But ultimately this ended up being a very rare side effect. The vaccination pause that the CDC and the FDA did in April of 2021 ultimately was lifted, and it was felt to be appropriate to continue vaccinating with the Johnson & Johnson vaccine, given the overall risk-benefit ratio at that time. Ultimately, we have kind of shifted in large part for other reasons as well towards the mRNA-based vaccines. A number of research studies have sort of subsequently come out that have really tried to demonstrate the safety of these medications. There had been concerns related, "Well, maybe there are some other thromboses "that aren't vaccine-induced "thrombocytopenic syndrome instances." And I think really what we've seen is the research is showing these mRNA vaccines don't cause VT and they don't seem to be associated with any more generalized thrombotic risk. And so I think we really do have a very safe vaccine, especially as it relates to venous thromboembolic events. And if anything, there's also some research showing that we probably are actually reducing thrombotic events by influencing COVID infection rates as well.

Dr. Bell: Okay, yeah, which gets us back to one of the points and impressions earlier in our discussion. So, unfortunately that's all we have time for today, Damon. So, really wanna thank you for sharing your experience. And obviously you've taken a very keen interest in this and have contributed to our understanding of this. And certainly from a personal note, I mean, it's much more reassuring your data and observations that we are hearing today compared to a couple years or so ago. Again, another example of applying sound scientific approaches to understanding not just, I guess, the epidemiology, but the pathophysiology and now the importance of anticoagulation. And it seems as though things have sort of been dialed down just a little bit. So, bringing clarity to this I think has been so helpful to, I guess all of us who are taking care of these patients, who come across these patients. So, Dr. Houghton, again, thank you so very much for taking the time to be with us and again to our listeners and viewers for joining us today.

Dr. Houghton: Thank you so much, Dr. Bell.

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