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Special Issue covering COVID-19 and thrombosis

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Thrombosis in COVID-19: What We Know, What We Don't Know and How to Treat?

During the course of the COVID pandemic, we've continued to learn about the disease and its multiple manifestations every week.

I would like to turn the attention to an issue that arose from the early observational reports of the disease and has continued to be a hot topic of conversation among clinicians taking care of COVID-19 patients, which is the associated problem of thrombosis. We've seen reports with ***varying degrees of incidence of thrombotic disorders***, both on the venous and the arterial side. We've seen reports coming out ***recommending thromboprophylaxis***. We've seen reports where people are starting to explore full-dose anticoagulation. We've also seen people worried about the risk of full-dose anticoagulation in this group of patients.

Let's start at the beginning. What has been observed in the area of venous and arterial thrombosis in patients with COVID-19 infection?

That's a really great question. From the macrovascular perspective, early reports suggested high rates of ***deep vein thrombosis*** ***(DVT)*** and ***pulmonary embolism*** ***(PE)*** in patients admitted to hospital with SARS-CoV-2 infection or COVID-19.

It's unclear as to what the actual incidence is, as I suggested in the introduction. Early reports suggest incidences ***of DVT and PE up to 30%***. I think that's probably incorrect.

The sicker patients get, the higher their risk, just like any medical inpatient where the risk is increased. Later studies coming out are ***suggesting lower rates*** closer to around 10%. There's a ***paper in press*** in *Blood* out of five hospitals in my beloved town Boston, which suggests this lower incidence of venous thrombosis.

We're not 100% sure yet, but we do know that there's something different about what this infection is doing to the clotting system compared with other infections, which is what we call COVID coagulopathy. This coagulopathy seems to be prominent and it seems

to predispose to thrombosis. Venous disease is the most important macrovascular complication.

What about the arterial side? I am interested in things like whether it triggers ***acute myocardial infarction*** or ***stent thrombosis.*** What about patients with ***atrial fibrillation***?
On the arterial side, I think the obviousness of an association is a little less. We are recognizing that people have elevated troponins and such. There have been suggestions that ***large-vessel stroke*** might be an issue in young people who have this infection. The epidemiology is not as prominent on the arterial side in terms of what exactly to expect.
If anything, there have been observations that ***cath labs are less busy***. The big concern is that the mitigation of infection in the population, including the stay-at-home measures, have been frightening patients from coming in for care. That may be a bigger problem than the arterial disease complications related to the infection itself.
That's been an issue that many of us have been talking about. We've seen somewhere between a ***30% and 50% decline in the acute presentation*** of suspected strokes and suspected myocardial infarctions.
Now that we recognize that the predominance of the observations are that COVID seems to be associated with an increased risk for venous thromboembolic disease, is the incidence higher than we see with critically ill patients with other viral infections? If we take a very sick person with flu, do we see the same association?
I think it is probably higher. Again, it's a little unclear. Risk adjusted for severity of disease compared with any other ICU patient, for example, it's probably higher based on the preponderance of evidence.
In the large hospitals that have a heavy burden of this disease, people are noticing that the standard DVT prophylaxis doesn't seem to be suppressing thrombus like it does for other patients.
Now, remember that in critically ill patients without any thromboprophylaxis, the rate of venous ***thromboembolism*** might be as high as 20%. We can reduce that perhaps by half with

thromboprophylaxis. Thromboprophylaxis isn't all that great in terms of its efficacy, but it's obviously better than nothing.
I'm going to come back to that again later.

What do we know about the biology? I'm going to comment on two things I've seen in the literature that have fascinated me, one of which focuses on the biomarker papers.
With an elevated IL-6, an elevated D-dimer, not so much what I would think of as the markers of DIC (disseminated intravascular coagulation) — the changes in PT or PTT due to thrombocytopenia — but this inflammation/D-dimer intersection is really interesting.
What can we take from the literature and what is it telling us about the pathobiology of COVID and thrombosis?
This is a story that we really need to solve. The first appearance of this idea came out of ***papers from China*** where the prominence of elevated D-dimer and proinflammatory markers, including IL-6, ferritin, and C-reactive protein, was described.
We all thought this is DIC, but it's not DIC like we normally think about it. The ***fibrinogen*** tends to be high, not low. Fibrinogen is an acute-phase reactant. It's a clotting factor, but from the biomarker perspective, it's more responsive to acute phase.
It's not like DIC where you see elevated prothrombin times, lowering fibrinogen, elevated D-dimers. You see high D-dimers and high proinflammatory biomarkers. You see mostly a normal prothrombin time.

Once patients progress to more advanced disease, they start breaking down and developing more consumption of clotting factors, whereby their prothrombin time will elevate and their platelet count might drop. Once patients develop the more classic picture, that's a really bad harbinger that they're dying, essentially.
So, it doesn't start as a ***consumptive coagulopathy***. Over time, it makes the transition to a consumption state, and that is, as I have said, a bad marker. I think it has become pretty standard that these biomarkers are checked when patients are admitted to the ward with this infection.

From the hematology community, they are recommending checking D-dimer, fibrinogen, and C-reactive protein levels along with the admission labs to see where patients stand. I think that can give you clues as to who is going to progress. We know that people who have higher D-dimer at the beginning have a more adverse course and a higher risk for death.

Someone may ask what this means for biology. We all think D-dimer doesn't really do anything. It's a marker of fibrin formation. That's really the key thing here.

D-dimer is not a fibrinolysis marker. When we study the epidemiology of D-dimer in healthy people, it's not marking fibrinolysis usually. It's marking increased fibrin formation. It is correlated with fibrinogen and with procoagulant factors like ***factor VIII***, which is also high on admission in these patients. It's also correlated with proinflammatory biomarkers in healthy people.

D-dimer is a marker of fibrin formation. If you just think about that for a moment and then consider some of the pathology findings that have come out, I think we're starting to understand that there's an intense stimulus with this infection to lay down fibrin.

That probably comes from endothelial damage. I haven't seen much on biomarkers of endothelial function or adhesion apart from factor VIII and von Willebrand factor, which I think of as biomarkers of endothelial function because factor VIII is stored under the endothelium. When there's endothelial damage, levels go very high. Remember, factor VIII is the clotting factor that's preserved in patients with advanced ***cirrhosis*** because it's stored sub-endothelium. Even though it's made by the liver, the levels can be fine when you have cirrhosis.

Now there is another ***paper*** that I wanted to talk about. It was in *The New England Journal of Medicine*, focusing on lung autopsy findings from a series of seven patients. They observed angiopathy and disruption of the endothelium.

What would you think of that, and how do we start to put that into the story?

Most patients who have died with COVID-19 have not had autopsies. We need to think about why those particular patients had autopsies

and other patients didn't. We don't know the extent of how much this means, but I think that it's really telling.
We're starting to believe that the coagulopathy marks people at risk for progressive lung disease, perhaps because it marks this possibility that the person is going to develop or is already developing microthrombi in the lung.
In fact, there's this idea that among people with this disease who present like they're having PE, it's not because they're having DVT associated with their PE, but they're having in situ thrombus, maybe even in the larger vessels.
Now, we would be able to distinguish the difference between the two potentially on a CT angio, but most of the patients can't get a CT angio because they're too ill and they can't go to radiology.
I think this is really telling and it raises the issue about the potential ways we could shut off the fibrin information.
There's a third ***paper*** just out that suggests that the virus actually could infect endothelial cells. If the virus is infecting the endothelial cells, then that's not typical in virology, from what I understand.

If this were to happen, this could explain a lot of these biomarker changes that we're seeing, because that endothelial disruption in the development of these microthrombi or maybe in macrothrombi, but probably microthrombi in the lungs, is where the virus is.
I think it's a really cool area to consider further.
It's really amazing, isn't it? Here's a disease that we weren't thinking about several months ago. Now, fast-forward to the amount of scientific information that's been pouring out daily, which is really extraordinary, and we've really learned so much.
During the first SARS epidemic, it was not as prominent, there was the feeling, at least in the ICU oh Harvard major teaching hospitals, that those patients were having more thrombosis as well. I think that wasn't as much of a global pandemic as this SARS-COV2 epidemic.
It may be that the SARS-CoV-1, the SARS virus that we were dealing with a number of years back, had a similar impact that we didn't recognize because it wasn't as severe. There wasn't as much of an outbreak, so we didn't have the urgency to study it.

I heard that at that time of the hematolgy fellows at University of Vermont Medical Center actually collected a bunch of samples from those patients and they never did anything with them. They kept them in the lab, so I think they should go back and try to dig those out. The hematologists had the sense that they were seeing more thrombosis with those patients as well. There was just less research at that time on that disease.

We may have seen that the ***AHA granted a series of rapid-[response] grants***. One of them is to study the thrombotic complications of the disease, given to investigators in New York City. Certainly there is a high volume of patients and a high likelihood that they have samples on those patients. It's going to be interesting to see what we learn from that grant about the thrombotic complications.

Let's turn our attention from observation in biology to clinical practice. Let us about thromboprophylaxis.

People have said we've got to use standard low-molecular-weight ***heparin*** in this group of patients to prevent thrombosis. It's a reasonable strategy. Is that what I am recommending? Now what kind of dosing?

I reviewed two consensus groups, one from the ***American Society of Hematology***, a relatively small group, and one from a much larger group of about 45 authors that was published in ***JACC*** last month. Bikdeli is the first author.

In both groups, the conclusion, based on expert consensus — because that's all we have right now — is that all patients admitted to hospital with COVID-19 should receive DVT prophylaxis using standard dosing. If it's ***enoxaparin***, it will be 40 mg once a day; for unfractionated heparin, 5000 units twice a day.

At the same time, there has been the emergence of these institutional protocols and other opinions about this, including that patients who have obesity should be given higher doses or all patients should be given higher doses. Some people suggest that those admitted to the ICU even be given full-dose anticoagulation empirically.

Those who are involved in creating guidance documents really have tried to stick with what they know from the literature to be effective and safe, because anytime you give DVT prophylaxis, there's a risk for

bleeding complications. They've stuck with recommending standard-intensity DVT prophylaxis. The International Society on Thrombosis and Haemostasis also put out ***consensus guidance*** just a couple of weeks ago that concluded the same thing.

People's emotions want to say "do more." I think this is driven by what's been observed in the large hospitals, and I respect that. For a given situation that you're in, based on your experience, if your hospital develops a recommendation that might differ from what guidance documents suggest, I think that's okay because everybody's just trying to do the best they can.

At this point, I really strongly believe that anything more than that should be documented in a randomized trial before it can be recommended broadly.

To me, the pandemic, in many ways, has shown us once again that clinicians are much more willing to make the sin of commission than the sin of omission. People think they have to do something.

I've never agreed with that because if you don't know, what you ought to do is study it rather than say, "Oh, I think this is the way," because you actually may be doing more harm than good. The only way you figure that out is by systematic study.

Hydroxychloroquine is a great example of that. People were passionate about its use. Now the randomized evidence is suggesting that you should not use it.

Cushman: The ***paper*** in press in *Blood* out of five hospitals in Boston looked at predictors of outcome. They replicated that higher D-dimer levels at admission were related to thrombosis outcomes. But guess what? Higher D-dimer levels at admission were also predictive of bleeding complications during the stay.

I think they have to conduct the trial to really answer the question. Emotions run high, especially because these patients get so sick so fast, and I understand that.

I understand that as well. We all take care of really sick people, and you want to do something. That's the nature of the work that we do. We want to do something, but we also have to step back and ask how we are going to learn about this in a way that we can help not only this patient, but also subsequent patients.

Let me another point. Are there particular patients or particular reasons to think outside the D-dimer story about who might be at highest risk of bleeding with the disease or is it the usual case with low body weight, elderly people, and comorbidities? Is it the usual things that predict bleeding in this group of patients?

I don't think we know enough about that yet. Honestly, in hospitalized patients, bleeding is common. Think about all the people who are at the hospital for one reason and then they have a GI bleed. We don't really understand the risk profile of those in the general medical inpatient population who are at increased risk of bleeding, apart from the fact that if you give people anticoagulants, they have an increased risk of bleeding.

It's an area of research that is underattended to. Again, COVID is magnifying everything. In the COVID setting, maybe we'll learn more because of the intense interest, resources, and creative thinking that are being put in that will be applicable to other patients as well. I don't think we have a good handle on that.

My final point for this issue is to make you aware of trials that are ongoing in the area of full-dose anticoagulation?

Recently a major trial was launched called the ***RAPID COVID COAG Trial.*** The Co-PIs are: Mary Cushman a hematologist at the University of Vermont, Michelle Sholzberg a hematologist at the University of Toronto, and Peter Jüni, who is also at the University of Toronto. They have over 40 hospitals in Canada, the US, and in other countries that are in various stages of getting activated.

It's a fascinating experience because they're testing the impact of full-dose anticoagulation with heparin or low-molecular-weight heparin in ward patients with COVID-19, who have elevated D-dimer or hypoxia with D-dimer elevation. The comparison group is standard DVT prophylaxis, so enoxaparin 40 or unfractionated heparin 5000 twice or three times daily.

The primary endpoint is not thrombosis. It's transfer to the ICU, or the need for mechanical ventilation, or death at 28 days. They went for the hard clinical outcomes. They are trying to see if the treatment will impact the progressive lung disease. It's going to be 462 patients, but it has an adaptive design. There'll be an interim analysis and then the

sample size can be modified as needed. With that sample size, we'll have 90% power to detect a meaningful difference between the groups.
The first cool thing about the study is the endpoint. The second cool thing is the biorepository that they're going to collect so that they can do correlative science. They will look at all of the variety of biomarkers I've been talking about, plus different ones. They've developed an assay for soluble ACE2, which has gotten a lot of attention, for example. Third, based upon the sites that they're prioritizing for activation, they are prioritizing sites that have very high racial minority representation. They really want this trial to have upwards of 50% nonwhite participants, primarily black and Hispanic.

I did give you a detailed discussion about COVID-19 and the risks of thrombotic disorders, particularly on the venous side, but not exclusively. I 've also talked about the biology and potential treatments.

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