Uhm, I know a lot of you guys already, but I'm one of the clinical hematologist here at the Cancer Center, and for the last nine years my main interest have been medical education and thrombosis or blood clotting. And then in mid March of this year Is everybody knows kovid hit and so early on when the first kovid patient arrived at Yale New Haven Hospital. A few of us in the hematology section were asked to join a multi-disciplinary effort designed to try to understand in combat the disease,
an one of the more interesting and kind of.

Unexpected features of COVID-19 infection was that there’s actually

a huge component of blood clotting,

and this is something that’s term

COVID-19 associated Coagulopathy.

So we became interested in the hematology section and trying to not just manage

this but also understand this,

and so that’s what I’m going to be

talking with you all about today.

So again,

this this whole feature of blood

clotting in Kobe 19 infection is

something that’s called COVID-19
associated Coagulopathy.

Its abbreviated CAC and at the laboratory level it’s defined by 4 basic things.

So one is that these patients have an elevated D dimer. That’s often very, very high.

The second is that they have a high fibrinogen level. Again, that’s often very high.

The third is that many of these patients have a normal prothrombin time, although some of them do have a
slightly reduced platelet count.

And again, as I mentioned before, clinically the main feature associated with code 19 associated Coagulopathy is thrombosis. So these patients have a very high risk of developing blood clots, predominantly venous thromboembolism or VTE, and in particular pulmonary embolism. There are some single institution studies that suggest that up to 37% of COVID-19 patients in an intensive care unit. Who are ready on prophylactic anticoagulation will develop a pulmonary...
embolism or a deep vein thrombosis.

And in addition Artur thrombosis an microvascular thrombosis on autopsies has also been described. So because of this very high rate of thrombosis are hospital system, our institution was actually one of the first in the country to develop what we call an escalated intensity anticoagulation regiment. So what I mean by this is that as most of you who are clinicians know, whenever patients in general get admitted to the hospital already there, blood clotting risk goes up and so most patients admitted to a...
00:02:33.842 --> 00:02:35.170 hospital center including Smilow

00:02:35.170 --> 00:02:38.522 would be on what we call a low dose of prophylactic anticoagulation.

00:02:39.700 --> 00:02:40.047 Typically, enoxaparin had a dose of 40 milligrams once a day.

00:02:42.129 --> 00:02:44.826 But in kovid patients, because of this increase risk of thrombo Sis we adopted this escalated intensity anticoagulation regiment so that patients with Cove in infection who had a D dimer level that was above a certain cut off which we ended up choosing us 5 milligram per liter would
00:03:00.935 --> 00:03:02.787 automatically get a higher
dose of anticoagulation.
NOTE Confidence: 0.888363063335419
00:03:02.787 --> 00:03:04.176 We would call this intermediate
dose of enoxaparin typically,
NOTE Confidence: 0.888363063335419
00:03:04.180 --> 00:03:05.990 which is at a dose of 0.5 milligrams
NOTE Confidence: 0.888363063335419
00:03:06.720 --> 00:03:09.608 and then again because of this super high.
NOTE Confidence: 0.888363063335419
00:03:09.608 --> 00:03:12.177 Risk of thrombosis in any covert
NOTE Confidence: 0.888363063335419
00:03:12.177 --> 00:03:14.390 patient in whom there is a suspicion for
NOTE Confidence: 0.888363063335419
00:03:14.390 --> 00:03:16.196 venous thrombotic event or confirmed
NOTE Confidence: 0.888363063335419
00:03:16.196 --> 00:03:18.821 V enus Don Bolic event we would
NOTE Confidence: 0.888363063335419
00:03:18.821 --> 00:03:20.521 recommend full dose anticoagulation
NOTE Confidence: 0.888363063335419
00:03:20.521 --> 00:03:22.872 typically again with enoxaparin
NOTE Confidence: 0.888363063335419
00:03:22.872 --> 00:03:24.432 and then twice daily so as I mentioned we
NOTE Confidence: 0.888363063335419
00:03:24.432 --> 00:03:26.009 were one of the first hospital
centers in the country to develop. One of these escalated anticoagulation dosing guidelines and many other hospitals if not most around the country have followed suit. One of the challenges that we’ve all had his clinicians. Is that even though most of us in the country are doing these escalated anticoagulation regiments, we don’t actually know if they’re safe or if there even affective and so at our group is in the process of analyzing this now as are many others and there are some clinical trials.
around different institutions in the country that are looking at this issue. This question as well.

One of the early studies that came out from China on covert associated Coagulopathy reported that it was essentially a variation of disseminated intravascular coagulations, or DIC, which as most of you all know as sort of an end point of a coagulopathic picture that’s characterized by pretty high rates of thrombosis and terminal disease.

DIC itself again as a lot of other clinicians know,
00:04:31.390 --> 00:04:33.706 has a very characteristic laboratory pattern, and to us it really didn’t seem.

00:04:33.710 --> 00:04:36.405 White covered associated Coagulopathy was similar to DIC at all.

00:04:36.410 --> 00:04:41.170 So early on when we start first started seeing kovid patients in our hospital,

00:04:41.170 --> 00:04:43.634 we decided to do a couple of studies to try to understand what the code associated Coagulopathy is.

00:04:43.634 --> 00:04:45.800 And so this first study that we did was led by one of our star first Hematology Fellows George Joshua,

00:04:45.800 --> 00:04:47.864 Hematology Fellows George Joshua,

00:04:47.864 --> 00:04:50.101 to look at the 1st 200 plus patients with Kobe, and what we did here was to look at the 1st 200 plus patients with Kobe,
we calculated what’s called a dic score at specified by the International Society of thrombosis and hemostasis, or IST age. And so the way this works is that the ice TH score essentially looks at different laboratory features of patients suspected of having DIC, and then it spits out a score. If your score is in the range of five and up, then that’s considered overt DIC. In anything less than five is not consistent with over DSD. And so in our first couple 100 patients with Cobain infection admitted to Yale,
New Haven Hospital when we calculated the IST FDIC scores, whether we were looking at patients who survived or patients who did not survive. As you can see, almost all patients had a very low IST HD score in this entire group. There was only one patient who had an IST HD score of six consistent with over DIC, but this is a patient who had helped syndrome after pregnancy, and we didn’t think that this is related at all to COVID-19 infection. So based on this,
we really started to feel that
Kovid associated Coagulopathy
was not consistent with DIC,
and so the next thing that we did
was to perform a somewhat large
study of a number of ICU and
non ICU patients with Cove it,
in which we measured lots and lots of
to see what exactly the mechanism of
covert Coagulopathy might be an weather.
Again this was distinct from DC.
This work here was carried
out by four people who are shown
at the bottom of the page.
Parveen,
but hell is one of the lab technicians in the Park Street Lab who did all of the quag elation.

testing and then George Joshua refers to your fellow Alex Pine, one of our star senior 30 or Fellows in he monk and then a super MD PhD student at my slash also together did this analysis.

So first I’ll starting at the top of the page. The first thing we measured were D dimer levels and something else called a thrombin, antithrombin complex or TI-80. So as most of you know,
the D dimer level is something that tends to go up on patients form blood clots, and it can often be a very useful measure of blood clotting, and one of the significant features of the D dimer is that encoded infection. the D dimer level seems to be one of the very very prominent markers of mortality and overall course clinical cores and so.

It’s a very useful and important marker in covert patients, marker in covert patients, both for thrombosis and also for their overall disease cores, and then thrombin, antithrombin complexes you can
NOTE Confidence: 0.877944767475128
00:07:34.089 --> 00:07:36.645 think of those as sort of a fancy
NOTE Confidence: 0.877944767475128
00:07:36.645 --> 00:07:38.390 and more specific D dimer that
NOTE Confidence: 0.877944767475128
00:07:38.390 --> 00:07:40.496 really looks at whether AD dimer
NOTE Confidence: 0.877944767475128
00:07:40.496 --> 00:07:41.888 elevation comes from activation
NOTE Confidence: 0.877944767475128
00:07:41.888 --> 00:07:43.578 of the Quag Elation Cascade.
NOTE Confidence: 0.877944767475128
00:07:43.580 --> 00:07:45.338 So when we measured D dimer
NOTE Confidence: 0.877944767475128
00:07:45.338 --> 00:07:47.200 levels an from an anti thrombin
NOTE Confidence: 0.877944767475128
00:07:47.200 --> 00:07:49.696 complex is both in ICU and non ICU
NOTE Confidence: 0.877944767475128
00:07:49.766 --> 00:07:51.718 patients with colon infection.
NOTE Confidence: 0.877944767475128
00:07:51.720 --> 00:07:54.424 We found that both of these were elevated,
NOTE Confidence: 0.877944767475128
00:07:54.430 --> 00:07:55.282 particularly in patients.
NOTE Confidence: 0.877944767475128
00:07:55.282 --> 00:07:57.912 We were in the ICU and on a separate
NOTE Confidence: 0.877944767475128
00:07:57.912 --> 00:07:59.942 analysis we found that the D dimer
NOTE Confidence: 0.877944767475128
00:07:59.942 --> 00:08:02.054 levels and from an anti thrombin
NOTE Confidence: 0.877944767475128
00:08:02.054 --> 00:08:03.466 complex is correlated together.
NOTE Confidence: 0.877944767475128

16
So this let us know that the source of the high D dimer encoded associated Coagulopathy is indeed activation.

The next thing we did was to measure a number of endogenous anticoagulants, antithrombin, protein C, and protein S, as well as a fire analytic enzyme called A2 Antiplasmin.

Whenever you form, activate coagulations through the coagulation cascade, the body has a natural mechanism to shut off coagulations and therefore prevent from boces from getting...
out of control and so that natural mechanism happens through two sources. One is through endogenous anticoagulants that are designed to turn off the Coagulations Cascade, and those are these first three up. The second way that the body regulates the Quag elation cascade is to turn on fiber analysis or the process of digesting blood clots that are formed and the principal enzyme that does this is called A2 Antiplasmin.
antithrombin protein protein S in ICU and non ICU patients with colon infection, we found that they were basically on normal. Normal is usually anything about 80% and as you can see. All of these patients had essentially antis arm approaching CN Protein showing levels around 100%, indicating that there was not excessive consumption of anticoagulants. Endogenous Lee and then we also looked at A2 Antiplasmin. The main fibrinolytic enzyme that I just mentioned, and again here you can see the levels in both.
I see you in an ICU patients with colon infection were normal, so this let us know that when we looked at endogenous anticoagulant San fibrinolytic enzymes, we were not seeing consumption. Of any of these, and the important feature here is that in most patients with DIC you should see consumption of endogenous anticoagulant. An fibrinolytic enzymes. So the fact that we were not seeing that. Let us know that CAC is probably mechanistically distinct from DC.
The next thing we did was to measure an enzyme called plasminogen activator inhibitor or Pai one. This is the main negative regulator of fiber analysis and what we found was that this was elevated both in ICU and non ICU patients. The significance of this is that whenever we see this elevated it sometimes will suggest that fiber analysis is inhibited and so it makes us wonder when we see this weather perhaps encoded associated Coagulopathy there may be an inhibition of Clock breakdown which might contribute to overall thrombosis risk.
And then the last thing we did was at the very bottom.
Here we measured three tests, von Willebrands Factor, Antigen von Willebrands factor activity and factor 8 coagulations level.
So what are these fun Willebrand factor?
Is a hemostatic factor that’s released by endothelial cells and the purpose in coagulations of fun.
Willebrand factor is basically to help platelets bind to sites of damaged endothelium and initiate primary hemostat stasis, which is important for blood
00:11:08.270 --> 00:11:09.416 clotting factor 8.
NOTE Confidence: 0.88461709022522
00:11:09.420 --> 00:11:11.778 Separately is a coagulations factor that.
NOTE Confidence: 0.88461709022522
00:11:11.780 --> 00:11:14.192 Wines to von Willebrand factor in
NOTE Confidence: 0.88461709022522
00:11:14.192 --> 00:11:16.667 the circulation and So what we
NOTE Confidence: 0.88461709022522
00:11:16.667 --> 00:11:19.037 notice when we measured levels of
NOTE Confidence: 0.88461709022522
00:11:19.037 --> 00:11:21.079 an willebrand factor in factor 8
NOTE Confidence: 0.88461709022522
00:11:21.079 --> 00:11:23.218 both in ICU and in ICU patients,
NOTE Confidence: 0.88461709022522
00:11:23.218 --> 00:11:26.162 we saw that the levels were quite high,
NOTE Confidence: 0.88461709022522
00:11:26.170 --> 00:11:28.228 and in particular the levels were
NOTE Confidence: 0.88461709022522
00:11:28.228 --> 00:11:30.230 super elevated in ICU patients,
NOTE Confidence: 0.88461709022522
00:11:30.230 --> 00:11:33.182 and I just want to show you another
NOTE Confidence: 0.88461709022522
00:11:33.182 --> 00:11:33.920 curve here.
NOTE Confidence: 0.88461709022522
00:11:33.920 --> 00:11:36.224 This right here are DOT plots
NOTE Confidence: 0.88461709022522
00:11:36.224 --> 00:11:38.165 showing Refactor Antigen one factor
NOTE Confidence: 0.88461709022522
00:11:38.165 --> 00:11:40.482 activity and factor 8 in ICU versus
NOTE Confidence: 0.88461709022522
00:11:40.482 --> 00:11:42.810 non ICU patients with the green.
Rose indicating what the normal ranges should be, so again based on this, one will benefactor in factor 8 levels are elevated both in ICU and non ICU patients with Cove it, but there are through the roof high, particularly for von Willebrands factor in the ICU patients. The significance here is that the major source of on lower end factor in the body as it circulates through the blood is endothelial cells and so whenever we see this sort of pattern where we have very very high levels of fun
Willebrand factor circulating in the blood. It tends to point towards a pattern of endothelial injury. In addition, von Willebrands factor can also be stored in platelets, can also be stored in platelets, and so looking at this pattern, it made us wonder if perhaps both endothelial cells and platelets were being hyper activated in the setting of coded infection. Particularly as patients progressed to critical illness. So in order to test this, we were interested in looking at specific markers of endothelial function and platelet activation and so for this,
we collaborated with Doctor Hengchun who’s an investigator in the Cardiology Section who, along with his two postdocs, doctor home Chang and doctor honey and Zhang performed a series of experiments on all of our ICU and non ICU patients looking at different endothelial and platelet activation markers and the specific ones we looked at were soluble key selecting. Which is shown up in the top left, which is a marker of both endothelial cells and platelets. And then we also looked.
at soluble CD 40 ligand, which is seen which is released by platelets and lymphocytes. And then Lastly we looked at soluble from a module in which is specific mostly to endothelial cells. Come here because these are all research tests. They don’t have normal reference range is so as a result we also got blood from 13 different control patients or control individuals, many of whom are listening to this talk right now. So the significance of this is that when we looked at all these three
different markers of endothelial cell

plus or minus platelet activation,

we saw in pretty much every single case

that the levels were higher in ICU

patients with kovid than they were.

Then controls in the case of

soluble thrombomodulin.

We did not see a significant change in

the level of soluble thermal modeling.

ICU versus control patients.

But what we did notice was that

there were several patients in the

ICU group who had a quite high level

of soluble thermal module in that

made us think that perhaps there
was something going on with soluble thermal modeling and therefore endothelial cells that might be specific to ICU patients. And so when we did a series of tests looking at all these different markers and comparing to mortality, we found that interesting Lee soluble thrombomodulin level segregated with mortality. Whether we looked at the entire population in our cohort or whether we looked at ICU patients. Alright, so putting this altogether, what did we learn from these studies? First in measuring different
levels of endogenous anticoagulant and fibrinolytic enzymes,
we found that antithrombin protein to protein S and A2 anti plasm overall preserved which is distinct from DIC indicating that indeed code associated Coagulopathy is not the same as DIC.
We also learned that Pai one is elevated, encoded associated Coagulopathy suggesting that fiber analysis might be inhibited.
Although we haven’t completely confirmed that.
In addition, we saw that on Willebrand factor, in factory levels, which are markers,
particularly endothelial cells and platelets, are elevated in both non ICU and ICU patients, and in particular are through the roof high in ICU patients, suggesting that there is a significant component of any Philly Opathy and platelet activation encoding infection, particularly as patients become critically ill. And then Lastly, we saw that when we measured specific markers of endothelial cell and platelet activation, we found that these were elevated in ICU patients with soluble thrombomodulin,
which is quite specific for endothelial function segregating with mortality. So In conclusion, what we believe our data shows is that code associated Coagulopathy is actually an Endo Philly Opathy where you see augmented von Willebrands factor release platelet activation and hypercoagulability all coming together causing an increased risk of thrombosis, including Venous thromboembolism, Artur thrombosis and also microvascular thrombus. In addition, we think that endothelial
dysfunction or injury is a marker of progression of critical illness, encoded infection and we find a specific endothelial marker seems to segregate with mortality. The importance of all of this is that it’s made us wonder if there might be a role for adding antiplatelet or even endothelial cell modifying therapy to our anticoagulation algorithm. And so early on while we were developing this story, we met with a number of the ICU directores, FDA only Haven Hospital Ann through...
a lot of discussion just I think
last week or the week before aspirin was finally added to our treatment
NOTE Confidence: 0.865365564823151
algorithm and now every patient who gets admitted to the hospital.
NOTE Confidence: 0.865365564823151
In the ICU with colon infection,
NOTE Confidence: 0.865365564823151
get started on aspirin empirically.
NOTE Confidence: 0.889760613441467
So I just want to acknowledge a lot of people who contributed to this work.
NOTE Confidence: 0.889760613441467
We have this gigantic, an amazing hematology team,
NOTE Confidence: 0.889760613441467
both on the research side.
NOTE Confidence: 0.889760613441467
In the clinical side,
NOTE Confidence: 0.889760613441467
on the left are all the trainees who are working with this.
NOTE Confidence: 0.889760613441467
George and Alex are start fellows in a particular a lot of our discussions. In fact pretty much every experiment that we've done really started with conversations at George and I had many months ago leading to what we have now. Matt, my salati as I mentioned, is a superb PhD student Eric Chang and Yu Shen Lu are both third year senior medical residents who are going to be our fellows this coming July. And then Rebecca fine is an intern who expressed some interest in doing immunology Hematology Research. Down at the bottom are the members of Doctor Chung’s lab who contributed this
worth hung Chang and honey Jang where both postdocs as I mentioned in the middle. We have a number of pharmacists, some of them are familiar to you guys who are part of our greater team looking at anticoagulation outcomes. Cajun mean Nick Difilippo, Dana McManus, Cantou Enedina frozen. Uh and then over on the right. Here we have our amazing, outpatient, benign hematology clinical team. Audrey Gina, Andrea, Joy, Ann and hope. Uh, and then finally the bottom. I just want to acknowledge Bob Bono,
who's our new chief of benign
team and then Stephanie Helene’s,
our section chief as both of them have been
incredibly supportive of these efforts.
So thank you guys and thank you
Charlie. Thank you and congratulations
to you and really the entire
team on working through this.
Uh, in a very short amount of time
and frankly making a difference
for our patients in the process.
Uh, in a very short amount of time
and I know we have some
questions coming through,
but let me start by asking you.
Your research seems certainly indicates that
this is a process of interfere with damage.
And do we? What do we know about the virus itself that lends support that? This would be a primary incident to the endothelium. Yeah, that’s a great question, so there does seem to be in autopsy studies. A certain component of endothelial leitis, which some people have shown might be related to direct viral infection. So there have been autopsy studies that have demonstrated viral particles within endothelial cells. Not every study has demonstrated that, but some people do believe that that is part of the incipient process that begins.
the end of filial pattern of injury.

One of the challenges is that.

A lot of people tend to think

of thrombosis as somewhat later

so it’s not clear if there may be a

second sort of hit to the end of Filium,

patients become critically ill that

might be independent of viral infection.

It might instead involve inflammation

and other things like compliment that

might trigger and a filial activation.

Thank you other questions

that have come through.

Do you have any information about
the specificity of these changes for chobit relative to other respiratory viral infections? For instance, are microvascular thrombi a finding in other respiratory viral infections beyond coated? Yeah, that’s a good question to my knowledge I’m not aware of a lot of other viruses that show microvascular thrombi. There are certain cases of influenza There are certain cases of influenza that can be characterized by massive inflammatory responses. Um dangi infection is also often brought up as an example of a
00:20:26.874 --> 00:20:28.728 virus that can cause a pretty
NOTE Confidence: 0.91236799955368
00:20:28.728 --> 00:20:30.530 awful coagulopathic picture,
NOTE Confidence: 0.91236799955368
00:20:30.530 --> 00:20:33.160 so I’m not sure if any of either of those
NOTE Confidence: 0.91236799955368
00:20:33.227 --> 00:20:35.857 in particular are classically associated.
NOTE Confidence: 0.91236799955368
00:20:35.860 --> 00:20:37.630 Microvascular phone by or not,
NOTE Confidence: 0.91236799955368
00:20:37.630 --> 00:20:40.045 but I’m not aware of a lot
NOTE Confidence: 0.91236799955368
00:20:40.045 --> 00:20:41.889 of other viruses that are.
NOTE Confidence: 0.86891633272171
00:20:43.320 --> 00:20:45.966 And then another question do that?
NOTE Confidence: 0.86891633272171
00:20:45.970 --> 00:20:48.090 Does the Coagulopathy correlate
NOTE Confidence: 0.86891633272171
00:20:48.090 --> 00:20:51.180 with the static on storm? Yeah,
NOTE Confidence: 0.876762747764587
00:20:51.180 --> 00:20:53.826 so that’s a great question Stewart.
NOTE Confidence: 0.876762747764587
00:20:53.830 --> 00:20:56.338 So one of the interesting experiments
NOTE Confidence: 0.876762747764587
00:20:56.338 --> 00:20:58.836 that that Young Chun started to
NOTE Confidence: 0.876762747764587
00:20:58.836 --> 00:21:01.461 do with our patient samples is to
NOTE Confidence: 0.876762747764587
00:21:01.461 --> 00:21:03.999 examine different proteomic profiles,
NOTE Confidence: 0.876762747764587
00:21:04.000 --> 00:21:06.210 and so we’re starting to
00:21:06.210 --> 00:21:08.420 get that data back now,
NOTE Confidence: 0.876762747764587
00:21:08.420 --> 00:21:11.507 and the hope is to see mechanistically,
NOTE Confidence: 0.876762747764587
00:21:11.510 --> 00:21:14.582 if any of the changes inside a current
NOTE Confidence: 0.876762747764587
00:21:14.582 --> 00:21:17.645 profiles that that are shown do correlate
NOTE Confidence: 0.876762747764587
00:21:17.645 --> 00:21:20.830 with robotic risk or endothelial dysfunction.
NOTE Confidence: 0.876762747764587
00:21:20.830 --> 00:21:23.196 One of the challenges we have in
NOTE Confidence: 0.876762747764587
00:21:23.196 --> 00:21:25.097 trying to interpret our data fully
NOTE Confidence: 0.876762747764587
00:21:25.097 --> 00:21:27.400 is that as most of you guys know,
NOTE Confidence: 0.876762747764587
00:21:27.400 --> 00:21:29.290 pretty much every critically ill patient
NOTE Confidence: 0.876762747764587
00:21:29.290 --> 00:21:31.216 in the hospital with kovid receives
NOTE Confidence: 0.876762747764587
00:21:31.216 --> 00:21:33.344 totalism AB before they reach the ICU,
NOTE Confidence: 0.876762747764587
00:21:33.350 --> 00:21:35.534 which is an interleukin six receptor blocker,
NOTE Confidence: 0.876762747764587
00:21:35.540 --> 00:21:37.780 and so there may be some effects of
NOTE Confidence: 0.876762747764587
00:21:37.780 --> 00:21:39.763 Totalism app not only on Coagulopathy
NOTE Confidence: 0.876762747764587
00:21:39.763 --> 00:21:41.797 but also on the sideline profile,
and so we’re trying to figure out how to interpret that.

Another question for patients on a ventilator for other causes of a RDS, do they have elevated levels of one willebrand factor? Yeah, even that’s a fantastic question, and so the answer is yes, sort of, but not quite to the same level.

There’s a few other diseases that are known to have very bad end of Philly Opathy, one of them being severe DIC with septic shock and VOD or SOS in transplant is another one. Um, and in fact a RDS is known
to also be characterized by NFL
dysfunction as somewhat of a control.
We separately worked with the ICU to measure von Willebrand factor levels in non-kovid ICU patients who are into baited and in those patients we did see elevated von Willebrand levels, but we did not see a consistently super high level of unrelated factor like we do in code and so we do think there’s some specificity to this particular Cove in response.

Makes sense since the last question from Stuart is you compared ICU versus non ICU versus controls?
What about these values in comparing patients with thrombotic complications?

For those without cloths,

You know, one of the challenges that we have at our hospital, and this is not unique to us, is that because of concerns about excess health care worker exposure, it’s not been routine for covert patients at Yale. New Haven Hospital to get imaging to confirm thrombosis. If you guys recall in the Cove anticoagulation algorithm, we said anybody.
Any patient in whom one suspects a Venous Roman Bolic event should automatically start photos anticoagulation. The reason we added that in there is because most patients are not getting imaging to tell whether they really have a Venous thromboembolic event. Therefore we don’t really have a good idea of how many patients in our own hospital system and which ones actually have a thrombotic complication and which ones don’t, so I can’t answer that based on our data.