[MUSIC PLAYING]

ROY E. SMITH: So this is the objectives of the talk, and you can just read those on your own. I have a lot of slides so I want to go through this fairly rapidly.

So the talk is going to primarily be based upon the DOACs that are clinically available at the present time. There are several that are pending approval yet. However, these are the ones that we commonly use.

As you know, the DOACs have been approved by the FDA for various disorders. The latest one, the trixaban, has been approved for prophylactic use. The other ones have been approved for various settings in post-operative patients as well as in patients who have acute VTE, or with non-valvular. Atrial fibrillation.

It's important to understand how these things work. The anti Xa inhibitors obviously are inhibitors to the activity of factor Xa. The oral direct thrombin inhibitors directly inhibit thrombin.

And all of these things have some sort of antidote or reversal agent which are presently available for the direct thrombin inhibitors. The agent that's primarily available is Idarucizumab or Praxbind. And for the Xa inhibitors, the latest one is Andexxa, as you know. It's made a lot of press recently.

There's also some standard things that been around for a long time, and that's FEIBA, or the 4-factor PCCs, or even activated Factor VII. And there's a lot of experience with these at this point. And whether they're going to be replaced by the new reversal agents is unknown at this present time.

The evidence for the use of the DOACs in the presence of non atrial fibrillation, non-valvular atrial fibrillation, is based upon these studies as indicated here. I'm not going to go through them in detail because they have all been in the literature in the package inserts.

But the point I want to make with this slide is that there's thousands of people that have been treated with these things. However, the indications for each of these studies is slightly different. The definition of non-valvular atrial fibrillation varied from one study to another. The frequency of patients who have a lupus anticoagulant or underlying malignancy varies with one study to another. And whether those malignancies were active or are simply reported as being present at some point in the patient's history is largely unknown.

And that number of people that have malignancies associated with these studies ranged from somewhere between 7% to 21%. So it's almost impossible to compare these studies one to another, and they probably will never be done. Therefore, when we talk about the comparison between the DOACs that are presently available to us in a clinical setting, a lot of people seem to quibble an awful lot about which is superior to which. But the reality of the matter is they don't know, and neither do I.

But what we do know is that it does appear that in the setting of atrial fibrillation, that the DOACs are safer to use than Warfarin. And we do know that perhaps there's a slight advantage in terms of whether these people have systemic emboli or stroke above that of Warfarin. But exactly how great that advantage is and whether it actually exists as a class is largely unknown, and probably will not be known anytime soon.

If we look at the forest plots of the DOACs compared to Warfarin, and the advantages and disadvantages as you can see, that there are some indications that the DOACs may be slightly better. But there's a large overlap between that and Warfarin, which makes it impossible to ascertain. So the major signal for the use of the DOACs in this day and age is really a safety signal. It's not a therapeutics signal, it's a safety signal.

And therefore, when trying to decide whether a patient is a candidate for a DOAC, one of the things you have to consider is what risk factors that patient may have for bleeding with these particular drugs. And that's based upon age, liver function, renal impairment, any history of GI bleeding or bleeding at other sites, as well as concurrent medications.

This plot shows you what the risk is in terms of-- what the efficacy is in terms of the patient based upon age. On the right side, there's-- I'm sorry, on the left side, there's people of the general population. On the right side, it's indicated individuals that are over the age of 75.

And as you can see, if you compare the different products that are indicated there, which are-- there does not appear to be any really significant difference between any of them. So again, the choice of the DOAC that you choose, I think is not really based upon what you think the efficacy is. It's based upon how you think the patient may tolerate that particular drug.

If you look at the efficacy again, very little difference, if any. What's been indicated so far is not based upon any particular clinical trial, but simply based upon comparisons. Is that it Apixaban may be slightly better, in terms of lower risk of bleeding. And it may have more-- may be more tolerable. Although it's given twice a day, adherence studies that have been done indicate that adherence to Apixaban is probably slightly better than to other DOACs that have been investigated.

It's important to point out that adherence to DOACs is highly variable, that that adherence may be as high as 80% or as low as 40%, depending on which literature you read. And of individuals that are placed on DOAC for non-valvular atrial fibrillation, clearly 40% of them revert back to Warfarin therapy at some point during their disease, for various reasons, including cost, and also fear of lack of access to a reasonable antidote in case of bleeding.

This is a slight review of patients who are treated with DOACs compared to low molec weight heparin, followed by VKAs in people that have VTEs. Again, I'm not going to go through all this stuff. But just to indicate, there's just thousands of people that have been treated with this stuff.

And again, in this sort of a setting, there is absolutely no signal at all that a DOAC is superior to Warfarin or to a low molec weight heparin for the treatment of patients, other than a safety signal. And if you look at a forest plot of the value of these drugs that we indicated here, if you look at the total DOACs are indicated, there's no indication of a clear advantage in terms of therapeutic uses for it. But there is a safety signal.

If you look at the individual DOACs the best that you can, based upon meta analyses, what you'll see is that there does seem to be, again, a slight advantage for Apixaban for both efficacy and safety. Although again, this is a meta analysis, and it's really based upon how well the original studies were done. And I point out again that virtually none of these studies have patients in them that are absolutely comparable. So even with a meta analysis of this type, the information that we have is relatively weak, with the exception of the safety analysis, which seems to be quite clear.

This is another way of looking at the same data in this particular meta analysis that was done by Cohen. It indicates that if you compare clinical relative non-major bleeding with its efficacy, that again, it would appear that Apixaban maybe have some slight advantage. Whether this is true or not, I haven't the slightest idea at this point. But it certainly seems that way.

So what we can say is DOACs are similar in efficiency with regard to prevention of recurrence of VTE or VTE related events. Apixaban seems to be the most desirable based upon the side effect profile. And it seems to be advantageous when compared to rivaroxaban and [INAUDIBLE], with a 50% to 30% decrease in significant bleeding.

If you look at patients who have hip and total knee replacements, there's been an entire series of trials that have been done looking at this, comparing them with enoxaparin, which many institutions is standard of prophylactic, standard for people that have these surgical procedures done. What we see is that-- let me get this to move-- is again that when you look at the value of these drugs, there seems to be some favorability for DOACs for the prevention of recurrent disease. And also, there seems to be a side effect profile which seems to be also advantageous.

Again, same limitations. Every one of these studies has different eligibility criteria for them. And therefore, they are not totally comparable. Which is again, a major limitation in this setting.

This is a study that we did here at the University of Pittsburgh for-- a retrospective study looking at 17,000 patients that had hip and knee replacements. In which we made an estimate of which therapy would be superior in terms of both cost as well as prevention of clot formation that can be detected by a Doppler examination. And what can be seen in this particular slide is that what we determined was that in the hip and knee replacement setting, aspirin as well as rivaroxaban seemed to be equally effective. And obviously, aspirin was more cost effective. As opposed to the other alternatives that were used at the time.

There is no data there about Edoxaban because at the time we did this study, there wasn't enough information to apply to the study. But this is supportive of what's now appearing in the literature. That in people they have hip and knee replacements, aspirin seems to be pretty effective. And so also do the DOACs that are used. Now obviously, in a post-operative setting the, DOACs will have a slightly higher bleeding risk, which is indeed what's been seen in the literature.

If you look at people in terms of who have had BTE and the opportunity to reduce the risk of recurrence, what you see based upon the following studies. Which include Apixaban, rivaroxaban, Dabigatran, as well as Edoxaban, is that DOACs appear to be effective in risk reduction. They obviously cause more bleeding than if you were treated with a placebo alone. And in this setting, rivaroxaban seems to be better than aspirin.

There is some literature out there looking at medical patients in terms of using aspirin for prevention of disease. And something I don't highly recommend. We use on occasion when people refuse to use anticoagulation. But very, very clearly, a DOAC is far more effective than aspirin use in that setting.

What's very interesting though is that when you take a look at the overall bleeding risk, that the bleeding risk with aspirin appears to be identical to that of rivaroxaban. And although these sites of bleeding may be slightly different, because rivaroxaban tends to predispose people to GI bleeding as well as Dabigatran.

If we look again at a plot of clinically significant bleeding versus efficacy, we can see again that it would appear that in this sort of a setting that Apixaban, a dose at 2.5 or 5 twice a day, appears to be the treatment of choice. Again, limitations in terms of comparability between populations that were studied in each of these studies.

If we look at the EPCAT trial, which was a study of patients who had hip and knee replacements with an extended therapy with either aspirin or with a DOAC, what we see is that there's no significant difference in terms of rate of symptomatic VTEs. And that the primary outcome of major bleeding or clinical significant bleeding were slightly worse for the DOAC than aspirin.

And so there is a reasonable debate right now in the medical literature in the post-operative setting for these orthopedic patients, what the best prophylactic therapy is. Whether it's just simply aspirin alone or whether it's a DOACs. I want to point out to you that probably the best therapy is just simply ambulation. And these various results that we get in which patients are treated with therapy that you would expect be relatively ineffective but shows great efficacy, is probably related to other factors other than those medications themselves. And most likely, the other factor would be ambulation itself.

When we've back and reviewed the rapidity of ambulation on our own hip and knee replacement patients, what we found was that the overwhelming number of patients were ambulated easily within the first 24, 48 hours after the procedure. And that probably is a major thing that makes the difference in terms of whether that patient has a long or short-term risk of a post-operative DVT in that setting. This is in contrast to medical patients who are in the hospital or relatively non-ambulatory for large periods of time because they feel sick and ill, in which they have a higher risk for developing a DVt, just simply because of relative immobilization.

This study is the APEX study, which is a study that was done to approve betrixaban. And what they were able to show in these high risk patients who were high risk for both bleeding as well as high risk for DVTs, that betrixabar therapy was able to reduce the risk of recurrence significantly, although there was some increase in major bleeding. So in this sort of a setting, it's important to understand that betrixaban has a very long half life. At the present time, there's no approved antidote for it. And the selection of patients have to be very careful because the population that was looked in this particular group of patients were people with very high D-dimers post when they were placed on the drug itself. And elevated D-dimers that are sustained after a DVT or after a procedure of some sort or after immobilization is a recognized risk factor for a thrombotic event at a later date.

The COMPASS trial has made a big splash just recently. This is a trial that was done looking at people that have coronary artery disease and [INAUDIBLE] vascular disease. And these patients were placed on aspirin and various doses of rivaroxaban. That trial indicated pretty clearly that low doses of rivaroxaban plus aspirin was effective in reducing the risk of stroke, coronary death, and loss of limb due to ischemia.

This is a game changing trial. And at this point, at least in my view, the treatment of choice for these individuals would be a combination of aspirin as well as rivaroxaban. Whether this applies to other DOACs is largely unknown. There are other trials that are looking at this right now that have not been reported as of yet.

If you look at people that have cancer, there's two trials that have been published. One is the Hokusai VTE trial for cancer. And in this study, they compared edoxaban with dalteparin. Dalteparin is a low molec weight heparin of choice for people who have malignancy, although nobody uses it. Everybody uses Lovenox. However, in this comparative trial, it was demonstrated that therapy with edoxaban was far superior to that of treatment with dalteparin. This is another game changer for those people that are candidates for this.

It's important to point out in this particular trial that there was a high risk of bleeding in those patients who had intraluminal disease. So it's relatively contraindicated, at least in my view, in people that have gastrointestinal tumors or any other sort of tumor that involves a visceral organ in which the lumen is involved. If you exclude those patients that have intraluminal disease, the bleeding risk is almost nil in this group of patients.

There is a SELECT-D trial that was done in Europe looking at rivaroxaban again compared to dalteparin. The design is almost identical to the Hokusai trial. And in this particular trial, rivaroxaban was superior to dalteparin in terms of efficacy. Obviously, there was more bleeding on those people that were getting rivaroxaban.

In this particular trial, with or without intraluminal disease, people had an increased risk of GI bleeding, about 30% or so. Of course, it depends on how you interpret the data. But about 30% or so people who are on rivaroxaban developed some sort of GI bleed. So there is a signal there that there are certain DOACs that might not be indicated in people that have a predisposition to GI bleeding for various reasons. One of them is obviously rivaroxaban. And the other one would be Dabigatran.

Dabigatran, very early on in the very early trials, was shown to cause GI upset because the drug itself is very poorly absorbed. It's coated with an acid product that decreases the pH in the GI tract, but also irritates the GI tract. And therefore, people have a predisposition to GI bleeding. So in that sort of a setting, you might want to be careful if you're using either rivaroxaban or Dabigatran.

There's also a couple of trials that have been done looking at DOACs as a preventative agent in people that have not had malignant DVT yet, but have a disease that has a high risk of it. For example, ovarian cancer or perhaps pancreatic cancer. And in these two trials, the AVERT as well as the CASSINI trial, looking at Apixaban and rivaroxaban, it it does appear that these drugs are at least as effective as the alternative that they were compared with. And also that they have a slightly increased risk of bleeding.

The interesting thing about the AVERT and the CASSINI trial is that although these trials also included people that had intraluminal malignancies, that there was no signal that these people had an excess amount of bleeding. So at the moment, it's open to question whether intraluminal disease predisposes people to bleeding or not with DOACs. As a matter of safety, however, it would be recommended that they not be used in that setting. At least not rivaroxaban or Dabigatran.

If you look at people that have GI bleeding and what the frequency is with the different trials-- I can't really see this slide right here-- but the whole point of this is that when you look at the frequency of GI bleeding, it seems to be that there is no difference with Apixaban, but there are disadvantages with the other DOACs that are available. So as I go these different comparison, it appears that Apixaban as sort of emerging in these non-comparative settings as perhaps being advantageous. Whether that's true or not, I don't really have the slightest idea. And neither does anybody else, despite what they might tell you.

If you look at that at the DOACs, there are differences in how they act. They're not all the same. They have different mechanisms of action-- not mechanisms of action, but they have different biochemical alterations that occur in the body when you take them. If you look at Dabigatran as an example, it has a very poor bio availability. And therefore, the ranges of the concentrations are very, very wide.

And there's a lot of inter-patient variability as well intra-patient variability. This is one of the difficulties with this drug. And it's also one of the difficulties with trying to figure out how you would monitor the drug, even if you wanted to do it. Because no one knows what the therapeutic range really is. All we know is what the expected range is, and it's very, very wide.

Also, the other thing with dabigatran is that it's highly dependent upon renal clearance, as you might expect. And also, it has a relatively poor protein binding. So what that means is that this drug is dependent upon, more dependent upon renal function than others. And also because it has poor protein binding, in a setting if a person has Dabigatran toxicity, one of the treatments that are available would be to dialyze the patient. Now that's not the ideal therapy, but nevertheless, it's something that's available.

If you look at Apixaban, what happens here is that Apixaban has a decreased renal clearance. And therefore, it very well may be, if a DOAC is-- for some reason [INAUDIBLE] DOAC and a person that's on hemodialysis or has renal failure, apixaban would be probably the treatment of choice in that setting just simply because the renal dependence is less. And there are clinical trials that I'll try to go to if I get to them, indicating Apixaban is probably safe in that setting.

The other thing is edoxaban, which is a drug I don't have a lot of experience with. But the problem with edoxaban is if you have very, very good renal function, that edoxaban concentrations actually decrease over time, and they seem to be less effective. So it's counter intuitive that if you have really good renal function that a drug's going to be less effective, but in this setting it is. And so you have to be very careful about that and aware of that if you're going to use that particular drug.

These drugs have different actions on the coagulation system. So we think of them as being factor Xa inhibitors, but they also affect other things in the coagulation system. And that's what this slide is supposed to show you. If you look at the pro time, PTT, the R time or the TEG, thrombin generation, they vary from one drug to another. So the idea that these drugs are completely interchangeable, it may be true. But there's a signal here that it may not be true. And I think we have to be very careful that because these drugs, although they've been around for 10 years, we're still pretty early in how we use-- determining how we use these drugs and what the best drug for each situation may be.

And as an example, when a person is placed on a DOAC, if we measure anti-Xa levels in people that have devices in place, the ante-Xa are highly variable. So there are certain settings, if you're going to try to monitor these patients or at least look at what the expected ranges are for the anti-Xa levels on these particular drugs, it's very difficult to interpret them or even have the slightest idea what they mean.

How you can detect these drugs, the activity of these drugs, as you can see, dabigatran is the antithrombin inhibitor. And therefore, you expect the thrombin time to be markedly prolonged. In fact, it's usually infinitely prolonged because thrombin time is extremely sensitive.

If you look at the pro time, PTT, they tend to be more affected by the anti-Xa inhibitors. In particular, the pro time is. But the amount of the effect on the common things that you measure in terms of the pro time, PTT, or other coagulation factors is variable between each of the drugs, and is variable based upon the dose, as well as just the drug itself.

So, again indication that these drugs are not identical, and you have to be somewhat selective in terms of how are you going to use them. And I think that selectivity is going to develop further and further as time goes by, as more information becomes available.

This is a plot of what happens if you have a person on a DOAC as compared to Warfarin. And as you can see, if you take a DOAC, they generally reach a maximum concentration in the blood in somewhere between two and four hours. And they're gone generally within 26 or 30 hours or so. Their half lives tend to be all about the same, except for betrixaban, somewhere between 12 and 17 hours.

So you get this peak effect, and then you get a rapid drop. And in general for all the DOACs, the expected range for your peak level would be somewhere between 150 and 250 nanograms per milliliter. And your expected trough would be something less than 50. That's of some importance because when you look at the bleeding risks to the extent that you can look at them, it looks like if you're trough level is below 50, then you're out of the woods in terms of a risk of bleeding from these particular drugs. That's of some importance.

Now likewise, if you take people that are on DOACs and you treat them with heparin at the same time for some reason-- and we've seen this on occasion. People are on DOACs someplace else. They get referred here or they're switched over to heparin to be sure that they're properly anticoagulated. What you see on the far left is the anti-Xa levels of people that are exposed to a DOAC as well as to heparin.

And what you can see is with the heparin exposure, the anti-Xa levels climb. This is artifactual increase in anti-Xa. And it will result in, especially if you're using one of these algorithms to adjust heparin doses, that it will result in a decrease in the heparin dosage you give a person because the nurse is going to readjust the dose based upon the algorithm.

So that's something. It's very important to keep in mind because you cannot use the anti-Xa levels in the setting of a mixture of these particular drugs with either low molec weight heparin or unfractionated heparin. But particularly with unfractionated heparin.

If we look at this next slide, this is a real world slide of looking at those people that are within a super therapeutic range. On the left side, on your left side, is a plot of those percentage of people that have anti-Xa levels within a super therapeutic range. And on the other side are people that are exposed to DOACs and heparin.

And as you can see, the number of people that are super therapeutic just simply explodes. So this is a real practical issue that we have to think about very, very carefully. And you should be aware of as you treat patients.

So what about in obese patients? Well, there's a lot of obese patients the United States. And it's estimated there's about 500,000 at any one time that require anticoagulation for various reasons. And this always is a debate about what you do in this setting.

There have been studies that have been done looking at the effect of DOACs on people that have so-called severe obesity Class 3. That is to say, a BMI greater than 40 or a weight greater than 120 kilos or 140 kilos. And what you can see here is that when you look at the efficacy of these drugs in the setting of atrial fibrillation and VTE, obesity has no effect.

If you look at real world experiences with registry studies done in Europe, again-- I'll just go through these very rapidly because they all say the same thing-- and that is in terms of efficacy and toxicity, there doesn't appear to be any significant difference from those people that are severely obese and those people that are not severely obese. With perhaps the slight exception of an increased risk of minor bleeding.

So the reason I'm bringing this up is because there is presently in the medical literature, recommendations from the American Society of Hematology as well as the International Society of Hemostasis and Thrombosis, strongly recommending that people that are severely obese not receive DOACs. And what's emerging-- those recommendations were given 2016-- what's emerging is that this is untrue. That DOACs are probably totally safe in people that are massively obese.

If you look at people that have a history of GI bleeding, again, what you'll see here is the incidence seems to increase with specific DOACs. But there seems to be an advantage, again with Apixaban. What about heparin induced thrombocytopenia? Well there's a whole series of patients who have been treated with DOACs, particularly rivaroxaban.

And in the setting of people that have stable disease, that is without progression and thrombosis or whose platelet count has recovered, it looks like rivaroxaban is as effective as putting people on argatroban. And I think this is presently a conditional recommendation, the American Society of Hematology, that DOACs be considered in this setting.

It will save a lot of money and a lot of hospital time. Because at this point, it looks like people with uncomplicated HIT could probably be treated largely as outpatients. That's a major change in therapeutic modality. So there's the recommendations. as they presently exist in 2019.

If we look at people in renal impairment, as you can see, renal elimination varies based upon the DOAC that's used. There's a lot of hesitation about using DOACs in people on hemodialysis or peritoneal dialysis or with renal impairment, as there is with low molec weight heparin. But I tell you right now that these are drugs that are safe to use in these settings if you know what you're doing. People have to be monitored for these drugs very, very carefully.

If you were going to choose a drug, then one of the drugs that you would choose is based upon this beta as shown in this forest plot, would Apixaban. And the dose Apixaban would be 5 milligrams PID. It seems to be highly effective. There doesn't seem to be a major increased risk of bleeding. And it seems to me to be efficacious.

Another look at Apixaban in terms of the risk of bleeding and efficacy in people that have atrial fibrillation, as you can see, it seems to be efficacious as Warfarin. And these are just recommendations of how you use the drug.

So what about with APLS, antiphospholipid syndrome? There's been one study that's been published looking at rivaroxaban in patients who are triple positive. That is to say they have evidence of a lupus anticoagulant, they have beta-2 glycoproteins antibodies, then you have anticardiolipin antibodies, and comparing them with the standard therapy, which is Warfarin. And what you can see is the risk of thrombosis is 19% on Warfarin and it's-- I'm sorry, 19% on rivaroxaban and 3% on Warfarin.

So at this point in time, I think all the DOACs are probably strongly relatively contraindicated in the presence of a lupus anticoagulant, until it can be proven that you can stratify patients based upon the severity of their disease, and which DOAC may be effective.

There's also a trial presently under way, which UPMC is participating in, called the ASTRO-APS trial looking at Apixaban in a similar setting of people with lupus anticoagulants. That won't be done for probably another two years. At that point, we'll probably have a better idea whether DOACs are effective. But right now, the treatment of choice would be Warfarin.

What about non-valvular atrial fibrillation? The definition is changing as time goes by. The RE-ALIGN trial was a trial looking at dabigatran in the setting of people that had mechanical heart valves. And the trial was a failure due to increased bleeding and lack of efficacy.

However, if you look at those trials that have been done in the past, for which the justification for approval of DOACs had been made, what you'll see if you compare them is that the definition of non-valvular atrial fibrillation changed from one trial to another. Some of them included people with severe mitral stenosis, some did not. Some included people with bioprosthetic valves, some did not. Some included people with more moderate valvular heart disease than others. So you can't really compare them with each other based upon that.

But the one thing that was common for all of them is based upon the fear that someone had valve disease that was severe enough that they would require a surgical intervention during the course of the trial, or who had mechanical heart valves in which it would have been probably unethical to withdraw therapy, to put them on a trial where they might get a therapy that you don't know is effective. These things were excluded.

And so when you now look at the present definition of non-valvular heart disease in 2019-- let met get to that here-- atrial fibrillation is really based upon the presence of the moderate to severe mitral stenosis or mechanical heart valves. And if those things are not present, then it's no longer considered to be valvular heart disease. It's non-valvular heart disease.

So what that means is that it's perfectly safe and acceptable to take patients who have mitral regurg, mitral prolapse, who has aortic stenosis, and who have non severe mitral stenosis, and who have bioprosthetic heart valves. To treat these people with DOACs. It's quite safe to do that and they're highly effective in that setting. And that's a different recommendation than has been published in the recent past. So the therapy is changing in this setting.

What about periopterative use for DOACs? I get these calls at least three times a week from various people about the abridged therapy, how long you have to wait before-- you have to stop before you do a colonoscopy or some other surgical procedure of some sort. The PAUSE trial was published just recently by James Douketis.

And what they did is they looked at people that had renal function with creatinine clearance of 30 cc's or greater. And in the setting of patients with dabigatran, they used a cutoff of around 50 cc's per centimeter. And they looked at what the risk of thrombosis and bleeding was in that setting. And they also looked to see when it was safe to restart anticoagulation after a procedure was completed.

What they were able to show-- this is the design of the study. There's a lot of patients, as you can see. And what they were able to show was the following thing. And that is that the risk of major bleeding was less than 1%. That the risk of some sort of thrombotic event, in this case primary arterial, because there were no venous events that took place at all, was very, very small. Again, less than 1%. These are perfectly acceptable risks.

And that if you measured the trough levels of your anticoagulant, greater than 90% of the time they were at a level that would essentially be considered be non-detectable, that is less than 15 nanograms per milliliter. I'm not done. And that nobody required bridging.

So this makes it easy. So if you have somebody that has a procedure that is of a low bleeding risk, then all you have to do is hold your Xa inhibitor for 24 hours before and restart it 24 hours after. And if you have a high bleeding risk, you do it for two days before and two days after. It's pretty easy. You don't have to think a whole lot about it. With Dabigatran, it's slightly different.

At any rate, I am going to go over this just for a second. And this is the reversal agents. As you know, the reversal agents that are presently available would be idarucizumab or Praxbind, in which treatment with Praxbind reduces your anticoagulant activity by easily 95% or so within minutes of receiving the drug. Likewise, available is this anti Andexanet, is a factor Xa decoy. And in this sort of a setting, your levels dropped to greater than 80% or 90% literally within 20 minutes of giving the drug.

The data that's been published that is highly effective for controlling bleeding both intracerebrally as well as peripherally, and that it's perfectly safe. That there does not seem to be a signal for recurrent thrombosis, at least not immediately. And the other alternatives would be the 4-factor PCCs that tend to overwhelm the system with increased thrombin production.

If you try to compare the efficacy of them, which no one has ever done in a clinically controlled trial, the data's right here. And that is that they all seem to be relatively equally efficacious. The difference is the cost. Because to treat a person with Andexanet, as an example, will cost four to five times as much as if you treat it with a factor Xa inhibitor. So that's the end of this discussion.