Laboratory Monitoring of Anticoagulant Therapy

As Laura has mentioned to you, I come by my training honestly. I was a medical technologist long before I got lost in my ways as physician in medicine, and I really think I have a true appreciation for what goes on in the laboratory, the issues in the laboratory, and as we heard from our most recent speaker, what the lab does and doesn’t do for the clinician.

And in that context, I hope today to reassure all of you that you all have a job even in the coag lab for a long time to come. You see there’s a lot of new anticoagulants out there. I’m going to talk about some of them.

Some you’ve heard of, most I bet you have, and why I think the lab is still going to be intimately involved in the treatment of these, using anticoagulants even though the professional physician has been shown the glossy photo that says, guess what doc, and you don’t have to monitor it, because that’s simply untrue in many settings.

And we’re going to talk about why that is today. And by way of making that point, gander at this, and raise your hand if you think you know what this is. I’m going to tell you about new drugs, new trade names, okay, in truth the issues are still the same old ones that you should recognize.
You just have to look at it in the proper perspective, and that’s what I hope to give to you today as a clinician, but as a person whose roots are in the laboratory, to show you why you’re still going to make a big difference in the coag lab even with new agents.

Title: Goals of presentation

1. Review new anticoagulant agents and their clinical uses
2. Review laboratory concerns regarding these new anticoagulants

So what I hope to do today for you is to review the new agents and their clinical uses and then to review the laboratory concerns. Now I’m going to go through, a lot of slides are there for your reference in part because previous participants have asked for them, but it’s really because for two reasons you’re going to care about what these drugs are used for.

And how it is that they’re working out clinically. One is because as a person who works in the lab, you’re going to wonder why in the heck the patient was getting this in the first place.

And the second reason is because you, your grandma, your brother, your nephew, someone that you know is going to get exposed to these agents at some point in their life. And you might be the only medically trained person in the family to whom everyone else turns when they have a question about a new agent or new treatment. So on a couple of levels, I hope to keep you engaged in the after-lunch hour.
NEW ANTICOAGULANTS

Heparin/Heparinoids
~ LMWHs (enoxaparin, dalteparin, tinzaparin)
~ Danaparoid
~ Fondaparinux
~ Idraparinux*

Direct thrombin inhibitors
~ Lepirudin
~ Argatroban
~ Bivalirudin *not yet FDA-approved
~ Ximelagatran*

The drugs that we’re going to review today, although fortunately Jay has done a lot of work with the heparin, is low molecular weight heparins.

As you’ve heard, there are three commercially available preparations, a drug called danaparoid, I figure I’m up in Detroit, near Canada, where danaparoid is still available, so I’ll touch on that; fondaparinux; and idraparinux.

And then a class of drugs called direct thrombin inhibitors of which there are three currently used in North America, certainly in the United States, lepirudin, argatroban, and bivalirudin, and then I’m going to spend a little bit of time talking about the new Coumadin.

And for those of you who make a part of your shift running PT and INRs, don’t panic. It’s not coming very soon. The FDA recently turned it down, and secondly it’s going to have a relatively limited clientele and we’ll talk about that.

Title: Drawing

So don’t get too comfortable, don’t think you’re going to have to find a new specialty in your laboratory. New agents are not going to obviate the need for a coagulation laboratory.
But if all those glossies say you don’t have to monitor it, why should you care? Well, firstly even if you aren’t measuring the coagulation test to see what the drug’s doing, it’s going to mess up potentially other tests that you’re doing in the world of coagulation.

Secondly, and you know it’s true because I’ve been there in the lab myself, the doc calls and says, the patient’s bleeding, I don’t understand, I gave him the dose the glossy said, what’s the problem, do they have too much drug on board, or the patient isn’t bleeding, they’re clotting, I gave the right dose, how come they’re still clotting.

And then finally, okay I have to do an emergency operation. You, a lab tech, are going to tell me when it’s safe to do so because you’re going to tell me when the drug is gone or no longer present. Even though the doc has been told you can’t or shouldn’t be monitoring.

So you know those situations do come. And then finally there are a-priori populations as we’ve heard talked about a little bit this morning, where you need to know, given extremes of weight, renal function or certainly in pregnancy and children, how drugs need to be dosed.

This is all very much a work in progress, however, and so I’m going to show you information that’s available. I’m going to perhaps in your mind raise as many questions as I am providing the answers.
And to give you a context for those questions, there are three cases we’ll talk about. This is a 46-year-old man with a deep venous thrombosis. He has a low platelet count on the fifth day of his heparin therapy, and the physicians are concerned about a heparin reaction called heparin-induced thrombocytopenia. So they switch to the drug argatroban.

The PTT is 55 seconds, and we’ll go through about the monitoring for argatroban. Two days into therapy on the argatroban, the guy crashes. He goes into shock, he’s got clotting everywhere in his intestine, and he needs to have that dead gut removed.

Now when they do a PTT though it’s 120, even though they’ve held the argatroban for a long time, the INR’s really high, and the platelet count is 85,000, and yeah, the surgeon’s calling you because you answered the phone and wants to know can he operate and why can’t he make these blood tests better.

The second case we’ll touch upon is a 76-year-old man with atrial fibrillation who, what’s he doing on the roof I don’t know, but he fell off the ladder and he hit his head. He’s in the ER; the neurosurgeon wants to drain his subdural hematoma, and he wants to know if it’s safe to proceed or does he have to give Factor VIIa concentrate (Novoseven), with a potential total cost of $60,000.

The patient took his last dose of ximelagatran 4 hours ago.

Why does he care, why is he asking, because he’s on this stuff called ximelagatran or something like that, he says, and he needs to know, it’s the new Coumadin.
Does he have to do anything about it? Can he operate? What’s the deal? And of course you’re the one answering the phone, so you get stuck with the question.

**Title: 85 year old woman comes in with GI bleeding**

**85 year old woman comes in with GI bleeding**

Started on LMWH 3 days ago for DVT, last dose given 4 hours ago

Physician gave FFP and protamine sulfate and wants to know why is she still bleeding?

- aPTT – 113 sec
- PT/INR – 30 sec/2.98
- Platelet count – 85,000
- Creatinine – 1.3

Well let’s start with this case. An 85-year-old woman who comes in with a GI bleed, she’s got ulcer disease. She was started on low molecular weight heparin three days ago for her deep venous thrombosis. Her last dose was four hours ago, but she comes in passing blood. The doc gave her fresh frozen plasma, gave her protamine sulfate, and wants to know why can’t they stop the bleeding.

They sent you some labs, the PTT is 113 seconds, the INR is 2.98, the platelet count’s 85,000, and her creatinine is 1.3. Fix it, he wants you to fix it. He’s tried, it must be the labs, what we were talking about at lunch, if it’s going awry, it must be something wrong with the labs or the measurements. So let’s talk about for a moment, heparins and low molecular weight heparins.

**Title: Coagulation balance: Activators**

**Coagulation Balance: Activators**

Intrinsic system

Extrinsic system

You knew there had to be a cascade coming some time today right? You’d been spared so far.

Here’s the coagulation cascade, and heparins tend to work on most of the activated factors, and low molecular weight heparins tend to work here at the crux, where the extrinsic and intrinsic pathway come together with factor Xa, and then down the bottom part of the cascade with factor IIa or thrombin.
Heparins, as you’ve heard alluded to, are ground up in these days of mostly pork gut; it used to be cow lung, but now it’s pork gut, and you grind it up, put it in a big vat. You chemically prepare it, stir it around until long chains of sugars fall out. If these five sugars as represented here are present, that combine with antithrombin to make this series of sugars an anticoagulant.

When, cleverly named, unfractionated heparin, all fractions of these long chains of sugars are put in a vial remarkably clear and not cloudy, you end up with old-fashioned unfractionated heparin.

If you shorten those chains so there’s less extraneous sugars and more represented the right five sugars in a row, you have a shorter chain of sugar which cleverly weighs less, hence the term low molecular weight heparin, and then finally if you take just these five sugars, the business end of heparin, we call it pentasaccharide, which is the smallest form of heparin that still works as a heparin or an anticoagulant.

Now, pentasaccharide makes sense, fondaparinux which is its now generic name was created by its company, I don’t understand, I would’ve called it pentasaccharide myself, but fondaparinux is its generic name, and it’s got a cousin that we’ll talk about called idraparinux, but they all work principally the same way.

They basically work with the molecule antithrombin, they cause it to change shape and become Pacman. And as Pacman, they can take activated factors, those on the cascade principally with an A behind them because they’ve been activated, bind them and thus make them in, unable to propagate clot.
Low molecular heparin is shorter, weighs less, and it principally focuses on factor Xa, which I’ll remind you is in the middle part of the cascade although it does affect the bottom. So these two cruxes in the cascade is where low molecular weight heparin works through antithrombin, just like the old fashioned stuff, it’s just more focused on this part of the cascade.

Title: Coagulation balance: Activators - LMWH
So it’s created from unfractionated heparin but it’s still a heparin, still ground up pork gut. But it can be given as fixed doses and so called without monitoring based on weight alone, because it doesn’t have all those extraneous sugars that get it stuck to all the kinds of places it doesn’t need to go, it’s much more reliably delivered and can be given under the skin more reliably.

Title: Unique attributes of LMWH

1. **Doesn’t change the aPTT (much)**
   ~ increased aPTT may imply significant overdose or some other influence on the aPTT (e.g. aPL antibodies)

2. **Difficult to reverse with protamine**

3. **Renally cleared (CrCl>20-30 ml/min)**

It doesn’t change the PTT, at least not very much, and the important point about this is so if you have someone who’s on low molecular weight heparin, remember 85-year-old PTT 113, it shouldn’t be changed, because none of the aPTT classically affected factors are affected by low molecular weight heparin.

So if her PTT is really high, something else is badly wrong. It’s hard to blame the low molecular weight heparin.

So if you see someone, and the physician calls and says the PTT, they’re on low molecular weight heparin and the PTT is 80, how come, it’s probably not from the low molecular weight heparin unless they have a significant overdose or something else is changing the PTT.

The unfractionated heparin that was hung at the bedside because the nurse didn’t know the patient was also getting low molecular weight heparin or the lupus anticoagulant is present. But the key is to recognize that the PTT shouldn’t change even on therapeutic doses of low molecular weight heparin, at least not much.
The second thing is low molecular weight heparin is hard to reverse with protamine, so docs need to get it right, because it’s hard to get rid of once it’s on board and overdosed. And then finally it’s cleared by the kidneys, which is something heparin you don’t think about.

And now you’ve heard the discussion earlier, Jay had mentioned that heparin’s going to disappear in some of our lifetimes. I’m not sure. When your kidneys don’t work, neither do these drugs. Heparin is just fine, the old fashioned stuff, with renal failure. Low molecular weight heparin is dicey business at best. There’s a lot of people on dialysis in this country. So I don’t foresee that it’s going to totally go away.

Title: LMWH currently available in the U.S. - Enoxaparin (Lovenox)

LMWH currently available in the U.S.

Enoxaparin (Lovenox)

Common uses:
- Prevention of DVT/PE around surgery
- 30 mg s.q. BID or 40 mg s.q. q day
- Treatment of DVT/PE
- 1 mg/kg s.q. q 12 hrs
- Treatment of unstable angina
- 1 mg/kg s.q. q 12 hrs

There are three agents and I’ll just list them for your consideration, enoxaparin and Lovenox, they’re used in various doses daily or twice a day.

Title: LMWH currently available in the U.S. - Dalteparin (Fragmin)

LMWH currently available in the U.S.

Dalteparin (Fragmin)

Common uses:
- Prevention of DVT/PE
- 2500 or 5000 U s.q. q day
- Treatment of DVT/PE
- 200 U/kg s.q. q 24 hrs or 100 U/kg s.q. q 12 hrs
- Treatment of unstable angina
- 120 U/kg s.q. q 12 hrs

Dalteparin or Fragmin is used, and again there’s treatment doses, and then tinzaparin or Innohep and the approved usages in treatment of DVT and a therapeutic dose once a day. In our hospital, we use all three interchangeably. Other institutions tend to focus on low molecular weight heparin usage with enoxaparin or with Lovenox.
Low molecular weight heparins are cleared by the kidneys. So if your kidneys are on the edge, you might accumulate the drug. How do you know if you’re accumulating? You measure it. Monitoring I think is indicated if you’re going to roll the dice and try and use it in someone whose kidneys don’t work, to be sure that it’s not accumulating.

You’ve heard already the discussion about very big people, who knows where the stuff goes, especially if you injected out here, where their pannus is sitting, where their big body mass is sitting, and so seeing how much actually gets into the circulation and works can be very critical.

Sometimes it doesn’t work so great if you have very active cancer. You might, you know, peaks and troughs. And if you trough too low, the bottom value, the nadir value, the low-point falls below that therapeutic range of 0.5 to 1.2. Maybe you’ll clot then.

How do you know if that’s the problem? You measure it to see if you got too low. There’s all sorts of situations where monitoring can be important, and then finally it’s important to get it right because it’s hard to get rid of, once you do, if you get it wrong.
Recognizing that, as we did hear earlier today, there’s an increasing focus to focus against the clotting cascade. And danaparoid, fondaparinux and idraparinux, all were quite specifically at this juncture in the clotting cascade.

Danaparoid, which is available now only in Canada and North America, no longer in the US, is a heparinoid, so it’s got dermatan, chondroitin and heparan sulfate. It works just like a heparin, through antithrombin against factor X. It doesn’t change the PTT.
The PTT test is really meant to measure the intrinsic pathway, and part of this influence, and so it doesn’t change at all the PTT. So again if the PTT is high, and they’re on danaparoid, something else is wrong.

When it was used it was approved for orthopedic surgery prophylaxis, but often we were giving it to patients who had heparin reactions, you could infuse it, you could treat it with subcutaneously, but it’s disappeared from North America.
So with due respect to my Canadian colleagues, I’m not going to spend more time on it because the company that makes danaparoid also makes the pentasaccharide, and they’ve switched that to this market.

Called again puzzlingly fondaparinux, it’s the ultimate low molecular weight heparin, it’s just the five sugars you need, nothing else, no extras, made recombinantly, it’s purely against the factor Xa, doesn’t change the PTT, and again the glossy says, doctor don’t you worry, you don’t have to monitor it.

It’s cleared by the kidneys on the other hand, so if you gave it someone with dead kidneys, you in fact may have it on board for weeks or days to come, and you won’t know if it’s gone away unless you measure a level to see if it’s gone away.
It’s used and approved for orthopedic surgery, although soon it will become approved for treatment of DVT and clotting in the doses that you see here. Are docs going to use it? Maybe, gets into pharmacoeconomic discussion because if it’s better and you don’t have to monitor it, you must have to pay more for it; at least that’s what we’re led to believe, and these new agents are expensive.

However, when compared to low molecular weight heparin like enoxaparin, in these studies that have involved nearly 7,000 orthopedic cases, hands down fondaparinux was superior to the enoxaparin or Lovenox.

Now there’s lots of reasons, lots of discussion, I won’t go into it about how come, it was timing, study design, but the fact is it’s better, so if it’s cheaper, your practitioners may switch, or if it’s the same price but maybe a touch better, your practitioners may switch.

And now on, maybe orthopedic patients aren’t going to get a lot of Lovenox anymore, they’re going to get fondaparinux, which is by the way the trade name Arixtra.
Fondaparinux - Matisse clinical studies

Matisse Clinical Studies

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<th>DVT Study:</th>
<th>2205 pts, compared to enoxaparin BID</th>
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<td>VTE</td>
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<td>Enoxaparin</td>
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<td>Fondaparinux</td>
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<th>PE Study:</th>
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Treatment for DVT and PE were studied in the largest studies ever done. And this agent was at least as good as IV unfractionated heparin for treating a PE except it’s a shot once a day.

So just like with low molecular weight heparin, if you’re not already doing so, practitioners might switch to this fondaparinux or Arixtra, and it was comparable to the low molecular weight heparin, so if it’s cheaper at your institution, your institution may start using Arixtra or fondaparinux instead of enoxaparin.

New anticoagulants - Idraparinux

Idraparinux

- side groups of pentasaccharide altered to increase binding to antithrombin
- half-life of 7 days after single s.q. injection
- cleared renally (CrCl>20 ml/min)
- under study for treatment of VTE

Idraparinux is a kissing cousin. It’s chemically changed by sulfation on a couple of those five sugars. And what that does is it takes the shot that you take once from lasting only 24 hours to 7 days. You take your shot this Saturday, you need nothing more until next Saturday.

It lasts for seven days straight. That’s great if you’re well. It’s not so great if your appendix ruptures tomorrow, because now you have six more days of anticoagulation in full dose in your future, but you need your appendix out today.

So it’s got upsides and downsides, but there may come a time where they’re going to have a shot on board that they took last Saturday but when they come to the ER, the PTT’s going to be normal, remember it doesn’t change the PTT, and yet they’re bleeding, how come, the clinician’s going to puzzled.
And maybe it’s because they have idraparinux in their system. The PTT won’t show that, the INR won’t show that, and the patient may be unconscious and couldn’t tell them that that little puncture mark was from their shot of long-acting anticoagulant.

So it is under study, it may come to pass that people will take a shot of something once a, once a week, that doesn’t change any of the usual monitoring tests that providers are accustomed to. So can you monitor stuff?

**Title: Laboratory considerations - LMWH, danaparoid. (fondaparinux)**

![NEW ANTICOAGULANTS](image)

**Idraparinux**

~ side groups of pentasaccharide altered to increase binding to antithrombin

~ half-life of 7 days after single s.q. injection

~ cleared renally (CrCl>20 ml/min)

~ under study for treatment of VTE

Sure. We’ve talked some about heparin assay. And I’m not going to go into all of this, it was discussed this morning, other than to weigh in with my opinion. This slide, I would say, is a bit outdated.

I do believe at your institution, it would be important to be sure that your heparin curve for unfractionated heparin behaves the same as for whatever low molecular weight heparins you’re using at your institution. At our institution, we still use two separate curves, one for unfractionated and one for any of the three low molecular weight heparins the patient may be on.

Because when they did the work, the tinzaparin, the dalteparin, and the enoxaparin, low molecular weight heparin curves were close enough for clinical safety, although different enough in our system from the unfractionated heparin curve, that they run the two separate, and the clinician is asked to specify are you doing unfractionated heparin or low molecular weight heparin, but we no longer ask them to say which low molecular weight heparin they’re using, because we use all three at our institution.

There are some differences that may occur, but in our instrumentation with our reagents, it doesn’t seem to matter. Having said that, people are going to want to monitor it, or should want to monitor it, renal dysfunction, in pregnant patients, and for the obese patients.
The levels, we’ve heard much discussion. This is just old information; you’ve got much more current stuff from our previous speakers.

Title: Antedotes for reversal

ANTEDOTES FOR REVERSAL

LMWH
~ only partially reversed with protamine sulfate
~ unclear if reversal occurs in vivo
~ calculation of dose of protamine challenging
  with s.q. dosing of LMWH
~ anti-Xa level may not change after protamine

Danaparoid
Fondaparinux
Idraparinux

} No specific antedote
Can use Factor VIIa concentrate or activated prothrombin concentrates

The key is that these aren’t reversible, we don’t want to overdose them, and if you’re going to try and reverse some of these agents, you have to use those very expensive concentrates that I alluded to in some of the cases earlier. The other catch about this is the clinician often relies on the clinical laboratory to help he or she out.

You see, when they have a person who’s bleeding on unfractionated heparin, they give protamine sulfate. And you know what happens, the PTT goes from 72 to 35. The bleeding stops, the clinician’s done, and the lab confirms the correction. The antagonism of that agent.

When protamine sulfate is given to a person with low molecular weight heparin, the heparin level, which is what we talked about this morning as you’re measuring, may or may not change. So the doc will say, well I don’t get it, I gave protamine, but you tell me that heparin level’s still 1.0.

Well it might be that the protamine is biologically working in the body, but the assay won’t reflect the antagonism that’s occurring there, won’t show the benefit that the patient has. So the provider can’t titrate down. He can’t say, I’ll give a little protamine and check a level, little protamine and check a level.
And that option is lost with the use of low molecular weight heparin because there isn’t a change in the Xa level like there was in the PTT with the old fashioned stuff.

Title: LMWHs/Heparinoids

The final comment I have is just something that I learned only relatively recently, and that at peak, despite what I said about a very high PTT means something’s badly wrong in a low molecular weight heparin patient, that the PTT especially with tinzaparin more than dalteparin or enoxaparin can be elevated in patients at peak with the therapeutic dose, not a prophylactic dose but a therapeutic dose of low molecular weight heparin.

So I take with a grain of salt, someone whose PTT is up just a little bit, if I know they’ve had a dose of low molecular weight heparin in the last three to four hours, so there can be some of that.

Title: 85 year old woman comes in with GI bleeding - aPPT - 113 sec

So back to our 85-year-old lady, she has GI bleeding, she’s already gotten plasma, she’s gotten protamine, why is she still bleeding? Here’s her coag parameters.
Title: 85 year old woman comes in with GI bleeding - aPPT - 80 sec

85 year old woman comes in with GI bleeding

Started on LMWH 3 days ago for DVT, last dose given 4 hours ago

Physician gave FTP and protamine sulfate and wants to know why is she still bleeding?

aPTT – 80 sec
PT/INR – 30 sec/2.98
Platelet count – 85,000
Creatinine – 1.3

Anti-Xa level – 0.98 U/ml (after protamine)

Her heparin level’s 0.98 after protamine, does that mean the protamine didn’t work, he needs to give more? Not necessarily because there is no correlation. And unfortunately at this point, the best the laboratorian can say is look, the PTT has come down, that must show some benefit.

Anti-Xa level may not change, doctor, don’t be chasing that, you need to chase the person clinically and continue to correct what other parameters you can, for example such as the INR and to keep going clinically with what you can do because unfortunately, there’s a limitation as to what the lab can help with as far as adjustment.

The bottom-line is this lady turned out to weigh less than her age, and her effective creatinine clearance was nearly dialysis level and she’d accumulated drug even though given therapeutically, and she ultimately succumbed to this hemorrhage because of basically an overdose of low molecular weight heparin.

Title: 46 year old man with DVT, develops low platelet count on 5 day of LMWH therapy

46 year-old man with DVT, develops low platelet count on 5 day of LMWH therapy

Started on argatroban for probable HIT - aPTT = 55 seconds

Two days into therapy goes into shock with extensive clotting of liver and ischemic gut, needs surgery

aPTT = 120 sec (after holding argatroban for 8 hrs)
PT/INR = 45 sec/4.5
Platelet count 85,000

Let’s get on to this fellow, 46-year-old with DVT, as I said, developed HIT. PTT was 55 seconds on argatroban, 2 days into therapy goes into shock, with clot everywhere. PTT is 120 seconds after holding the argatroban for 8 hours, remember he’s in shock, he’s got DICs, he’s a mess, but the PTT is high, INI is, INR’s high, and the platelet count’s really high.
So argatroban, leech spit. The reason the leech can continue to feed, and let me tell you, I grew up in Minnesota, it was a good day in the lake when you waded and didn’t rip the leeches off from between your toes, leech spit is what hirudin is, and that’s the way the leech can continue to feed after it attaches.

Clever coagulationists that we are, we like leeches, bugs, ticks, and other things, we said there must be something valuable in that, and we found a way to purify the direct thrombin inhibitor in that saliva, and it’s an agent that directly binds to thrombin in the bottom part of the cascade to provide the anticoagulation.

**NEW ANTICOAGULANTS**

*Direct Thrombin Inhibitors*

~ agents that bind directly into the active site and or substrate recognition site of thrombin

~ binding to those sites may be reversible or irreversible
So here’s a thrombin molecule, has to attach to three different places to work as a clotting mechanism, the bottom part of the cascade. Lepirudin or leech spit works in two sites, here your log is now called by bivalirudin or Angiomax, which is approved for use in the cath lab by our cardiology colleagues, and then argatroban or PPACK you may be familiar with in terms of inhibiting thrombin in various coagulation assays as a monospecific site of inhibition here on thrombin.

And just as a reminder that’s all down here at the bottom part of the cascade. Now the drug, new Coumadin, ximelagatran or Exanta is also a direct thrombin inhibitor. It, as an oral tablet, is converted into a direct thrombin inhibitor called melagatran after digestion in the stomach.
So lepirudin or Refludan, it’s recombinant hirudin, it looks just like the leech spit except for one change, its dosing is recommended, and its goal aPTT for therapy is 1-1/2 to 2-1/2 times baseline. Now we just spent an hour this morning trying to sort out the vagaries of unfractionated heparin.

Can you use ratios, we shouldn’t, we should use actual drug levels, for decades we’ve been chasing people erroneously around with PTTs, here we have a brand new really expensive, really excellent, really potent anticoagulant that we’re light years behind the heparin mess as regards monitoring.

So all the studies did is wherever you are, wherever you live, make your PTT 1-1/2 to 2-1/2 times baseline when you do drug on this study, and we’ll see what happens.

It’s used as an alternative to heparin in HIT, and here’s what happened clinically. When you did that, when you chased people around, this is the people who got historical treatment, a bunch of them still went on to die or to clot or to actually have an amputation because of clotting up here, but down here is what happened when they got lepirudin.

Fewer of them did that when you gave an anticoagulant, monitored, I would put in quotes by doing aPTT ratios, at a fairly consistent group of folks and centers in Europe. So clinically, it got better when you did that.
Argatroban, done about the same time, a similar study, it’s the small synthetic molecule I showed you, this time we chased a PTT of 1-1/2 to 3 times baseline, whose lab didn’t matter, wherever you worked, whoever you saw, that’s whose aPTT they used, and they said not to exceed 100 seconds.

Okay except at the time that we did the study, 100 seconds was just barely therapeutic for heparin at my institution. Was it therapeutic for argatroban? I don’t know, our people did pretty well, but that’s the kind of, we got all these new drugs, in this case calling for monitoring that we don’t know quite where we’re at yet.

Title: Treatment of patients with HIT (argatroban)

Here’s what happens. On argatroban, fewer people ended up with problems as compared to those who didn’t get argatroban or an anticoagulant for this heparin reaction.
These drugs are very short half life, which is good. You have to pay attention, the clinician does, so that the liver’s working to clear argatroban or the kidneys are working to clear lepirudin. You know what, that clinician never ever thought about that before with unfractionated heparin.

So the ICU person who has a dead liver and dead kidneys, guess what they’re going to get if they can, they’re going to get unfractionated heparin or something that isn’t cleared by these two organs. And guess what, if they’re started on an agent, and their liver goes to heck, they’re going to ask you how’re we doing with the drug levels.

And in this case, at least we’re using a test we’re familiar with, which is a PTT, but no one’s really done with the same validation studies that we’ve talked about this morning with either unfractionated heparin or low molecular weight heparin. So it’s a whole new era.

Finally there’s bivalirudin, also called Angiomax, that’s approved for use in the cath lab. It’s reversible, although it doesn’t have an antidote, and it goes away very quickly, that is provided your kidneys work okay, so once again, things we never thought about with unfractionated heparin.
Does it work? It works well. I’ve understood that 30% of North America now uses bivalirudin instead of unfractionated heparin in the catheterization lab. So for what it’s worth, it’s here. You might even be monitoring it and not knowing it, although mostly they’re doing ACTs point of care in the cath lab.

**Title: Laboratory considerations - Direct thrombin inhibitors (i.v.)...**

**LABORATORY CONSIDERATIONS**

*Direct Thrombin Inhibitors (i.v.) – Argatroban and Lepirudin*

1. Monitored by aPTT for common clinical uses

2. May be better monitored by the ecarin clotting time (ECT) when use for bypass or for PCI

So thrombin inhibitors, monitored by a PTT, although for very high uses, like for percutaneous coronary intervention for catheterization, an ACT might be used or a test called Ecarin clotting time when it’s used on the bypass pump.
So the goal, I already said, is 1-1/2 to 3 times baseline for argatroban and not to exceed 100 seconds, 1-1/2 to 2-1/2 times baseline for lepirudin, although the guy who kind of brought this to the market and did all the research, Dr. Greinacher in Germany, says oh you should never have a PTT greater than 60, that’s not even therapeutic in my hospital Dr. Greinacher, how can I not have a PTT greater than 60 with an anticoagulant?

So there’s lots of statements out there that clinicians have heard about how to use these new anticoagulants, but whose lab are they talking about, your lab, my lab, Denver’s lab, Detroit’s lab? So what do we know about that?

What we know is that there’s variation with heparin, and at least there you can do a Xa level, get patient samples, devise a nomogram based on the Xa level and compare it with the PTT. There is no anti-Xa level. You can do by HPLC, argatroban and lepirudin, but there’s no easy, alternative way to assess how much drug is in the test tube to compare it with your PTT to devise a curve, to devise a nomogram.

We haven’t gotten there yet. Now if you have HPLC or want to send out samples to do that, you can, and of course you can always spike samples and set up a curve, and actually I would advocate that, but it’s not the same as getting some drug measurement in the tube and then see what the PTT is getting you.
And this has been looked at with various instruments and various reagents, so an old paper from 1993, it’s cutoff, couple of agents including a point of care test, here’s the lower therapeutic concentration of hirudin and these were studies where they could do measurement by HPLC or other biochemical methods.

Here’s the variation. From 53 to 103 is the lowest PTT you’d ever want. The highest PTT that you’d want for highly therapeutic values ranges from 60 to 114. Look at this range with this reagent. High variability.

But you know that wasn’t, and what he showed was that the slope of the response curves were different, so they’re not just parallel, it’s not just shift your range up and down, once you got over a moderately therapeutic value, it’s a nonlinear relationship with PTT and this hirudin, and so for the high dose like cath lab and bypass, you can’t use a PTT, course they don’t anyway for heparin. Right? I mean they use an ACT in the cath lab anyway.
Title: Relationship between Argatroban dose, plasma concentration, and anticoagulant effect

For argatroban, there’s a pretty good correlation across the usual infusion doses, there’s a fairly solid correlation with the aPTT, at least with the one reagent and the one instrument that they used to derive this curve.

Title: Argatroban in patients with Acute Ischemic stroke (ARGIS-1) aPTTs

And in clinical studies, and this study actually involves stroke victims, with various institutions. So various reagents, and look at that, pretty consistent PTTs, depending upon the goal they had. They got pretty consistent PTTs and good outcomes, but no one is standardizing the PTT ranges.
And this is some good work out of California that it came to publication this summer, that looked at 14 different reagents, using a couple of different instruments, so look at the PTT curves with increasing concentrations, and you can see that the majority of reagents used do cluster in a somewhat linear fashion, and the aPTT ratios are pretty consistent.

And the author suggests that the differences, although I’d submit to you, this is very different from this, but that, for the most part, agent, reagents you’re likely to use and instruments you’re likely to use, that probably an aPTT at 60 at my hospital is the same as yours for drug concentration.

I don’t share the author’s confidence, although clearly certain reagents stood out. The pathromtin, I apologize the R is missing, the pathromtin, the TAS-aPTT reagents seemed to be the most sensitive, and the flattest curve was with Actin FSL.

Again, spike some samples, see what your reagent’s responsiveness is, even if you can’t measure drug levels to see what your response in this curve looks like, or pull the article and see what they’ve found if you’d like, but I think it’s important to look for various thrombin inhibitors what the response is.

Title: ACT during PCI with Argatroban

You know for point of care, the ACT nicely responds to these agents like argatroban. But the truth is what probably needs to be done for some of our colleagues in surgery is not the aPTT, which flattens out with very high concentrations, and certainly not the thrombin time, which looks like this with increasing concentrations, but a test called the Ecarin clotting time.
And that’s outlined in a recipe for you here, and I say that again, and this has now become inaccurate again, I learned at the last symposium that Baxter has now pulled this cartridge, so it used to be that you could do Ecarin clotting time if you could do an ACT, do it on the point of care testing to monitor direct thrombin inhibitors if you were so inclined.

But I understand that this is no longer available even on compassionate release, so there is a way that you can do an Ecarin clotting time, but whether you want to apply that for routine clinical use, firstly it’s cumbersome and secondly it poses a lot of regulatory hazards I think. But that’s the way to measure them in high concentration.
The other thing that direct thrombin inhibitors do of course, remember that it’s the bottom of the cascade, right, so the INR is affected. So there are all these, I would call them somewhat convoluted ways to approach for the clinician how you get someone safely onto warfarin with a therapeutic INR if the agent you’re giving already changes the INR in the first place. For lepirudin, they say well shoot for an INR greater than 2, while the aPTT is 1-1/2 times baseline, okay, in whose lab.

And then check the INR later after you stop the drug. For argatroban, you want to get an INR greater than 4, because argatroban affects the INR to begin with without warfarin effect. Depending upon what the dose is, clinicians just go ahead, I thought this was an easy drug. I thought we were in the age of no monitoring, you guys are hurting me.

And here’s in fact what happens with direct thrombin inhibitors on INR determination. It depends upon what reagents you have, and these were done on a couple of different instruments.

So I just picked out of, literally it’s another paper again, I gave you the citation to review. You can pick your reagent, pick your instruments, see if they’ve studied it or do so yourself, but here’s an instrument that as you have increasing concentrations of direct thrombin inhibitors, especially argatroban, the INR or the protime ratio doubles.

On the other hand, if you’re using this ratio, this reagent, it changes hardly at all. And it depends upon which thrombin inhibitor,
argatroban, which is the dark bars, changes more; lepirudin and bivalirudin don’t change hardly at all, although they do a little bit, and all this is going to confound the ability to assess what Coumadin is doing in the system as compared to what these agents are doing in the system.

And so the least variability is seen with low ISI and they’re listed for you here. The higher the ISI, the greater the variability. So if you use a very low ISI, you’re likely to be not, it’s significantly been impacted by the presence of thrombin inhibitors on the INR, but it all has to be accounted for, and they all affect the INR.

**Title: Direct thrombin inhibitors: Effect on INR**

![Direct Thrombin Inhibitors: Effect on INR](image)

The concept that you can help clinicians with is the following. When they get an INR at 2.8, there’s not a chance in heck they’re going to operate, 2.8, my gosh, what that means to them is all these vitamin K dependent factors are low because that’s what I, that’s what warfarin does to your INR.

When you have a direct thrombin inhibitor, all these factor levels if you could measure them, are normal, except for thrombin after it’s gone from II to IIa, and that’s what’s inhibited in a very pharmacologic way.

So convincing a surgeon, no really it’s okay to operate, just turn the stuff off for a couple of hours, you’ll be fine, can be hard to do, but conceptually, the INR change is a laboratory phenomenon, not a change in actual factor levels, which is a concept that really confounds the use of these drugs clinically.
So back to our person, 46-year-old guy with a DVT, develops a low platelet count on the fifth day of heparin. They think he has this heparin reaction which is very hypercoagulable state. They run this PTT at 55 seconds on argatroban. Two days later, despite being therapeutic, he’s got a big old blood clot. How come? 55 not good enough in your lab? How do you know? Do you ever look, do you ever spike a sample?

Do you ever see if 55 was therapeutic for your PTT reagent and your instrument with direct thrombin inhibitors? I think although there aren’t clear standards to do so, it’s important to be sure. It could be that that’s perfectly therapeutic at a drug concentration associated with success, but it’s a bad disease, and they clot anyway.

Secondly he’s clotted off his liver. His liver function has now gone totally to heck, this drug is cleared by the liver. So it should go away in like 40 or 50 minutes, but eight hours later, it looks like it’s accumulating still, and that’s because his liver has gotten sick and it’s not going to go away.

And remember the INR is whacko maybe because the liver is sick, maybe because we know it affects the INR, and it’s just a lot of drug hanging around, and of course he’s sick to begin with because of his low platelet count. So the issue really is is if we had had a PTT at 70 in your hospital at your lab, would he have had the clot?

Maybe, maybe not. It’s a question for you to consider as you help to monitor these thrombin inhibitors, and then secondly keep in mind that the drug may linger a very long time if the organ that clears it isn’t working.
Final case, 76-year-old man with atrial fibrillation, up on the roof, fell and hit his head. Subdural hematoma, surgeon wants to drain it, but wants to know if it’s okay to proceed. He took his last dose of ximelagatran four hours ago, and he’s calling you because he called the primary care doctor, and the primary care doctor said, what lab test, they told me I didn’t have to monitor it. I don’t even know what lab test to order. So now I’m going to help you tell them what to order.

Title: New anticoagulants - Ximelagatran (H376/95)

Ximelagatran is oral, but it converts to a drug that you could give IV, called melagatran, it’s cleared by the kidneys, and it’s irreversible, as I said.
It works, and there’s going to be a lot of attention if it becomes approved eventually because it works better than low molecular weight heparins in preventing DVTs in people who’ve had hip surgery.

It works to prevent clotting just like Coumadin does if you take it instead of a placebo after you’ve been treated for your DVT; the second indication they sought from the FDA where they’ve markedly changed the chance of having a clot after six months by continuing to take ximelagatran instead of a placebo, akin to what warfarin can do for you.
And in terms of, it doesn’t seem to be associated with a lot more, there’s some more hematuria, and a little bit more bleeding, but not major bleeding. You can see here the bleeding is a little bit more, but not really clinically significantly by taking this pill instead of nothing to keep your DVT away. Which is similar to the benefits seen with Coumadin.

But Coumadin, you’ve got to do those INRs, and the new recommendation for long-term prophylaxis includes one strategy which is 1-1/2 to 2 for an INR. Now, how easy is it to hit 2 to 3, we’ve all seen them go up and down in the labs everyday, right? So to hit 1-1/2 to 2 is even more of a challenge in some cases.

The beauty of this stuff is you don’t have to monitor it. You just take the same amount, no matter who you are, no matter how much you weigh, theoretically no matter how old or young you are, and you can go ahead and have this drug and prevent DVT. They went to the FDA for these three indications.

Interestingly what held it up was that somewhere between 6% and 10% of all persons who take the drug for long enough, end up with liver damage, including one fatality as I understand, that was otherwise unexplained with development of cirrhosis over this period of time.

And so the FDA, you might’ve heard it’s coming, it’s supposed to have been coming for a long time. Just a month ago, the FDA said no thanks to approval of use of this drug in this country, although it’s been approved in Europe, because of the hepatotoxicity.

They say come back to us with a better plan, once a month LFTs is not good enough to monitor the, this drug for safety, so whether that means we’re going to have to do liver function studies more often or exactly what the plan is of the manufacturer of this drug is unclear.

But ximelagatran or Exanta is not coming anytime soon. So take a sigh of relief for those of you who make a living doing your INRs and that keeps your lab going or at least fruitful because you’re still going to be doing INRs for some time to come. Principally this is what has held it up.
The other indication they went for was stroke prevention, comparing warfarin. I mean isn’t that the plethora of the INRs that we do, where the older folks who need to have something to prevent stroke and a-fib. In the European studies, it did at least as well if not a little bit better than warfarin without a lot of major bleeding that was different, so that the liver got sick in 6% of the folks who took it.

In North America, okay, warfarin did a little bit better, but principally they're almost the same as far as having a stroke if you use this new stuff instead, although once again, there’s a tenfold increase in liver injury which has kept it, but just imagine the beauty, same dose, no matter who you are, you’re good.
So it’s to be given unmonitored. And the problem is that you’re going to have with your providers is they think oral pill INR. You know it, right they’re in a rut. Okay, they’re going to call you up. The guy fell, I need an INR, get me an INR. Please keep in mind that the INR is not the way that you’re going to follow this, it’s a thrombin inhibitor, if you’re going to try at all, it’s going to be with a PTT, and when you look at INRs in the use of melagatran or ximelagatran, they’re highly variable.

So an INR of 2, depending upon the reagent and the instrument that you use, may represent a 0.5 level which is just a little below therapeutic to a fourfold increased toxic level, that same INR of 2. The INR is not the way to monitor this, but you know your clinicians are going to call you, and say, look it’s a pill and it’s for a-fib so I must want an INR, and that is not true with the new agent. What has been looked at is an aPTT because remember that’s like argatroban and lepirudin, all these other agents, it’s in that same class.

**Title: Plasma Melagatran levels and aPTT**

And here what are the few data that are available? An aPTT will go up after it’s absorbed up to around 70, and within 12 hours, will drop to between 40 and 50. And this was derived from 12 patients who had thrombosis with normal kidney function. By the way, this is cleared by the kidneys just like other agents.
So you can see that it comes up and goes down. So the clinician calls and says, you know, did the lady overdose, is there too much, can I operate? These are the sorts of curves that you can extrapolate from, although it’s based on only 12 patients. I mean thousands have had this drug; we got published data on 12, but at least there seems to be reliable albeit highly variable response in aPTT. And so if you’re going to take a crack at trying to judge where your ximelagatran is at, it’s the aPTT and not the INR.

Title: 76 year old man with atrial fibrillation fell off ladder and hit his head

So here’s a 76-year-old guy with a-fib, fell off the ladder. Neurosurgeon wants to know, can he operate, took his last dose six hours ago. His INR is 2. Doc says, oh I know a little plasma will be good to go. That could be toxic ximelagatran, that could be subtherapeutic ximelagatran.

The answer’s the aPTT, and it’s 80. Now assuming it’s the only reason for a high PTT, the clinician’s responsibility to sort out. Because the ximelagatran, that guy is still hanging on to it in a fully therapeutic dose. And it’s like you can tell the neurosurgeon, it’s like operating fully therapeutic on heparin or fully therapeutic on warfarin.

The creatinine, by the way, was 1.5, and I think what this drug is going to lead to laboratory investigation for, because once it’s out and available, those docs are going to give it to everybody.

And this drug is highly dependent on renal clearance, much more so than low molecular weight heparin, and they’ll start giving it to all their 70 and 80-year-old people who have, who’re nearly on dialysis and they’re going to have very high levels because everybody gets 36 mg; tall, short, big, wide, small, dialysis, not.

And they’re going to, you’re going to see people coming in with spontaneous bleeding now with very high PTTs even though it’s been 12 hours since they took their dose because the drug may accumulate unless we do a very good job of educating clinicians about the renal clearance issues with these drugs.

Never mind the hepatotoxicity and maybe the INRs too, because the guy’s liver’s now failed from the drug. A host of things for docs to think about, but you guys won’t be off the hook, even if it comes to pass, because there’s a new Coumadin.

Because there’s always reasons that you’re going to have to try and figure out whether or not there’s a problem. And in fact, this person got about $65,000 worth of hemophilia concentrate that bypasses inhibitors called NovoSeven in order to have the subdural drain.
NEW ANTICOAGULANTS AND THE LAB

Laboratory has to know how to assess effect

- bleeding patients
- preoperative evaluation
- unexplained test results
- special populations
  (obese, renal, pregnant)

“Old” anticoagulants won’t go away

So even in the lab, where you’ve heard you’re going to be out of a job in coag, because all these new anticoagulants don’t need to be monitored. In fact, in a patient who’s bleeding, even though they think the drug is gone, they want to operate, is the drug gone?

Unexplained test results in special populations, you’re going to have to know what the drugs do in those situations. So you can help answer the important clinical questions, and to be able to follow the very special populations and because of that, and because with the new stuff, you have to have good kidneys and good liver, and a lot of folks who need anticoagulants don’t, the old stuff isn’t going away.

So don’t throw away the INR manual yet. Because you’re still going to need it. Same for the PTT.

NEW ANTICOAGULANTS AND THE LAB - LMWH/Fondaparinux/Idraparinux

LMWH/Fondaparinux/Idraparinux

- recognize aPTT may be slightly altered, if markedly altered, may represent overdose
- anti-Xa levels (with appropriate standard curve) may be important

Direct Thrombin Inhibitors

- recognize interaction with INR determination
- establish aPTT ranges specific for each drug??
- consider ecarin clotting time??

Remember with the low molecular weight heparin, fondaparinux and idraparinux, the PTT can be off, even though it’s not supposed to be, and anti-Xa levels are important in many settings.

Direct thrombin inhibitors, remember they mess up the INR even though you’re trying to follow the PTT, and if you could get the cartridges, the Ecarin clotting time may ultimately be a way that it goes in specialized centers using them in very high doses.

I don’t foresee a lot of places making it from scratch, and we’ll see if they become available again. But recognize that it’s going to interfere with some of the other assays that you’re trying to do.
Now I know this is a lot, it looks like a pile of rocks, but I hope I put it in a little bit more order, even though Stonehenge is still kind of mysterious, and I’d be happy to take any questions if I can clear up any mysteries that I’ve begotten this afternoon and I’ll stop there. All right and thank you all very much.