The Integration of Safe Practices Related to Anticoagulation Management

Good afternoon, everyone, and welcome to today's New York State Partnership for Patients' ADE Reduction webinar, with a focus on Anticoagulant Safety. We want to congratulate and encourage all hospitals in the Partnership to continue their efforts in tracking and reducing adverse drug events. We know that some of you have seen an increase in your ADE rates. But want to remind you not to be discouraged because this may just be a reflection of the fine-tuning of your monitoring methods. But in the end, your efforts will allow you to identify and improve your processes and reduce your ADE rates overall.

In continuation with the New York State Partnership for Patients' focus on the three major high-alert drug categories: insulin, opioids and anticoagulants -- we have asked our speakers today to share with us some of the latest best-practice recommendations to prevent harm across the board and readmissions within 30 days by focusing on successful anticoagulant management of both Warfarin and the new oral anticoagulants.

Dr. Kelly Rudd is our first speaker and is the Anticoagulation Clinical Specialist at Bassett Medical Center in Cooperstown and has expansive expertise in anticoagulant management. Among her many distinguished accomplishments, she holds Board certification in pharmacotherapy and is credentialed as a certified anticoagulation care provider. And most notably, the U.S. Department of Health and Human Services honored Dr. Rudd with the Life Saving Patient Safety Award in 2013 for her work in anticoagulation safety.

Our second speaker, Vicky Agramonte, is well-known in New York State as a Project Manager with IPRO and was the project manager of the AHRQ-funded QIO Learning Network project. Through this project, she distinguished herself as a national expert in the dissemination of evidence-based practices in clinical topics such as blood clot prevention and treatment, hospital-acquired venous thromboembolism reconciliation and management. She also has an expertise in hospital quality reporting, care transitions and other clinical topics.

And so with our introductions complete, I will turn the program over to Dr. Kelly Rudd.

Thank you for that kind introduction.
It's my pleasure to be here today to talk about anticoagulation safety. With such a vast topic and the time allotted, we thought that we would pare this down and talk specifically about the target-specific oral anticoagulants. And with the Partnership for Patient's initiative, one of them specifically focusing on VTE, I thought I would tailor my comments today to specifically in that realm. Certainly I will be able to be contacted afterwards if folks have questions about other indications. But in the essence of time, I thought we would best limit our comments to that today.

With this topic, certainly there has been a plethora of information out there about these agents. We've all seen them, and hopefully we don't have alert fatigue. My hope today is to provide a little bit different perspective on that and think about how we can use these agents in our safety programs and certainly across the transitions of care.

Specifically looking at deep vein thrombosis, I guess it's no surprise that we focus in on this. Certainly in many patients across the United States, expecting about 300,000 first-time cases of DVT in the United States every year. A fair portion of these patients have inherited thrombophilia, so a predisposition to clotting. And many of these patients go on to either require lifelong anticoagulation or have a second thrombosis. Estimates are perhaps up to two million patients, give or take, are chronically on anticoagulants for VTE.

VTE in and of itself, as we know, can be pathogenic. Patients have a lot of postmorbid problems from that, post-phlebitic syndrome, pain. But really the reason we focus in on VTE is the development of pulmonary embolisms. Pulmonary embolisms are blood clots that travel to the lungs and preclude the lungs from delivering oxygen to vital organs – such as the heart and the brain and others – which can be incompatible with life if done to a large extent.

So really when we think about DVT, our primary objective is to prevent the pulmonary embolism and is why we also focus so much on DVT prophylaxis. A fair number of pulmonary embolisms, which makes me cringe, estimates are about 10% of symptomatic pulmonary embolisms become fatal within one hour of symptom onset. So unfortunately, these patients often don't survive to get to our institutions to be treated.

But likewise, with the onset of a pulmonary embolism, mortality greatly increases in the first 24 hours that these patients are anticoagulated. So that first 24-hour period is absolutely critical, but that mortality risk does not mitigate instantaneously; and those rates can stay high over the immediate treatment period and through the first three to six months. So getting patients
adequately anticoagulated is not only a safety standpoint from the bleeding end, but also from the morbidity and mortality associated with a blood clot.

Thinking about appropriate treatment, traditionally what we have seen in that initial treatment period in the first seven to ten days of patients requiring parenteral anticoagulation, typically what we think of as low-molecular-weight heparins or fractionated heparin, so specific targets that we've all probably implemented at this point in our safety programs. But patients also go on to require long-term or extended anticoagulation as part of their treatment regimen.

Historically, we've done that with Vitamin K antagonists. In the United States, that equates to Warfarin. This from the Chest Guidelines included other agents as these target-specific oral anticoagulants are coming to the market. So typically, we've done parenteral anticoagulants in that first treatment period, largely because we're all fairly familiar with the pharmacokinetics and pharmacodynamics of Warfarin equating to Warfarin not becoming therapeutic or effective until usually about the first 5 to 7 days, and certainly not reaching steady state until about 10 to 14 days.

So I've added the caveat here that with the approval of these new oral agents, this could potentially eliminate the need for bridge therapy – bridge therapy meaning parenteral anticoagulant transitioning to an oral anticoagulant. And I say potentially because as we'll examine some of the literature, it may not completely eliminate the need for the parenteral anticoagulant.

I can't be a pharmacist and not put up a pharmacology slide. So looking specifically at the target-specific oral anticoagulants, you may also see the nomenclature Novel or New Anticoagulants or NOACs. That nomenclature has fallen a little bit by the wayside because these agents have been out long enough now, several years, that they're not quite new. And as we gain more and more of these agents on the market, they're not quite novel anymore.

So for the bulk of the presentation I'll try to refer to them as TSOACs. But in case I flip back and forth, that's my old school coming out.

Looking at this coagulation pathway, this is how clots form microscopically through our bodies. Warfarin pharmacologically inhibits the production of clotting factors VII, IX, X and II. So why there is that delay in the onset of activity for Warfarin is because it reduces the production of
these that naturally are produced through the liver. So those that are circulating already out in
the system are well and active and able to form a clot.

The newer agents – Apixaban, Rivaroxaban and Dabigatran – bind directly to the active clotting
factors. So we don't have to wait for that production to be diminished. As soon as they're bio-
available through the system, they combine to that Factor X or that Factor II, depending upon
their respective mechanism of actions and halt clotting propagation and growth nearly
instantaneously. So that process typically happens within 30 minutes to an hour, give or take,
depending upon the agent. We think of them working similarly then to unfractionated heparin or
low-molecular-weight heparin, both in target and in timing by being more readily available and
instantly working.

The title of the presentation today is: Truth or Dare. We have all seen the advertisements out
there, either in print or on TV and the headlines that they garner. And really, all that matters is
your version of the truth. We've seen what's out there. Pradaxa got kudos from docs as being a
very effective advertising campaign. And certainly the folks who do this are very clever. Get the
monkey off your back by using our drug, and you'll have no more worries.

I'm hoping to present to you today the clinician's view. We've all seen what's out there. We've all
seen the conclusions for the literature. But I want to walk you through how I view these drugs as
a clinician and how that allows me to target my safety programs through these transitions of
care and as patients are going onto and off of these medications.

As I think about that from my clinical approach, these are the main categories in which I tend to
target my safety intervention. In the first phase, it's initiation. When we see those patients, when
they come to our institutions, how do we get them on the right drug? How do we get them at the
right dose? And how do we mitigate their drug-drug interactions to keep them safe on this drug
so it will both work and keep them from having an ADE, bleeding event of some sort, that might
prompt them back to our institution?

In the maintenance phase, we're all focused in on that transition period. But as patients
transition to the community, and likewise transition back and forth out of our institutions for other
health-related problems, how do we make sure through those changes that we're doing the best
we can by our patients? And certainly, last but not least, how do we assure that patients are
being safe as we transition them on and off the drug, starting and stopping it correctly for a
multitude of procedures and things that patients are going to experience whether they're on anticoagulation or not?

The first step to this is – How do we get the dose right? The order comes down to the pharmacy, or the provider is ordering is through CPOE. How do we make sure that we're doing the best right from the start of this anticoagulation therapy?

And I promised that I wouldn't go into too much about the various indications for the new target specific oral anticoagulants, but I did include stroke prevention and VTE prevention on this slide as a matter of point in looking at how we're dosing these new agents. For this indication of VTE treatment, the dosing is pretty much dramatically different than what we've started to become accustomed to for stroke prevention.

So in our CPOE here when a provider pulls up Pradaxa, it doesn't tell them that there are special dosing requirements potentially that they need for VTE treatment. Likewise for Rivaroxaban – you notice that the dose is dramatically higher, 15 mg twice a day for the first 21 days. How do you distinguish in that CPOE or remind providers that as they're ordering this that this needs to be done? In our Phase II trials, looking at these medications, there is a rhyme and reason behind this dosing, is that there was treatment failure when using these drugs at the maintenance doses right off the bat.

So it's vitally important to get patients for the first five to ten days on parenteral anticoagulants with Dabigatran, and at the higher dose on Rivaroxaban, so that we don't lapse into those recurrent DVTs or extending to PEs or potentially to fatal PEs.

You can build best practice alerts. IPRO has a paper pending about using your electronic health record to prevent some of these problems and strategies for that. So look for that in the coming months. But something definitely to think about in your safety program, even from the start, is how we get patients on the right doses.

Likewise when you look at the package insert, even if you get the right dose, using it appropriately perhaps may not always be clear. This is the package insert – the newest package insert for Dabigatran, which was just approved last month for this indication of VTE treatment. So cutting edge – we might be the first ones out here to be talking about these – Pradaxa officially for this indication.
May 7, 2014

But looking at this column, treatment of DVT and PE is pretty clear. Last week I heard a clinician talking about these, the DVT and PE for prevention or prophylaxis of DVT, which immediately threw up my flag wondering what new was out there in addition to this indication. The clinician, thinking about the reduction and risk recurrence of DEACTIVATE, is not the same potentially as prophylaxis; but that was what was being done interchangeably.

This prompted a call to the drug company to check to see if there was a new press release or a new indication even beyond DVT or PE coming. And I can assure you that it's not being used or not approved through the FDA. And there is no application out there to seek that indication. But from simple misinterpretation of this wording, I had clinicians approaching me about the use for a potentially inappropriate indication.

So this was compounded by looking at our drug information database, Micromedex, cross-reference to several others out there. Among all of the FDA-approved indications for the drug, you'll notice here an indication for post-operative deep vein thrombosis, prophylaxis and repair of the hip.

Immediately my concerns went up. If my providers are looking at this and if you don't notice these footnotes here, reference #5 or #6, is a piece of primary literature that was done several years ago and not an FDA-approved indication, you might be misled. Likewise, looking at these doses – this is not commercially available in the United States. So it could precipitate a whole plethora of errors if providers are trying to force this into the dosage forms that we have available.

Taking this a step further, we know what's being approved or what the approved doses are through the FDA. Now we can build those potentially into our electronic health records. My concern, a bit theoretical if you will even beyond that, comes back to simple biostatistics. This here is a bell-shaped curve, and is much of how much of life is distributed. So much as with anything, you see mean score there. There's an average or a mean for most things. Myself as a woman, there's an average height that I should be. But we know that there is variation within the human species; and some women are taller, some women are shorter.

We see this with drug dosing, with Warfarin. The average dose for a 65-year-old person should be 5 mg. As a clinician, I know that not every 65-year-old patient is going to require the same dose. Some need more; some need less. And if we think and apply this to our target specific
oral anticoagulants, I have to wonder – and this is my wondering and my pondering – if that same theory applies to these fixed doses of these new agents.

We tout them to be much like low-molecular-weight heparins, which are a fixed dose based upon weight. We know that there are populations that that fixed dosing doesn't work for. And we have a test that we can do to check for that. With our target specific oral anticoagulants, there is no test. There is no test commercially available and/or validated to assess a patient's response. So if we think that humans on these target specific oral anticoagulants follow the same distribution as humans do in other things, there could potentially be a fair amount of the population that these fixed doses may not be the right dose for.

In clinical studies with thousands of patients, it appears these are the right doses for the majority of patients. But as I think about the statistical application of this, when I'm counseling a patient, I want to disclose this to them. I have no way to double-check this dose. My best estimates are that I'm 64% certain that this is the right dose for you. And how I achieve that is that in this middle column here, Same as Others, that should be the right dose. But if I look at the 16% that the dose might be too low and the 16% that the dose might be too high, I potentially have concerns that I might not have the right dose for that patient.

If you're less conservative than that, and you say, "Well, maybe we're just looking at the extreme," so that plus or minus 2 standard deviation, potentially 2% of patients above and below, this may not be the right dose for. So is it, "Mrs. Jones, I'm 96% certain that this dose is right for you, I'm 4% unsure," that's a conversation that I have with my patients. And my caution to that is even if we are less conservative and just use that 4% number, 4% of two millions patients with VTE potentially on these drugs is still a heck of a lot of patients. So take that at its worth, but this is how I think about some of these new agents and not having this monitoring test to be able to double-check that.

Thinking about our FDA-labeled doses, we know that there are patients, based upon their pharmacokinetics, that probably do require dose adjustments. And if you look at the package inserts, this is what is labeled for those dose adjustments. You'll notice that the dose-adjustment recommendations are again different, depending upon the indication, which again, can lead to a fair amount of confusion.

To make that even more complex, if I digress a little bit and talk about stroke prevention, it can be a little daunting to remember all of the nuances to this. If you look at Pradaxa, we're dose
adjusting at a creatinine clearance below 30. But for the counterpart Rivaroxaban, that's 50. The
dose adjustments are different. It's not a 50% reduction for all agents. And if you're thinking
about building this into your EHR, I hope you have a very technologically-savage person when it
comes to looking at some of these criteria for Apixiban, because it's not as straightforward. You
have to meet two of those criteria to qualify for dose adjustment.

As a clinician, I know this is FDA-approved; this is what's in the package insert; this is what we
should do. But looking at the science behind this is, again, where I have concerns. If we look
specifically at what's been clinically studied for dose adjustment, this is what the picture
changes to. The long and the short of it is that all of these dose adjustments that are
recommended by the FDA are based upon pharmacokinetic modeling. So when the
pharmacokinetic studies are done -- typically on young, healthy, male college students –
applying what their pharmacokinetics are versus a computer program that says what the
 clearance should be as patients' renal function changes, as hepatic function changes – entering
all of that into a computer model, this is what we get.

So if you feel comfortable in using these numbers, essentially we're saying we're fairly certain
that our patient is going to act like a computer model says that they should. And I'm going to
take that on faith because I don't have the ability to monitor it and make sure that that happens,
these are the dosing recommendations that you use.

But if you're a little bit conservative and want to know how patients are going to respond and
want some data behind that to assure yourself and your patient that they are not going to
bounce back for a bleeding event, that they are not going to bounce back because the drug was
ineffective because they didn't respond the way that the computer model said and you wanted
evidence, this is the picture that we're left with.

So I say that a little bit tongue in cheek. And I do feel a little bit let down, I have to admit, by our
FDA that with many drugs preceding these, we waited until we had the clinical evidence to put
out those dose recommendations. But in this case, that they're out there. And if you don't know
the rationale and the data behind them, I think it could lead you into potentially some unsafe
situations.

That same trend comes through with drug-drug interaction. Pulling the package inserts for
Pradaxa and Xarelto, because those are the two that I'll focus on as both approved for VTE, this
is what the structure looks like. This is what we'll see. These are the types of things that IT
professionals around the country are pulling from the packet insert to load into our drug interaction checkers, both within our electronic health systems and within our drug-checking databases.

Much of this, unfortunately again, is fairly limited. These drugs are new. We're doing the best we can with what limited data that we have. But to give you an example, Dabigatran, in the package insert it says, "Avoid for Rifampin." But it doesn't comment on Carbamazepine and Phenytoin, which have a similar mechanism of action. Later on in the packet insert it says, "Do not extrapolate this data to other agents." So it leaves you a little nebulous in that the interpretation potentially could be no drug interaction exists because it's not stated in the package insert, when one might certainly possibly do.

Complicating things is that lack of data. These agents are not only approved in the United States, but are approved in other countries. Looking at the package insert differences between the United States and our neighbors to the north, so in Canada, cross-referencing the package inserts, the areas in red that I have highlighted are areas where the package inserts between the two countries differ. So if I believe that patients in Canada as human beings are pharmacologically different in how they might respond to these drug-drug interactions, that could possibly explain why the packet inserts are different.

If I had a Canadian patient come down to my clinic, I wouldn't treat them any different than an American patient. But it again leaves us with several more questions potentially than we do have answers.

So having trained your staff, how do we combat this potential both as patients start on these drugs but as they go through the continuum of patient care, how do we assure that patients end up on the right drug or on the right dose when we're using these in combination? Making the point here that as I put them through my drug interaction checker, you recall that we said that Phenytoin had a major drug interaction and to avoid potentially with both Pradaxa and Xarelto, putting that interaction through Micromedex, I only come up with a major drug interaction for Rivaroxaban.

And this is actually a true story. I had a patient a couple of weeks ago want to switch off of Warfarin to one of these new agents who takes Phenytoin for a history of seizure disorder. So looking at the two agents, had I only relied upon what my drug interaction checker might tell me
or what my EHR might pop up as I enter the new drug into his medication list, I potentially could have been led astray if I wasn't thinking about this as globally and pharmacologically.

So to combat this, at our institution we do quite a bit of training with our pharmacists. Many of these new things obviously do bounce through me as our anticoagulation "expert" for double-checking, just because the literature is continually evolving. And it certainly makes a challenge for all of us who are trying to use these drugs safely in thinking about reconciling the differences between what the packet insert says, what our drug databases might say, and what we know to be true through our training.

At this point I want to transition a little bit -- hopefully I've raised some awareness and given you reason to stop and pause and think about the safety of these agents – and focus a little bit now on the safety and efficacy comparison versus Warfarin. What we hear coming through the media and what gets translated to what we think based upon the truths that we know.

The truths from the clinical trials are that Rivaroxaban is non-inferior to Warfarin in the acute phase, and there's no statistical difference in the clinical or major bleeding. I believe that to be true. When we look at the evidence-based medicine, we've seen that Dabigatran is actually inferior to Warfarin to the acute phase. But if you can make it to the chronic phase, after three months, it's non-inferior and thought to be no different than Warfarin for patients both in terms of efficacy and safety.

I just want to explore a little bit of this. Going through all of the data with a fine-tooth comb is certainly not possible in the timeframe that we have to talk about this. But I want to hopefully leave you with a few places to ponder and to consider. And certainly we are available for questions and comment offline, if necessary.

The Rivaroxaban study, EINSTEIN, was an open label, randomized, non-inferiority trial that looked at comparing Rivaroxaban versus our standard, so bridge therapy with Enoxaparin plus Warfarin. We said that there was no difference in the outcomes. Rivaroxaban is non-inferior to Warfarin, so we think it works as well and is as safe.

The caveat that I want to make to that is about the Warfarin management. When we do Warfarin management, we measure how well we do that by a quality measure called Time in Range. So it's a quality measure which essentially, if you're not familiar with it, looks at what percentage of the time the patient is within the desired range over the total treatment period.
So in this study, about 58% with our time in therapeutic range. So on Warfarin, patients were within their desired target range 58% of the time. Time in therapeutic range is a marker that we use that has a wealth of data behind it, noting that it is a surrogate marker not only for anticoagulation control but also the safety and efficacy of the drug. And this makes a lot of sense. If the patient is within their target range, the therapy should work. And if patients are within their range, they're not clotting or bleeding, depending which side of the range they're out of.

So this marker becomes very important. 58% in the grand scheme of things is actually not very good when we're talking about such a narrow therapeutic index drug, but unfortunately what we see about the same marker when patients are not managed by an anticoagulation clinic. So the recommendations are out there. IPRO has done a ton of work to try and improve the time in therapeutic range, particularly if we're not using an anticoagulation clinic. But the literature is very clear that anticoagulation clinics are typically those, including a pharmacist – I have to put that plug in there -- can really optimize the time in range and improve the safety and efficacy of care.

So in my anticoagulation clinic, so a focused, dedicated, specially-trained team, we're able to achieve a time in therapeutic range over 70%, usually closer to 80%. With an AC clinic, that's our target, both to mitigate the problems with safety but also to keep patients most efficacious on their therapy.

When looking at the recover trial for Dabigatran, the time in therapeutic range here was 60%. So again, very similar to what we saw with Rivaroxaban; but again, a very low time in therapeutic range.

How does that equate overall? We talked about those truths. So thinking about that in relation to how effective these medications are and how safe they are compared to Warfarin, I have to put that asterisk on there that this is compared to poorly-managed or moderately-well-managed Warfarin. This is a meta-analysis out of an article that was published in the *Journal of Thrombosis and Hemostasis* back in March, a very well done meta-analysis. They controlled for several variables. So I would advise folks to go and take a peek at this. This is a table that I extrapolated from that, pooling these thousands of patients together to try to eliminate what just might be happening in one study versus another.
What we have here on the left is the outcome of interest. So these are our EDEs that we're looking to prevent and comparing the rates of those versus the target specific oral anticoagulant versus Vitamin K antagonist Warfarin managed to that suboptimal level. The fourth column is the absolute risk difference, and then the right-hand side is the number needed to treat that the authors reported.

So with the number needed to treat, that gives us an estimate based upon the differences between the two categories about what the treatment effect difference might be. For example, if we look at fatal PE, the number needed to treat is 10,000. What that number means to me as a clinician is that I will have to treat 10,000 patients with a target specific oral anticoagulant to prevent one fatal PE, versus patients who are managed to a time in therapeutic range of 55% to 60% on Warfarin. So thinking about these numbers, you see several in the thousands. That helps me guide where I think these agents might fit in, in terms of safety and efficacy compared to what I know about Warfarin.

As a purist, looking at the confidence intervals in these absolute risk differences, technically if those numbers cross 1, there is no difference between those two agents -- the target specific oral anticoagulant and the Vitamin K antagonist. So I've extrapolated this in my clinical interpretation to mean that all of these markers are no different -- target specific oral anticoagulants, Vitamin K antagonists, measured to a TTR of 55% to 60% -- are the same number, the only difference being major bleeding where the number needed to treat works out to be 149.

So my question then is, these Vitamin K antagonist patients, these Warfarin patients, are not patients in my clinic. Some of them are. But the bulk of patients have a much higher time in therapeutic range and have less bleeding and less negative outcomes because in an anticoagulation clinic, I can optimize their therapy. Unfortunately, I don't have any data to show about what happens in VTE as we optimize that time in therapeutic range. But I do with Pradaxa and with afib.

The RE-LY TTR trial was published shortly after the RE-LY trial and looked at what happens to the efficacy of anticoagulation care as we march up that time in therapeutic range. So what happens to those outcomes of interest -- you can see here -- as we increase that patient's time in range? So I caution you about extrapolating this to VTE because in the relay trial Pradaxa was shown to be superior to Warfarin in both efficacy and safety. Keep that in mind.
But look at what happens to these outcomes of clotting events and bleeding events as that TTR is increased. We see no difference in most or all of the major outcomes when that TTR is optimized. Keeping in mind this was for a drug that was superior at a lower time in therapeutic range.

So I always caution about extrapolating this data to a different indication or to a different set of indications or data. But the thought is still there lingering in my mind about what truly happens when we optimize patient care. We're not really comparing the best therapy to the best therapy.

Likewise, this is only for a limited amount of data in limited duration. What happens in VTE or stroke prevention as we march out in time? Particularly for thromboembolic disease, our data is limited to 12 months with Pradaxa, essentially up to 36 months with Xarelto. But how does that risk versus benefit shift change the further out we go when VTE risk gets lower and lower and lower the further we are out from the initial event?

So really I'm hoping to leave you with a word of caution today about these new agents. This is data from the Institute of Safe Medical Practice. And I am running short on time, so I won't belabor this point too much. But just look at the rates of death compared to some of these newer agents versus Warfarin when we get out in the real world setting.

So many of the places that we can go wrong, we've talked about. And hopefully I've planted a few seeds so that we can all evaluate when we leave this presentation today about where in our processes we can do better. Talking specifically about transitions of care – so we got the patient on the drug. But patients still need to come on and off that for procedures, or because they've been admitted to the hospital and it's not safe to give that to them. All three of these new agents have a Black Box warning about the risk of rebound stroke or thromboembolic events when they stopped, and to consider bridge therapy with parenteral anticoagulant while they're off.

The majority of the questions that I get from providers – and we're trying to build this into our transitions process through our perioperative setting – about how to most effectively do this temporary interruption of these therapies the safest way possible and to do it according to what is recommended. And it is confusing. Pulling up all the different packet inserts, you see 48 hours, 24 hours, 5 hours, 1 to 2 days, 3 to 5 days. So how do we make this a systematic process so that we always do this correctly?
And likewise, back to that patient who wants to transition off of Warfarin onto one of these new agents or between these new agents or they're on their parenteral anticoagulant. How do you approach that systematically with all of these nuances? The package insert for Pradaxa – four separate bullets about how to do this, just for converting to Warfarin. Eliquis and Xarelto – the labeling is very different between the two about the strategy and how you do that systematically.

So to keep all of that straight is a job in and of itself. How do you put those processes into place and to follow it? My counterpart, Vicky, really our expert in how to implement this and bring this from research to practice and the New York Anticoagulation Coalition has been instrumental in helping us across the state implement this in a systematic manner and these best practices and overlapping our safety processes so we don't have to reinvent the wheel. And really, she's the expert on that. We've used their tools and partnered with them.

So at this point, I wanted to turn this over to Vicky Agramonte to take this from here.

Thank you, Kelly.

Thank you, everyone.

If we could just pass the ball, Joanie, I'd appreciate that.

This is a perfect segue into the work that's been done by our Drug Safety Team at IPRO and just a moment of acknowledgement for them. Our Drug Safety Team is run by Dr. Darren Triller, along with Anne Myrka and Susan Weimer; and, as Kelly had mentioned, have run a very successful anticoagulation coalition in New York State and nationally, and through the efforts of the experts in this coalition have developed a periprocedural tool that we call MAP. This is available on the IPRO website. I've provided you with the link. We urge you to try to adopt practices where we have simplified those very complicated regimens that Kelly has very wonderfully pointed out for us.

And we know as we move forward in this project in working together, again with our Partnership for Patients, we're going to have more opportunity to talk about these tools that IPRO has created and also help you implement them in your hospital.

Again, along with some of the great work that the Partnership for Patients has done, my colleague and friend, Anne Myrka, and I have been working diligently across 4 communities, 20 facilities, to really make a patient-centric cross setting medication management of
anticoagulation project work. And we’re going to demonstrate how we were able to weave the safe use of anticoagulation into safe care transition.

We're also in the process of developing a tool to support our providers – not only our prescribers, but the nursing staff that is the safety net for the patient for medications that are used, and also for our care transition partners where our rehab facilities can be assured that if a medication is being used, that it's being used at the proper dose for the proper indication for the right duration for the right patient. And as soon as we have completed this tool, we will be sharing it with anybody who wants it.

And again, putting in place mechanisms in which you don't only use our tools, but that you actually have a system for updating them. As Kelly said, this information is changing faster than we can update our documents; but we do. Every single time that there is an update, our tools will change. But then someone needs to be responsible for making sure that we're on top of those documents.

So what we're asking is a change in practice. Again, doctors are taking advantage of the simplicity or the presumed simplicity of the noble anticoagulant agents. But we need to take this a step further. We need to put systems in place to identify patients on any anticoagulant. We need to determine and use tools and resources that are easy to use if the patient is on the right medication for the right condition. We need to ensure that if there is an interruption to anticoagulation therapy, it's done thoughtfully and very carefully.

In our future work together, we know that a great place to focus on our improved interruption is in our inpatient and outpatient surgical settings where we commonly see the interruption of anticoagulants. We see the medications put on hold. And then when the surgical procedure is complete that the patient has that interruption of possibly days before someone has resumed that oral anticoagulant. In certain cases, patients are high-risk and not being bridged. As Kelly had pointed out beautifully, and our team has noted, and through the work of Dr. Triller, we know that this is a high-risk period for patients.

We need to confirm that the patient's insurance will pay for a prescribed therapy. Unfortunately, we're in a situation right now where a switch of an agent may be a thoughtful process in the hospital. Once that patient is discharged to a short-term rehab, there are denials from insurance claims that the patient can go on this medication. And what those short-term rehabs are doing is
switching the patient back to Warfarin. This is very unsafe. We need to put in place the mechanisms that have the patient at the center of our decision.

We need to also think about, and what many of our partners are doing right now is providing a comprehensive discharge summary that addresses all the components of anticoagulation therapy that we'll share with you later in our programming and in this project.

Some of this critical information that we’ve adopted at IPRO based on the literature and the consensus statement of the Anticoagulation Forum Board of Directors, we have compiled what we believe is critical information that has to be collected during an inpatient stay, and we know to an extent that it is. But we know for a fact that it is not being transitioned with the patient as they move forward.

Very commonly, orthopedic cases who have a bridge therapy happening, a nursing home or a rehab department is using a calendar to determine when that therapy was initiated. At this day and age, we need to make sure that we're not only providing the date and time of the day and when the medication was last administered, but we have a time; and we actually have it in real time, where it's valuable -- that we're not missing a day.

Therefore, as we're identifying patients who are high-risk for readmission, the use of anticoagulants makes them a high risk for readmission. We're not going to go through each of these elements, but certainly we're available to talk you through if you'd like to talk more about it.

I mentioned the AC Forum Consensus Statement. Again, this is what we consider the nation's experts of anticoagulation experts; and we follow the guidance of this group very closely. And as you'll recognize, Dr. Alison Burnett has been part of working with New York in the past; and we hope to engage her in the future in our work.

I'm going to just briefly touch on – we're running out of time – but this is certainly a webinar in and of itself, what the adequate patient education for any patient on an oral anticoagulant is. We know what we are required to do by CMS for the VTE-5 measure, and we know that that's just basic, really skimming the top of what the patient really needs to be properly educated.

Dr. Rudd has also done a tremendous amount of work in this area. What we can tell you is that patients need far more education. And not only more education, but far more coordinated education among any provider that touches that patient on any encounter, they need to be
instructed on the safety of the use of any anticoagulant, not just Warfarin. And we'll be emphasizing that point through our work together over the next six to eight months.

Again, those of you who know me very well, this is my contact information. We are here to support you in your efforts.

Just a final thought that I have before we open the line up for questions, -- and I do see that we did receive one question through the Chat -- we need to begin to think about conserving our energy, conserving the energy of our staff. As Dr. Rudd had described earlier, alert fatigue, where we're alerting everything. We need to be thoughtful with those alerts and find a common thread through all of our initiatives where we can help our staff keep this together as one initiative. This is safe practice and safe care.

And what we've described at IPRO, and some of the work that we hope to be doing with our Partnership for Patients group, is really weaving through anticoagulation safety through the VTE prevention and treatment effort through readmissions, which will hopefully be some of our work in the future to reduce internal adverse drug events.

And I know a lot of your measures are focusing on the safe use of Warfarin; but we really need to begin to monitor the safe use of other oral agents, as well as antiplatelet agents. Looking at anticoagulation as part of our inpatient/outpatient surgical safety – are we using that as part of our Surgical Safety Checklist that we've identified that this patient had a history of bleeding events or has a history of being on oral anticoagulants. I'd want to know more about the patient beyond what their bleeding risk may be for that procedure.

Certainly, as Dr. Rudd has pointed out, the impact on mortality is one. I can spend the next 20 minutes or so explaining to you cases that I have audited personally of things that have gone wrong from hospitals to nursing homes or home health. And we can talk about those down the road. But what we can tell you is that horrible things are happening to patients as they leave the hospital.

In one event that we were informed of was that a patient was switched from Warfarin to Pradaxa in the hospital. The Warfarin was discontinued, and the Pradaxa was never started. That patient was a TIA patient, was discharged to short-term rehab and died within 48 hours. These are real events. These are happening every single day. And we need to put mechanisms in place to mitigate some of these risks. And we hope to really be able to strengthen a lot of what you've
been doing with the Partnership with additional type of really deep dive areas for the next six to eight months that we'll be working together.

Med Rec – I know I've talked to pharmacists who are like, "You know what? If I hear Med Rec one more time, I'm going to scream." And I'm here to tell you we're not going to stop talking about it. Med rec is huge problem. The accuracy and quality of the initial list that we collect from a patient is at the very center of why adverse drug events occur. Again, beyond the fact that we know that med rec is being done, we need to know – Is it being done correctly? And so we'd like to be able to offer, for those who are willing, to maybe take a deeper dive and maybe hear some of the work that we're doing with our Health Quest system to really strengthen their med rec process by reducing unintended discrepancies. That's where we get the biggest bang for our buck, and we'll be sharing some of those interventions with you down the road.

Falls with injury – we know from the work that my colleague Anne Myrka and I have done that we all do fall risk assessment in every care setting. Yet there is no link to whether that patient is on an anticoagulant of any type. Certainly that is an opportunity that we really need to know through any mechanism that's decided. I know many of you are using wristbands and electronic triggers for fall risks. But we need to find a way to interrelate those elements that we collect on a patient so we're seeing the whole picture of the patient.

We wanted to really just illustrate this point. I know your Partnership Project Managers really bring this home quite often of how we're doing all interrelates. There's nothing separate. We just need to involve as many people as possible. And as we go on in this project for the next six months or so, we want to regenerate your VTE prevention and treatment efforts. And we hope that we're doing that today by offering ourselves to work with you. And stayed tuned for project programming that the IPRO team and the Partnership for Patients' team are working together to put forth for our state.

And with that, Joanie, I'm going to actually turn it back over to Deb or Alissa for opening up for some questions.

Vicky, thank you so much. This is Alyssa Beers, and I can't thank you enough for taking the time to spell out the integration of improvement efforts that you have just walked us all through as it relates to anticoagulant safety. I think that was such a great way to illustrate, as you said, how these are all so interrelated. And we sincerely appreciate you making that connection for everyone.
We, through the Partnership for Patients, have been sort of living this mantra of our guiding principles which, as you know, include ways to innovate, integrate, engage and hardwire best practices to optimize care. And I think that this is just such a great way of showing that integration theme, which is actually the theme that we're in right now in the month of May. So I really appreciate that.

I want to thank you and Dr. Rudd as well for talking through and providing some examples of safety precautions to keep in mind related to the target specific oral anticoagulants. I think that you both mentioned some pretty eye-opening questions to consider in terms of evaluating where in our processes that we can do better and take particular caution around. So really great presentations, and we thank you for being with us today.

I know a couple of people have already started to Chat in. Just a reminder, you can type your questions in for either Dr. Rudd or for Vicky through the Chat window on the right-hand side of your screen. Or you can also click on the raised hand icon, and we can unmute your line to ask your question directly.

I'm going to just start to feed some questions that I'm seeing to both of you while we're waiting for others to queue in their questions.

The first one is directed at you, Kelly. It is with regard to the slide that you put up on the biostatistics. This individual is wondering if that slide was referring to one particular drug or to all target specific oral anticoagulants.

The biostatistics slide is meant to be thought-provoking. There is no data out there about how these agents – or I've not been able to access any data either through what's been commercially available or through the drug companies – to look at those doses and what, across those standard deviations, the right doses should be. That's more of a thought-provoking slide illustrating my concern that maybe for these target specific oral anticoagulants, the one-size-all approach might not be the best approach. And those are my concerns about the dosing of these agents and not having a test or a means to double-check that.

The other question that partnered with that was regarding the package inserts regarding these medications. And certainly I can provide those to the group so that they can be distributed. But to parlay that with Vicky's comments, the data is rapidly changing. What we know is rapidly changing. These indications are rapidly changing.
And likewise with the package inserts and any of the wonderful IPRO tools. IPRO is wonderful about keeping all of that updated. Dr. Triller, Anne Myrka – they’re right on the top of their game. But the piece that we as institutions are going to have to look at is -- Who is going to be charged with making sure we have the most up-to-date information? Providing them once is not enough. We need to continually look – even from day to day some of the wording on these package inserts can change. And how do we keep current? Because what we know today may not apply a week from now, a month from now. There might be new information that we can use to keep these things safer.

Great, thank you so much, Kelly.

The next question is: "What recommendations would you give to make sure anticoagulants, including the new orals, are not started too soon after surgery or after epidural catheter removal?"

Again, this is one of those grey areas where the data in the literature is not overly wealthy. We have recommendations from the package insert, and the American Society of Regional Anesthesia has a few recommendations. But mostly what we've extrapolated together, at least at our institution, is what our best estimates are based upon what limited data we have. What the package insert says, parlaying that with an interdisciplinary team, sitting down – This is what I know about the drug and what I could possibly expect. You as a surgeon or as a spinal interventionist or as the anesthesiologist, we need to sit down and figure out what we think our risks versus benefits are and make that ideally a standardized procedure.

We've done that here. We've had a tool in place that's approved by our TNT Committee prior to those target specific oral anticoagulants coming out. And it is very difficult. (inaudible) has a great question because so many of us are struggling with a lot of these same issues. And I don't think anything has a great solid answer. I know our surgery folks are scared to death of these agents, as are our community and our dentists and things just because, quite frankly, we don't know for sure.

Much of this, again, is just based upon pharmacokinetics. Hopefully, as time evolves, we'll get more information. Again, if we have a monitoring test, I can assure my surgeon that the effect is gone; but perhaps I can't. And sometimes rationalizing the pharmacokinetics doesn't always
match what I would expect is printed in the package insert. So it is a little bit more of an art right now than a science.

But again, coming back to Vicky’s comment of trying to put something in place and follow it and keep it updated, I think when these grey areas are, looking at what is AC Forum recommending, what are other institutions doing. I think that's why the Partnership is so great about bringing us together to share where we're at is so vital as we all face these same issues.

That was really well said, and thank you for that. I think we all appreciate some of the up-to-date information as you presented it today. And of course we'll continue to monitor any new data or new literature that is published in this area so that we can ensure that all of our tools and processes are up-to-date and reflect new changes as they come.

And, Vicky, we really appreciate you presenting on some of the tools that you already have and those that are also in development currently. And we all really do look forward to taking a closer look at those when they do become available. So thank you for mentioning that.

I see one last question that is coming in the queue. And this one is with regard to elderly patients over 85 years old. And I'm guessing this is just referring to, in general, some of the safety precautions around the target specific oral anticoagulants.

Looking at our very elderly – this is Kelly – we know that patients, as we age, our pharmacokinetics profile changes and our response to a variety of different drugs change. And I think what's been clear across the literature is that patients in this age group are definitely vulnerable, both because of their limited inclusion in clinical studies. It's hard to include patients in that age group potentially, to recruit them, to keep them in the study long enough. If they perchance expire during the study is that related to drugs? There are all sorts of issues regarding that.

But I think what is clear when we look at some of these subgroup analyses, particularly with Apixiban, if we look at the dosing recommendations, that certainly does make the list for patients who could be candidates for dose reduction -- noting mostly because we're concerned that the dose might be too high because those patients on average tend to bleed. If we look at the Has-Bled scoring system, a variety of older patients are just more prone to bleeding complications anyway. Parlay that with the pharmacokinetics.
Looking more so at the afib data for Pradaxa, which is a bit older, there were countries across the world that were banning the use of this medication or making it contraindicated in these patients. Australia was going to pull the drug from the market if they were going to use it in that population because of the risk of bleeding.

So I think at any point with any drug, from my geriatrics training, we have to be careful with our older patients, but especially these medications, the target specific oral anticoagulants, because we're not exactly sure what's happening pharmacokinetically in those patients. It could just be one factor. There are certainly a multitude of factors that could predispose those patients to bleeding. But compared to Warfarin, those patients are bleeding higher. So that's a great question in a great population that I think we, again, need to go to the patient-specific level and evaluate risk versus benefit.

Thank you so much, Dr. Rudd.

We are at the top of the hour. So I just want to say another big thank you to both you and to Vicky for presenting today, as well as Deb Cole and Kathy Wray [sp?] and the rest of the New York State Partnership for Patients team and, importantly, to all of the attendees who listened in today. If you do have any additional questions, I encourage you to reach out to your Project Manager. And we'll be sure to respond quickly and continue to work with you not only around your adverse drug event-related initiatives, but also around all of the Partnership for Patients areas.

As Vicky so eloquently illustrated, this is all so very interconnected. And I also just wanted to reiterate something that Deb mentioned at the top of the call in terms of continuing to monitor your potential adverse drug event data with your Project Manager and your internal teams. As you move forward, we're happy to work with you closely on that.

And we look forward also to working with everyone on your VTE prevention efforts as well moving forward, as Vicky mentioned. We will be announcing some more details around future programming in that regard as well, so please do stay tuned.

And so with that, I just want to thank everybody for joining. Have a great afternoon. Take care, everyone.