**MARC REICHERT:** I went to school in Wisconsin, did residency in Michigan, and came here 18 years ago. So now my daughter who just started at UNC-Chapel Hill was born when I came here. So I know how old my daughter is based on how long I've lived here. It's a little easier that way.

And so I've been a specialist with cardiac surgery at Wake Forest for all those 18 years and just the last two years I've been what's called a team lead for heart transplant nephrology. So I still run with card thoracic. So I taught Dr. Lot all he knows about aortic stitches. I always tell Dr. Lot if you ever see me with a scalpel in my hand something's gone very wrong at Wake Forest. So I'll stick to the medications, and I'll probably be better off that way.

I don't have any conflict of interest with any of the things I'll discuss. It's best for me, since I do sit on several committees looking at adding drugs to formulary if I don't have any stocks or anything in the companies I talk about. If you want tips afterwards, I'm available for consult. But I can't influence that too much. And I have enough electronics on my belt right now to pull my pants down, so if that happens I apologize to the front row.

So annually in the US when you talk about drugs, we're talking about almost 100,000 people admitted each year just because of adverse drug events-- and people over the age of 65. So when you think about what kind of drugs are those, we're talking about mostly it's 50% other, but when you look at 33% is due to Warfarin alone. And this is in 2012 so we really haven't even added the new agents yet.

So you think about 33%. So 30,000 people a year in the US over 65 are admitted because of Warfarin. And about another 23% are due to platelets. You know that's almost half of your adverse drug events right there. So we talk about antiplatelets, anticoagulants, it's a very, very big topic for preventing people from having adverse outcomes, as well as doing what's best for them to keep them out of the hospital in terms of being compliant.

When I used to call people at 30 days after heart surgery, what's the first drug they said they stopped? Anybody have a thought? Aspirin, and why do they stop aspirin first? Because they say it's so cheap, it can't really work.

And so if I charged them $10,000 for the aspirin, they'd say this stuff is great. But a bottle of 100 for $5, it must not be any good. So the education component is really big into why we're giving them these things. And that the aspirin is not the first drug that you want to be stopping.

So antiplatelets-- I start with this because University of Wisconsin Pharmacy School has one of the first History of Pharmacy sections. We had to take a semester of History of Pharmacy, which I know all of you look like that sounds really thrilling, Marc. But it came with a $300 textbook which was my favorite.

But if you look at where we come from in drugs, it's amazing to me that we are where we are. Because if you look at this aspirin ad from probably the late '20s, early '30s, you can see here that it says aspirin-- it does not affect your heart. So it's safe, it's effective, it says. And it says it won't affect your heart, so it's really good for you.

So then we come another seventy years later, until somebody figured out in the 1970s actually why aspirin works. And then we finally come around to now. We understand how good it is for your heart. So every time I think we know a lot about pharmacology and how drugs work, we get reminded that I just take this back, and say, it takes us many, many, many years to really figure out how something works exactly and what it's doing for us.

So I always say that pharmacology was easier when I was young, because we had aspirin. The list right here got a little longer as I got going in training. But we added dipyridamole or Persantine. We added Plavix or clopidogrel. And now we've added the newer agents, prasugrel or Effient, cilostazol, we have Pletal now, we have ticagrelor and Brilinta. Now I'll talk about some of these other ones at the bottom, because they are the future or upcoming type agents.

So mechanism of action-- we're all going to have a test on this afterwards. This kind of diagram is what gives me nightmares, because when I was studying I would be thinking, they could ask me anything in this whole entire diagram, and I don't know what I'm going to answer. The main thing is, as we find out more and more about how a platelet is activated, we get more and more potential targets for drugs. And that's the new way of drug development, is look for the target, and then develop the molecule around that to help fit that target.

So if we look at aspirin or other agents, they work by cyclooxygenase. We talk about all of our new agents that work by ADP receptors. You have your 2B3a antagonists that work to help prevent platelets from binding to each other.

But if you look at all these other targets, we have thromboxane, they have epinephrine, they have platelet activating receptor. They have different GB-- when the platelet is rolling down to the blood vessel, there's all these glycoprotein molecules that get exposed that could be targets for drugs. And so when you really think about where is the industry headed, it's drugs that are working for anticoagulation, antiplatelets, drugs that really tend to face the upcoming population.

Clopidogrel is a-- they call it a P2Y12 antagonist. But it's actually just ADP. It's a lot easier to say ADP than to say that big long name. It's available generically. We all knew the day when I was talking to people about-- Plavix is so expensive, clopidogrel is so expensive. I don't know if you can pay for this or not.

Nowadays, it's like on the $4 list at most pharmacies. It's amazing, the generic equivalent now. The efficacy was demonstrated in multiple studies. If you want to look at one antiplatelet that's been studied extensively, it's clopidogrel.

But when you really look at the data for it initially, they looked at heart. They looked at stroke. And they looked at peripheral vascular disease. Does anybody remember what population really had the benefit from clopidogrel?

It was peripheral vascular disease. So if you took the outcomes-- heart by itself, stroke by itself-- there's really not that big a difference between that and aspirin. But when you added in peripheral vascular disease, that converted almost all the data over to positive.

So clopidogrel is really great for peripheral vascular disease. Now when you add it on to aspirin, again, like in dual antiplatelet, it's a great addition to aspirin. But by itself, in heart, it wouldn't be a great agent by itself without aspirin being onboard.

Now it's metabolized by cytochrome P450, 2C19. And so when I was in school, we only had 3A4. So thank goodness there was only one discovered by that time, because now there's so many.

But the problem with that is that there are many different metabolizers. And now there's a whole-- I could do a whole fellowship in pharmacy in pharmacogenomics, looking at people's genetic makeup and then determining what drugs are you going to react to. So when I talk about future, that's kind of the future. It's looking at what is your genetic makeup and then which of the antiplatelets do I best give you based on how you metabolize drugs or how you respond to different agents.

And so this accounts for the fact that some people just don't convert Plavix from its inactive form into its active form in the liver or in the intestinal wall. And so you'll get Plavix resistant patients. We have aspirin resistant patients.

And so limitations, and why the market decided to keep going with antiplatelets, was because inadequate responses can be seen in 4% to 34%. You see people that come in with stents multiple times that have restenosis. And the question was-- we always assumed it was maybe noncompliance. They didn't take their Plavix and aspirin, maybe they didn't take it correctly. But probably, it's the result of, again, genetics.

And then it has a slow onset and a long duration. So when Dr. Lotto wants to do a surgery with Plavix, it has to be off for five days. You always hear the waiting for Plavix washout. Patient's going to go home for five days and come back for the surgery.

Well, that's not very convenient for the patient. Even for me-- if you tell me I have a strep throat culture out for 24 hours, I spend the whole day worrying about whether or not it's positive or not. So I can't imagine going home for five days waiting to have your heart surgery.

So again, that long onset-- you can't really use Plavix for emergency use, again, because it's such a slow onset of action. It may take 12 hours, 8 to 12 hours for onset, whereas aspirin is almost five to 30 minutes in onset.

Prasugrel, you give a 60 milligram loading dose, and then 10 milligrams a day. So this is the second agent, the newer agent. It's metabolized by cytochrome P450, but much more efficiently. So it doesn't have all the multiple steps that it takes for clopidogrel and it's much more efficient. So much more of the prasugrel active drug gets developed in the first pass.

Its efficacy was demonstrated in the TRITON-TIMI 38 study. The interesting thing about cardiology is all these names make me laugh, because now it's all space. It's Aristotle, and Jupiter, and Mercury studies. I want to make ones that come out to something really funny acronym when I'm done. But I haven't found that one yet. The efficacy-- oops, I might have to back up one.

There are more bleeding side effects, as compared clopidogrel. So this is one problem. It may be more potent. It may be more efficient at its action. But again, the problem is you end up with a little higher rate of bleeding.

And so there is still some thought about prasugrel. Is it the best drug to add on to aspirin? Will I have more bleeding? Will that offset my decreased risk of platelet activation, the stent? There's a lot of discussion about that.

And again, we're kind of early in to these drugs. We're talking about one or two studies. We're not talking about studies with multiple thousands of patients that we can say, like with Plavix, we understand what population will probably benefit the most. It's actually also contraindicated in patients with a history of stroke or TIAs. Now it was interesting, that-- I think of this as the first time that I saw-- the FDA actually looked at subgroups of patients and said, these patients are good to have the drug. And these ones aren't.

Usually we say subgroups are not what you use to conclude about a drug. Those are future study type things. But the FDA went ahead and said, if you have a history of stroke or TIA, or if you're over the age of 75, that prasugrel is not the best drug. And I'll show you why in this slide.

If you look at death from cardiovascular causes, nonfatal MI, nonfatal stroke, non CABG related bleeding, you see if you got prasugrel it was 23% versus 16% for Plavix. So again, much higher rate of these bad outcomes if you took prasugrel versus clopidogrel, if you had a history of a stroke. And then if you're over the age of 75, what they found is that there was actually no difference. So it's kind of the first time that-- it's almost as if the FDA was saying, there's no cost benefit to giving it to people over 75, so don't give it to people over 75, because there's no benefit and it's going to cost you a lot more money. And so that's the two things in the package insert. If you look at under contraindication, it says don't give it to people history of stroke or TIA and don't give it to people over the age of 75.

Ticagrelor is the latest one on the market. It's probably the preferred agent right now, at Wake Forest, as far as being added to aspirin. We do still use Plavix, we still do use prasugrel at times. But I'd say our most common agent with aspirin is ticagrelor.

It's a reversible inhibitor of P2Y12. So what I mean-- Plavix is irreversible, meaning when it binds to the platelet, it's there for the life of the platelet. So if the platelet lasts for five days, the Plavix lasts for five days.

The difference with ticagrelor is it binds to the platelet, it falls off the platelet, it binds to the platelet, it falls off. So there is some thought that maybe you can take people to surgery earlier because the drug is kind of variable. And there have been people that needed to go to surgery within two or three days.

The question was, is the ticagrelor gone? And at our hospital, I send a platelet function test that tells you how much is still blocked of the platelet. So maybe in two days you could take somebody, if you really needed to emergently, if it shows that that drug is no longer active. So we're really looking for the antiplatelet that actually has a very fast onset and a very fast offset, so that these kind of things would balance out.

Metabolism to its active form is not needed. Again, a great benefit-- there's no drug interactions as far as the liver is concerned, then. The efficacy was demonstrated in the PLATO study. Again, we go back to some good acronyms. The use with low dose aspirin-- and again, this was one of these issues that came up with the studies is looking at ticagrelor. Does anyone recall what happened to the US population who got ticagrelor versus Europe and the rest of the world?

It had worse outcomes. And so when they looked at the US population alone, they found that the drug actually had harm. And then they looked at the rest of the world and the drug had great benefit.

And so, the question was, what's wrong with Americans? And I can start. We all could stand up right now and talk about 20 things that are different about our diet.

No. The question, the real issue that they found, was that the difference was due to the fact that we like high dose aspirin. Americans like 325 aspirin, whereas Europeans use 81. And for years and even still now today, we try to get people who are appropriate on 81 of aspirin, because really, if you look at the studies, 81 to 162 of aspirin-- baby aspirin to two baby aspirin-- are probably all anybody needs as far as antiplatelet effects. But we give people the adult dose.

Does anyone know how the baby aspirin ever got developed? It's trivia. It's one fourth of an adult aspirin. So a baby is one fourth of an adult. That was the thought process at the time. So 81.25 is one fourth of 325, if you do the math, and that's a baby aspirin.

I wouldn't get away with that in court, nowadays, explaining how I got that dose. But that's how they got it. And don't confuse Brilinta with Brintellix, which is actually an anti-depressant, so there's been a lot of adverse events of people filling the wrong thing because they think it's for an anti-depressant instead of an antiplatelet.

Usually the FDA doesn't let drugs that close get named the same. Darbepoetin, the drug, wanted to name itself carbopoetin. But it sounded too much like carboplatins. The FDA said, now your name is darbepoetin, not carbo.

Here's the outcomes based on dose. And if you look at the lines, the high one is ticagrelor plus high dose aspirin. And so you can see the harm here going up because of people that got high dose aspirin. And then if you look at the clopidogrel with high dose aspirin is here, ticagrelor with low dose aspirin is about the same.

So again, now you've seen the package insert. It says you have to dose ticagrelor with low dose aspirin. Again, something, always to check, as we look at people going home, to make sure they're on the proper dose of aspirin for the most benefit.

And then this study is based on these newer agents. If you look at death, MI, or stroke, it's probably 12% if you're on aspirin and Plavix, and they go down to about 9.8 if you're on one of these new agents, which is significant. So again, more efficacy, maybe some more bleeding. And again, this goes back to the more tailored approach, perhaps, of antiplatelet regimens.

My father-in-law just got a drug eluting stent. He's put on aspirin and ticagrelor and had a significant bleed. And now he's on aspirin and Plavix. So it kind of talks of the fact that there's going to be people who are going to have adverse events. There's going to be people who-- this combination is great for efficacy, but I still think we're in the tailoring mode to decide who is most likely to benefit from which drug.

And so just as an antiplatelet summary, clopidogrel-- we mentioned it's irreversible. It's a pro-drug. Its onset is relatively slow, five to 10 days for offset. And they say withhold it for five days. Prasugrel, irreversible, 30 minute onset, so very fast. But again, seven days you have to wait for surgery, because again, it is much more potent against the platelet.

And then ticagrelor is a reversible agent. You can wait probably three to five days. The package insert says five, but most studies looked at three to five. So I have a little play room in there if we need to. If someone needs to go earlier to surgery, I usually say that three days is probably off. I hate to tell that to-- it's fun to say that to a surgeon, because I don't have to worry about it. I'm like, I'm sure it'll be off.

When you get in there, if something-- well, don't call me. I could never be a CT surgeon because-- I love sleep, one. But two, that's a lot of pressure. It's easier to be the consultant sometimes.

The future agent says-- you see this blows up, because again, when you think about-- if you're blocking one or two receptors on the platelet, but there's 15 there, well, the platelet could still be activated by multiple other ways. And so if you're thinking about the PAR1 antagonist, we have drugs now like [INAUDIBLE], that's actually FDA approved-- not by itself, but with other agents, still trying to figure out where it belongs.

We have cangrelor, which is an IV antiplatelet drug. It's IV ADP inhibitor. Again, there's a lot of problems with bleeding. But you have all sorts of drugs being developed against the platelet activating receptor-- epinephrine. More thromboxane receptor antagonist like aspirin. People are trying to find a super aspirin type drug. But when you look at the market right there, antiplatelet, anticoagulation tends to be where it's focused.

So now we'll go on to anticoagulation, the opposite part of the system. So we have warfarin-- been around for a long time. And I'll take credit for it the next slide, being from Wisconsin. But the dabigatran or Pradaxa, rivaroxaban or Xarelto, apixaban or Eliquis, and maybe coming edoxaban next. The easiest way for pharmacology to remember is if it has an "xa" in the generic name, that's a Xa inhibitor. So if you look at rivaroxaban has the xa in there, that apixaban has the xa, edoxaban has an xa so it's a factor 10A inhibitor.

Dabigatran did me wrong and named its brand name Pradaxa. And so it's a thrombin inhibitor. So they kind of try to goof with us with the xa there. So all the ones that have an xa in their generic name are Xa inhibitors, whereas dabigatran is a thrombin inhibitor.

So Warfarin was first approved as a rat poison in 1948. So does anybody have warfarin rat bait at home? Hopefully not, because then you'd have a rat problem. But-- yeah. That'd be the first problem you have. The funny thing is you go back to the story, and this Dr. Karl Link was at Wisconsin in the 40s. And this farmer brought him, in his pickup truck was a frozen cow and a jug of blood from the cow that wouldn't coagulate. And he told the PhD at Wisconsin, why are my cows dying of bleeding?

And I said, well, what a great way for a scientist to be handed a project, you know? It's like, here's the cow, here's the blood, they won't coagulate, figure it out. So years later, they figured out that the problem was dicoumarol in the field. It was like, sweetclover-- that when they ate the sweetclover, the cows did, they would bleed to death.

And so they made dicoumarol into coumadin or Warfarin. Started off as a rat poison, eventually became a medication. So if you look at for Warfarin, it stands for Wisconsin Alumni Research Foundation. So there's a WARF building right on the lake in Wisconsin that's built based almost totally on the money from Warfarin sales.

It's amazing that still today, there are-- it's hard to believe that a drug that was developed in the 40s is still around in 2016. And we are learning a bunch about it. Who would have thought that with mechanical valves, that you would almost have to have Warfarin and not some of these newer agents? But that's where we're at.

Indications for the new anticoagulants-- so they've been adding weekly. So every time I make the slide, I have to update it to the next time I talk because there's a new indication for one of them. But with dabigatran, rivaroxaban and apixaban, they have the same indications, just like warfarin. You can use it for a-fib DVT treatment, DVT prophylaxis, pulmonary embolism, and for pulmonary embolism prophylaxis and like orthopedic surgery.

So lots of new agents. And again, it's become very, very nice to have patients that cannot get INR monitors. They live somewhere where they can't INR monitors. They are not capable of doing their home INR monitors and calling them in. So some of these agents have been great for people to transition to home with. They, of course, are expensive.

But again, monitoring is a lot less the-- we used to call them NOACs. That was the first term, is they would call them novel oral anticoagulants. The problem is that, again, with abbreviations-- the people saw this and they said, it probably means no anticoagulation.

So you can see what that would look like is no AC. Oh, they don't want anticoagulation, this patient, will not treat them. And then people are developing pulmonary embolisms and stuff in hospital. So now the term preferred is DOAC or direct oral anticoagulant. So instead of warfarin working against factors 2, 7, 9, and 10, we have either directly on thrombin or directly on 10A itself.

So mechanisms of action again, just like what I was mentioning, warfarin is working on several parts of the coagulation cascade-- 2, 7, 9 and 10-- whereas these agents are working against 10, 10A inhibitors. And then thrombin, you have down here. We also have the antifibrinolytics and some other agents that are much more directed towards the final step of coagulation. Or in the case of heart surgery, you have antifibrinolytics trying to keep people from bleeding during surgery.

So the coagulation cascade-- the more we understand, the more we develop new drugs for that. Pharmacologic properties-- again, looking at dabigatran, it's oral. It about 80% bioavailable. Half life of about 15 to 17 hours. You usually have-- the clearance is usually renal. So again, with people with renal impairment, it can become difficult to use dabigatran.

And then we have multiple other studies. There are some drug interactions based on, again, down here, looking at genomics itself and how they clear. Rivaroxaban is a once a day drug, unless you're loading it for like DVT or PE, then it's usually a 15 twice a day. And then after three weeks you go to a once a day regimen. Again, only available orally. Its max concentration is two to four hours. So it's great, again, you can get the drug, maybe turn off your heparin very quickly, and then you're on your oral anticoagulant.

Not based, like on warfarin, where some people you'll try for three days to leave them in health, trying to get their INR about two. And again, it could be much more. We've done some studies looking at length of stay issues with some of these drugs. And you can have a much shorter length of stay converting people, appropriate patients, to these drugs. And then apixaban, a little longer half life. A lot of these drugs have some renal clearance and again. It's steady state very quickly.

So looking at these as a whole, this is actually looking at efficacy in a-fib. So I want to give you a slide that looks at all these together and how good they are for a-fib versus Warfarin because I think that's the hard thing for me-- is I hear the words, dabigatran, rivaroxaban, edoxaban-- which one is better for a-fib or PE or is there one or the other that's better for which indication? And if you look at the rely trial is dabigatran, for your hand out, if you want to write that. The ROCKET AF is rivaroxaban. Then we have apixaban and then finally we have edoxaban on the bottom.

So when we talk about these studies it's kind of these are the trials with each medication. And you can see for efficacy of these direct oral anticoagulants versus Warfarin, they tend to favor the DOAC on this side. If you put them all together, it does not cross that midline. So it's actually better than.

So we see that in a lot of these drugs. But some cross over, which means they're not worse than. But the new thing in pharmacologic studies is the "were not inferior". So you can't say that you're superior. You can just say you're not inferior. So we're not better than, what we're no worse than.

I wish I could have done that in sports, you know. I'm not inferior to that guy over there. But no, they wanted him to be superior to me, and beat me. So that was a problem.

But that's the new terminology. So a lot of times I can't say that Warfarin is superior. A lot of times I can't say these drugs are superior. I could just say that they're not inferior, meaning probably that they are pretty much alike.

In a-fib bleeding, we see that a lot of these drugs have actually like similar bleeding rates to Warfarin and the ROCKET AF study. The rate for rivaroxaban was just a 0.2 higher. If you look at some of the studies with the edoxaban was actually lower than with Warfarin. And that comes up in a few places.

You'll see that with-- did I say edoxaban? That one was with apixaban. There's actually a little lower bleeding rate than with Warfarin. And so that's a big thing we're looking at is, do you get the efficacy? But also you want to make sure that we're not adding to it by increasing bleeding rates at the same time.

And so what's the big drawback to these drugs currently as compared to Warfarin? Cost is one. Yeah, no reversibility, except for right now we have dabigatran has one. But again, you come into that emergency room on Warfarin. I have about three different ways to reverse the Warfarin.

The cheapest probably being vitamin K or FFP and things. The most expensive being blood factors. So I have to look at somebody and say, well, is the risk of a severe bleed that I can't reverse different than the efficacy that I get over Warfarin? So that's the current thought process.

For DVT/PE, if you look at-- with dabigatran again, not Inferior to warfarin. So they crossed the midline several times. But again with these agents, and again I'll just give you the idea. The top one is pooled together so that more solid line is if you put trials together.

And this is the DVT one and this is the PE. So if you go down for each one, you can see the different rates compared to Warfarin. And again, they're not inferior. They're probably the same as, as Warfarin for these treatments.

For DVT and bleeding, again the one thing you see here again is that I mentioned with apixaban or eliquis seeing a much lower rate of major bleeding as compared to dabigatran. Rivaroxaban is actually good. Apixaban is great. So again, maybe apixaban has less risk of bleeding as compared to some of the other drugs. And then you do have rivaroxaban having a little lower risk of bleeding as compared to Warfarin.

So little things we have to think about with each patient. Does the person have risk factors for falls? Do they have risk factors for not being able to get their INR checked? Do they have issues with compliance? Is a once a day drug better than twice a day drug? And all these types of things go through your head for each patient.

Discontinuation for procedures-- so we have a whole guideline now. If somebody comes into the emergency room on one of these drugs, what do you have to do for emergency, for emergent, for urgent, for routine? Just to talk about-- because again each one has its own little nuances right now.

If you talk about Warfarin now, you have Kcentra. It has factors 2, 7, 9, and 10 in it. So you can actually reverse your Warfarin-- but again, very, very expensive. So you don't want everybody who walks in with a cut to be getting Kcentra.

But then we also have all the other agents now. If they come in with rivaroxaban, if they come in with a edoxaban, apixaban-- what's going to be your algorithm. And a lot of times, the question is a big question mark. There's not a whole lot-- we could use this, but we're not sure if it's going to reverse it. We could put them on dialysis, maybe that will take some of it off. But there's still a lot of questions when it comes to reversing some of these newer agents.

And so again, most of the time it's supportive. Let the drug wear off and then see where we are. Unless it's life threatening, and then we have to do things like using blood factors-- Factor VIIa. I've always thought that if it blocks thrombin, maybe we could actually add a drug that has activated thrombin in it. But we're still stuck there.

So reversal agents, you've heard about the new agent for dabigatran. It's a monoclonal antibody. It binds to the same receptor that dabigatran should bind to and so it takes its place. And so I think we used it once so far at Wake Forest for someone in a life-threatening bleed due to dabigatran.

I don't see as much dabigatran in our community as there is in some others. And I think it's a preferred agent for the VA, if somebody needs an anticoagulant besides Warfarin. But I don't know how many-- people seeing a lot of the people in the community on dabigatran? I don't see as much of it.

And then we're talking about andexanet is the next one that's kind of on the market now, I mean in studies. It actually went to the FDA last, I think, April. Because this is an agent that can reverse all the Xa inhibitors. So if you think about somebody that would come in on a rivaroxaban or apixaban or eliquis you need a reversal agent, this would be your one. So it would be a great agent to have.

April, the FDA said we need more information. They rejected it the first time. I'm sure it's going to come back to the FDA. And based on its need, I wouldn't doubt if it gets approved. And so again, it would be great to have this recombinant human factor Xa inhibitor.

Because we see a lot more people now on rivaroxaban in our community. And again if they come in with a life threatening bleed it would be great to have an inhibitor. I would just be interested to see what the cost will be on that end. Because again, I've never seen a reversal agent or anything like that that they say, hey, we'll get it to you for $0.10, Marc. We spent four years developing it, and we really want to give it to you for $1.

So we'll see how that works into the equation when we talk about what's the best agent for an [INAUDIBLE] person. Now I mentioned just before-- all these new agents can't be used in patients with mechanical valves as compared to Warfarin. The reason being is that they think that probably blocking Factors 2, 7, 9, and 10, as opposed to a single factor, is the reason that people clot more and have more bleeding problems in patients with mechanical valves.

So again, based on the kind of population that we work with with heart surgery, a lot of times it's just not an option. We have to go to Warfarin. And the hardest thing is to get a patient who says I just will not take Warfarin. It's terrible for me. I can't get my [INAUDIBLE] ever under control. And the drawback is that's all we have right now for mechanical valves.

So again Warfarin still seems to find a way. I remember there was a slide once that had a box of Warfarin that had cobwebs and spiders all over it, like it was old and dusty. And it said someday pretty soon Warfarin will not be around anymore. And it seems like it's funny as a drug. It finds a way to find a population that it still is the preferred for based on the others.

Now when you talk about the new agents, they can run anywhere from probably a $100, $200 a month. You know it depends on insurance. Some people have zero co-pays based on their insurance, and so it's great.

We do have a great service in our pharmacy that I can actually have technicians run test scripts on these newer agents, and say based on the patient's insurance, what is their co-pay? And that's been very helpful, because I can come back and say, the co-pay's $200 a month. The person's like, oh, I'll take Warfarin, thanks.

Or it comes back at $4 a month. And they say, well, that's great. Because I don't have to go get my [INAUDIBLE] checked. Then I'll take that. That's a great option. So it gets very confusing with each insurance company and what they'll handle and what they won't.