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Secondary Stroke Prevention in Focus: Addressing Residual Thrombotic Risk

Chapter 1. Introduction

Dr. Johnston:
Hi, everyone. it's, good to join you this evening.

So I'm a stroke neurologist and spent most of my career at UCSF, then moved to start a new med school in Austin, and then now have moved on to start a learning health system with insurance and care in Austin.

And these are my disclosures. I'm the co-chair of the Librexia STROKE trial, which we'll, talk about a little bit later.

Chapter 2. Residual Risk After Stroke: Why Current Secondary Prevention Falls Short

I'm going to go through a case that kind of runs through the entire presentation. it's an epic case, I'll warn you already, and it's not my case. This is Deborah Kerrigan's case from Vanderbilt, but it's just a really good illustration of a bunch of the points that we wanted to, wanted to make today.

This is an 83-year-old woman, DQ, who presented to the ED after a two-hour episode of word finding, but also with some subtle right arm and leg weakness. And all this fully resolved before she arrived in the emergency room four hours later. and she's got a history of lots of vascular risk factors, as you can read there, and some, chronic kidney disease, with her creatinine of one point seven.

And then her medications are there listed, antihypertensives, metformin and, atorvastatin. Her blood pressure on presentation was elevated in spite of her two meds. NIH stroke scale score and in fact, her full exam was completely normal. and a head CT without contrast showed, nothing really.

Looked quite good. and the CTA just showed a little bit of atherosclerosis at the bulbs, and the carotid bifurcations, but, but, intra-carotid bifurcation, but nothing much so she was admitted for further workup and some observation, and, had an MRI. and it really was normal.

Didn't show any acute infarct. did show, some, diffuse hyperintensities, not, kind of minor for somebody her age. and her TTE also wasn't too revealing. She has, concentric LVH. and her systolic, her systolic function was absolutely fine. No valvular disease.

A moderately dilated left atrium. her LDL was nicely controlled at eighty-three. Her hemoglobin A1C was also not so bad. and her blood pressures came down on their own. acutely elevated with the, with that event, but, but then back into control on her, her usual meds. So that's a TIA, right?

I mean, like by the old definitions, one could argue, and I have, that maybe we retire the term TIA, but it's one that won't be easy to retire. a TIA because there's no infarction and because the symptoms have resolved. and, depending on whose definition you like to use, whether you care about twenty-four hours or not is a separate question.

But regardless of whose definition, this is a TIA. So then with a TIA, we have, the potential, the ability to, to assess risk. and this score that I helped create years ago is still works. It's not perfect, but it works pretty well. So the ABCD2 score. and it's super simple.

I think most of you have used it or understand it. Might just remind you about it here. some people have said, it's antiquated, it's too

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simple, it can't work." But it does over and over again. I think it's working, predominantly by identifying who had a real event and as opposed to some, mimic for an ischemic event.

That's mostly how it works, and there's a few studies that have confirmed it definitely is associated with finding infarct in people who have transient symptoms, which argues, again, the only ones that are going to go on if you've got an infarct, you had a real ischemic event, right?

that, it nicely aligns with that. some have added an I after the ABCD² score to say, gosh, if you have infarction on a, on a, MRI scan or acute or old infarction on a CT, you can add three points. I think the reality is if you have an infarction, just call it a stroke, and that's a high-risk event regardless of the other components of the ABCD² or score.

And then you can see those risks. Those are actually the two-day risks, for having a stroke afterwards, so a lot of acute risk. It's probably come down a little bit since this paper, but remains quite high in that acute period we keep showing these, this slide. It hasn't changed very much, The seven ninety-five, people a year in the US. The reality is that the age-adjusted rates have come down some. That's kind of plateaued in recent years, but has come down some. But we're an aging population, and so that has, because stroke is more frequent in the older folks, of course, that the numbers themselves have stayed relatively the same for the, about the past decade.

So not much movement on numbers, a little movement on age-adjusted rates, some increase in age-adjusted rates in the young. most of these are first strokes, but a lot are recurrent strokes. roughly a quarter, twenty percent to a quarter are recurrent strokes. So stopping second strokes really is an important thing for us to do.

These are the ones we get involved in. They're not primary prevention, they're secondary prevention. We see them. It's our job to prevent these second strokes. so these are happening all the time. and, death is still frequent and mortality rates really, they came down a lot when we first started using thrombolysis, thrombectomy, but they've kind of stabilized as well.

We still have one in six deaths from cardiovascular disease due to stroke. As a cause of death worldwide, we're still two. it's come down in the US, but not, as other countries are living longer and not dealing with their chronic disease, predictors. Their rates are coming up.

So worldwide it remains super important even if, we've got it under better control here in the US. After a stroke, what happens? So this is from one meta-analysis. A little confusing presented this way, but it just shows that, just so depends on the cohort that you've included in the trial.

One-year risks, anywhere from six to eighteen percent. Two-year risks, ten to twenty-two percent. three-year risks up to thirty-six percent. five-year risks here it says up to twenty-six percent. Obviously, that doesn't make any sense. But the, reality is these are all different trials.

There's a, a big hump of risk in those first few days, first three months, then first year, and then it's pretty stable after that first year, but still remains a couple of percent after that. and, in spite of all the things that we do. It's come down some, as you can see, quite a bit actually since when I first got into this we first, found this high risk in TIA and stroke.

But not so much that we can ignore it. it remains really high. And the risk for recurrence, so this is now in the long term. So in the short term, ABCD² score, we've got that. That's fine. It predicts to two days, seven days, thirty days, ninety days. After that, hypertension, diabetes, atrial fibrillation, or if the stroke is now your second, then that's also an additional risk

And then of course, the risk differs and what we do differs by subtype. and I mean, we could spend a long time on this. I know you've all learned this before. I'm just reintroducing it to talk about some things that are changing now. But large artery athero, cardioembolism, small vessel occlusion, so lacunar strokes, other determined etiologies.

So this would be things like, you know, cancer, a PFO, a paradox going both through a PFO, dissection. And then undetermined etiology, so if they've got two and you're not sure which one, if the evaluation's entirely negative, if nobody did an evaluation or it was incomplete, those are all reasons why it might be undetermined, and that includes, of, potential embolic source, right?

So the ESUS subgroup that's gained some interest recently so where are we with secondary prevention? Well, of those subtypes, the large artery and, cardioembolic groups have really high risks of recurrence, particularly the large artery, whether it's intracranial or carotid, those risks are high.

And then cardioembolic as well. and then, the others are kind of variable. but small vessel in general, the risks of recurrence have been lower, and their, follow-up strokes have been more diverse, not necessarily another small vessel event, but more likely to be another small vessel event than if your,initial one was a, a large artery atherosclerotic stroke.

And over the last, 20 years or so, there hasn't been that much. that's partly why I'm here is because we are getting more excited about

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the potential of this opening up again. But, one is this, is antiplatelet therapy and the evolution. I've been very involved with that.

But also there's this, development of novel anticoagulants, first the DOACs and now a new generation. All right, so just quickly going through what has been a long arc of many studies. the first real, good randomized trial of aspirin was this one from the Canadian Cooperative Study, and it was just aspirin versus, sulfinpyrazone.

And it showed aspirin worked. So this is, 19% relative risk reduction, a tiny trial by modern standards, but they did it. and, it was significant, and it established aspirin for this indication with a bunch of other studies kind of confirming that aspirin does work and produces about that kind of, of, of, risk reduction.

So then that kind of stayed there. I mean, this is like a really shortened version. There were some other, attempts to make to, you compare clopidogrel to aspirin, not specifically in secondary stroke prevention, but more broadly. And then we had dipyridamole and aspirin versus aspirin, and then we had dipyridamole and aspirin versus clopidogrel.

I mean, it was just like a whole array of those trials. Bottom line is we were left with aspirin or clopidogrel. You could use that as a single agent as well, and it was perfectly justified. but then in twenty-thirteen, the CHANCE trial was published. So you can even see I was part of this and helped to plan it.

The trial, though, was executed completely in China, and this took, high-risk, TIAs, so ABCDs grade scores, four or greater, and minor ischemic strokes and enrolled them within twenty-four hours to clopidogrel and aspirin or, aspirin alone. And then they treated with clopidogrel and aspirin for twenty-one days and then switched to clopidogrel alone in that group.

And the aspirin group was just aspirin placebo and then aspirin alone. nicely done trial, super fast. We weren't sure if we could believe it at first, but because it was just so good. So the results of clopidogrel and aspirin, I mean, you can see that it was an 11.7% ninety-day risk of stroke.

So this is ischemic and hemorrhagic In the aspirin group. And that was reduced to 8.2% in the clopidogrel aspirin group. So that's a thirty-two percent hazard reduction. That's a, I mean, that's a huge reduction. And they didn't see much bleeding, really not anything significant in terms of bleeding.

A really nice result. it didn't change practice very much because again, I think there was a lot of anxiety about, a trial just in China, particularly back then. Now we know the Chinese are producing a whole bunch of trials in there. we produce them and, we all feel good about them.

But there was more anxiety about this at that point. So then five years later, it took us that long. We planned these two trials at the same time, but, this was funded by the NIH, and we didn't have the same resources, and it's just really hard to do. I mean, China's just got it figured out how to do trials even back then.

And, so a similar design to what I just described, but we had to get them in within twelve hours. We had a larger load of clopidogrel as well. We loaded with six hundred milligrams. People really aren't doing that anymore. and, CHANCE, loaded with three hundred. We had good reason for loading with six hundred, again, I think three hundred, six hundred, it works, as you'll see.

So our results were actually pretty similar to theirs. So the primary efficacy outcome was this composite outcome that included a combination of ischemic events. Most of that was driven by ischemic stroke. Our total event rates were lower, but the effect was quite large again, twenty-five percent relative risk reduction.

and you can see most of that is ischemic stroke. We didn't see an effect on myocardial infarction or any of the other components of the primary outcome measure. And then I should go back. we did see, some increase in hemorrhage, which makes sense. the phase things are working on platelets are going to-- they should cause hemorrhage.

And so we did see that, a doubling in hemorrhage, but the absolute risk was quite small. So the absolute risk was much smaller than the absolute benefit. And a lot of these hemorrhages were GI and just not, I mean, easy to control not that relevant.

So how long should we treat? We treated for a full ninety days in POINT. in chance, again, as I mentioned, the dual antiplatelet therapy was twenty-one days. So we went back in, in POINT and said, "Okay, do we have to treat for ninety days? Is ninety days the right amount of time?" So this is now, it's randomized data, but this is a secondary analysis.

We always be a little careful in interpreting secondary analyses, but I think this has been, kind of widely accepted in recommendations and guidelines. so what we saw is that, here you've got weeks after treatment. So we're just looking at the impact of treatment, the number of events in the first week, second week, third week, fourth week, fifth week, sixth week.

And you can see that in the first week, there was a huge impact and a benefit of clopidogrel aspirin. Not much benefit in the second

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week, but then in the, and again, these are small numbers, so it just could be chance, some benefit in the third week, and then no benefit after that in terms of reducing ischemic events.

But then when you look at major hemorrhage, the major hemorrhage rates were always greater, and that persisted out through week six. So constant increased rates of hemorrhage and really the ischemic benefit predominantly in the first three weeks. And I'm going to show you another illustration of that which is here.

So this just shows that this favors clopidogrel and aspirin. This is 40 fewer ischemic events in that first week, and then you gain another 10. and then the hemorrhage again is, tiny compared to these benefits, but it continues to be elevated, the hemorrhage. And so this argues you're really not getting much by extending treatment to four weeks.

So most people have stopped treatment, have continued to stop treatment at three weeks, even though that wasn't the, the primary way in which POINT was designed. The guidelines say, 2190 to 90 days for, dual antiplatelet therapy with clopidogrel and aspirin I'm not showing you a bunch of other trials.

They're interesting, and if we had more time, I would do that. we looked at, ticagrelor, another 2B3A that doesn't have a lot of genetic variability in the way it impacts platelets versus aspirin. That was a failed trial called XOCRITES. We looked at ticagrelor and aspirin versus aspirin.

That was a positive trial. But We never had a direct comparison of that to clopidogrel till recently. that was called the TALUS trial. And then the direct comparison just looked at the group of people who don't convert clopidogrel to its active form. There's a, pretty big subgroup that doesn't.

And those people do benefit from ticagrelor and aspirin versus clopidogrel and aspirin. That was CHANCE-2. So that is worth kind of knowing and seeing and thinking about. The reality is we're underutilizing ticagrelor currently. we've made it so complicated. you know that's why.

I think the key is to get somebody on dual antiplatelet therapy early on when the risk is particularly high, and that's what the guidelines reinforce.

Chapter 3. Beyond Platelets: Rethinking Thrombosis in Secondary Stroke Prevention

So back to our patient. This is what DQ got. So she got, aspirin and clopidogrel and was treated for twenty-one days and then switched to aspirin monotherapy afterwards.

Atorvastatin was increased, and, was kept on her, metformin, kept on the same, blood pressure meds. Because it wasn't clear, where this came from and because it felt like an MCA event and it could have been big, there was concern that it might have been an embolism. So she had a loop recorder placed, and was sent out.

What can you tell her about her risk? Well, the residual risk in somebody like this remains actually quite high. This is just one of many studies that look at residual risk, but, it's asking the question, what happens for people who are adherent versus non-adherent? And, and this was in, a Chinese study, so the event rates are quite high, probably.

They generally are higher than they are in the US. but you can see there, there is a benefit of adherence and even, you know, trying to adjust what predicts adherence away that, benefit, persists. And it makes sense, right? We'd expect, given the trial results, that if you do all the things that we've proven, it should be even better.

The benefits here should be even better. But of course, there's some biases probably in the other direction as well. So I would say though, if you look at with adherence what those numbers are, these are the one-year risk. a one-year risk of eight percent of stroke, that is quite high.

That is not something that we should be satisfied with. Maybe that number is six percent in the US, seven percent, but it's, it's still way too high, even with people taking the meds that they should be taking, even with the dual antiplatelet therapy. So question, do we have the right, therapies?

Are we targeting all these things that I've just mentioned are targeting platelets? Is that the right thing for us to be targeting? the other mechanism is this, is the clotting cascade. And I know, I think all of us were feeling happy that we didn't have to look at these numbers and know how they're interlaced and everything again.

But sadly, it's come back. the clotting cascade is important again. So it basically, just to remind folks that-- and I think there's easier ways to simplify this, but you have your extrinsic pathway, and this really helps you with, with, stopping bleeding. you cut a blood vessel, and this is what you need.

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Tissue factor is triggered, and you get your clot. So you need this to stop extrinsic bleeding, a lot of the bleeding events that we see. And then the intrinsic pathway is really what gums us up. It's what leads to thrombosis. It's what leads to, escalating from plaque rupture into, a complete vessel occlusion or a thrombus that gets thrown from the heart.

And part of this is this feedback loop from thrombin back up to the top of this thing. And you can see the factors there on that side, and eleven happens to be one of them, and that's the one I'm going to, I'm going to talk about that's been, an interesting target recently. The ones that we've been using really hit everything.

So warfarin, of course it hits all of those factors in common and in both extrinsic and intrinsic. And then heparin, enoxaparin, those are towards the end. And then, most of the DOACs are hitting, at Xa or at thrombin. So that's kind of the array. Everything's hitting-- everything's impacting something that might come from the extrinsic pathway, everything that we're using today And no surprise, those are going to come with, bleeding risks.

And those things have to be balanced. So in AFib, this is one setting where we know anticoagulation works, right? So I'm not reviewing all those trials. in AFib, we can risk stratify, right? So we can pick who really needs to be treated. for us, they always get two points for stroke or TIA, right?

So they're always weighted towards, being higher risk, and most of our folks are older, and most have hypertension, and many have congestive heart failure, and many have vascular disease, and many are female. So you can see, we end up getting a lot of points in the CHADS-VASC score, and I'll show you, those are strongly correlated with the risk of, the annual risk of having a stroke with AFib.

And then the HAS-BLED score is kind of the counterpart for bleeding risk. And unfortunately, many of the same factors that are in the CHADS-VASC are in the HAS-BLED. So in other words, that same group who benefits the most from treatment with anticoagulation, reducing, thrombotic risk, also is the one at greatest risk for bleeding on an antithrombotic anticoagulant.

So how does that play out? I mean, you don't have to, you can always look these up, right? Or just calculate them on your phone with the tools that you pull up. but, the CHADS-VASC, it's not uncommon to be towards the top of that scale. And you can see, you get to really scary event rates up there.

six and seven. Oof, I mean, those are really high rates. It is also true that it's not hard to get that high up on the HAS-BLED score. Those are also quite high rates. Particularly, you can see there's a huge range. and, and so that's not, Those aren't intracranial bleeds, by the way. Those are just major hemorrhages.

So those could be, completely reversible, whereas the thromboemboliments, those are mostly strokes and mostly irreversible so what do we know about these various agents that are out there? I am not going deep into this. I know you guys have seen this before. This is really just a reminder of, the background evidence that exists today.

And I'm not going through the individual trials, but these are trials of DOACs in a meta-analysis. These are the major trials, initial ones versus warfarin. And you can see for reducing stroke or systemic embolism, they work. they reduce the risk somewhere between... Well, overall, in the meta-analysis, about twenty percent.

So it works better than warfarin. And, and they have generally a lower risk of, bleeding. Not all of them, but, but generally that risk is lower. And in meta-analysis it's lower, so about, fifteen percent lower risk. So clearly superior to warfarin. No surprise. Warfarin's horrible. just dosing and all the things that impact it and,that how it changes and, diet and adherence is a problem and all the blood testing is a problem.

It's a terrible drug. So no surprise that a simpler drug would work better. and, some of this was just sort of getting doses right for what we wanted it to do. and, we have. And, obviously DOACshave, dominated in the US. Not in every country, but we're fortunate enough to have the resources to make them available.

And now as pretty much all of them are shortly coming, becoming generic, that's, that's making them even more attractive. So back to our patient. so she came back, at our three-month follow-up, and it was discovered that she'd had a six-hour run of AFib, so paroxysmal atrial fibrillation.

So stopped her, aspirin and started her on, apixaban. you have the, choices here. Given a renal failure, you just don't want to have to worry about renal function, so apixaban is a great choice, And, obviously it's become like kind of our kind of go-to DOAC anyway based on its other characteristics.

So what happened? So she started on the apixaban. it's always reassuring to know, okay, that's what caused her event and now we've got it and she's on the right thing. So unfortunately, she returned six months later, and, had a fall. not a huge fall at all, but had a fall,

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And again, she's on her apixaban and, But you're about to see that she had the consequences of a fall. So she was reversed and sent out, as she did not do well, so she ended up going to rehab to recover, and obviously she's got a little bit of subarachnoid blood there as well, and, and sent out off of anticoagulation back on antiplatelet therapy alone.

four months later, unfortunately, so now she's off anticoagulation, so she comes back in and found down again, not clear about, the fall or the circumstances of it, has a new bleed. and this one's big. and again, this one's now off anticoagulation. I'm not going to go through these scans, but bottom line, she didn't have any diffusion-weighted imaging positivity that could be seen, and she did not have other signs of hemorrhage elsewhere, so didn't have amyloid angiopathy.

But she did end up having left atrial appendage thrombus. It's almost like why even look? But she did have it, so the thought was maybe she had an ischemic stroke underneath that led to her fall, and then a much bigger hematoma that obscured the ability to see the ischemic event.

So based on this, after lots of conversations with the family, they decide to start, heparin, seeif they, could at least get this controlled and stabilized. And unfortunately, two days later, she had, just gotten into range and was controlled, and she ended up with, with this, finding.

You can already see there's additional blood there in the subarachnoid space in a big extension so she, actually deteriorated after this, really didn't wake up, and was actually, discharged to hospice. I mean, obviously that poor woman, it wasn't like you can go back and say, "You shouldn't have done that. You shouldn't have done that."

I mean, everything followed the guidelines, but obviously we have these really blunt instruments to treat people with. And again, as we talked about before, the existing anticoagulants that, that we have in our armamentarium is, are all impacting both the extrinsic and intrinsic pathways. And again, we'd love to spare extrinsic to reduce that bleeding risk.

Chapter 4. FXI Inhibition in Secondary Stroke Prevention: Interpreting the Emerging Evidence

So now back to factor XI. So factor XI is, converted by factor XIIa, the activated form of factor XII to factor XIa, the activated form. And then that continues on this cascade that, it accelerates thrombosis, and again, this-- with this feedback loop, that acceleration can really, multiply and lead to vascular occlusions there's a ton of data on XI, and it's super interesting.

So there's a lot of genetic data that's really interesting. So people who don't have factor XI, so they're born without functional factor XI, they, they have a form of hemophilia. They call it hemophilia, but the reality is they don't really have major bleeding problems, and they have fewer strokes.

They have fewer DVTs as well. and the data's pretty compelling. so that had a lot of folks interested in, gosh, can we target it? and first out of the gate were two, oral, small molecules. so one is this one, called, Milvexian, and, this was the phase two trial of it.

It took some high-risk TIAs and minor ischemic strokes, not dissimilar to the ones that I was describing in the antiplatelet trials. And, they all got antiplatelet therapy, and then they randomized them to Milvexin or placebo over a whole range of doses. And the bottom line was the, this is a, a phase two trial, so there wasn't really signal for efficacy.

That's the way I would read the trial. Little clany trend there. it, does impact clotting factors for sure, and, and there was no risk of hemorrhage. So at least it looked encouraging. It was clearly safe over a large range of doses. They did another study with Milvexin on DVT prophylaxis, and it, and they did find that it worked for DVT prophylaxis.

So that also in a phase two trial. So that encouraged everybody to, move forward, with, Milvexin. So that's the program I'm engaged with. The other program, is of Acodexin, so a similar molecule. and they also did a phase two trial, and it remarkably similar to the other one in terms of design and in terms of outcomes.

very safe. you could hallucinate a trend, but essentially flat, but safe over a large range of doses. and this led them to want to keep going as well. So the huge thing is, we just had presented, the results of the asundexian trial for secondary stroke prevention. So this is a gigantic trial.

So over 12,000 people recruited worldwide. Again, it's high risk TIAs, and ischemic strokes up to, 15 recruited in the first 72 hours after their event. And, they are receiving background antiplatelet therapy and either asundexian or placebo. so it's against placebo.

It makes sense. we wouldn't, shouldn't normally get an anticoagulant in that setting. and then followed for a long period of time. And the primary outcome was ischemic stroke in this trial was positive. It was nicely positive, just almost the same amount as like the initial, dual antiplatelet therapy.

So 26% hazards reduction for ischemic stroke. So that's a really nice effect. And again, a gigantic trial. So highly significant. and you can

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look through, it's, also true for any stroke. It's true for, if you add in other, death and other CV causes. So it, remains, highly significant.

Not within 90 days they had to stop their secondary analysis, because they were tiered and, it wasn't, there weren't as many events in 90 days, and there wasn't as much of a separation in 90 days, and so that didn't end up being significant and then in terms of the bleeding outcomes, their primary bleeding outcome was this ISTH major bleeding, which is just, I'm not going to go through the specifics of it, but major bleeding.

You can just figure, not necessarily life-threatening, but close to it, and it includes, cranial hemorrhage as well. And you can see they just didn't see an impact. There's not an impact. I mean, it's bizarre. no significant elevation in major bleeding. Event rates are obviously smaller.

so could there be one there that, the hazards, the confidence intervals are just too big to show it? Maybe. But, but wow, I mean, for that big an effect with an anticoagulant without bleeding, that's kind of crazy. so and pretty awesome. So another, bleeding events, you can see them all kind of listed below.

There really wasn't one that, popped out even down to minor bleeding. There really wasn't much of, an impact. So again, this kind of disconnection between, bleeding and ischemic events that we hope, had hoped could happen by just hitting the intrinsic pathway through factor XI, and it looks like, wow, it looks like for asundexian it worked.

So these are the survival curves. So the, primary outcome incidence of ischemic stroke there on the left. And you can see the curves are very... Actually, I didn't show you the curves for any pleiotropy, but they, those curves separate immediately and dramatically and then kind of are more parallel after, twenty-one days or so.

And this, you can't see much separation in the first thirty days or so, and then you see delayed separation. So whether it was important to recruit within seventy-two hours or not, maybe not, and maybe just prevalent stroke may be an, indication as opposed to within seventy-two hours.

And then you can see the bleeding. was there initially an increase in bleeding? That maybe, but, you can see the curves kinda cross again, so you can see why then it wouldn't be significant. Notice the scales are quite different to just, that's up to two percent at seven hundred and eighty days versus, up to ten percent in the placebo group for ischemic stroke.

So fewer hemorrhagic events as well So what else is going on? So this is just the beginning. there's a bunch of other stuff that's going to come out and, and it's super exciting to have another group of agents that we can look at and maybe retire these hor-- Just like, warfarin was such a horrible drug.

Wouldn't it be great to retire all the DOACs? I mean, it'd be awesome. It's too early to say we can do that, but that's the kind of excitement that, we're, feeling in the stroke world right now. Librexia STROKE is similar to OCEANIC, the one I just showed you. It's for and, it'll report out, fairly soon.

that's all I can really say about it. but, it's coming up. and then AF. So this is Milvexian higher dose versus, apixaban in patients with atrial fibrillation, another gigantic trial. there, there was an asundexian versus a-apixaban trial in that was negative. that may have been the, just the dose that was used, or it may be that, that's just not enough to hit, just the intrinsic pathway to prevent thrombus in AFib.

We don't know. This trial is going to be super important, to, demonstrate that. It's done recruiting and and follow-up, and this will report out fairly soon. OCEANIC's got a follow-up trial that's now been announced, This is going to be for, patients with AFib who are deemed ineligible for standard anticoagulation.

Obviously, that's a huge population, right? Really frustrating one. And so that's a nice indication for them. And since, it's still wide open whether they, that could work well in that group. and then, LILAC-TIMI seventy-six. So abilimab is, is an antibody that blocks, factor eleven, and it's being compared to, placebo again in those deemed unsuitable for standard anticoagulation.

But this is not the, the full list. no surprise with the results of OCEANIC. There's a lot of interest in this space. Other pharmaceutical companies are coming forward as well, with new agents, variety of different pathways and mechanisms that are being tested. so all of this is great for the field, right?

Chapter 5. Applying Evidence to Practice: Managing Residual Thrombotic Risk After Stroke

To have things being studied and, and potentially a whole new class that, that could make the lives of our patients much better. who remains at risk despite current maximal medical therapy? Well, we still have a ways to go. I didn't show you, but in OCEANIC, one of the cool things is that in the subgroup analyses by toast criteria, it seems to work in all the subgroups, so including lacunar.

And we weren't sure that anticoagulants were going to work or should we even call it an anticoagulant. There's a, a lot of discussion right

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now about that. But, a targeted anticoagulant, we weren't sure that it was going to work in, lacunar. I thought it probably would, just, TPA works in lacunar strokes, there's thrombus there.

but we weren't sure, and, it does. so that's kind of-- that's cool. hopefully we'll, reproduce that for other agents as well. but, we still have to flesh out a lot of stuff, right? So what about those at increased bleeding risk? We saw the ones, the AFib subset's going to be tested, but, there are others too that are-- that would be interesting in that category.

Is this good as adjunctive for moderate, carotid artery stenosis where, a surgical or a stent, intervention is not, felt indicated? intracranial atherosclerotic disease, obviously very high risk for recurrence. It works in that group, so is, but is that the right dose or the right combination?

lipoprotein A now with the recent trial, who knows? But yeah. And then, people with more than one stroke etiology, we really struggle with that too, right? Like aspirin and anticoagulation? Well, do we need to worry about that anymore? does, does that combination, is that combination safe?

We know it hasn't been so safe with DOACs So what is the ideal treatment? I mean, obviously we're still working even in,the placebo groups in OCEANIC, that's not a zero event rate, right? It's still too high. But we're chipping away at this, which I think is great. But we definitely want agents that prevent stroke.

Of course, that's why we're doing this and preferably of multiple etiologies, 'cause often we don't know what the etiology is and, atrial fibrillation surprises us and, we often just kinda make up a diagnosis or we never pretend. We never say that we do that. But the reality is it can be hard or impossible.

It has lower bleeding risk. I mean, even antiplatelet agents have bleeding risks as, as you saw in, even in the long term. I didn't show you that, but they do in the long term as well. It's easily administered, it has few side effects. By the way, in OCEANIC, there isn't, there wasn't another signal of an SAE or anything that popped out at this point, and that's with a lot of people studied.

We can see maybe, and we certainly don't know that for milvexian yet. but we certainly want drugs that have no side effects. and then, the, the case just again reminds us how important it is to think multidisciplinarily. the indications for these drugs are likely to cut across disciplines as well.

I should also say the trial of acute coronary syndrome of milvexian versus placebo was negative. There was no impact of milvexian in acute coronary syndrome. we do not have a drug that's working across that space as well, and that was, just reported, what? Two weeks ago.

but vascular medicine's important, vascular surgery, neurosurgery, primary care, all of them, and we're going to be important to educating them and keeping everybody up to date. I think there's going to be a lot coming out, and it's, an exciting time to see, what's new and to think that, some of the things that have plagued us in the past with poor therapies might be a thing of the past.

So that's it for my presentation.

Chapter 6. Audience Q&A and Conclusion

So there's a few questions here. and again, we just have three minutes, so I'm going to try to address them as quickly as I, can.

So one question is, how frequently should renal function be assessed to ensure that DOAC dosing remains appropriate? I mean, it depends on which DOAC you're using, and this is another reason to use a, apixaban. I mean, there are other reasons to use it as well, so I honestly just think that's the simpler choice in somebody who has, renal function that's fluctuating.

Could factor, XI, XIa inhibition eventually have a role in patients who are considered unsuitable for conventional anticoagulation, due to prior intracranial hemorrhage or another major bleeding risk? A hundred percent. Yeah, I think that's a super interesting group. regardless of the ischemic stroke etiology, if we're ruling them out because of hemorrhage risk, I think that's a really interesting group to study.

There were some hemorrhagic risks that were, used as exclusion criteria in the trials that we have. So my guess is that a lot of us will be using these drugs for people like that, and that we'll have registry data pretty soon to, confirm efficacy or, safety in that group. But I think it's a perfect group and perfect target for this.

And, another group that we've been really frustrated not to have, alternatives for treatment. the next one, how should we approach secondary prevention in patients who have more than one potential stroke mechanism, such as both atrial fibrillation and clinically significant, atherosclerotic disease?

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It may be once you identify the atrial fibrillation, we know that patient needs anticoagulation. What to do on top of that, again, we kind of debate that. I would say if the AFib trials are positive for the XI, XIas, then antiplatelet therapy plus, an XI, inhibitor, XIa inhibitor, is probably the right solution.

Will we have data that shows that? No. But we know that in the, in, patients with ESUS from OCEANIC that, that XI works. So we know it has impact in that group, and likely, I mean, we'll have to see what the AFib trial shows. for a patient with atrial fibrillation who has both high thrombotic risk and a history of intracranial hemorrhage, how do you determine when the benefit of restarting anticoagulation outweighs the bleeding risk?

Yeah, that's a great question. There's been a number of trials that have looked at the timing of anticoagulation, reinitiation and, earlier probably is better for most people. But what I would say is I think, that's where things are today. Let's see. I think this calculus could be very different, in the, in the future with new agents.

Okay. I want to thank everybody. I got through the questions I think pretty well, but pretty fast. I'm sorry there's like, I can't see you or hear from you or anything, but I appreciate you all joining tonight and have a good dinner and a good evening and, thank you.

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