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Factoring Solutions to the Management of Stroke Care in the Settings of Secondary Prevention and AF

Announcer:
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Chapter 1: Clinical Insights Into Stroke Pathophysiology and Advanced Prevention Strategies

Dr. Gurol:
As vascular neurologists, we want to really minimize the number of strokes, and we want to use the appropriate approaches, medications, diagnoses to make this happen. But we still are seeing a lot of strokes, both ischemic strokes and brain bleeds in our practices.

Our first talk is from Dr. Robin Novakovic, the professor of radiology and neurology at University of Texas Southwestern Medical Center, and she will discuss the physiopathology of ischemic stroke and intracerebral hemorrhage, and where things stand right now for their prevention. Dr. Novakovic?

Dr. Novakovic:
So I'm so excited to be a part of this session and to start us off with some of the basics of strokes and hemorrhagic stroke. It is a sobering fact to recognize that stroke is a leading cause of disability in the United States. Every 40 seconds, someone in the US suffers the consequences of a stroke. Stroke remains the fifth leading cause of death, and every 3 minutes and 14 seconds, someone in the US dies as a consequence of a stroke.

When we think of the different stroke types in the United States, the vast majority are ischemic strokes. Hemorrhagic strokes, including intracerebral hemorrhage and subarachnoid hemorrhage, make up a small proportion of the stroke subtypes. Meanwhile, globally, hemorrhagic stroke, especially intracerebral hemorrhage, have a much higher incidence.

Intracerebral hemorrhage is the deadliest stroke subtype with the highest associated disability. The annual rate of anticoagulant-associated intracerebral hemorrhage is 0.3% to 0.6% for vitamin K antagonists, and 0.1% to 0.2% for DOACs. DOACs, however, are associated with about a 50% reduction in the anticoagulant-associated intracerebral hemorrhages. We know that the 30- to 90-day mortality rate for anticoagulant-associated intracerebral hemorrhage is 40% to 65%. Oral anticoagulants are associated with a larger baseline hematoma volume, more frequent secondary expansion, and poorer functional outcome and higher mortality. In one observational study, treatment with an oral anticoagulant was independently associated with lower odds of a favorable outcome and higher odds of mortality at 3 months.

When we think of strokes of all subtypes, only about 57% of patients will return to work at 1 year. And at 2 years, it's only about 2/3. Functional cognitive impairments as well as dementia, are common in patients that suffer stroke.

When we think of the healthcare impact of stroke in the United States alone, we saw direct healthcare costs of $34.5 billion in 2019, and

when you add together the direct and indirect costs, you see a further $56.8 billion was spent in that same year. And if we try and project what healthcare costs will be in 2035 for direct costs alone, we're looking at $94.3 billion, and that's in 2015 dollars.

So before we focus on stroke prevention, it's always helpful to take a moment to think about the stroke classification, as well as the mechanisms of ischemic stroke. Based on the TOAST classification, ischemic stroke can be divided into lacunar and non-lacunar stroke. Non-lacunar stroke can then be subdivided into cryptogenic, cardioembolic, large artery atheromatous disease and other. The other category is what is characterized as our nonatheromatous vasculopathies or hypercoagulable states or even our hematologic disorders.

Now, lacunar strokes are subcortical strokes measuring less than 1.5 cm in diameter. Most, but not all, lacunar strokes are due to small vessel disease. Meanwhile, small vessel disease is still a subcortical stroke, but without evidence of a concomitant cortical infarct.

As we discussed, non-lacunar strokes are divided into the 4 main categories. Most of the categories are self-explanatory, but cryptogenic stroke warrants a little further discussion. Cryptogenic stroke is a stroke with unknown source, but despite a very thorough diagnostic assessment. And when we talk of a stroke that's nonembolic of undetermined etiology, these can be strokes where we have not identified the mechanism, but they may have multiple comorbidities that could separately each explain a stroke. For example, a patient with Afib and a carotid stenosis on the ipsilateral side. An embolic stroke of undetermined etiology is a non-lacunar stroke without clear embolic source.

Now, in terms of the mechanisms for ischemic stroke, we typically think of them as either thrombotic, hemodynamic failure, or an embolic stroke. Thrombotic strokes,
as we know, are occlusion right at the site of the vessel wall. And these can be mediated by things like endothelial injury from either a dissection, vasculitis, or infection, or it can be from stasis or turbulent blood flow, like in a fusiform aneurysm that has stasis within the aneurysm. And thrombotic strokes can also be mediated by a hypercoagulable state, whether it is a genetic or acquired hypercoagulability.

Hemodynamic failures really come from a hypoperfusive process, and this may either be global, like in a cardiac arrest, or it can be localized, like in a narrowing of a blood vessel, either from an atherosclerotic stenosis, a dissection, or even vasospasm.

And finally, embolic strokes are either going to be mediated from an artery-to-artery embolus or something from within the heart, whether it is an arrhythmia or some underlying pathology within the heart that is prothrombotic.

In terms of prevention, when we think of non-cardioembolic strokes, we know that the mainstay of treatment for secondary and primary prevention is an anti-platelet agent. Here, we either think of aspirin, clopidogrel, or aspirin in combination with dipyridamole.

More recently, DAP therapy, dual anti-platelet therapy, has a strong indication for minor to moderate strokes. Of the trials, though, that demonstrated benefit in DAP therapy over monotherapy, it is important that most beyond the CHANCE trial showed that while there was benefit in DAP, there was an increase in major bleeding complications. And the major bleeding complication could range with DAP therapy from 0.3% to 0.9%.

So again, this is a reminder that all of our interventions for prevention are going to
come at some risk, even while they are affording a reduction in the risk of stroke.

Atrial fibrillation is important to remember that it is the most prevalent arrhythmia worldwide, impacting over 46 million individuals. About 25% of those embolic strokes of undetermined source will later be determined to have atrial fibrillation. And as we all know, the current recommendation for high-risk atrial fibrillation is to use anticoagulation. But no anticoagulation to date has been proven to provide absolute protection against stroke without increasing the risk of bleeding. DOACs, therefore, over warfarin, are the first-line therapy for stroke prevention in patients with non-valvular Afib and have that elevated risk of stroke.

In one meta-analysis of 4 randomized controlled trials demonstrated that DOACs, while they were equivalent in risk reduction, also had a lower incidence of intracerebral hemorrhage. As I mentioned earlier, they saw a 50% reduction in that major bleeding complication. However, DOACs were associated with a higher risk of GI bleeding.

Factor XIa inhibitors may offer a promise in decoupling the hemostasis from thrombosis and thereby offering a superior safety profile over the current anticoagulants used for stroke prevention in atrial fibrillation. Currently, we know with the oral anticoagulants that are in use today, there is fear of bleeding that leads to underutilization, underdosing, and noncompliance of the medications. Thus, looking to the future, factor XI may be a promising treatment for stroke prevention.

We know in mouse models, factor XII and XI are integral to the formation, growth, and stability of thrombi. Factor XIIa, it actually initiates the intrinsic pathway of the coagulation cascade. And factor XI is converted to XIa by the factor XIIa. Factor XIa is going to contribute to thrombin generation by activation of several factors, most notably factor IX. And it is factor XI that is really this bridge between tissue

factor-initiated thrombin generation and other coagulation system activation. There is evidence that factor XI contributes to platelet activation and accumulation in flowing blood that's exposed to thrombogenic surfaces.

So the holy grail of treatment and prevention of thrombosis and thromboembolism would be a drug that is highly efficacious without carrying a substantial risk of bleeding. From this hematological standpoint, the inhibition of factor XI represents this promising target for the future. And for the remainder of this session, you're going to get to learn more about some of these promising drugs. Thank you.

Chapter 2: Stroke in AFib: Past, Present, and Future in a Nutshell

Dr. Gurol:
Thank you very much, Robin, for this excellent presentation. So I'm going to discuss the past, present, and future of stroke and its prevention in patients with atrial fibrillation.

Atrial fibrillation is the most common etiology of cardioembolic stroke. It might increase ischemic stroke risk by 2- to 5-fold, and it might be paroxysmal, persistent, or permanent. This is a gross classification but still used, but temporality does not change need for stroke prevention measures in most cases. Even in a patient with paroxysmal atrial fibrillation, we still use anticoagulation to prevent strokes. Afib is diagnosed with a 12-lead EKG, but validated monitoring tools are available.

So in the past, we were diagnosing atrial fibrillation with a pulse check, EKG, Holter has been used for a long time, but it was only used for up to 48 to 72 hours, mainly 24 hours. And the mainstay of stroke prevention in people with atrial fibrillation up until 2009, 2010, it was warfarin. Warfarin showed in multiple studies superiority over nothing or aspirin for stroke prevention, and meta-analysis showed that in people with atrial fibrillation, warfarin would reduce the risk of strokes by 62% versus placebo.

As you guys know, INR needs to be checked, and the sweet spot for INR is between 2.0 to 3.0 for the very reason that Robin very nicely mentioned. Essentially, we want good prevention of ischemic events, ischemic strokes. We do not want disproportionate increase in the risk of major hemorrhages and intracranial hemorrhages. You're going to discuss this a bit further.

Aspirin does not really have any more role in stroke prevention, but in these old studies even aspirin prevented, again, some strokes. About 19% prevention with aspirin against placebo was seen, but warfarin was a lot more efficacious than aspirin, at least a 33% risk reduction, which later studies proved even much higher risk reduction with anticoagulation than compared to aspirin.

So now, we are moving to present. We have smart watches, we have other variables, external prolonged written monitors that can be used over the left chest up to a month, insertable cardiac monitors that can detect atrial fibrillation for up to 4 years for detection. So we are detecting a lot for atrial fibrillation now than before. And right now, the mainstay of stroke prevention and systemic embolism prevention among patients with atrial fibrillation is direct oral anticoagulants. Left atrial appendage closure is an existing FDA-approved modality, but it is a second-line prevention method. DOACs are now absolute first-line prevention method, including warfarin.

I'm running a high-level stroke prevention research policy meeting, and we do come up with consensus guidelines, and quite a few of the things that we are going to discuss now have been discussed in those Roundtable of Academia and Industry for Stroke Prevention meetings.

So while coming to end of 2000s, our other study included patients deemed to have some problems with warfarin use, and the randomization was between apixaban versus aspirin. So in this study, the mean CHADS2 was 2.1. CHADS2 is an embolic risk score that's being used to understand how high the embolic risk is in people with atrial fibrillation. It goes from 0 to 6; 2.1 was not very high, but in this patient population, apixaban proved to be much superior to aspirin, and it prevented 63% of strokes when compared to aspirin. It was the first study that showed a clear superiority of a new oral anticoagulant.

Around the same time, RE-LY for dabigatran, ARISTOTLE for apixaban, ENGAGE AF for edoxaban, and ROCKET AF for rivaroxaban, these 4 randomized control trials were conducted as phase 3 studies. And as you can see here, mean CHADS2 in RE-LY and ARISTOTLE was 2.1, and dabigatran and apixaban used in these studies resulted into really low ischemic stroke rates, 0.92%, 0.97%. The rivaroxaban study was done in a much higher-risk patient population with a mean CHADS2 of 3.5 and they were also a bit older. But still it proved to be noninferior to warfarin for ischemic stroke prevention. The annual ischemic stroke rate on rivaroxaban in this study was 1.34%.

Unfortunately, the discontinuation rates were pretty high for all of these new drugs, as well as Coumadin, but the intracranial hemorrhage rates were much lower with these direct oral anticoagulants, ranging from 0.3% for dabigatran, 0.32% per year for apixaban, up to 0.5% per year for rivaroxaban, obviously again, the ROCKET AF, which studied rivaroxaban against warfarin, had the highest risk and oldest patient population.

Phase 4 studies showed that when you use these direct oral anticoagulants in similar patient populations, people with atrial fibrillation with the mean CHADS2 of 2, you get very similar results, which is great news. When you can reproduce randomized controlled trial

data in phase 4, you are happy. So the incident rate of ischemic stroke, the systemic embolism, even TIA, was about 1% per year in this Japanese study, which was a Japanese government-mandated study to prove that apixaban would be good for Japanese patient population, and it worked great. But once again, in this study as well, a lot of the patients excluded from ARISTOTLE trial were excluded. So this is part of our problems in our current methods to prevent strokes in people with atrial fibrillation. There were a lot of exclusion criteria, and many of them were related to increased bleeding risk, past history of intracranial hemorrhage, frailty, renal failure, liver failure, so these high-risk patients were not included into the phase 3 studies.

Overall, warfarin is the only alternative for stroke prevention in the presence of mechanical heart valve, moderate to severe mitral stenosis, or rheumatic valve disease, concomitant antiphospholipid antibody syndrome. INR should be checked at least weekly until stable in therapeutic range, and then monthly thereafter. Warfarin is a difficult medication to use. It's saved perhaps hundreds of thousands or millions of lives since 1950s, but it's still a medication that we love to use.

We as physicians, both in cardiology, stroke neurology, general medicine, we love the direct oral anticoagulants. So in patients with relatively low based on risk of hemorrhage, they have been much easier to use than warfarin. No blood tests needed, much less drug and food interactions than warfarin, and they have a fast onset of action, which is very important. When you give the first dose of apixaban or rivaroxaban, the patient is anticoagulated within the next hour or 2. That's a huge advantage. The disappearance of the anticoagulant effect is also relatively quick, which might be a disadvantage in patients who miss doses, but it is an advantage when the patient bleeds because when you stop the medication, the anticoagulant effect decreases within 24 to 48 hours.

DOACs are currently the mainstay of stroke ischemic embolism prevention in patients with nonvalvular atrial fibrillation, which is the great majority of patients with atrial fibrillation, essentially.

Now, the set truth is that major, clinically relevant, and minor bleeding events were common among warfarin and DOAC users, even in those randomized controlled trials. Major bleeds happened in 2.1% to 3.6% for DOACs, 3.1% to 3.4% for warfarin in those DOAC RCTs. Clinically relevant, no major bleeds happened anywhere between 9% to 17% for DOACs, and 10% to 16% for warfarin among those 4 randomized controlled trials for DOACs. And inevitably, and all of these numbers are per year, so any bleeding happened between 15% to 25% per year for all oral anticoagulants, and these are huge numbers.

And we need to remember that even minor bleeds matter as they might result in the discontinuation of the oral anticoagulants, and for people who take oral anticoagulants, patients have no protection after 24 hours and hemorrhages are major contributor to the extremely high permanent discontinuation rates seen in phase 3 and also in post-marketing studies. Some post-marketing studies have shown 35% to 58% permanent discontinuation in 2 years. So bleeding, despite the fact that we have made progress, bleeding is still a very big problem with the current direct oral anticoagulants. And with the current agents, there is no oral anticoagulant, warfarin, or DOAC that decreases ischemic risk without increasing the hemorrhage risk, and the location of the hemorrhage matters.

So this study from Danny Singer clearly showed that warfarin-related extracranial bleeds had a mortality of 5.1%, whereas warfarin-related intracranial bleeds had a mortality close to 50%. And no patient with a past history of intracranial hemorrhage has ever been included in any direct oral anticoagulant, warfarin, or left atrial appendage closure study.

DOACs increase ICH risk by 2- to 5-fold, even in very-low-risk patient populations, and when an intracranial hemorrhage happens in people on DOACs, the mortality is still super high. These data are directly coming from the phase 3 studies of the direct oral anticoagulants. And for apixaban and rivaroxaban, the mortality of ICH on those agents was between 45% to 50%. For this reason, 2 randomized controlled trials were conducted in Europe, and they enrolled over 300 intracranial hemorrhage survivors with nonvalvular atrial fibrillation. Only very few had cerebral amyloid angiopathy, which is a very high intracranial hemorrhage condition of the brain. And randomization was between direct oral anticoagulants versus aspirin or no antithrombotic. These patients were followed up for 1 to 2 years.

There had been 15 recurrent intracranial hemorrhages when DOAC was started after ICH, with 70% mortality for DOAC-ICH in SoSTART, and only 2 recurrent intracellular hemorrhages when oral anticoagulant was avoided and none of the 2 was fatal.

As a result, direct oral anticoagulants failed to show noninferiority against aspirin or nothing in intracranial hemorrhage survivors with nonvalvular atrial fibrillation. If a medication fails to show noninferiority against aspirin or nothing in atrial fibrillation, we have to be very careful. And our team looked at the markers, brain imaging markers, especially if they are associated with the risk of direct oral anticoagulant-related brain bleeds. Several microbleeds in the presence of cortical superficial siderosis were very highly associated – their presence was very highly associated with the risk of brain bleeding on DOACs. And prior ischemic stroke, diabetes, smoking history were also significant predictors

Here, in people who sustain intracranial hemorrhage, they have very high rates of recurrent intracerebral hemorrhages, but we also have all of these MRI markers, such as white matter disease, enlarged perivascular spaces, cortical superficial siderosis, lacunar infarcts. And middle-aged to older patients who have any of these are also at very high risk of having a brain bleed.

So there is no currently available anticoagulant that decreases thrombotic embolic risk without significantly increasing the risk of major and or clinically relevant bleeding, and that includes brain bleeds as well, unfortunately. And as neurologists, we see these intracranial hemorrhage patients, we know that oral anticoagulant with ICH is our big problems, major cause of mortality and morbidity. We care for this problem.

Others also do, and this is why this one is a relatively recent study that shows that, okay, DOAC use has increased, and rat poison or warfarin use, has decreased over the years since 2013, but still among patients who need oral anticoagulants, a lot of them are no treated. As you can see in this large-scale study, unfortunately, about 50% of people who need anticoagulation are treated with oral anticoagulation and the main fear factor is oral anticoagulant-related bleeds, including intracranial hemorrhages. Left atrial appendage closure is being used. The initial studies, PROTECT AF and PREVAIL, showed a very significant decrease in hemorrhages and especially, hemorrhagic stroke. The problem is that ischemic stroke was higher with left atrial appendage closure against warfarin. But even if that was not significant, this difference was nontrivial. That's what led people to think that left atrial appendage closure may not be working.

More recent studies show that it is working, and PRAGUE-17 study showed noninferiority of left atrial appendage closure against direct oral anticoagulants. But there are still a lot of issues that we are working on in that space. There are challenges. So efficacy data, CHAMPION AF and CATALYST studies are looking into efficacy of the left atrial appendage closure over the direct oral anticoagulants. These are large-scale studies. We will see. If they succeed, they might move to a higher space, a higher place in guidelines. Right now left atrial appendage closure is a secondary prevention measure in patients who are at very high hemorrhage risk or moderately high hemorrhage risk.

Device leaks are a problem. Device-related thrombi, even if not very common, remain a problem, and certainly, these are operator-dependent procedures. So despite the fact that the risk of procedure-related complications decreased, they are still present, and for now it is clear that even if these large-scale studies show noninferiority of left atrial appendage closure, they are not going to replace oral anticoagulants by any means.

Okay, what is the future? So Robin very nicely explained factor XIa inhibitors. I'm not going to discuss the futuristic ways of detecting atrial fibrillation, but factor XIa inhibitors are in clinical trials and factor XI is important for thrombogenesis, but not that important for hepatocytic function, and this is why the thinking that inhibition of factor XIa might decrease pathologic thrombus formation without necessarily touching the healthy hemostasis, it's an important and scientifically sound thought.

The studies so far approved some support to the view that factor XIa inhibitors would be efficient, at least for DVT prevention in people who underwent knee arthroplasty, and that happened. That was proven. So they work; they can work. And there is also some data suggesting that they would cause lower risk of hemorrhages than compared to even existing direct oral anticoagulants.

Asundexian was trialed in a large phase 3 study, the OCEANIC AF study, to see whether it would prove noninferior to apixaban. It didn't happen that way. We might discuss this a little bit more. We don't know whether it was the agent or whether it was problems with dosing, whether it was underdosed, whether it was incomplete inhibition of factor XIa. All of these questions are out there, and we have a great expert who might discuss these issues with us. Jeff can certainly comment more on that. But the primary safety endpoint, that happened a lot less with asundexian compared to apixaban. Okay, the medication didn't work. Maybe it just acted as a placebo, we don't know.

But what we know, the milvexian is a molecule. It was studied in a very large range of different doses, and against a prophylactic dose of enoxaparin, milvexian provided very good protection from DVT, and it was not associated with a high risk of major hemorrhages.

And these are the doses studied and the bleeding results. As you guys can see, both for any bleeding and clinically relevant bleeding, milvexian, even at high doses, performed very well against a small dose of Lovenox, or enoxaparin.

LIBREXIA AF study is going on, so this is milvexian 100 mg twice a day compared to apixaban 5 mg twice a day. All-comers with atrial fibrillation who fulfill criteria for anticoagulant use are enrolled, and again, randomization is between milvexian and apixaban, and the idea is to prove noninferiority for ischemic events and superiority for hemorrhage, which is a very important objective.

So we discussed the past, present, and future of stroke prevention in people with atrial fibrillation. We heard already about the very common occurrence of atrial fibrillation. The numbers are increasing exponentially because we are detecting Afib much better. An anticoagulant that can efficiently lower the risk of ischemic events without increasing hemorrhages will be a big breakthrough in our care of patients, and hopefully we will be preventing a lot more stroke if factor XIa inhibitor studies are successful in the field of atrial fibrillation.

So here, I finished my talk, and next up is Dr. Shadi Yaghi from Brown University and Rhode Island Hospital who will discuss. And now, we are going to shift gears and discuss the role of antithrombotic therapy in secondary stroke prevention.

Chapter 3: The Role of Antithrombotic Therapy in Secondary Stroke Prevention

Dr. Yaghi:
Thank you very much. Great to be with everyone here. And I'm going to focus on non-cardioembolic stroke. My colleague, Dr. Gurol, discussed cardioembolic stroke and AF. So non-cardioembolic stroke could be from small vessel disease, which would be a lacunar stroke less than 2 cm in size, affecting the deep structures in the brain. In addition, large R3 atherosclerosis, when you have an atherosclerotic plaque ipsilateral to the stroke causing more than or equal to 50% stenosis. Also, patients could have a diagnostic evaluation, and you may not find the etiology and they're labeled as embolic stroke of undetermined source.

Or you could find another mechanism like dissection. So I'm going to discuss antithrombotic therapy and these different subgroups of stroke.

So I'll start with the platelet activation and aggregation process. So endothelial injury is the first step, and then there's platelet adhesion. Then there's activation, secretion, and then there's platelet aggregation. And after platelet aggregation, there's the thrombus formation and that's through the clotting pathway that leads to activation of fibrinogen into fibrin, and then there's cross-links, and those would form the thrombus. And this is the pathophysiology of most of our ischemic strokes.

And there are several medications or molecules that can inhibit platelets. Aspirin works on the COX enzyme that inhibits arachidonic acid transformation to thromboxane A2 that activates platelets and causes platelet aggregation. Also, cilostazol and dipyridamole, they're phosphodiesterase inhibitors. They inhibit the transformation of cyclic AMP to AMP. AMP activates platelets and causes platelet aggregation.

And then you have the agents or the medications that work on P2Y12 receptors. P2Y12 receptor, the ADP binds to it and causes platelet aggregation. So ticagrelor is a reversible inhibitor of P2Y12 and clopidogrel is another one, as well.

And there are anticoagulants as well, and my colleague, Dr. Gurol, discussed some of them. There are the factor Xa inhibitors – rivaroxaban, apixaban, and edoxaban – and thrombin inhibitors. The one that is currently used is dabigatran. And then there are factor XIa inhibitors that are anticlotting but doesn't affect homeostasis.

So let's start with the different regimens that we use for secondary prevention. Antiplatelet monotherapy has been the most commonly used regimen for most strokes if the patient doesn't have atrial fibrillation. And there are several trials. They are pretty old trials. I'm not going to go through the details of them, but aspirin was shown to be superior to placebo in IST, ESPS-2, and CAST. The trial looked at Aggrenox, which is the combination of aspirin and dipyridamole. It showed that it's superior to aspirin, ESPS-2. And then, PRoFESS compared aspirin plus dipyridamole, or Aggrenox, to clopidogrel and showed no difference between the 2. There were more side effects from aspirin and dipyridamole, Aggrenox. Mainly, it's headaches. But also, it's a twice-daily dosing, so clopidogrel is more commonly used.

Ticagrelor is another new medication that's used for secondary stroke prevention, and the SOCRATES trial compared ticagrelor to aspirin and showed no significant difference between the 2.

More commonly used regimens nowadays are dual antiplatelet therapy. They started with the CHANCE trial, and we're talking about a short duration of dual antiplatelet therapy followed by a transition to a single agent. The first trial that looked at that was CHANCE. It was done in China. A large randomized controlled trial of 5,170 patients who had a minor ischemic stroke, NIH 0 to 3, and high-risk TIA, and they were randomized to receive aspirin versus aspirin plus clopidogrel for 21 days, followed by aspirin monotherapy. And it showed that the combination treatment significantly lowered the risk of recurrent stroke, and the major bleeding risk was similar in both groups; 0.3% versus 0.3%, and the P-value was not significant. So very promising treatment early on in minor ischemic stroke and TIA.

The results were similar to the POINT trial that was done in the US and Canada. POINT enrolled 4,881 patients with TIA and minor stroke, randomized them to aspirin versus aspirin and clopidogrel. The difference between POINT and CHANCE is the loading dose was 600 mg of clopidogrel versus 300, and POINT continued the regimen for 90 days and then switched them to single agent.

The results were slightly different in POINT. So in POINT, there was a significant reduction in subsequent ischemic stroke risk with combination treatment versus aspirin – reassuring. However, there was an increased risk of bleeding with dual antiplatelet therapy versus aspirin. This was statistically significant. When they further analyzed the data, this was not significant at 30 days. The curve separated more and more as time went on, so it was thought that maybe we should give a shorter duration of dual antiplatelet therapy and then switch to aspirin before 90 days.

The THALES trial looked at ticagrelor. Again, we're talking short-term treatment here. It randomized 11,016 patients with mild to moderate ischemic stroke, so NIH 0 to 5, or high-risk TIA within 24 hours to aspirin plus ticagrelor versus aspirin. And they treated patients for 30 days here, and then switched to single agent, and they showed a significant reduction in subsequent ischemic stroke risk with combination treatment versus aspirin but an increased risk of major bleeding as well, and it was mainly extracranial bleeding.

And there's some concerns with clopidogrel, which is clopidogrel resistance. And clopidogrel has to be activated into the active form via CYP2C19, and some individuals have loss of function of CYP2C19, so they don't have this activation process and, therefore, they may be resistant to clopidogrel.

CHANCE looked at this group of patients who may be resistant to clopidogrel based on CYP2C19 testing, and they randomized them to receive clopidogrel, the medication that needs activation, versus ticagrelor that does not go through this pathway and does not need activation. So they did dual antiplatelet therapy, aspirin plus clopidogrel, versus aspirin plus ticagrelor, and they showed that the combination treatment of aspirin and ticagrelor in these patients who have evidence of CYP2C19 loss-of-function allele, where they're resistant to clopidogrel, this combination of aspirin and ticagrelor worked better than aspirin and clopidogrel.

Triple therapy was studied in the TARDIS trial. So we're giving 2; 2 works better than 1. Does 3 work better than 1? So TARDIS was a trial that was published in *Lancet* in 2018 that randomized 3,096 patients with ischemic stroke or TIA within 48 hours to aspirin plus clopidogrel plus dipyridamole versus standard of care treatment for 30 days, and it didn't show a difference between the 2 treatments. But it did show that there was more bleeding with triple therapy, so perhaps 3 is too far; 1 may not be sufficient. Dual antiplatelet therapy is the way to go short term for these patients.

What about long term? Should we continue dual antiplatelet therapy long term? This was looked at in the MATCH trial and SPS3 trial and showed that there was no reduction in the risk of recurrent stroke. However, there was increased bleeding with continuing a dual antiplatelet therapy long term.

On the other hand, cilostazol was studied in Japan as an add-on treatment to any antiplatelet regimen the patient was receiving. This was studied in the CSPS.com trial in Japan. It randomized 1,879 patients with ischemic stroke within 180 days to aspirin versus clopidogrel in addition to cilostazol. Whatever regimen they were on, they added cilostazol. And they showed that dual therapy, adding cilostazol long term, significantly lowered the risk compared with monotherapy without increasing the risk of bleeding.

So let's talk a little bit about anticoagulation and non-cardioembolic stroke. Once warfarin was proven in AF, the stroke community and others said let's try warfarin in other strokes; maybe it works better. So WARSS looked at warfarin in patients with non-cardioembolic stroke. It compared warfarin and aspirin. It didn't show a significant difference in stroke or death between the 2. There was more minor bleeding complications with warfarin compared to aspirin, and there was no significant benefit.

WASID looked at warfarin in patients with intracranial atherosclerosis. We know these patients are very high risk for recurrent stroke, so WASID said let's check warfarin versus aspirin and see if it worked better. In fact, warfarin did not work better than aspirin. There was no significant reduction in ischemic and subsequent ischemic stroke; however, there was significantly more major bleeding events with warfarin.

What about in DOACs? DOACs were looked at in ESUS. There were several randomized controlled trials looking at direct oral anticoagulants in patients with embolic stroke of unknown source, thinking that these patients have a clot, some of these are coming from the heart, some of these have some sort of clotting problem, some may be coming from the artery, some have a PFO. Let's put them all in one category and say: These are embolic strokes; let's test DOACs on them. The ESUS trials were all negative. This is a meta-analysis of all the trials, showing no significant benefit of a DOAC over aspirin in patients with ESUS.

Dissection showed a slightly different finding. So in patients with cervical artery dissection, this is an updated meta-analysis of observational studies and RCTs showing that anticoagulation, in fact, is superior to antiplatelets in lowering the risk of subsequent ischemic stroke in patients with dissection, but it carried a higher risk of major bleeding, arguing for an individualized treatment approach, weighing the net clinical benefit of ischemic stroke prevention versus bleeding complications.

So anticoagulation, as we saw in most of these trials, carries a high risk of bleeding. Dual antiplatelet therapy short term is better than a single agent. However, we're still seeing high risk of ischemic strokes even on dual antiplatelet therapy, so this led to starting to think, should we think about dual pathways inhibiting antiplatelets and potentially adding low-dose anticoagulation? This was looked at in the COMPASS trial. COMPASS looked at low-dose rivaroxaban plus aspirin versus aspirin alone versus rivaroxaban alone, and it showed that the combination treatment had a significantly lower risk of cardiovascular death, stroke, or MI compared to each one of these agents separately.

There are ongoing trials looking at factor XIa inhibitors, promising treatment, and again, looking at the concept of dual therapy. Maybe if we inhibit anticoagulation or if we inhibit clotting and we inhibit platelets without increasing the risk of bleeding, maybe that will lower the risk of subsequent ischemic stroke without increasing the risk of major bleeding. So these trials are ongoing.

So I know I've talked a lot about antithrombotic therapy, but these are really important things to also think about and definitely talk to the patient about. Getting active, exercising, eating healthy, losing weight, stopping smoking, definitely looking at other avenues for stroke prevention like lowering cholesterol, managing blood pressure, and reducing their blood sugar.

So as a conclusion, along with other secondary prevention strategies, adequate platelet inhibition is a very crucial aspect of secondary stroke prevention, particularly early on after a non-cardioembolic ischemic stroke. No benefit of anticoagulation therapy overall, except in the patients with dissection, and most trials actually showed an increased risk of bleeding.

Dual inhibition of platelets and coagulation may be a promising strategy that's currently being tested in trials.

Thank you.

Dr. Gural:
Thanks, Dr. Shadi, for this excellent and detailed overview. Now, the only thing that I don't like was about being overweight and such. So, I mean, it's true that this risk factor control is very important, but in situations with atrial fibrillation and such, unfortunately, risk factor control is never enough to prevent stroke, and we need medical approaches to prevent stroke in those cases, we can afford to discuss.

So now I have the pleasure of introducing Dr. Jeffrey Weitz from McMaster University in Hamilton, Canada, and he's the big expert on medical management and anticoagulants, and he will tell us about the new therapies in secondary stroke prevention, a glimpse into the future.

Chapter 4: Innovative Therapies in Secondary Stroke Prevention: A Glimpse into the Future

Dr. Weitz:
So the direct oral anticoagulants were introduced 15 years ago and they're already generic in almost every country except the US. So we have these agents, we've got a lot of experience using them, and although they come closer to that magic bullet of providing a reduction in thrombosis without increasing the risk of bleeding, there's still a significant increase in bleeding with the DOACs. They're better than warfarin, we're using them widely, but we still have a problem with bleeding, as you've heard so far.

And this, either, the fear of bleeding or, in fact, bleeding, has led to the systemic underuse of anticoagulants for stroke prevention in atrial fibrillation, and if they are used, there's an overuse, an inappropriate overuse of the lower-dose regimens of the direct oral anticoagulants with the false belief that that will reduce the risk of bleeding and still provide stroke protection. But both of these lead to unprotected patients. So there's still a need for safer anticoagulation therapy, and that's where factor XI comes in.

So remember that there are 2 separate pathways by which coagulation can be initiated. There's the tissue factor pathway; this is the pathway that's initiated when atherosclerotic plaques are disrupted and tissue factor in the core of the plaque is exposed to the blood and triggers coagulation via this extrinsic pathway. There's also the intrinsic or contact pathway, and this is the pathway that's traditionally initiated when blood comes into contact with a negatively charged surface. That might be a mechanical heart valve or a stent or a catheter. And this leads then to activation of coagulation through that intrinsic or contact pathway. And these pathways converge at the level of factor X and result in the common pathway that leads to clot formation.

Now, all of the currently available oral anticoagulants target that common pathway. They either reduce the synthesis of factor X and prothrombin, such as warfarin, or they inhibit factor Xa or thrombin, but they're blocking that common pathway. So now we want to move upstream to the level of factor XI, which resides in that intrinsic pathway. And let me show you. You've heard a lot about uncoupling thrombosis and hemostasis. Let me show you how this works.

On the left side, we see hemostasis; on the right, we see thrombosis. Now, both of these pathways lead to the formation of a blood clot, but location, location, location. In the sense of hemostasis, we're talking about a blood clot that's forming to seal a hole in a blood vessel. That's a predominantly extravascular event. It's triggered when there's an outside-inside damage to the blood vessel and that then results in exposure of the blood to the very high concentrations of tissue factor that surround the blood vessel in that hemostatic envelope. That leads to explosive thrombin generation and fibrin formation, and factor XI is mostly redundant in that process.

Look to the right at thrombosis. This is intravascular blood clot formation. Here, we get exposure of a little bit of tissue factor when, say, an atherosclerotic plaque is disrupted. That little bit of tissue factor induces the formation of fibrin, which covers up the injury site. So what results in expansion of that clot? Well, that's feedback activation of factor XI by thrombin, which generates more Xa and more thrombin. So factor XI is important for this amplification step that results in clot expansion, and if that intravascular thrombus expands, it blocks the blood vessel and can lead to a stroke or a heart attack.

So here's where our current anticoagulants work, the DOACs and warfarin. They block factors in the common pathway at the level of Xa or thrombin, and that common pathway is important both for the hemostatic process and for the thrombotic process. So as a result, the inevitable consequence is, as you get more drug on board, you're also going to increase the risk of bleeding. Contrast that to factor XI inhibitors. Factor XI is essential for thrombosis for clot expansion, but mostly redundant for hemostasis. So by blocking factor XI, we can attenuate thrombosis but not have much effect on hemostasis, and this gives us safer anticoagulation.

So what evidence do we have that factor XI is a good target? You've heard about some of this already. We know that people with congenital factor XI deficiency rarely have spontaneous bleeding, but they're protected from thrombosis. We know from large genetic epidemiology studies that persons with low factor XI levels rarely have an increased risk of bleeding, but they're protected from thrombosis. Those with high factor XI levels are at increased risk for thrombosis. And finally, in animal studies, if you knock out factor XI or you inhibit factor XI in rodents or in nonhuman primates, you attenuate arterial and venous thrombosis in response to injury, but you don't get bleeding. That's very different from the DOACs where you attenuate Xa or thrombin activity, you attenuate thrombosis, but the more drug you give, the more bleeding you get.

So we have factor XI inhibitors that come in different flavors. We've got antisense oligonucleotides to reduce the synthesis of factor XI and now sRNAs. We've got antibodies that block factor XI activation or factor XI activities, and we've got the small molecules, asundexian and milvexian. Now, traditionally, we start the assessment of new anticoagulants in the orthopedic surgery model. We use this model because these patients are at risk for postoperative deep vein thrombosis that can be readily detected on a venogram, an X-ray of the veins, about 10 or 12 days after the surgery, so this is a very efficient way to look at different doses of the anticoagulant and assess its effect on thrombosis. And when these various factor XI inhibitors were compared with enoxaparin, in that orthopedic model, you see that there was about a 40% reduction in the risk of postoperative venous thromboembolism and that was associated with about a 60% reduction in clinically relevant bleeding. So in fact, there is some evidence that we can dissociate thrombosis and hemostasis. We can get better antithrombotic activity without paying the risk of more bleeding.

We've heard already that the COMPASS trial showed the benefit of dual pathway inhibition, so if we add a very low dose of rivaroxaban on top of aspirin, and I'm focusing here on recurrent stroke in patients who'd had a previous stroke, you see a marked reduction in recurrent stroke with dual pathway inhibition. The problem is rivaroxaban's associated with an increased risk of bleeding. So can we do better with a factor XI inhibitor?

And we had the AXIOMATIC secondary stroke prevention study with milvexian. It evaluated a 16-fold range of milvexian doses from 25 mg to 400 mg for secondary stroke prevention on top of antiplatelet therapy. The PACIFIC-Stroke, a 5-fold range of asundexian doses from 10 mg to 50 mg, again on top of antiplatelet therapy, and in both studies, the drugs are compared with placebo.

What did we see? Well, the primary efficacy outcome of those studies was the combination of secondary symptomatic stroke and recurrent covert stroke detected on repeat vein imaging. We didn't see a reduction in that primary outcome, but there was no evidence of an elevated risk of hemorrhage, and both studies showed a trend for a reduction in recurrent symptomatic stroke, although not a reduction in the recurrent stroke detected by imaging.

So these studies have led to the ongoing OCEANIC-STROKE study which is looking at asundexian versus placebo on top of antiplatelet therapy. Notice the dose: 50 mg once a day, the highest dose tested in the asundexian program.

The LIBREXIA-STROKE study: 25 mg twice a day of milvexian versus placebo. The same total daily dose in both of these trials. A low dose of these drugs because you want a low dose on top of potent antiplatelet therapy to get the benefit without increasing the risk of bleeding.

What data do we have about the safety of long-term factor XI inhibition? Well, we have the recently published AZALEA trial which compared 2 different doses of abelacimab with rivaroxaban in patients with atrial fibrillation and showed a significant reduction in bleeding with abelacimab compared with rivaroxaban, and this is over a median of 18 months of factor XI inhibition.

So we've got safety. Do we know about efficacy? Not yet.

We have the OCEANIC AF trial results. You heard about that already. We had a failure there. More strokes with asundexian than with apixaban. Is this a class effect, or is this a dose effect? And what I want to tell you is I think it's a dose effect and not a class effect. We have ongoing trials in atrial fibrillation with factor XI inhibitors. We have the LILAC trial, abelacimab versus placebo in AF patients who are considered not candidates for an anticoagulant, and we have the LIBREXIA-AF trial looking at 200 mg total daily dose, not 50 mg. It's still ongoing. Almost 20,000 patients enrolled. I think if we were going to see an OCEANIC AF result, we would have seen it already.

So we have a number of trials ongoing. You've heard about them already, and the future here is that targeting factor XI or factor XIa has the potential to reduce the burden of thromboembolic cardiovascular disease while preserving hemostasis and we're eagerly awaiting the results of the phase 3 trials.

Thank you very much for your attention.

Dr. Gurol:
Thank you very much for the excellent review of factory XIa inhibition and how that compares to currently available classical oral

anticoagulants.

Announcer:
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