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The DOAC Revolution: What Have We Learned?

Announcer:
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Dr. Granger:
Good evening. I'm Chris Granger from Duke University. And I'm delighted to co-chair this symposium with Manesh Patel, who will be here in a little while. But I hope we'll have a really exciting and informative session that goes over kind of updates on where we are with stroke prevention and AFib, and it looks towards the future.

So, the basic theme that we're going to go over in the next hour and 15 minutes or so is that we have really good treatments to prevent stroke and AFib, but they're not being used very well and at least a large proportion of the population is not getting them. And the proportion that's not getting them are the highest risk for stroke and bleeding. And the main reason they're not getting them is because of concern over bleeding. And factor XI as a target has the potential to substantially address that problem.

This is kind of where we are on a slide. If you take the warfarin data that Mike Ezekowitz and Danny Singer, you know, we have some real luminaries here in the audience. It's like, pretty exciting. Stefan James, he's like doing all the guidelines for Europe. This is like an all-star audience. So, they're going to correct me if I'm saying anything that's off base. But the guys who did these early trials of warfarin versus control showed that warfarin is a very effective treatment to prevent stroke, like two-thirds of strokes are prevented.

Then we had the series of trials, including Mike Ezekowitz led one and Manesh, and Elaine, and others, that we had the DOAC versus warfarin trials, that showed another 20% reduction. So, then you do the math, and we can prevent 70% of strokes. And Elaine makes the point, and she'll make it I'm sure, that these strokes are not like minor things. These are like big, disabling, devastating events. And to have a treatment that can prevent 70% of those is like remarkable. And but again, the challenge is how do we get used more consistently?

So, this is the best. I just wanted to highlight this, this was put together by the group of people who led the DOAC trials, including Mike is part of this and others, it's called the COMBINE-AF dataset. We got all the individual patients, it's the way to do the highest quality assessment of data that you put together from various randomized trials. And this is pretty remarkable, because each trial had the same control, had the same warfarin control. So, you can do this in a high-quality way. And you can look at time to event, you can look at subgroups, you can look at rare events in a way that you could never do looking at individual trials. So, this is just the topline results that stroke and systemic embolism is prevented 20% more effective prevention compared to warfarin, which is already highly effective. By the way, these trials also showed that warfarin reduces mortality by 25%. And then look on the right-hand side of this slide, you get another 10% relative risk reduction, 11% relative risk reduction in all-cause mortality. That's a great summary of the aggregate effect of DOACs versus warfarin on both stroke and bleeding and everything else. So that really is reassuring that DOACs are really good in aggregate. And you put those two together and you realize compared to no treatment, that DOACs, if you look at warfarin and then DOACs on top of warfarin, probably reduce mortality by 30% in this population. So, these are big - these are big effects. And then there's somewhat less bleeding, there's kind of heterogeneity according to trial in this particular parameter. But intracranial bleeding and

serious life-threatening bleeding is consistently lower with DOACs, over a 50% lower rate of intracranial hemorrhage. So, that tells you we got really effective treatments. But again, they're not being used so well.

So, a couple of points. This is like the most important thing I'm going to tell you tonight to be able to improve the care of your patients on Monday or Tuesday, whenever you get back to your clinical duties. This is the simplest thing we can do. We still see about 20% of people who have atrial fibrillation and are on an anticoagulant are treated with it with aspirin or an antiplatelet agent. And in the – and then you can really - for most of those patients, you should stop it on Tuesday, and you'll improve the care of your patients. And I'll show you a little bit more about that. And there have been a number of analyses that have demonstrated that when you add antiplatelet agents on top of anticoagulants, you increase bleeding substantially, and there seems to be no associated further reduction in thrombotic events.

But the randomized trial that most graphically shows us, it's the single trial, maybe it's a little bit of an overestimate, but I still think it's probably true. This is the AFIRE trial, it was a trial done in Japan, it was taking patients who were on rivaroxaban and had stable coronary disease for at least a year. That means no MI or revascularization within at least a year. And it randomized them to either rivaroxaban alone or rivaroxaban plus an antiplatelet agent; 2,200 patients. And the results, maybe not surprisingly, are that when you added an antiplatelet agent to rivaroxaban, you got a 70% higher rate of major bleeding. So clearly a substantially increased risk. This was the surprise though, you also had higher risk of thrombotic events and you also had higher risk of death. In fact, an 80% increased risk of death with hazard ratio 1.8 from all-cause mortality. You know, you might ask how could this be? Stefan, we did a lot of work with this, right? About – in acute coronary syndromes, you use more intensive antithrombotic therapy, paradoxically, you actually can get more thrombotic events. Part of the reason for that is when you get bleeding, we tend to stop the antithrombotic therapy and then you get ischemic events.

So bottom line here is, you know, we have a lot of data now that for patients even who have coronary disease, as long as it's stable, anticoagulation alone is what we should be using. Elaine is going to cover the issue of bleeding in some detail, I'll just make a couple of points. First of all, it's pretty common. The yearly rate even in patients enrolled in trials who are lower risk than patients in unselected general practice settings, is like around 3% per year of major bleeding across the randomized trials.

This is work that Elaine published from ARISTOTLE, showing that the risk factors for bleeding are over on the right. And they're kind of the standard things that you would predict, including concomitant aspirin. It kind of confirms or it reinforces the randomized data. And but then these are the causes of bleeding. So, the number one site of major bleeding in these trials is gastrointestinal. So that's – and it's mostly upper GI bleeding, and then intracranial the most devastating, hematomas and a variety of other things like epistaxis can be pretty common. These are the other factors. And then the bad news about GI bleeding is not only is it the most common, but it's also a type of bleeding that is not lower with DOACs and warfarin. The other types of bleeding tend to be lower, but not GI bleeding.

So, Stefan James' group at Uppsala, with Lars Wallentin and Ziad Hijazi and others, have done I think the best work ever done with integrating biomarkers with clinical factors to predict bleeding and stroke for patients with AFib. So, this is the bleeding risk score, the ABC, that stands for age, biomarkers, and clinical factors. And it's really interesting, the number one factor is a biomarker that maybe some of you have never heard of called GDF-15. It's growth differentiating factor-15. It seems to be a marker of like vascular aging and vascular integrity.

And then the second most important factor, high-sensitivity troponin, this is for predicting risk of bleeding. And, you know, those that were somewhat surprising. But the clinical factors, if you want to remember three clinical factors to assess, these are the only independent factors once taking biomarkers into account, their older age, low hemoglobin, which probably is somewhat of a marker of prior bleeding and general health, and previous bleeding. So those are the three most important factors for predicting risk of bleeding.

I don't know if Danny and Elaine will agree with this. Maybe you'll comment on this, but I - like the HAS-BLED score I don't think it's particularly helpful. It's got a C-index of like a coin flip. And so, I don't really recommend people to calculate the HAS-BLED score, but I think it's really important to be familiar with, especially modifiable factors but also with these three factors that predict bleeding.

So why is bleeding important? This is from a Swiss analysis of their registries. So first of all, bleeding is very common, 20% at 4 years major bleeding, hospitalization for bleeding. So, we want to prevent and reduce the risk of bleeding. And then patients who bleed are at higher risk for thrombotic events. I made this point earlier. So, there's a 36% higher risk of MI, stroke, and death in those who bleed, so we need to, again, decrease bleeding, so avoid nonsteroidals, antiplatelets, choose safer anticoagulants. And then finally, it's common that these drugs are not restarted after a bleeding episode. And that's a challenge clinically, right? If you have someone who had major GI bleeding, 5 units of transfusion, hospitalized, you know, when do you restart the anticoagulant? And how do you feel about it? So, these are tough questions. But it's an important part of the issue.

How about the elderly? You know, we get concerned about the elderly, because it is one of the most important risk factors for bleeding.

And we have – I just want to mention two sets of randomized data in the elderly of anticoagulation with DOACs versus control, either placebo or aspirin.

So, the first is ELDERCARE. This is a Japanese trial about 1,000 patients, edoxaban at the lower dose that's commonly used in Asia versus placebo. There was this 70% reduction in risk of stroke and about a doubling in risk of bleeding. But clearly the net effect was beneficial in this population of 80 years of age or older, mean age 87. So, this is really an older population that had clear benefit.

And then the AVERROES trial looking at that subpopulation, which was 2,000 patients who are at least age 75. By the way, most of these got the full dose of apixaban, 5 mg twice a day, only had one dose reduction factor, and/or 1 or 0. And here, you also see about a 70% reduction in risk of stroke. And in this case, not much bleeding compared to aspirin. Elaine makes this point a lot that aspirin is not safe in the elderly. And in fact, it's really not safer than apixaban. Then this is the other interesting thing, intracranial hemorrhage, numerically fewer with apixaban than aspirin. Now there's tiny numbers. But anyway, this is kind of consistent now, we're seeing this in a fair number of trials that intracranial hemorrhage does not seem to be increased compared to aspirin for DOACs in general.

Another reason we withhold anticoagulation is because of falls, like my mother. I talk about my mother a fair amount and she fell a lot and stayed on anticoagulation, and I think it really reduced her risk. And she never had major problems from the falling. But the bottom line here, this is a study that included Graham Nichol from Ottawa a long time ago in 1999, but – and it used a Markov model, and it estimated you have to fall 295 times a year before the benefit of warfarin would be outweighed by the risk. And then if you double that, because the risk of intracranial hemorrhage is - even traumatic intracranial hemorrhage is, you know, 50% or lower percent compared to warfarin, then you'd have to fall basically, I don't know, basically, like 3 times a day before you shouldn't use an anticoagulant in these patients who are falling. As long as they're not hitting their head and getting intracranial hemorrhage, that's a different situation. But basically, if a person falls a few times, which is all too often a reason that people withhold anticoagulation, don't withhold anticoagulation.

So, the guidelines are pretty clear. If your CHADS VASc of 2 or greater and sex doesn't include as one of the factors, then treat with a DOAC. Don't treat if your CHADS VASc 0. If you're CHADS VASc 1, then that's kind of what we call shared decision-making, which is a euphemism for we don't know what to do in that situation.

But one of the things that I really recommend that you can do is check a pro-BNP and look at the left atrial size, because those are factors that are not incorporated into these risk models. And if the patient's pro-BNP is high, these again are data from Uppsala. There's a complementary increased risk with high pro-BNP and risk of stroke with the CHADS VASc score. So, if it's greater - if you're pro-BNP is greater than 700 to 1000, then you're getting in a range where that's meaningful information that it's a higher risk of stroke and consider anticoagulation.

And then the clinical factors, again from the same ABC risk score approach, in addition to biomarkers, were prior stroke and TIA. That's the single most important factor that predicts risk of future stroke on an anticoagulant, prior stroke or TIA in older age. Those are the two most significant risk factors.

Another question, this is relatively recent information, but this is a common question that usually neurologists deal with, but we deal with it also, is somebody comes in with a stroke, let's say they're on an anticoagulant, and they come in with a stroke, then as a variety of questions, should you switch to a different one? You know, make sure you know they're adherent. Or a new stroke as a first diagnosis of AFib, which happens a fair amount too. Then when is it safe to start anticoagulation with a DOAC? And so, this was addressed in this trial that was recently published in *New England Journal*. And the bottom line is, compared to what we thought was the case, this is work that Chris Diener had done, where you should wait like 12 to 14 days after a major stroke before starting anticoagulation. Patients did really better if it was started earlier, 48 hours after a minor or moderate stroke, and 6 to 7 days after a major stroke. So, you can start it fairly early after strokes as long as they're not hemorrhagic transformation. And then it's a little bit of a trickier issue.

Chronic kidney disease is another factor that you'll hear more about, I think from Cecilia. But basically, we don't have much data when kidney disease worsens. So, this another opportunity, I think, for factor XI as a possible target. Because what we know is, as kidney function declines, risk of stroke increases, risk of bleeding increases, and it's trickier to use DOACs. So, we have randomized data with DOACs down to an estimated GFR of 25. We have limited data below that. But basically, we really have uncertainty about what we should do.

One of the things though that we definitely should do is do what the trials did for dose reduction. So, if you have two of the three criteria of the dose reduction criteria for apixaban, reduce the dose. If your GFR is less than 50, your creatinine clearance less than 50, then go down to the 15 mg. And likewise for edoxaban, do what was done in the trials. And then you'll get results in that low creatinine clearance group that are comparable in terms of safety compared to warfarin as normal GFR, but only down again to a creatinine clearance of like 25 to 30.

Finally, let me raise this issue which will be addressed by a randomized trial tomorrow morning, by two randomized trials actually

tomorrow morning, NOAH and ARTESiA. And that is what should we do with this AFib that wasn't diagnosed, like by someone coming into a doctor's office or an emergency department and getting a 12-lead EKG, but was diagnosed because they had an implanted device, usually a pacemaker? But there's also questions about like implanted cardiac monitors, like the LINQ monitor, or even Apple Watch, or Fitbit, or Samsung watches now that are giving like millions of people every day – well, I don't know about millions, but let's say tens of thousands of people every day are getting alerts on these devices that they're having some AFib. And what do we do with that? We still don't know, right, Elaine? Still not really sure. But this is data that's beginning to lend some light on the issue of subclinical AFib.

So, this was the data that was presented and published by Paulus Kirchhof at ESC. And it showed that in a modest sized trial, 2,500 patients who had pacemakers or ICDs, and who had risk factors for stroke, and on average they had 2.8 hours was their longest episode of atrial high-rate episodes, which 90% of the time is subclinical AFib, it showed there was a 19% non-significant relative risk reduction in a composite outcome that included stroke, systemic embolism that included MI and DVT, CV death. So, there was some hint of a benefit, but it was not really impressive. And then there was a clear increased risk in bleeding, not surprisingly with edoxaban, versus placebo. The other thing that was shown here is overall this population has a fairly low annual risk of stroke, only about a 1% risk of ischemic stroke. And ischemic stroke likewise was reduced by about 20%. Not significant, but only 49 total strokes.

Salim Yusuf, in his famous 1985 manuscript in *Progress in Cardiovascular Disease* said, less than 50 events for a modest treatment effect is totally inadequate in terms of power. So, my main conclusion about this trial is this trial is in underpowered. But that's not the way it was presented. But anyway, I think it's really underpowered. And if you come tomorrow morning at 8 o'clock to the hotline session, you'll see whether or not I was right. It was underpowered, because of that ARTESiA trial that's - has three times a number of stroke events in it and much longer follow-up in 4,000 patients will be presented by Jeff Healey about whether apixaban is better than aspirin in that population for reducing risk of stroke. This is the design of that trial.

I'm not going to go over factor XI as a target and what's currently available because Manesh is going to cover that in some detail. I will say that at least theoretically and based on data to date, including the AZALEA trial recently with the topline results recently announced and with the presentation will also be at that same session tomorrow morning. Factor XI as a target really looks like it's safer than DOACs, so far at least. And that's because - and people like Scott Berkowitz could explain this much better than I can, that there seems to be this unlinking of the intrinsic and extrinsic pathway with a theoretic construct that factor XI inhibition may reduce pathologic thrombus but allow hemostatic thrombosis to occur. And so, that's - it's an exciting area that again Manesh will cover.

So, my summary since 2009, it's not that long ago, like care for AFib has been transformed. DOACs have become the standard of care to prevent AFib for most patients, a couple exceptions, but most patients. They're more effective at preventing stroke, mainly through reducing intracranial hemorrhage, but also ischemic stroke somewhat reduced, less serious bleeding, consistent benefit across nearly all subgroups, including these high-risk subgroups, but they did not have lower risk of gastrointestinal bleeding, which continues. And bleeding continues to be kind of like the Achilles heel of these drugs in terms of their implementation in care and they're still substantially underused, mainly related to that concern over bleeding.

So, I will stop here.

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