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Time needed to complete: 1h 35m

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While the DOAC Revolution Has Occurred, 40-50% of Patients Remain Untreated... Why?

Announcer:
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Dr. Hylek:
Thank you, Chris. And hi, good evening, everyone. Nice to see some old friends. So, in the next 15 minutes, I will try to go through all of the reasons that I think underlie this incredible underuse of anticoagulants.

Let's just look for a second at the 2019 AHA/ACC/HRS Focused Update of the 2014 Guidelines for the Management of Patients With AF. And the big change here was that warfarin or NOACs had been recommended in the 2014 guideline. But in 2019, for a variety of reasons, I think particularly the reduction 50% and intracranial hemorrhage, that the NOACs were recommended over that standard for 50 years warfarin.

So, one would think with this - all these new agents that you didn't have to monitor, you didn't have to worry about diet, you didn't have to be concerned about the amount of vitamin K that you were consuming. What is the influence of this paradigm shift with anticoagulation? In this particular study, PINNACLE, these were outpatient cardiology practices convened through the American College of Cardiology to say, well, what is the impact of these new drugs on use of anticoagulation for patients with AFib? So, you can see they started with a cohort of 740,000 individuals across the U.S. Their final cohort was 655,000 individuals. And you know, this should be a bit shocking, because it's not surprising that we've been chipping away at warfarin now for many years. I think prevalent warfarin use is probably about 25%, 30%, depending upon where you look. And there is an increase in DOAC use but appreciate that there's still 35 to 40% of individuals with atrial fibrillation documented in the PINNACLE registry, cardiology outpatient practices where we're still not using anticoagulant therapy.

Let's look at this paper published in the *American Heart Journal*. This was looking at international trends in clinical characteristics and oral anticoagulation treatment for patients with AF. This was the results of GARFIELD, as well as the ORBIT-AF and AF II registries. And appreciate that GARFIELD was through 2010 to 2016, ORBIT-AF the second wave of that was also through 2016. GARFIELD was worldwide. And you can appreciate the number of individuals enrolled there, 51,000 patients.

This particular paper focused on the new onset atrial fibrillation. So, what did they find? Again, I think it should be a bit striking; these are individuals newly diagnosed with atrial fibrillation all meeting the current guidelines to be on an anticoagulant. And you can see with GARFIELD, 71% were prescribed an anticoagulant. And as you follow through over the years, you can appreciate a reduction in vitamin K antagonists use, which one would anticipate. But we still have this about 30% of patients that are receiving either nothing or this persistent use of aspirin.

With ORBIT-AF, it looked a little bit better. This was solely a United States, different volunteer practices wanted to be part of ORBIT. But again, you're still faced with about a 20% use of nothing or aspirin among individuals with newly diagnosed atrial fibrillation and appropriate CHADS scores. These numbers get rather dismal when you follow patients out over a year or two. And I'll show you that data.

So, what are the factors driving underuse of anticoagulant therapy? I think we all see these, we're all in clinical practice, we all scratch our heads, but there's two, definitely perceive bleeding risk and true bleeding risk. And say to yourself, what are the absolute contraindications for use of an anticoagulant? And there aren't many. There are some, but there aren't many. And what about the perceived bleeding risk? So, fall risk, obviously. Chris has already talked about this older age, history of bleeding. But what are the absolute contraindications? And in here, this is where I see the use of left atrial appendage occlusion devices or individuals with AVM, GI bleeding, gastric antral vascular ectasia, these patients are almost transfusion dependent, clearly thrombocytopenia, usually platelet count less than 50, prior intracranial hemorrhage, and severe hepatic or renal impairment. And I think these are the groups of patients that I think we would all struggle to maintain on an anticoagulant.

In addition to that, and I think one of the perhaps more prominent reasons that we don't see this, is the uncertainty regarding paroxysmal AF, uncertainty regarding the burden of atrial fibrillation, we see patients in the hospital that develop runs of AF with or pneumonia. Many of these patients leave the hospital without anticoagulation because we're attributing it to something temporal, something that's going to change. Certainly, there's uncertainty regarding success of rhythm restoration. This is also common. Patient preference and mixed messages that patients get from the media, as well as nonadherence.

So, how frequent is bleeding with DOACs? This is a squishy number in a sense, because it really depends upon the group of patients that you're studying. Older patients absolutely are at higher risk of bleeding. But this was the bleeding percent per year across the four phase 3 AF DOAC trials. And you can see major bleeding is on the order of 2 to 3%. We really amazingly hit a homerun with intracranial hemorrhage, incredible with the DOACs, 50% reduction across the board. Everyone thought the dabigatran finding couldn't be real, but then that was subsequently seen with each of these. And as Chris has alluded to, we didn't get everything we had hoped for, because the gastrointestinal hemorrhage is still an issue. And this is the site of bleeding that we see most among individuals who were older with atrial fibrillation.

So, this is Christian Ruff's meta-analysis of the four AF trials, really well done. And you can see that again, hemorrhagic stroke, a dramatic reduction in hemorrhagic stroke, thought to be maybe due to the lack of factor VII being in the area with tissue factor in the brain parenchyma. But if you look at the GI bleeding, 25% increase in gastrointestinal hemorrhage. So again, this is something we're not going to get away from and I think this is one of the other potent reasons that we're going to see the factor XIa development programs.

How can we be smarter about using these drugs? I mean, I'm talking to the choir, I'm sure with all of you being in the professional realm. But clearly, if you have poorly controlled hypertension, you shouldn't be on an anticoagulant. There can't be a more potent risk factor for intracerebral hemorrhage than poorly controlled hypertension. Certainly, a labile INR, these patients were all transitioned to DOACs very early on after these studies were finished. Medications, remember that non-steroidal anti-inflammatories increase the risk of upper GI hemorrhage by 19-fold, huge risk. So, it's really a contraindication to use non-steroidal drugs with patients on these drugs. Certainly, excessive alcohol risk.

If you look at the potentially modifiable bleeding risk factors, I think, again, this is common sense. If your patient has an anemia you've got to figure out why. You know, isn't an occult GI lesion? Should this patient have their GI tract worked up? And then the non-modifiable bleeding risk factors. And I have to credit the individuals who, ERA and the ESC guidelines who kind of took the HAS-BLED score and made it something a little more useful in the sense that there are things that we can do to try to minimize the risk of bleeding on these drugs so that patients don't stop the drugs. They don't want to restart them after a big GI bleed. So hopefully, this will help.

Non-modifiable bleeding risk factors, obviously, dialysis. I'll speak briefly about that. We have zero data about severe - moderate or severe liver impairment. These patients were not enrolled in the trials, that would be the Child-Pugh B and C class, so we don't know really how to handle their hypercoagulability, as well as the hemorrhagic diathesis that comes with patients with liver disease. Malignancy, and then genetic factors.

So, the Cochrane Database of Systematic Reviews, we all respect these reviews, they're rigorous. And this was a look at the direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among AF patients with chronic kidney disease. And shown here on this slide, you can see across ARISTOTLE, ENGAGE, J-ROCKET, RE-LY, and ROCKET, that the estimate of the benefit, I think you can see at the very - I don't have a pointer, but at the bottom, was really suggesting that even though some of these agents were cleared more by the kidney, I think apixaban is about 25%, that it looked as if there was enough exposure in this group, that we should feel okay using these drugs among individuals with a creatinine clearance of 30 to 50. But of course, the problem comes, and what the author stated, that our findings indicate that DOACs are likely as warfarin to prevent all strokes and systemic embolic events without increasing the risk of major bleeding. But the issue being that these results really reflects stage 3, or moderate renal impairment. And as Chris and I think Dr. Bahit will talk in more detail about what can we do with patients with endstage renal disease?

What about fall risk? I think that the paper by Brian Gage was still the best paper that I've read, looking at fall risk. They looked and

randomly selected individuals at six different states in the United States. They looked at the charts, and they designated these patients based on very rigorous criteria as to whether or not they were a high fall risk or a low fall risk. And you can see that he absolutely documented a higher rate of traumatic subdurals and traumatic intracranial hemorrhage among these individuals, mean age of 80. And remember with warfarin, intracranial hemorrhage is a particular issue, 48% were on warfarin. Perhaps surprising was the very strong conclusion was that despite that, the enormous risk of ischemic stroke and the mortality related to ischemic stroke weighed heavily in favor of anticoagulant therapy. And that was the conclusion of Brian Gage's paper.

Paroxysmal AF, we know, this was a good study, looking at the highest risk of not receiving anticoagulation is if you have been diagnosed with paroxysmal AF. This risk of not receiving therapy was even higher or greater than being aged 80 or older. So again, paroxysmal AF, what are we doing with it? It looks like there's a lot of confusion and gray area in the literature and among practice, practicing physicians.

Misconceptions are that paroxysmal AF is due to something else. It was the alcohol you had. It was the pneumonia that you had. It was the stress that you had. You know, we're not going to buy into that being a real entity. It's not as serious as permanent AF, but hey, checking your pulse after ablation is enough, get your watch, you'll be good to go. We'll use the pill-in-the-pocket approach. This notion that it's safe to stop anticoagulation after cardioversion or ablation regardless of stroke risk. Patients go for these procedures; they think they're going to be cured. They expect to come off of these drugs. And this notion that aspirin is an alternative.

One other very brief thing here. This is an interesting paper published not long ago looking at this notion of persistent AF and paroxysmal AF, stating that the burden of atrial fibrillation clearly, as we all know, still remains something that we haven't really nailed down quite yet as far as what is the burden that mandates anticoagulation therapy. We may know more tomorrow.

Treatment persistence and time to discontinuation. This should be shocking. If you look at individuals on rivaroxaban, apixaban, dabigatran, and warfarin, at 12 months, about 60% of individuals are still taking these drugs. A variety of reasons for that, but that's a shocking number. Long-term persistence to any cardiovascular drug is really suboptimal.

The mortality in patients who are deliberately and intentionally prescribed the lower doses of these agents to sort of get away from the bleeding risk. This was a really good paper published by Dr. Camm and colleagues from GARFIELD. And it showed that when you're using the nonrecommended low dosing, look at the all-cause mortality. Striking. So, you're able to lower the risk of bleeding at the expense of death. And I think this is a very important message for those individuals who cut back on the dose because they're afraid of bleeding.

My last few slides. This should be concerning patient-directed information and mixed messages. These are some of the ads that came out when the DOACs were being used. Worst Pills, Best pills, Bleeding on Your Brain, 1-800-BAD-DRUG, and this is really what our patients are bombarded with. This one, the Worst Pills, Best Pills actually recommended warfarin over the DOAC for intracranial hemorrhage risk. Which, I mean, who puts the feet to the fire for these individuals? I mean, it was just purely not true.

It's important for our patients to be their own advocates to be educated. There are so many resources now. The EHRA Consensus Document on Patient Values and Preferences clearly shows this. In addition to that, I wanted to give a little plug for StopAFib.org. Mellanie True Hills is a patient that actually took this forward and now it's an international organization and it's only purpose is to educate patients about atrial fibrillation. What is your doctor telling you? Do you understand what they're even saying? And I would just encourage you all to get those patients educated.

Thank you.

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