Practical use of ANTICOAGULANTS to manage patients with ATRIAL FIBRILLATION

Preventing Thrombosis, Minimizing Bleeding, and Exploring Reversal Agents

FACULTY SLIDE REVIEW

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Slide 1 – Title Slide

Slide 2 – Reminder Slide: Syllabus, Participant Survey and CME Evaluation

Slide 3 – Disclosures

Slide 4 – Learning Objectives

To start out with the learning objectives: number one is to identify atrial fibrillation patients who are at risk for developing ischemic stroke and comply with the treatment guidelines for their management; then we'll evaluate options to overcome the limitations of vitamin K antagonists to reduce the risk of new and recurrent stroke; and, finally, how to individualize antithrombotic treatments to find the right drug at the right dose, for the right patient.

Slide 5 – Polling Question 1

Slide 6 – Lecture Overview

As a lecture overview, we'll be starting with the prevalence and incidence of atrial fibrillation.

Slide 7 - The ECG of Atrial Fibrillation

This is a slide of the electrical circuits of atrial fibrillation. On the left, we know that when patients are in normal sinus rhythm, they have nice, organized electrical activity initiating from the sinus node, going down to the AV node, and then you get coordinated contraction of the atria and ventricle.

In atrial fibrillation, we don't just have a single, organized electrical circuit but multiple abnormal electrical pathways that often lead to this irregular – irregular rhythm with patients often, frequently presenting with a fast heart rate and palpitations.

Slide 8 - Stroke and Atrial Fibrillation Burden

When patients present with atrial fibrillation, they often don't feel well, they may be short of breath, have chest discomfort, feel the palpitations. But what we really care about when we're treating patients with atrial fibrillation is obviously making them feel better, but we're worried that atrial fibrillation significantly increases their risk of stroke. We know patients who have atrial fibrillation, compared to other patients their age who don't have atrial fibrillation, have about a fivefold risk of stroke. But this risk of stroke is not homogenous. There are underlying risk factors that can increase or decrease this risk.

Slide 9 - Atrial Fibrillation: An Epidemic

Now atrial fibrillation strokes actually are the worst types of strokes that you can have. They're more likely to be fatal and they're more likely to translate to permanent neurologic disability. If you look at all strokes, about one in five, one in six are due to atrial fibrillation. If you look at the elderly, particularly people who are in their eighties, this can approach almost one in three strokes. So these are very, very common. Of course, this has staggering implications for our healthcare system.

Atrial fibrillation is quite common. In fact, if you live to the age of 40, you have a one in four chance of developing atrial fibrillation, and it really is one of the epidemics of medicine, not just cardiology. In fact, the incidence and the prevalence of atrial fibrillation atrial fibrillation worldwide is increasing about 20% to 30% over the last 20 years. And there is an increase in mortality that's seen as our population ages and is more likely to develop atrial fibrillation.

Slide 10 - Lecture Overview

We'll move on to risk stratification for stroke and bleeding.

Slide 11 - Efficacy and Safety of Warfarin

This is, of course, the famous curve of the efficacy and safety of warfarin. And warfarin is a very difficult drug to use because we have to manage it in this very narrow therapeutic window with an INR of 2 to 3 by routine, frequent blood testing. And the reason why that is important is, though warfarin can be very effective, when the INR dips below 2, you see that there's an exponential increase in the risk of stroke. But when the INR goes above 3, particularly when it goes above 4, we see an exponential increase in the risk of intracranial hemorrhage. And so being on either side of this range has very serious health implications for patients.

Slide 12 - Nonvalvular Atrial Fibrillation

Obviously, when we have a therapy that could be potentially very effective but does have side effects, particularly serious bleeding, we only want to give it to patients whose risk of stroke is high enough to warrant the risk in bleeding of giving any blood thinner or anticoagulant.

When we look at these slides, we see that patients with non-valvular atrial fibrillation, if they have underlying risk factors for stroke, it significantly increases their individual risk per year, and that is how we got the original $CHADS_2$ score.

The $CHADS_2$ score is an acronym. It stands for very common clinical features that increase the risk of stroke in patients with atrial fibrillation. C is for heart failure, and that's any history of clinical heart failure, systolic or diastolic; H is for hypertension; A is for age greater than 75 years; D for diabetes; and S for prior stroke or TIA. And we see that, when we look at these risk factors, they all tend to increase the risk of stroke about the same except for prior stroke or TIA, where we really see a twofold increased risk of stroke with that particular risk factor. That's why, in the $CHADS_2$ score, all of those factors get one point except for prior stroke or TIA, which gets two, because having a prior stroke or TIA is the biggest risk factor for having another stroke.

Slide 13 – Polling Question 2

Slide 14 - Redefining Risk: CHA2DS2-VASc

The $CHADS_2$ score is a very, very good, simple-to-use bedside risk assessment for stroke, and, generally, we've given patients with atrial fibrillation an anticoagulant if they had a $CHADS_2$ score of 2. But it turns out, if you looked at patients who had a $CHADS_2$ score of 0 to 1, so those who we normally wouldn't consider for anticoagulation in the old guidelines, we saw that approximately 40% to 50% of those patients fell into that low-risk group. And that really begs the question, "Is it really not appropriate to provide an anticoagulant -- which can reduce the risk of stroke by close to 70% to 80% – to almost half the patients with atrial fibrillation?" And people wondered whether we were being too conservative in our cut point for anticoagulation, and that really led to the development of the CHA_2DS_2-VAS_C score, which you could see on the slide.

Now, the CHA_2DS_2-VAS_C score, as you can determine, has all of the original elements of the $CHADS_2$ score, but it adds additional risk factors. So instead of having a single age cut-off of greater than/equal to 75, it now adds a lower-risk age category of 64 to 74. This is nothing magical that happened on your 75th birthday. The risk of stroke due to age is a continual risk.

It also adds a point for having vascular disease, and that is having coronary disease, cerebrovascular or peripheral vascular disease, and also another point for being a female. Now, it's important to remember that females have higher stroke risks when they have atrial fibrillation, but you only get a point for being a female if you have another risk factor. And so, if you have no other risk factors for stroke in the CHA_2DS_2-VAS_C score, and you're a woman, your $CHADS_2$ score -- CHA_2DS_2-VAS_C score is zero. If you have a single other risk factor and you're a woman – say, if you just have hypertension – your CHA_2DS_2-VAS_C score would be 2.

And as you could see on the right-hand side of the slide, that the CHA_2DS_2-VAS_C is a much better arbiter of risk, and that patients with a low CHA_2DS_2-VAS_C score seems to have a much lower risk.

Slide 15 - CHA2DS2-VASc Refines Stroke Risk

What this really translates to is a refinement of risk for patients who are on the lower end. So I don't routinely use the CHA_2DS_2-VAS_C score, but I use it in patients who have a $CHADS_2$ score of 0 to 1 when I'm unsure whether they're truly low risk. Because, in this slide, you can see that you could be $CHADS_2$ score of zero and have a CHA_2DS_2-VAS_C score of zero, 1, 2, or 3. And so where we would lump all of these patients together as a $_2$ zero – very, very low risk – that turns out not to be true. These patients, when stratified by a CHA_2DS_2-VAS_C score, can have a stroke risk of 0.84% per year to as high at 3.20% per year. Remember, this is a per-year risk. And so there is definitely a significant grading of risk that we can pull out with the CHA_2DS_2-VAS_C score, and that's why we've really moved to the CHA_2DS_2-VAS_C score, because it is – makes almost all the patients you see eligible for anticoagulation, probably about 90% of the patients you'd see in clinical practice.

Slide 16 - Initiation of OAC to Reduce Stroke Risk in Patients with AF

And so we see how to approach anticoagulation in patients with atrial fibrillation, and this is from the current guidelines. You should be using the CHA_2DS_2-VAS_C score. And, again, if someone's $CHADS_2$ score is 1 or 2, they're automatically going to have a CHA_2DS_2-VAS_C score of 2 or greater. The new guidelines incorporate not just warfarin but the new or non-vitamin K oral

anticoagulants, which we're going to talk about in a little bit. And we see here that, if you have a CHA_2DS_2-VAS_C score of zero, your risk of stroke is so low that you don't need any antithrombotic therapy, no aspirin, no warfarin, no NOAC.

On the other side, if you have at least two risk factors for stroke – so a CHA_2DS_2-VAS_C score of 2 – you clearly should be on an anticoagulant whether it's warfarin or one of the non-vitamin K oral anticoagulants.

And, now, in the American guidelines, if you have a CHA_2DS_2-VAS_C score of 1, the guidelines lead you to say that you can do a range of things, either having on warfarin or being on a non-vitamin K oral anticoagulant. The ACC-AHA Heart Rhythm Association guidelines saying these CHA_2DS_2-VAS_C 1 patients, you can also give aspirin, but we'll talk a little bit later how that's probably not a good idea and that, at least, we should be considering oral anticoagulants for all patients with a CHA_2DS_2-VAS_C score of 1 or greater.

Slide 17 - Bleeding Risk: HAS-BLED

We've talked a lot about risk stratification for stroke, but, obviously, when you give an anticoagulant, the main side effect is really bleeding. Should we be using risk scores to identify patients at high risk of bleeding? And there are many common bleeding risk scores; probably, the most widely used is the HAS-BLED score. Works very similar to the CHA_2DS_2-VAS_C score in that it's an acronym. H is for hypertension. A is for abnormal liver-renal function. If you have both of those, you would get one point each. S is for stroke. B for bleeding. L is labile INR, so that's only relevant for patients who are on warfarin. E is for elderly; in this case, it's age greater than 65. And D is for drugs or alcohol.

Now the drugs here are antiplatelet medications such as aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs, because those types of drugs all increase the risk of bleeding when being on an anticoagulant. And we see here you've got a maximum score of 9. And high-risk, at least according to the HAS-BLED score, is really having a score of 3 or greater.

Now, the question comes up, "Should we be using the HAS-BLED score to identify patients at high risk of bleeding and then withhold an anticoagulant to say, "There is such a high risk of bleeding that it's not worthwhile for them to be on an anticoagulant, even if their $CHADS_2$ score is elevated." Well, the problem is that patients who have an elevated risk of bleeding are also usually the patients who have an elevated risk of stroke. You see that many of the common factors found in CHA_2DS_2-VAS_C are also part of the HAS-BLED score: prior stroke, elderly, hypertension, etcetera. And the only reason to use the HAS-BLED score is really just to identify patients who might be beneficial to modify their risk factors but not deny anticoagulation. So if they have untreated hypertension, treat it. If they're taking aspirin and clopidogrel, maybe you could stop one of those medications.

Slide 18 - Net Clinical Benefit of Warfarin

But don't deny patients anticoagulation because, even if you take patients who have a relatively low risk of stroke -- and just focus on the top left-hand panel with the CHA_2DS_2-VAS_C score of 0 to 2, so that's the lowest risk of stroke – and who have a high HAS-BLED score, a HAS-BLED score of 3 or greater. We see here those patients on oral anticoagulant therapy – and that's the

OAC – have better outcomes – and this is a composite of mortality -- ischemic stroke and intracranial hemorrhage – than not giving an anticoagulant. So you actually can't find a population where their risk of serious bleeding on an anticoagulant outweighs their risk of having a stroke, as long as their CHA_2DS_2-VAS_C score is at least 1.

Slide 19 – Lecture Overview

Now, we're going to move on to the clinical properties of warfarin.

Slide 20 - Stroke Prevention in AF

It's interesting. We've been using warfarin for over 60 years. Warfarin was approved for human use in 1954, and so anyone who, in the healthcare profession who's been practicing since the 1950s is used to using warfarin. And warfarin is a very effective medication. And this is from the sixth randomized placebo trials of warfarin. And we see here that warfarin is highly effective. It reduces the risk of stroke by about 64%, so very dramatic reduction compared to placebo.

Now, it is interesting to point out that this clinical trial data, since we're all very comfortable using warfarin, is in less than 3,000 patients. I want you to contrast that when we talk about the clinical trial evidence that underlies our support of the NOACs, the non-vitamin K oral anticoagulants.

Slide 21 - Limitations of Warfarin

Now, warfarin survived for many, many decades because it is highly effective but it remains one of the most difficult and dangerous drugs that we use in clinical practice for a variety of reasons. There is delayed onset and offset. It interacts with multiple food and drugs that these patients are on. There is a tremendous amount of genetic variability in how we metabolize warfarin; that is why some patients are on 1 milligram of warfarin a day, other patients are on 20 milligrams of warfarin a day. And, of course, due to this narrow therapeutic index, it requires frequent blood monitoring of the INR. And, of course, warfarin is associated with an increased risk of significant bleeding, that being intracerebral hemorrhage and fatal bleeding.

Slide 22 – Polling Question 3

Slide 23 - Modest Use of Vitamin K Antagonists

So even though warfarin's highly effective, we don't use it as much as we should in patients who have atrial fibrillation and a risk of stroke because it's a difficult drug to use. And this is data from the European Hearts Survey from 2003 to 2004, showing that, regardless of a patient's risk, that we don't seem to be using warfarin higher than about a 60%. So there are still many patients who are eligible for anticoagulant therapy, who are not receiving it.

Slide 24 - Lecture Overview

Let's talk about the clinical properties of the non-vitamin K oral anticoagulant, or warfarin.

Slide 25 - Properties of an Ideal Anticoagulant

So I've already told you about some of the limitations of warfarin. Now, if we were in a pharmaceutical lab in the 1980s or late 1970s, and we wanted to develop an ideal anticoagulant, what are some of the features we would look for? Well, once-daily dosing would be nice. The patients prefer once-daily dosing if all things are equal.

Rapid onset or offset, so you wouldn't have this issue where it takes a while for warfarin to get effective, then, when you stop it, it takes several days to essentially a week for it to be out the system. Minimal food and drug interactions not requiring routing monitoring. Safe in patients with renal disease. Rapid offset of action, so if a patient is going for a procedure or has a bleed, you can stop it and it'll be out of their system. And, of course, an antidote or specific reversal agents, although we know the risk of serious bleeding is low, there will be patients who have these serious bleeds and you certainly would like to have a reversal agent.

Slide 26 - Non-Vitamin K Oral Anticoagulants

Due to this desire for an alternative to warfarin, there was a tremendous amount of research done to development of specific inhibitors, the factors, and the coagulation cascade. And there were two points in the coagulation cascade where these inhibitors had been developed. There are the Xa inhibitors, and three are approved -- rivaroxaban, apixaban, or edoxaban -- and then there is one factor IIa, or thrombin inhibitor -- dabigatran.

Slide 27 – Polling Question

Slide 28 - Comparison Overview of Non-vitamin K Oral Anticoagulants (NOCAs) with Warfarin

If we compare the NOAC to warfarin, this is the class of NOACs – we see that they're rapid-onset, unlike warfarin. They're given in six doses. There is no significant food effect. There are much fewer drug interactions. They don't require routine monitorings. They have a much shorter half-life. And there wasn't an antidote, actually, we just had the approval of our first specific reversal agent or antidote for one of the NOACs.

Slide 29 - Comparative PK/PD

These are the four NOACs. They have a lot of similarities and some important differences. First, they're all rapidly active. If you swallow a pill of one of these agents, you will achieve a full therapeutic anticoagulant effect in about two to three hours. Their half-lifes are broadly similar – around 12 hours; although, interestingly, the drugs are given once or twice daily. But remember a half-life does not equal biologic effect of the drug, so the once- or twice-daily drugs are given at different dosing to provide a full anticoagulant effect over the 24-hour period. So a half-life of 12 hours in a once-daily medication doesn't mean that 12 of the 24 hours they're not therapeutically anticoagulating.

The most important difference from these drugs is really their renal clearance. They all have some degree of renal clearance, and so adjustments in dose are indicated for all of them depending on their renal function; although, where you lower the dose differs across the agents. And the most renally cleared drug is dabigatran, so that's a drug you'd probably have to be the most careful about in patients with moderate renal dysfunction.

Slide 30 - Stroke Prevention in Atrial Fibrillation Trials

There are four landmark trials that studied the NOACs versus warfarin in atrial fibrillation: the RE-LY Trial with dabigatran, the ROCKET AF Trial with rivaroxaban, the ARISTOTLE Trial with apixaban, and ENGAGE-AF-TIMI 48 Trial with edoxaban. These were huge trials – between 14- to 21,000 patients – so a tremendous amount of data that were ascertained by these trials to give us insight whether these drugs are an effective and safe alternative to warfarin.

Slide 31 - Meta-analysis of All NOACs vs Warwfarin

I think it's important to know that these drugs may have differences between them that would cause you to select one drug over the other. But, in my opinion, these drugs are much more similar to each other and different from warfarin. And so the most important decision you can make is whether to prescribe an anticoagulant versus not an anticoagulant, because all of the drugs will lower your risk of stroke by approximately 70% or more.

The second-most important decision is between the NOACs or warfarin. There are some important differences, and probably the least important decision is which NOAC you would prescribe. Now, if we look at all of the trials and look at how this new class of drugs – the NOACs – compare to warfarin, we see that, in addition -- remember, warfarin reduced stroke and systemic embolism by about 64% – the NOACs, as a class, tend to be more effective. They reduced stroke and systemic embolic events by another 19%, so that's pretty dramatic improvement on warfarin, which is already highly effective for this outcome.

Slide 32 – Polling Question 5

Slide 33 - Meta-analysis of All NOACs vs Warfarin

Let's look at a little bit of the details regarding the efficacy of the NOACs. They're about as good as warfarin in reducing ischemic stroke. The hazard ratio is favorable at 0.92, although that's not statistically significant. And remember warfarin is very, very effective for ischemic stroke in particular with a risk reduction by – of about 70%.

What was interesting is these drugs are dramatically better with respect to hemorrhagic stroke. They cut hemorrhagic stroke in half. They're about the same as warfarin for preventing myocardial infarction. Remember, warfarin has been shown in the old days to be as effective if not more effective than aspirin in preventing MIs. And I think probably the most important is people who get a NOAC tend to live longer than those who are on warfarin. Remember, warfarin reduces mortality in the AF population by about 20% to 25%; the NOACs give you about another 10% reduction in mortality, so that's quite important.

Slide 34 – Polling Question 6

Slide 35 - How Frequent is Bleeding with NOACs?

Of course, the flipside of preventing strokes is bleeding. And we see here that, overall, bleeding with the NOACs is actually less frequent, statistically, than warfarin, and so patients have less bleeding. Although, no matter which anticoagulant you give, the risk of bleeding is less than 3% per year. You do tend to see more GI bleeding with the NOACs compared to warfarin, and that's because the NOACs are active anticoagulants in the gut. Warfarin's inert in the intestine, and so if you were to happen to have a bleeding polyp or an ulcer, as this NOACs travels down the intestine, you may get local anticoagulant effect.

It is important to note – and this is data that's been evolving, recently presented at the major cardiovascular meetings – that the type of excess bleeding you see with the NOACs tends to be mild bleeding, And so when you look at serious bleeding or life-threatening GI bleeding,

actually, you tend to see, numerically, less of those types of bleeds than warfarin, so this excess in GI bleeding tends to be minor or mild.

And, of course, the dramatic advance with the NOACs is they essentially cut intracranial bleeding, or bleeding into the brain, by 50%, and that's pretty important. Because, remember, bleeding is kind of a loosely defined term. There are lots of things that can count as a major bleed. What you really worry about when you write a prescription for a anticoagulant is intracranial hemorrhage because 50% of patients who have an intracranial hemorrhage don't survive, and many of those who do have permanent neurological ability. So there is something fundamentally different about the NOACs that cause less bleeding into the brain.

Slide 36 - AHA, ACC, and HRS Guidelines for the Management of Patients with AF

Based on these findings, the AHA, the ACC, and the Heart Rhythm have developed guidelines for the management of patients with AF, and it was published in 2014. And, again, along similar lines, as we talked about, they now advocate using the CHA_2DS_2-VAS_C score instead of $CHADS_2$ and to at least consider anticoagulant therapy in all patients who have a CHA_2DS_2-VAS_C score of 1 or greater. Now, certainly, this is a strong indication for patients who have a CHA_2DS_2-VAS_C score of 2.

Now, I did mention that the U.S. guidelines here for CHA_2DS_2-VAS_C score of 1, they kind of give an equivocal recommendation where they say you could either give nothing, aspirin, or an oral anticoagulant. In my opinion, you should consider giving an anticoagulant to all of these patients, and we'll talk a little why giving aspirin may not be a good recommendation. And I think the U.S. guidelines gave no preference to which anticoagulant you would use. It gives equal treatment of warfarin and the NOACs, and they're certainly all reasonable options for patients.

Slide 37 – Is Aspirin as Effective and Safe as NOACs?

I think there has been a movement worldwide, and the European guidelineshave already endorsed this, and I do think that the U.S. guidelines will soon follow – that aspirin really no longer has an role primarily for stroke prevention in atrial fibrillation. And aspirin is very, very effective for treatment and prevention of vascular disease such as, say, coronary events, but we see here in data from the AVERROES Trial, which was comparing apixaban, not to warfarin but to aspirin in patients who were intolerant of warfarin.

Now, what being intolerant of warfarin really means I'm not sure, but the trial is very interesting because this trial was stopped early, and it was stopped early because aspirin was woefully inadequate compared to apixaban, so it was actually unethical to continue this trial because aspirin was so ineffective. And I don't think that surprised many of us because I think we've sort of known aspirin for stroke prevention in atrial fibrillation really doesn't do much. But what was shocking was that the major bleeding profile, in this case of a – of a NOAC – and this example is apixaban – was as safe with respect to major bleeding as a baby aspirin. So that begs a question, "Why would you give aspirin to prevent strokes in atrial fibrillation when it's not effective and it's not any safer than our current agents available?" And so I think that, really, we should move as a society to say that aspirin really no longer has a role *at all* for stroke prevention in patients with atrial fibrillation. If you want to prevent strokes, you need to give an anticoagulant.

Slide 38 – Lecture Overview

Well, what about the current guidelines in management of AF.

Slide 39 - Choice of Anticoagulant in Patients with AF

This is now the European Society of Cardiology guidelines, and they're taking a little bit more aggressive stance than the ACC-AHA-Heart Rhythm Association guidelines, where they say that, for all patients with a CHA_2DS_2-VAS_C score of 1 or greater, they should be on an anticoagulant. So no more of the hedging on a CHA_2DS_2-VAS_C score of 1. They say everybody with one risk factor gets an anticoagulant.

And I think, because of the better safety data and, really, the better efficacy data with the NOACs, the European guidelines favor the NOACs compared to warfarin and other vitamin K antagonists. I don't know if we can necessarily make as strong a statement in the U.S., primarily because of the cost different issues. The NOACs probably are a better drug for most patients, but, obviously, because warfarin's generic, it ends up being much cheaper and that's certainly an important consideration.

Slide 40 - Japanese Circulation Society 2014 Guidelines

The Japanese Circulation Society also had very, very similar recommendations to the ESC and American guidelines -- with patients who have at least one risk factor of stroke, we should at least consider anticoagulation.

Slide 41 – Lecture Overview

Let's move on to preventing and managing bleeding and, specifically, to comments on the use and availability of reversal agents.

Slide 42 – Are We Using Too Much Aspirin in Patients with AF?

Actually, when you're talking about managing bleeding, we focus a lot on how to manage the bleed, but, actually, the biggest thing that you could do is to prevent the bleed from happening in the first place; that's the best management of bleeding. And if you look at patients who bleed on an anticoagulant, the unfortunate thing is that a lot of it could have been prevented because a significant proportion are due to inappropriate use of concomitant antiplatelet therapy with anticoagulation.

We know that the use of aspirin or any other antiplatelet medication essentially doubles your risk of having a bleed. And this is data from the RE-LY Trial showing that, if you add aspirin, you get a significant increased risk of bleeding. If you add *two* antiplatelet agents – in this case, aspirin and clopidogrel – you get almost a 200% to a 250% increase in bleeding. And so we really should only be giving antiplatelet therapies in combination with an anticoagulant if we absolutely had to, patients who, say, have acute coronary syndrome or get stenting. But routine use of antiplatelet therapy in patients with stable vascular disease can lead to disaster because you are dramatically going to increase your risk of bleeding.

Slide 43 - Renal Function and NOACs

Now, what about renal function? Renal function is very, very important because we know that patients with impaired renal function will have elevated levels of drug, and that would potentially

increase their risk of bleeding, so we want to make sure that we appropriately lower the dose in patients with renal impairment if they qualify for dose adjustment. But, remember, you have to make these dose adjustments as they are indicated in the label because that's how these drugs are studied. Inappropriately giving a lower dose to a patient that doesn't qualify for dose adjustment, say, who has normal renal function, you could actually be providing an inadequate dose and level of drug for that patient. So all the NOACs require dose adjustment for patients with renal dysfunction.

In patients who are on dabigatran, you give 150 milligrams until their creatinine clearance drops below 30, and then you give 75 milligrams twice a day if their creatinine clearance is between fi-- between 15 and 30.

Rivaroxaban the starting dose is 20 milligrams once a day for patients with a creatinine clearance above 50. Once it falls below 50, you reduce the dose to 15 milligrams once daily.

Edoxaban – the starting dose is 60 milligrams once daily, and that's given to patients with a creatinine clearance above 50. There's actually upper-limit cut-off for edoxaban of 95 milliliters/minute, and that was because, in the Phase III trial, for edoxaban, it looked like edoxaban might not have been as effective as warfarin in patients with very, very high renal function, so creatinine clearance above 95. If patients with edoxaban have a creatinine clearance below 50, they should get the reduced dose of 30 milligrams once daily.

Now, apixaban – the starting dose is 5 milligrams twice daily. But, remember, apixaban's the least renally cleared drug, so, actually, to reduce the dose on apixaban to 2.5 milligrams, you need two of three risk factors. So all of the other agents are dose-adjusted based just on renal function, and, apixaban, you actually need two of three, either weight less than or equal to 60 kilograms, age greater than or equal to 80, or serum creatinine greater than or equal to 1.5. So just having renal dysfunction alone is not enough to reduce the dose of apixaban.

Slide 44 - Managing Bleeding with NOACs

Although using the NOACs, we get 50% as less serious bleeding as we do with NOACs, and if we stop antiplatelet therapy, we even further reduce the risk of bleeding on NOACs, there are going to be patients who bleed if you give a blood thinner, and so we need to know how to manage them.

I like this article from Kovacs in *JAC* in 2015, and it is really the four Rs. When you have a patient who is bleeding, you review those patients, and that's really reviewing their records, stopping their drugs -- both their anticoagulant and their antiplatelet agents -- and providing routine management as far as volume resuscitation and identifying the source of bleeding, transfusing with – as necessary.

Then we move on to "remove." And I think it's important to at least consider whether the ingestion of drug has been in the last two hours; if that's the case, you can use oral charcoal for the NOACs. I will say you can theoretically dialyze dabigatran; it's the only dialyzable NOAC. But, to be honest, usually, this situation occurs when you have a patient on dabigatran who

goes into acute renal failure, and arranging for them to be dialyzed, bleeding and acute renal failure on dabigatran is actually fairly challenging.

Number three is to assess, repair, and so surgical evaluation and whether there needs to be an intervention to manage the bleeding.

And it's really only the fourth step, once we go through all of those, that we have to think about reversing. And, now, with the vitamin K antagonists, we are sort of used to giving vitamin K, fresh/frozen plasma, or 4-factor PCC, or prothrombin complex concentrate. Up until recently, we would sort of manage the NOAC bleeding, really, the same way. Vitamin K is totally ineffective in patients who are bleeding on a NOAC, but you can use the 4-factor PCC, or prothrombin complex concentrate.

And so, really, their PCCs are non-specific reversal agents that you can give to both VKA bleeding patients and NOAC bleeding patients, which is basically giving them clotting factors to allow them to clot. Now, remember, any time you giving clotting factors, you are potentially increasing a patient's risk of having a clot, and so you do have to, at least, think about that in your bleeding patients.

Slide 45 - Non-specific Reversal Agents

Again, these are non-specific reversal agents. Right? They can be given to bleeding NOAC patients or vitamin K antagonist patients. They are not antidotes or specific agents, but they provide clotting factors to enable that patient to clot. There are various types of PCCs. There is 4-factor or 3-factor. There is activated PCCs. It really doesn't matter which one of these you use, whatever is available at your local hospital or clinic. There also is another non-specific reversal agent – recombinant factor VIIa. I would probably use the PCCs before recombinant factor VIIa just because the limited data that we have for all of these agents, it seems to be that there may be more of a prothrombotic effect with recombinant factor VIIa.

Slide 46 - New and Emerging Antidotes

Unlike the non-specific reversal agents that we have for warfarin, and the NOACs previously, we now, at least, have antidotes or specific reversal agents for the NOACs; there are three. The first one is idarucizumab. It's a monoclonal antibody, humanized antibody fragment to dabigatran. It's actually made by the same company that makes dabigatran. This drug was actually FDA-approved in October of 2015. So if you have a patient who is bleeding with life-threatening bleeding on the dabigatran, or needs an urgent surgery, you actually have a specific reversal agent, or antidote.

There is in late-stage clinical development a specific reversal agent, a common one, for the factor Xa inhibitors. This is called andexanet alfa. It's basically a factor Xa decoy. It looks like factor Xa but it lacks the catalytic binding activity, and so the factor Xa inhibitors bind to andexanet alfa and it just sequesters them, allowing your own native factor Xa to initiate the clotting cascade. Theoretically, this compound will work for rivaroxaban, apixaban, and edoxaban. And, again, not yet FDA-approved but it's given breakthrough status by the FDA, and it is possible that'll become available next year.

And then the third agent is much further along in development. We do know less about it. It's now either called PER977 – it has several names in the literature; the most common one being used now is ciraparantag. This is an interesting molecule. It's a small molecule and, theoretically, it actually reverses all anticoagulants, so it's been purported to work for low molecular weight heparins, NOACs, and so kind of a universal anticoagulant, and it works by charge- -- charge interactions and non-covalent bonding. But, again, this agent is much further along than the other two.

Slide 47 – Lecture Overview

What about considerations for choosing an anticoagulant? So I think, first, it is important to know that the biggest decision is really anticoagulant versus no anticoagulants; that's the most important.

Slide 48 - Patients Not Well Suited for an NOAC

The first-most important thing is whether patients are eligible for an anticoagulant, because no matter which anticoagulant you give, it reduces their risk of stroke by about 70% to 80%. The next-most important decision is whether you're going to use a warfarin or the NOACs. And it is important to remember that there are some patients who are – warfarin remains the standard of care. In patients who have: a mechanical heart value, moderate to severe mitral stenosis, pregnancy, who have stage IV chronic kidney disease, moderate to severe hepatic failure, children, extremes of body weight or age, or a malabsorption system in the gut, warfarin may be a better choice.

I would like to just comment on several of these features. One, I didn't mention all valvular heart disease, because you hear this term "non-valvular atrial fibrillation." What does that mean with respect to eligibility for a NOAC? Really, the only thing that means is patients who have a mechanical heart valve or moderate to severe mitral stenosis – those patients should be on warfarin because these agents are not approved for those individuals. All other types of valvular heart disease, it's fine to use a NOAC.

This issue of end-stage renal disease or stage V CKD is a challenging one. I will say that apixaban is approved for use in these patients, for patients on dialysis. This was not made based on clinical outcomes data; it was based on PK modeling from the Phase III trials that said, in patients with end-stage renal disease, that, because apixaban's the least renally cleared of the drugs, that the levels did not seem to be too elevated in those patients. But I would say most guidelines' treating physicians are uncomfortable using a NOAC in patients with this severity of renal dysfunction until clinical outcomes data are available.

Slide 49 - Optimal Candidates for NOACs

Who are the optimal candidates for the NOACs? We've talked about who you might still want to use warfarin in. Well, actually, it's most patients who have atrial fibrillation. And, again, there is this term "non-valvular." But, remember, "valvular" for the case of NOAC only means mechanical heart valves or moderate to severe mitral stenosis. Certainly, patients with good renal function are ideal candidates, and so I think that, really, the NOACs apply to most patients with atrial fibrillation.

Slide 50 - Renal Function and NOACs

Again, we talked about this, that the NOAC trials did not allow patients with very severe renal dysfunction, so, really, below 25 or 30, we have very little data on the NOACs. I will say that the NOACs appear to perform very well in patients who have moderate renal impairment. So, certainly, from 30 to above, the NOACs seem to have distinct efficacy and safety advantages over warfarin even more so than in patients with normal renal function.

I will say, you do have to be careful, though, with dabigatran in patients who have really impaired renal function because the drug is significantly renally cleared.

And we've already spoken about that all the NOACs required dose adjustment for renal dysfunction. And, on a prior slide, we walked through what those lower doses are as well as their relevant dose reduction criteria.

Slide 51 - Important Factors when Considering an NOAC

What are important factors when considering a NOAC? Really, all patients with atrial fibrillation should be considered for anticoagulation. And a NOAC is certainly -- I think, have been proven from the Phase III trials to be as effective if not more effective than warfarin, with significant reductions in serious bleeding and mortality. The NOACs are an excellent agent except for patients who have a mechanical heart valve/rheumatic mitral stenosis, women who are pregnant, and there is no data for their use in children.

The real advantage of the NOACs, in my opinion, is that they reduce intracerebral hemorrhage and actually intracranial hemorrhage, in general, by 50%; that's a dramatic advance. They also are safer with respect to major bleeding. They reduce at about 14%, so you will see less bleeds overall with the NOACs. They are more effective, on average, reducing stroke and systemic embolism by 19%. Of course, they reduce mortality by another 10% compared to warfarin.

I don't want to say that there aren't differences of the NOACs that are important. They aren't the same. They are much more similar than they are different from warfarin, but there may be individual patients where you might choose one NOAC or a particular dose over another.

Slide 52 – Polling Question 7

Slide 53 - "Pointers" Regarding Which NOAC to Choose

If we went through what are some of those features, and then if you bring up all of the choices on the slide, this is just our opinion. Again, this isn't science; this is sort of the art or medicine, but if you were given practical advice on what would make you choose one NOAC over another, or one dose over another, what are some features that might push you in one direction? And, again, this is really expert opinion. I think, for patients who have a high risk of bleeding, whether that's the very elderly or patients with a HAS-BLED score of 3, you probably want to use the agents or doses that appear to cause the least amount of bleeding; that would be the lower dose of dabigatran 110 milligrams -- that's only available outside the United States – or edoxaban and apixaban. And remember, edoxaban and apixaban were the two agents that have significantly less major bleeding, in general, compared to warfarin in their Phase III trials.

The patient who has GI issues, whether it's bleeding or dyspepsia, I think you'll use agents that have good GI profiles, and that's apixaban, which had similar GI bleeding, to warfarin or lower-dose edoxaban, as that had significantly less GI bleeding than warfarin. Although, remember, the higher-dose edoxaban was the only drug that was approved as a dose by the FDA; although, the 30 milligrams was approved as a dose adjustment for the high dose.

If patients have a high risk of ischemic stroke and a low bleeding risk, I think dabigatran 150 milligrams is probably the best agent. Remember, dabigatran 150 milligrams was the only NOAC or the only dose of a NOAC that was significantly better than warfarin in reducing ischemic stroke in particular.

We talk about previous strokes, and now this is secondary prevention, someone with atrial fibrillation has already had a stroke; you would use an agent that had the best data in that group. And then there are several options here: rivaroxaban, apixaban, or high-dose edoxaban.

In a patient who had prior coronary disease, agents that have good data in that group are rivaroxaban or high-dose edoxaban. In patients who have renal impairment, you'd choose drugs that are either – either less renally cleared, such as apixaban – or the reduced doses of the other Xa inhibitors, so the lower-dose edoxaban 30 milligrams once daily -- that's a dose-reduced dose – or rivaroxaban 15 milligrams once daily.

If they're on a concomitant CYP inhibitor, these are frequent drugs used for patients who have concomitant AF and atrial fibrillation – I mean, AF and coronary disease. You'd use the two NOACs that don't have any interaction with the cytochrome P450 system in the liver – that's dabigatran and edoxaban. And, of course, all things being equal, if you're – if you feel comfortable with the efficacy and safety profile of the NOACs and your patient strongly prefers once-daily medication, the two agents that are approved, that are once-daily are rivaroxaban and edoxaban.

Slide 54 – Conclusions

And so, to conclude...

Slide 55 - Properties of Ideal Anticoagulant

What are the properties of an ideal anticoagulant? I think NOACs fit the bill. They certainly have proven efficacy and a low bleeding risk, and this is in over 72,000 patients who had been randomized to one of the Phase IV trials – one of the Phase III trials. They could be given in fixed dosing. They have very good bioavailability. They don't require routine monitoring, so if you know their renal functions, in some cases body weight and age, you can pick the appropriate dose in all of these agents without measuring any blood tests.

With respect to reversibility, they had, at least up 'til now, the same reversibility was warfarin because, for warfarin, we did PCCs, as well. You also do have to give vitamin K for warfarin. But, unlike warfarin, we do have specific antidotes and reversal agents that have either been approved or will soon to be approved, so you actually *do* have an antidote for at least one NOAC and, hopefully, for all of them soon. Really, there is no true antidote for warfarin. They do

have rapid onset of action -- all the NOACs -- and much fewer food or drug interactions. But I do think they met all or most of the criteria we outlined for an ideal anticoagulant.

Slide 56 - Additional Issues Regarding Direct OACs

What about additional issues? I still think we're learning how to fit the NOACs into a clinical armamentarium. These are some important questions we're still struggling with. How to really compare one drug to another, for that, you need a head-to-head trial which – that's very unlikely today, and so I think we're still uncertain which drugs are really the perfect drugs in a specific patient group.

Would more flexible dosing improve efficacy and safety? I think we're still learning how to use these agents in patients at extremes of age or body weight.

Are NOACs better if patients are well controlled at warfarin? The answer appears to be, for the most part, yes, that NOACs tend to preserve their efficacy and safety even in patients of a good time and therapeutic range.

How do we incorporate measuring drug concentration or anticoagulant activity? This is very hotly debated. All these drugs were developed not to need routine monitoring, but as soon as they were approved, everybody wanted to monitor it. I will tell you that we – we're going to start to be able to measure drug concentration or anticoagulant levels, but we have yet – have any data on what therapeutic ranges are for these NOACs or what clinical decisions we would made if we measured something. So just because you should measure something doesn't mean we know what to do with it once you get the value back.

I think these drugs are unique in that they have a shorter half-life, a fast onset and offset. But, remember, compliance becomes ever more important, because, if a patient misses a dose or, certainly, two doses, they have almost no anticoagulant in their blood. Missing doses on warfarin is not nearly as big a deal due to the long biologic activity.

Are there specific adverse drug reactions? There appears really not to be. The main and only side effect of these drugs really appears to be bleeding. Dabigatran does have some GI side effects, particularly dyspepsia, as that might be the one thing that you may see outside of bleeding.

A big question that we're asked frequently – what do you do in patients who *do* require antiplatelet agents, particularly two of them, such as they had a heart attack or a recent stent? Remember, I said don't use antiplatelet therapies if you don't need to, but what about if you do? And I think there are ongoing trials with *all* of these agents in combination of different antiplatelet regimens, to try to figure out what to do in patients who require both, because they're very, very challenging, because bleeding risk on both antiplatelet and anticoagulant medications is very high.

And how do we best value cost effectiveness? This is a challenging issue. Remember, it's not just the cost of the drug. And, for the NOAC, they're – they're all more expensive than warfarin, *much* more expensive. But, also, what are the costs of preventing strokes and bleeds? And so,

as a healthcare society, the NOACs all appear to actually be quite cost effective because they tend to be more effective and safer. But they do come with a higher out-of-pocket cost to the patient, and if that's an issue and the patient is not going to refill their prescription, you shouldn't be using the NOAC; I would use warfarin. Although, fortunately, all of the NOACs are becoming more competitive with respect to pricing discounts for insurance and Medicare.

Slide 57 – CME Credit Slide

That's the end of our presentation. Thank you.

