GAYATRI ACHARYA: Greetings. I'm Dr. Gayatri Acharya, cardiology fellow at Mayo Clinic. During today's recording, we'll be discussing the recently released FDA Drug watch list with advisories on the direct-acting oral anticoagulants, or DOACs. I'm joined today by my colleagues, Dr. Robert McBane, cardiologist, and Dr. Ariela Marshall, hematologist at Mayo Clinic who both specialize in this area. Welcome.

ARIELA MARSHALL: Thank you.

ROBERT MCBANE: Thank you. Good to be here.

GAYATRI ACHARYA: Great to have you today. So Dr. Marshall, we'll start with you. What are the DOACs used for, and what are the FDA-approved indications?

ARIELA MARSHALL: Sure. So when we talk about the DOACs as a class of drugs, we're actually talking about a number of different medications. So one of them is dabigatran, or Pradaxa, and that's in a class called the direct thrombin inhibitors.

And the other medications are all in a class called the direct Factor Xa inhibitors, and that includes rivaroxaban, apixaban, and edoxaban. So we group them all together because they're all oral agents and call them the DOACs and that's the class of medications that we're referring to. And while there's differences in the mechanisms of action, most of the FDA-approved indications and the way that we use them clinically are similar.

So the first is where a lot of the big initial clinical trials are studied is in the setting of atrial fibrillation. And so just as you may have a patient who is on warfarin for stroke prevention in the setting of atrial fibrillation, the DOACs can be used for that indication as well, as long as it's for non-valvular atrial fibrillation. And the second is my area, and that's patients with venous thromboembolic disease.

And so whether that's a deep venous thrombosis, usually in the lower extremity, or whether that's a pulmonary embolism, so any of that class of VTE you can use the DOACs for as well. And the third indication that FDA-approved for many of these medications is actually for clot prevention, and that's primarily after orthopedic surgery. So a hip replacement or a knee replacement, and they can be used usually at lower doses for clot prevention.

GAYATRI ACHARYA: Great. And Dr. McBane, Dr. Marshall mentioned that there's different medications. What are the differences between these medications?

ROBERT MCBANE: So I think the first thing, and this has really been a godsend to us who have been treating these patients, the first thing is that now for the first time in 50 years, we have medications that don't need to be monitored. So as a class, in comparison to warfarin, we don't need to monitor these medications. The second thing, which is also a great benefit of these medications, is they don't tend to interact with food substances and they don't tend to interact with very many medications.

So for many reasons, these are very attractive medications and, in fact, quite easy to use. Of the four, there are some subtle differences, however. The first medication FDA-approved, which was in 2010, dabigatran, is predominantly cleared by the kidney, and so the vast majority of this drug is cleared by the kidney and therefore, makes it a little bit tougher to use in patients with renal impairment.

Then as you add the Factor X inhibitors, as Dr. Marshall has mentioned, these tend to be less cleared by the kidney and more cleared by other routes of metabolism, such as the liver and enteric secretion. For example, specifically apixaban and edoxaban. And so one of the big differences among this class is just how they're cleared.

They all have about the same onset of action, which make them very attractive. So within an hour to three hours of taking these medications, they will be fully therapeutic. And this is important when thinking about using these medications, particularly in individuals who've just had maybe a major surgery.

You need to know that within an hour, they're going to be fully anticoagulated. The half-lives of these medications are also long and defer to some degree. But in general, 10 to 17 hours for the half-life of metabolism of each of these medications. They have differences in their efficacy, though the efficacy differences are subtle.

The major differences amongst these drugs, I think, is their rates of bleeding, and they can have rates of major bleeding which were more similar to warfarin. And with some of the medications, such as apixaban, their advantage is that their rates of major bleeding are actually quite a bit less than warfarin. I think as a class, these medications, each and all, have a very attractive benefit that compared to warfarin, in general, they're much safer drugs, so make them very attractive for practitioners wanting to use them.

GAYATRI ACHARYA: Great Dr. Marshall, are there any other pros or cons in comparison to warfarin or standard medication that we've been using for anticoagulation previously?

ARIELA MARSHALL: Sure. So I think Dr. McBane has really outlined a lot of the benefits, and we'll talk about some of the risks a little bit later on, but I think the major things are oral availability. So for instance in comparison with something like a low-molecular-weight heparin, which can be very painful for patients and very expensive.

Obviously, the oral-acting agents are much easier to use. The ability to go without monitoring, so patients who are having their INR monitored every couple of day often on warfarin or whose INR changes rapidly with other medication interactions or with the food that they eat. So these are all things that make them very attractive to patients, especially for those who might have a little bit more active lifestyle, do traveling, not be able to get their INRs checked.

And in terms of cost, it varies, obviously, based on insurance coverage from individual-to-individual. But in general, they're less expensive probably than the injectable agents. Probably still more expensive than warfarin in many cases, but if you take into account all of the monitoring that's required for warfarin and the visits with practitioners and the nursing with the dose changes, the overall cost may actually be lower as well.

GAYATRI ACHARYA: Absolutely. And I know from any of us in our practice, this is a very attractive option for our patients, and one that they often ask about. Dr. McBane, you mentioned bleeding risk for these new agents, the DOACs. How do these bleeding risks compare to warfarin?

ROBERT MCBANE: So when thinking about effectiveness, the efficacy of these medications across the spectrum, really they don't offer a huge benefit to warfarin. The big benefit for these medications, in addition to the things that Dr. Marshall has mentioned, is the benefits of bleeding. So lower rates of intracranial hemorrhage, lower rates of major hemorrhage, bleeding from other sources.

Unfortunately for gastrointestinal bleeding, two medications can be problematic. So if you have a patient who is having difficulty or has a history of GI bleeding, then the dabigatran and rivaroxaban probably are not the best choices. And in fact, compared to warfarin even for GI bleeding, lose-dose edoxaban has been shown to be superior from that standpoint.

Apixaban, probably a wash or perhaps a bit better than warfarin therapy. So again, effectiveness-- probably similar to warfarin. However, if you're looking for the major advantage, it definitely would be a reduction of major bleeding. So that's where, I think, the biggest sell for these medications is.

GAYATRI ACHARYA: And Dr. Marshall, the next natural question is, Well, if we have a patient bleeding, how do we reverse it?

ARIELA MARSHALL: Sure. And I think there has been a lot of hesitation when these medications were first released and approved because, initially, they were thought to be irreversible in the setting of a bleed. Whereas with warfarin, the bleeding complication can be reversed within minutes with the use of a 4-factor PCC, and even within a couple of hours with the use of fresh frozen plasma.

And for heparin, obviously, if it's an unfractionated heparin that's being given continuously, just turn off the drip and protamine can be used to reverse that. So there's a lot of medications that are quite easily reversible, and the fear was, with these newer medications, that they're not reversible. So if the patient five to 10 years ago had come in with the a bleed while on dabigatran, say, knowing that this is mostly excreted by the kidney, one of the things that we could do really in a pinch is to actually try to dialyze the dabigatran off. And other things have been used-- fresh frozen plasma, PCCs have been used, but none of those are really specific to the agent that you're given.

So more recently, we've actually had the benefit of a specific reversal agent that has been released for dabigatran. And this is called idarucizumab. It's an antibody that actually binds to dabigatran and removes it from the system. So you can actually think of it as DIGIBIND, or the anti-digoxin antibody, but this is "DABIGABIND" essentially.

And so it is idarucizumab is actually a specific anti-dabigatran antibody that removes it from the system within a couple of minutes. There have been some clinical trials that have shown-- most of them are actually looking at more laboratory endpoints, so time-to-clot generation. But the clinical trials that have been looking at more patient-centered outcomes in terms of bleeding have shown that it is efficacious in reversing within a very short period of time.

So that's definitely a benefit, and something that's become available only in the last year or so. And then for the Factor Xa inhibitors, there actually is a reversal agent that's in the pipeline. So this is called andexanet alfa and, again, the initial clinical trials were more in a healthy patient populations just looking at that capacity to reverse the agent and show that it was reversible in a period of minutes.

And then more recently, we've actually seen clinical trials come out in patients who have required reversal in the setting of either of emergent surgery or trauma-related bleeding. And that actually has been efficacious in reversing. So their early trials, so we don't have the benefit of having hundreds of thousands of patients like we do in the efficacy trials for these agents.

And andexanet alfa is still not yet FDA-approved, but it's certainly in the pipeline. And I think that for all of us, we'll feel a bit better when there is a specific reversal agent available. But because, as Dr. McBane was talking about, the risk of bleeding with these events is actually somewhat lower than with warfarin, even though there isn't a specific agent available for reversal yet for all of the agents, I wouldn't use that as a reason not to prescribe them.

GAYATRI ACHARYA: Absolutely, and that's very important for us to know as providers to convey to our patients because that's also a very frequent question from patients. Dr. McBane, who would you consider to be a good candidate to prescribe a direct-acting oral anticoagulant, or the DOAC?

ROBERT MCBANE: Yes, that's a really good question and somewhat of a intricate question. I think the first question to ask is, Who doesn't need a DOAC? And so there are a number of patients who have been taking warfarin for years and they're doing fine.

They've never had a bleed, they've never had a clotting event. And so often times patients will come and say, Gee, do I have to switch? And the answer is no.

There are many, many patients who are doing just fine on warfarin. They don't mind the INR monitoring or maybe they have a home INR monitor, and they're just doing very well. And for those individuals, we definitely don't need to switch, and we have a lot of those individual in our practice.

The second group who are not candidates for DOACs are those patients who have mechanical heart valves. We have some very early phase 2 clinical trial data for dabigatran and, honestly, it was a bust. Dabigatran did not work for mechanical heart valve so I think, if anything, one of the take home messages would be if you have a patient with a mechanical heart valve, they should not be on a DOAC.

They have to be treated with warfarin. So if you get to beyond those conditions and if we talk about the FDA-approved indications, which are atrial fibrillation and venous thromboembolism, as Dr. Marshall has mentioned, then these medications are very advantageous. For the individual who is considering a DOAC and if they have an underlying indication of a paroxysmal atrial fibrillation or chronic atrial fibrillation, then the issue is which nuances of each of these drugs would best serve that particular patient?

So for example, if it's a young individual and they have a high risk of thromboembolism but a reasonable risk of bleeding, then I think dabigatran is a very reasonable option. For the patient who maybe has suffered a peripheral embolization, maybe an embolism to a brachial artery or maybe to a popliteal artery, there's clear evidence from the ROCKET trial that rivaroxaban is the preferred agent for that patient. On the other hand, if you have an older individual who may be at increased risk of bleeding, then ELIQUIS would be a reasonable option.

Whenever thinking about prescribing these medications, we have to push compliance and adherence to our patients. So we have an individual who might be very busy, a young executive for example, with a high likelihood that they won't be able to do twice-daily dosing, for that individual once-daily dosing with either rivaroxaban or edoxaban is particularly attractive. This issue of compliance is a very big deal and something we all have to grapple with.

And one of the things that we talked about for years was just how painful it was to monitor INR in our patients who are on chronic warfarin therapy. And yes, it definitely was a setback and a disadvantage for this group of individuals. However, the advantage of regular INR monitoring was that you promoted compliance.

If a patient came into the office and their INR enter was 1, you don't have to guess often to see, Gee, are you really taking your medication? With these newer medications, we won't be checking compliance by doing regular monitoring. But we have to ensure that they are both filling the prescription and that they're taking the medication.

So if you have a patient who you're prescribing one of the DOACs, you still have to follow them. And the European guidelines would say that you should see them at least quarterly. Do pill counts, maybe have some kind of a written document that you have them sign to say that, in fact, they are going to be taking the medications.

The worst possible scenario would be to accept a phone call from the emergency room where your patient with afib comes in with a new stroke and they haven't been taking their medication. So compliance and adherence. Just because we're not doing iron are monitoring, we have to be diligent with these patients and ensure that they're both picking up their prescription and filling them.

GAYATRI ACHARYA: Definitely. And, Dr. Marshall, from a hematology perspective, any other insights onto who would be a good or poor candidate?

ARIELA MARSHALL: Sure. So it's a very important question. We see many patients who come in, either with deep venous thrombosis or pulmonary embolism.

And per the recent guidelines by the ACCP or the CHEST guidelines, actually the DOACs are the preferred initial agent for treatment of DVT and PE for ease of use and safety considerations, as we were talking about. But there are certain populations of patients that we still do not prefer the DOACs. So one of them would be antiphospholipid antibody syndrome.

So this is a very pro-thrombotic condition, and there have been case reports of patients with antiphospholipid syndrome who were managed with these DOACs and actually have recurrent thromboses. Now there's only case reports, and there's also case reports of patients who have been safely managed on the DOACs as well, but until there is more clinical data from ongoing trials, we generally prefer to treat these patients with warfarin. And the other even bigger population is actually the cancer population with ETE.

So up to 20% of ETE are actually cancer-related, and so it's a large population. And from the ongoing studies comparing warfarin with low-molecular-weight heparin, we actually know that low-molecular-weight heparin is the preferred agent for treatment of cancer-related venous thromboembolic disease. And there's many trials actually going on now to compare the DOACs with low-molecular-weight heparin.

The DOACs have been compared to warfarin in cancer and they're thought to be at least as efficacious as warfarin. But since we know that the low-molecular-weight is actually still preferred, we need data from these ongoing trials before we can recommend DOACs for cancer-related VTE. And the last thing that I'll mention is actually VTE in the setting of pregnancy.

ROBERT MCBANE: Very good point.

ARIELA MARSHALL: And so, obviously, warfarin is contraindicated during a pregnancy unless it's a very tough case of somebody with a mechanical heart valve. But generally, warfarin is not used and we use low-molecular-weight heparin. There is not data from clinical trials in pregnant women.

It's actually contraindicated at this time, and that's just because of the lack of available data. So There is a registry that's open for patients who are pregnant and are, for some reason, treated with a DOAC and looking at the outcomes both for the mother and the child. But for now, it's actually not recommended in pregnancy. And so those are specific situations, but very important to consider.

ROBERT MCBANE: Agree. Absolutely.

GAYATRI ACHARYA: Fantastic. Well this was a very educational discussion, and I thank you both so much for being here.

ROBERT MCBANE: Thank you for having us.

ARIELA MARSHALL: Absolutely.

GAYATRI ACHARYA: So thank you to Dr. McBane and Dr. Marshall for these very important insights. And thank you for joining us on the heart.org on Medscape.