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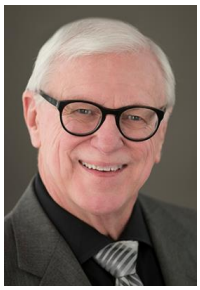
Transcript – Coag Conversation

Managing the Direct Oral Anticoagulants (DOACs)

Part 1: DOAC History and Clinical Use

Featuring:



Moderator
Mr. George Fritsma, MS MLS
Laboratory Scientist

Guest
Karen A. Moser, MD
Medical Director, Hemostasis and Thrombosis Laboratory, ARUP Laboratories

Transcript of the Conversation – Part 1:

Mr. Fritsma: Hello and welcome to COAG conversations, an educational series sponsored by BioMedica Diagnostics of Windsor, Nova Scotia, Canada.

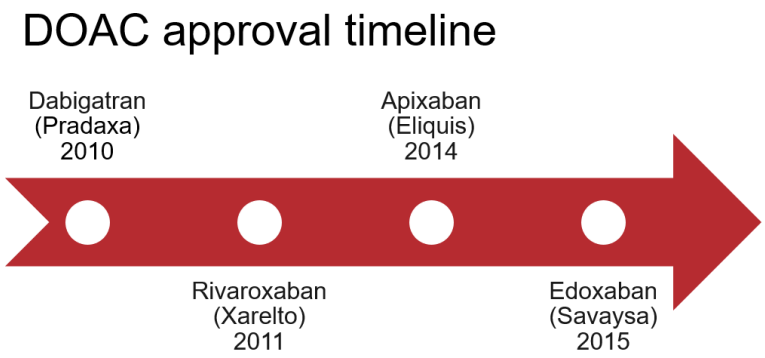
I'm George Fritsma faculty at the University of Alabama at Birmingham School of Medicine, Division of Laboratory Medicine, and proprietor of the Fritsma Factor, your interactive hemostasis resource where we exchange current information on coagulation mechanisms, clinical observations, and the role of the laboratory in diagnosis and management of disorders.

We welcome you to our three-part series. **Managing the Direct Oral Anticoagulants,** commonly named the DOACs. Part one is entitled **DOAC History and Clinical Use**. Parts two and three will be posted in subsequent months.

Our guest is Doctor Karen Moser, Medical Director of the Hemostasis and Thrombosis Laboratory at ARUP Laboratories in Salt Lake City, UT. She's also Associate Professor of Pathology at the University of Utah School of Medicine. Doctor Moser received her medical degree from Saint Louis University and served her residency at the University of Utah School of Medicine. She also served a fellowship in Hematopathology at the University of Utah School of Medicine. She is certified by the American Board of Pathology in anatomic clinical pathology and hematology. Her research interests are in laboratory hemostasis and thrombosis testing and medical education.

Mr. Fritsma: Doctor Moser, let's start by summarizing the development of the DOACs.

Dr. Moser: I'm sharing a timeline of the history of DOAC development, and you'll notice that the first direct oral anticoagulant or DOAC, dabigatran, was approved by the FDA in 2010, and it was followed by rivaroxaban, apixaban, and edoxaban within the span of a few years.



There's another direct FXa inhibitor, betrixaban, which was approved, but is no longer manufactured nor used in the US. It had a much more narrow indication for use than the rest of the DOACs, which probably contributed to less use of that agent, and it's no longer available.

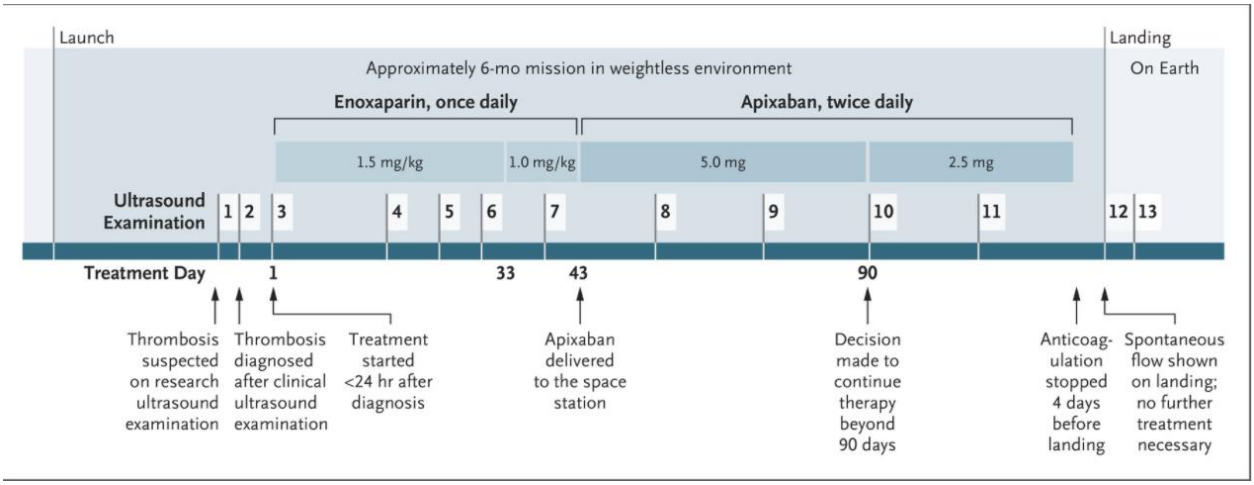
It looks like this is a pretty compressed timeline, but when you consider the scope of anticoagulants on a larger scale, thinking that heparin was initially discovered in 1916 and warfarin in the 1940s, the DOACs are relative newcomers to the scene. They're approved for use without laboratory monitoring (unlike heparin or warfarin).

So, this is really a new paradigm for anticoagulation, and we've been on a steep learning curve for the past decade or so. As increasing numbers of patients switched to or started on DOACs, it became clear that there are some clinical scenarios where making a measurement of the drug level could be informative in choosing the next step in clinical care. So, laboratories have been working in real time to develop and optimize assays for the purpose of measuring the DOACs. Again, we've been learning, kind of in real time, and so that's been an interesting journey over the past 10 or so years.

So, as it relates to the lack of laboratory monitoring, one story that I find interesting is the relative degree of confidence we have in not needing to monitor these drugs. There was an interesting story shared in the New England Journal of Medicine in 2020, describing the use of apixaban in an astronaut while on the International Space Station. So, during a research protocol involving ultrasound examination, this astronaut incidentally discovered a possible thrombosis which was confirmed with a clinical ultrasound.

And initially what was stocked on the space station was a low molecular weight heparin, enoxaparin. And that's what was used for initial anticoagulation. But, as you can imagine there are some challenges in handling liquid materials in space and so the idea arose, in consultation with hematologists back here on earth, to use an oral anticoagulant for ease of administration. And so apixaban was shipped up to the International Space Station and this astronaut was treated over a period of months. Over time the thrombus resolved. There were no bleeding complications, and again, management was a close partnership between the space station team and hematologists back here on earth. So that's an example of a success story where the particular properties of an oral anticoagulant and the relatively stable pharmacokinetics not requiring laboratory monitoring really came in handy and saved the day.

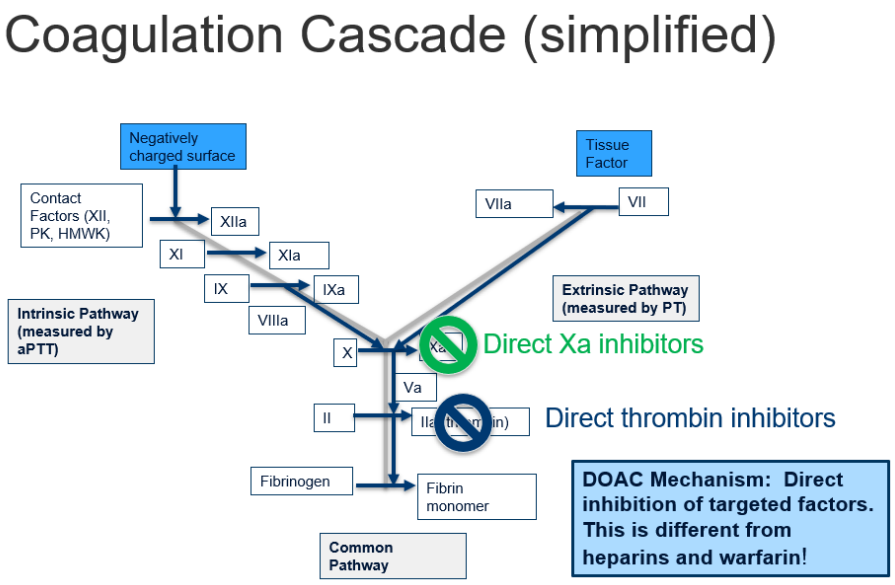
How confident are we that monitoring isn't needed?
Well, someone in space was treated with apixaban:



Mr. Fritsma: Thank you, tell us how the DOACs work. Do they work the same way as good old heparin and warfarin?

Dr. Moser: Not exactly. So, the main difference is the direct oral anticoagulants, as you might guess from their name, directly inhibit coagulation factors. Whereas heparin works by potentiating antithrombin and warfarin works by inhibiting formation of active vitamin K dependent factors. It inhibits a carboxylation reaction that's necessary for those factors to fully participate in the coagulation cascade.

So, those have relatively indirect actions, whereas the DOACs again, as their name says, directly inhibit the factors they target.



It wouldn't be a coag talk if we didn't look at some version of the coag cascade, right? So, I have that here and then we can look at where the different agents target, so direct thrombin inhibitors target factor IIa. And the Xa inhibitors target activated factor X.

Mr. Fritsma: How are the DOAC's being used? Are they used in all the same applications as heparin and warfarin?

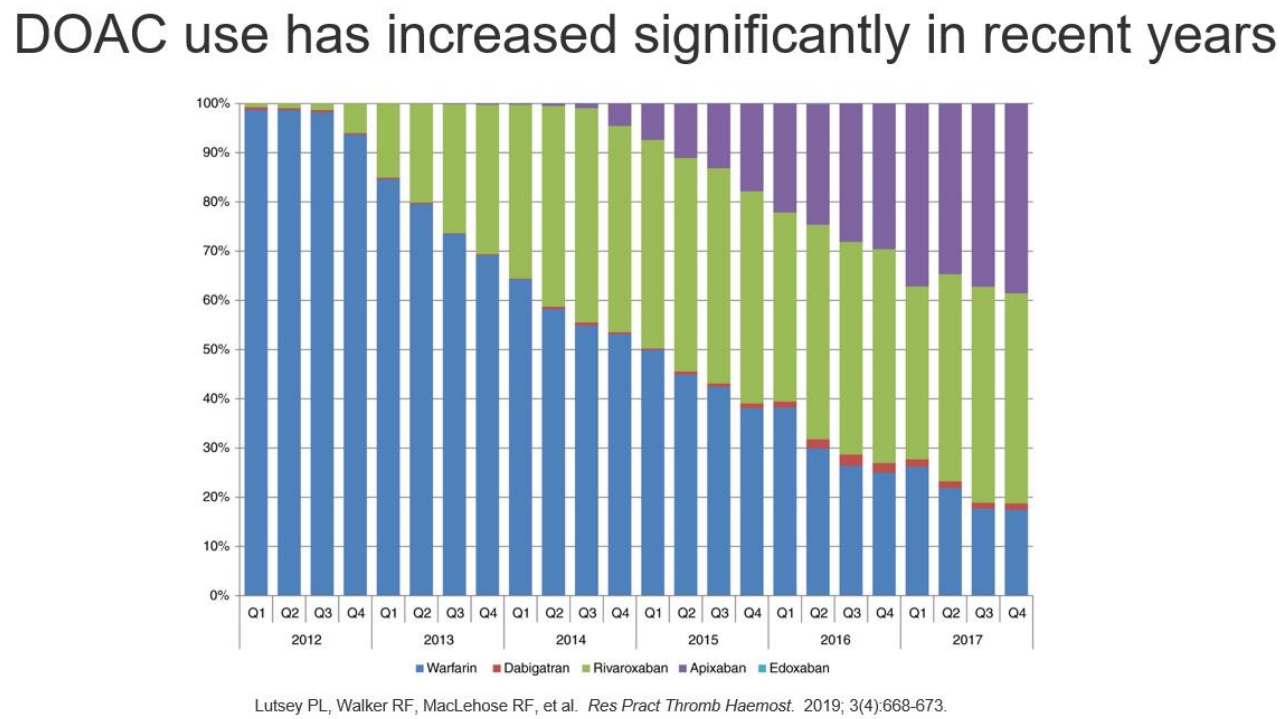
Dr. Moser: They do share many similar indications. All of the DOACs are FDA approved for different combinations of actions. Many are approved for prevention of thrombosis and atrial fibrillation, or potentially for prevention or treatment of DVT or PE, but the exact indications vary by drug, so it's important to consult the package insert to know exactly what is approved for each individual drug.

Mr. Fritsma: Have they been approved for only for non-valvular atrial fibrillation? Or can they be used also if there is a mechanical heart valve?

Dr. Moser So, that's an interesting question. We actually have some data to address that question. Mechanical heart valves are a contraindication for use of DOACs. DOACs are not used at all in patients with mechanical heart valve replacements. Warfarin is used in this setting instead. There are data from the prematurely stopped RE-ALIGN trial showing that dabigatran is associated with higher risks of thromboembolism and bleeding than warfarin in the mechanical heart valve patient population. We don't have data for direct FXa inhibitors at this point, and we likely won't because of the data we do have from RE-ALIGN.

Mr. Fritsma: Thank you. Are we still using warfarin at all or is it now obsolete?

Dr. Moser: Yeah, after I'm telling you about these exciting new agents, you might think that, right? I have a slide here that I will share to address that. So, many people have asked that same question George, and it turns out that when we look at new prescriptions in pharmacy databases, we see a clear trend of increasing use for the direct oral anticoagulants. What I'm showing here is a slide detailing prescriptions over time from 2012 through 2017. Warfarin is shown in the blue bar, and you'll notice that initially when the DOACs were just coming on the scene, warfarin accounted for the majority of new prescriptions for anticoagulation.



Lutsey PL, Walker RF, MacLehose RF, et al. *Res Pract Thromb Haemost.* 2019; 3(4):668-673.

But over time, as the DOACs became available and also as we gained experience with those anticoagulants, warfarin gained a lesser and lesser share of the market. And drugs like rivaroxaban and apixaban gained a relative proportional increase in market share. The landscape is definitely changing. I will say though there still are some indications like the mechanical heart valve example we gave, or for anticoagulation in patients with lupus anticoagulants, where warfarin remains the preferred anticoagulant of choice.

Mr. Fritsma: Just as an aside, I had a friend who had been on warfarin for several years. He had had a PE back in about 2005. When the new DOACs came along, I asked him, wouldn't you like those better? You don't have to have the lab work done every month? He said, well, I appreciate the discipline. By going back for lab work all the time, it kind of keeps me straight. So, I thought that was an interesting observation.

I knew another person who was on warfarin and when the DOACs came along, he thought that, given the cost of the DOACs, that he would rather stay on warfarin even though it was insured. His insurance company and Medicare were paying for it.

Dr. Moser: So, you highlight the variety of factors that play into decision making involving costs, involving patient preference and involving physician preference. So, there are a lot of factors that influence the decision of an anticoagulant. Certainly there are data to guide us. Cost remains an important consideration, and I too have known of patients like you say, George ,where they've been on warfarin for a long time and for whatever reason don't want to mess with success, which is totally understandable. So, I do think there's a lot of factors that play in.

You know, wearing one of my other hats, I'm a medical educator and I teach a session on anticoagulants. That's a team-based learning session, a really interactive session with one of my hematology colleagues. That's something that we really try to convey, the complexity of decision making. The many factors that go into choosing an anticoagulant for a patient.

Mr. Fritsma: Thank you. Most recently, various anticoagulants have been attempted for management of COVID and the progression of COVID. Talk a little bit about what anticoagulants we're using and how DOACs play into COVID management.

Dr. Moser: I like where we're going. Now**, y**ou're really combining some hot topics here. So it turns out this is a timely question. The ISTH just released a guideline for antithrombotic treatment in COVID-19 that will be published in the Journal of Thrombosis and Hemostasis. But there's an initial electronic version available for review now. For patients with symptomatic COVID-19 who are either not hospitalized or who are hospitalized but not critically ill, the DOACs don't appear to reduce the risk of hospitalization, thrombosis, or mortality. The guideline, in its current form, does not have data to address DOAC in critically ill hospitalized COVID-19 patients. Heparin, low molecular weight heparin, or unfractionated heparin are used in that patient group. There might be a role for prophylactic rivaroxaban to reduce the risk of venous thromboembolism in patients who have persistent VTE risk factors after they're discharged from the hospital. But the data supporting this weak recommendation are pretty limited at present. The recommendation doesn't address the use of prophylactic rivaroxaban beyond about 30 days after discharge from the hospital, and there aren't results of studies of the other DOACs in this clinical setting yet. But there may be more information to come. We're definitely still learning about COVID-19. The ISTH guideline doesn't address the role of DOACs in long COVID, but that certainly could be an interesting question for the future.

Mr. Fritsma: Yes, from everything I've heard, it seems we are really at sea where management of long COVID is concerned. And I have two relatives who have long COVID and they think I might know the answer, so they'll contact me. I said I just don't have any answers right now if they're using anticoagulants. I know one individual

was really quite ill and he is getting. two antiplatelet drugs, aspirin and clopidogrel, and I think rivaroxaban. All three of those. That seemed excessive to me.

Dr. Moser: Yes, that sounds a little unusual. I'm not sure that would be a typical treatment plan. But, you're absolutely right. That this is an area again where we're sort of learning as we go. Can't really prepare for a novel coronavirus that spreads as a worldwide pandemic, so every day we're learning how to take care of these patients better and better.

Mr. Fritsma: Exactly. Well, that concludes our first section. Dr Moser, thank you for your expertise and also thanks to our audience for your participation. And we will encourage your questions and comments. There will be a spot on the BioMedica Diagnostics' website or an email address that you can use to forward your questions or your comments. This concludes today's conversation.

Please join us next month as we continue our discussion and we focus on **DOAC Measurement.**
Thank you.

Questions or Comments? Please email us

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