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Expert Panel: Evidence-Based Medicine and Current Clinical Guidelines — How Do We Evolve Our Clinical Practice Paradigm With the Latest Clinical Data?

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Dr. Young:
Hello, everybody. My name is Guy Young. I'm a pediatric hematologist-oncologist Children's Hospital Los Angeles and University of Southern California and specialize in coagulation disorders. And we're here today to discuss direct oral anticoagulants and what we can learn from the clinical trials. And we've reviewed some of those data for you in the previous talks. And today we're going to have a panel discussion about those with two of my colleagues. So for starters, let's have Dr. Jaffray go ahead and introduce herself.

Dr. Jaffray:
Hi, I am a pediatric hematologist. I also specialize in pediatric coagulation. My research though is really focused on pediatric venous thromboembolism.

Dr. Young:
Thank you, Julie. And Neil, tell us a bit about yourself.

Dr. Goldenberg:
Hi everybody. I'm Neil Goldenberg. I'm a pediatric hematologist as well, professor of pediatrics and medicine at Johns Hopkins University, but I am based on the Florida campus at Johns Hopkins All Children's Hospital. And like my colleagues, I have a special interest and research focus in coagulation and specifically for myself in venous thromboembolism treatment prevention and prognostic factors.

Dr. Young:
Great. Well, thanks to you both. I think we all know that the era of, or we're moving into a new era in pediatric anticoagulation with the recent approval of two oral anticoagulants in children after many, many years of study. Let me start by asking, actually Neil, the first question about the previous anticoagulants. And can you tell us what was the unmet need? Why did we really need, or why do we really need these new oral anticoagulants in children? What are they providing that we didn't have before in what we were using?

Dr. Goldenberg:
Well, it's a really important question, Guy, and I think there's some pragmatic aspects for families and there are also some challenges that we have as prescribers with our conventional historical anticoagulant armamentarium in children, and so low-molecular-weight heparin as one of the most common historical anticoagulants administered in kids is an injectable and therefore there's discomfort, there's invasiveness, there's challenges in making sure that one is drawing up the appropriate dose and administering the full dose through an injectable. And so, from a patient satisfaction, parent satisfaction, that can be very difficult. And so, then when we look at

warfarin and vitamin K antagonists in general as the conventional oral option for anticoagulation, there are a host of challenges with warfarin with regard to dietary interactions, drug-drug interactions, challenges with dosing, especially for pediatric patients who can't swallow pills and the need to crush up and try to give an oral solution. And so all of those aspects really call for an agent that can be given noninvasively with a very stable profile, with minimal drug interactions and minimal dietary interactions. So I think that was a key unmet need. And beyond that, just getting to the idea of how the agents are approved, we still have an ongoing unmet need to really study certain populations and indications in pediatrics. And so I think even with the approval of new oral anticoagulants, we need to really pursue some of the ongoing unmet needs in special populations.

Dr. Young:
Thank you, Neil. And so Julie, with these new agents being now available and indeed some of them, not all of them, but some of them licensed for use in children, how do you see this evolving into the real world clinical use?

Dr. Jaffray:
Thanks, Guy. Yeah, I'm actually really interested to see, and as you know, there's some centers like at CHLA and Neil at Johns Hopkins that we've been involved in these newer anticoagulant phase one, phase two phase three trials, and I think for us, it's a little bit easier to adapt these new medications, to start using them in our patients. But what I think will be interesting are the other centers who weren't involved in the trials and may not feel as comfortable using them in children. And I think the other big, the question is who are we going to start with? You know, so we've got neonates, we've got those children in the neonatal ICU versus a 16-year-old patient that was maybe not even hospitalized and had a thrombosis. And I think it's going to be very interesting how each of us decide which patient might be appropriate to start on these medications. And I know for my practice, I plan on being a little picky, not just deciding all right, no one is getting a low-molecular-weight heparin anymore, we are going to switch everyone over to these newer oral anticoagulants. My view is that I think I will pick those who I feel is okay that we don't have ways to measure the level of the anticoagulant. I think that's the biggest plus and minus of these new medications. So they, you know, at this point, there are no standardized laboratory test to decide if the level is good enough, which is pretty normal for most of the other medications we take, but this is a new place for patients on anticoagulants. So I want to pick a patient that I am okay if their level, I don't know it, I'm not that worried about bleeding. And I also want to make sure that I choose patients that I'm really confident in their absorption. So perhaps not someone who needs a lot of help getting vitamins absorbed and things like that. So I'm personally going to, I'm excited, but I'm also going to step cautiously at the beginning.

Dr. Young:
Thank you. Neil, what are your thoughts on Julie's answer and the clinical use?

Dr. Goldenberg:
Yeah, I think it's a really important question and I share a lot of Julie's perspectives on that. And I think a lot of us have been starting to use these agents on label and as is often the case in pediatrics, obviously sometimes departing from what we know is a proved practice, because there are real pragmatic situations in clinical care. I think one thing that's important to me, and I think all of us as researchers have a bit of this in us, is having that careful dialogue with the family and the patient, depending on their age, around what we know and what we don't know about various agents. And so I present conventional anticoagulants as options to all of my patients in 2022. But I also present to them, do we know that something appears to be as effective, as safe? Do we have any evidence of superiority? And I think largely we don't. And so presenting it as here's another option, here's what we know from the large trials, and here are some of the pragmatic aspects, and then presenting them as options and letting the family have a lot of input in veto or ultimate decision. And often, I think all of us have situations where parents will say, "Okay, hey doc, well, what would you use if this was your child?" And certainly, if that's what they're asking after I've presented it, then I'll say, "Well, here are some of the reasons for which I think options A and B might be best out of the four in this circumstance, because of some pragmatic aspect or because of the evidence." So to add to Julie, I think just presenting the options and the evidence in a succinct fashion is really important, because I do think what we have now is expanded options rather than largely evidence of superior options when it comes to kind of phase three data.

Dr. Young:
Thank you. And then we'll close with Julie. Are there specific or any types of patient populations for whom these new agents are not appropriate?

Dr. Jaffray:
Yeah, I think I just briefly touched on it. When you look at especially the phase three trials that have been published, there are a couple of populations that I think we as thrombosis treaters have noticed that aren't on these. And those are really, especially the neonates, but especially the premature neonates, which goodness gracious, a lot of our clots are in the neonatal ICU. I think those children, we really need to be careful with, is, you know, the three of us understand, but maybe other pediatricians don't, is their developmental hemostasis is still developing. Their pro and anticoagulants are still being formed, are increasing levels. And so it is really important that if we are trying new medications that are anticoagulants in this particular group of patients, that we study them specifically versus just hoping that

well, it worked in a one-year-old, I expect it'll work in a 28-week infant. So that is who I'm not going to start and I would not recommend anyone else giving these medications until we have a little bit more data. I think the other population that is interesting, and I think we need to be a little bit careful with are those who are new surgical cardiac patients. So this is another group who have had a lot of thromboses. There is an agent that has been approved for prevention of future thromboses, but there really wasn't a study on newly, out of the OR, cardiac ICU patients, you know, especially those with single ventricle physiology or cyanotic heart disease. But unfortunately, they get a lot of thromboses. But I would also be hesitant in starting anything on them, especially they have, you know, can tend to have a higher risk of bleeding. So those would be the two main populations I would not want to start anything on yet.

Dr. Young:
All right. Thank you. And then we'll close with Neil just having a little bit of thought on the safety issues.

Dr. Goldenberg:
Yeah, I think one thing that we've learned predominantly from the adult data is to have caution with regard to patients with prior arterial events who have antiphospholipid antibodies, or those who have multiple positive antiphospholipid antibodies, regardless of whether it's an arterial or venous event, to be cautious about use of DOAC agents, as opposed to some of the conventional ones until we have more data.

Dr. Young:
All right. Thank you. I think the other area that I think data's still emerging is mechanical heart valves. And for that, probably warfarin is still the go-to agent when we can use it. Well, thank you to both of you. I think there is really valuable information and insights there for clinicians who really do need to learn about these agents, cause they do offer lots of advantages as we discussed, but we do want them to use them in the proper manner and in the right patients. Well, thanks very much, and hope everybody learned something and goodbye.

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