THINKING THROUGH AMYLOID-RELATED IMAGING ABNORMALITIES

A Case-Based Exploration of Recognition, Evaluation, and Reporting of Novel Imaging Events of Alzheimer's Therapeutics

- Good afternoon, everyone, or good morning or good evening depending where you are across the country and around the world. My name is Don Melady. I'm an emergency physician in Toronto, Canada. I'm a member of the Geriatric Emergency Department Collaborative and along with our partners Efficient CME, we're bringing you this webinar this afternoon. This is probably new territory for most of you, and in fact, for most of us, we're looking at a completely new topic, Amyloid-Related Imaging Abnormalities and how we can manage them in the emergency department. So that mouthful is typically reduced to ARIA, Amyloid-related imaging abnormalities, and it relates to an entirely new class of medications that are now available for the management of early Alzheimer's disease. That class is called Amyloid-targeting therapies. Now, it's certainly, I suspect that most of the people on this webinar as usual are our emergency department colleagues from around the world. And it's certainly true that we will not be prescribing these medications probably ever. But it is certainly true that we will be seeing patients who are on these medications and sometimes people who are in our emergency department because of these medications. So it's essential that for high quality care of older adults, emergency departments be ready to receive this new group of people. We hope that by the end of the webinar you'll have a better understanding of Amyloid-targeted therapies and this topic of Amyloid-related imaging abnormalities and especially how you can change things in your emergency department to better manage those people. So let's start with a case. So this is a person who could show up in any emergency department anywhere. A 77-year-old man with a headache and slurred speech. He comes by an ambulance and he is not accompanied by any family or friends. He has limited medical history in your institution's electronic health record. Naturally you go immediately for a CT scan. So far this is pretty easy and straightforward and the CT scan appears normal and naturally new person with new neurological symptoms and a normal CT, you're ready to activate your stroke protocol and you're thinking, you know, you've done a great job so far. Then his daughter arrives and shares that her father is on lecanemab and you say, "What's that?" And she says, "Oh, that's the new medication for treating early Alzheimer's and it has something to do with Amyloid." So what would be your next steps in his management? This case clearly presents the challenging scenario that we're all gonna be facing at some point when patients who are on Amyloid-targeting therapy appear. We'll be discussing how to care for these people who will all have Alzheimer's disease and are prescribed these new therapies that can lead to Amyloid-related imaging abnormalities, which we'll be talking more about after, and which we will refer to as ARIA. We've got a fantastic panel. This is your opportunity to really hear from the top experts in the field. I've already introduced myself. Dr. Kevin Biese is the Vice Chair of Emergency Medicine at the University of North Carolina and one of the two leads for the Geriatric ED Collaborative. Dr. Gayatri Devi is a clinical professor of neurology at the Zucker School of Medicine and very knowledgeable about

this new class of medication. Dr. Gloria Chiang is the vice chair in the Brain Health Institute at Weill Cornell Medicine. And Dr. Jennifer Sutherland is one of our pharmacy colleagues who works also at University of North Carolina where she's an Assistant Professor. So we definitely wanted to include a pharmacist on this panel because those are the people who know most about the medications. If you're wondering what the Geriatric ED Collaborative is. We're a group of clinicians and hospitals around the United States and the world who focus on improving the care of older people in emergency departments. We are involved with education, quality improvement, dissemination of best practices and evaluation of those interventions. If you're interested in that or want to join us either as an individual or as an institution, please check out the website or take a picture of the QR code there. These are the topics that we'll be covering today and there's gonna be a lot of material, most of it new to everybody. Don't fear that you have to get it all on the first pass. There will be a full toolkit available to you. It should be, I think on your home screen there should be a tab that reads Clinical Toolkit. So I'd like to start with a poll so you can tell us what you know. Have you seen patients with complications from Amyloid-targeting therapy in your emergency department? We've got a quorum of answers there, and this was more or less a rhetorical question. It may surprise some of us that even up to 8% of emergency clinicians on the call today have already seen patients on this completely new class of medication, which I think is rather impressive and I'm pleased that they're here to find out more and maybe share their experience. And significantly, 92% of of emergency clinicians have not seen anybody in their emergency department. I'd like to send this question out mostly to our emergency department based people. That's Jen Sutherland and Kevin Biese. Why do you think this is gonna matter to emergency departments? And Kevin, why don't you go first?

- Oh, thank you so much, Don. I think this is a really important topic because the bottom line is that patients present with a relative high degree of frequency. I think the number is 10 to 20%, I'll defer to Dr. Chiang and Dr. Devi on that. With microbleeds, a small amount of bleeding secondary to the utilization of these medications. And you can only see these microbleeds on MRIs, we'll talk about in a second. And so that has a lot of ramifications for our workflow. It has ramifications for stroke as we'll talk about soon. It has ramifications for diagnosis more generally. But if I was to be really succinct, I would say it's because most of the time when we think about acute neurological presentations that we need to figure out real quick in the ER, we get a head CT. And in order to figure out patients on these monoclonal antibody against the Amyloid, you need an MRI. And that has really significant implications for how we diagnose these patients and how we make sure we don't cause harm, say by giving TPA in the setting of what looks like an acute stroke. Jen, what would you add to that?

- I would echo what you just said. I think it's very challenging when a patient rolls in and they look like a stroke and they sound like a stroke, but we know that if we treat this patient just like any other stroke patient, we potentially miss something or we can cause harm. And there are many considerations that hospitals are gonna have to make and there's gonna be very institutions specific obstacles that they have to overcome. For example, academic medical centers might have very different problems than a community hospital. Is the patient receiving that medication at our institution or are they receiving it somewhere else? So it's important that we get out in front of it, make a plan ahead of time before this patient even shows up so we can anticipate

what kind of problems we might see and be prepared to go down a different treatment pathway.

- Jen, how good are we currently in emergency departments at getting medication histories in general?

- That is a tough one. I'll get into the challenges a little bit later, but a lot of the information that we need, especially on these patients, is not gonna be available in our electronic medical record when they roll through the door. And EMS crews might not be prepared to ask the questions that we want answers to. So I think we have a lot of improvements to make in this process.

- Thanks, so in summary with any novel therapy, the whole thing about it is it's new, and when something is new, something else has to change and this is a completely new set of medications and completely new set of problems that patients are arriving with and we are gonna need to do something different in our emergency department. This sort of echoes the whole idea of a geriatric emergency department. As we're seeing more and more older people, we need to start doing things differently. It can't be just like in the old days. Significantly, it's gonna have a big impact on our stroke protocols as our case just demonstrated, what used to be kind of clear pathway now would hold extra set of path side branches to it. And you know, emergency departments interaction with the MRI department is not always smooth and easy and so there's clearly going to be more MRIs in the future. So we do have our resident experts and once again, if you have questions specifically for a neurologist about these topics, please put them into the chat. And I'm gonna turn this over to Dr. Devi to give us a high perspective on this whole class of medications.

- Thanks, Don, so the first thing I'm gonna say is these drugs are tongue twisters, lecanemab, donanemab, and the first drug aducanumab, they're all mabs, monoclonal antibodies that target Amyloid in the brain. And by targeting brain Amyloid where our hope is by dissolving the Amyloid over time, we're then not only going to slow progression of Alzheimer's, but we may in, you know, actually very, very early on if you institute the drug early enough, you may even be able to prevent. That's the ultimate goal. So it's very exciting to be in this era. Unfortunately, as with all good things, there are side effects. So the big issue with the monoclonal antibodies used for treating Alzheimer's disease and mild cognitive impairment is that it can cause brain bleeding and brain swelling. And so we have the side effect in lecanemab for example, it's up to a quarter of patients can have the side effect and in donanemab up to 40%, a little over that, will have the side effect of brain bleeding and brain swelling, which Gloria will get into. But this is a very exciting class of drugs and I'm very excited about it. I've been a proponent of this class of medications for all the benefits it can give. And it's the first class of medication that's actually disease modifying. It alters the pathology, clears the plaque, and because it also clears the plaque in the blood vessels, the Amyloid in the blood vessels, that is why you have some breakdown of the blood brain barrier and have the brain bleeding and the brain swelling because of leakage and damage to the vessel walls. So it's exciting times but also scary times and it's important for emergency rooms to be aware of the various ways patients can present and how to treat patients differently in this situation.

- Thanks for that overview and actually there's a really great question has already come in from our audience, which is probably best directed to you and that is,

"Do these drugs have an online electronic monitoring database?"

- Sadly not, and right now the administration of these drugs is far flung. I mean it's actually possible that a neurologist may not know that the drug is being prescribed by a geriatrician and it's being given at an infusion center and place C so that that kind of centralized database is not there yet. But I know there's a momentum, there's a move to try to have that happen.

- And then the second part of this very good question. And since you are as a neurologist, somebody who would prescribe this medication, right? Like this is...

- Yes. So when you are prescribing it, what kind of advice do you give the patients and/or families about possible risks?

- So I was an early proponent of these drugs. So I started using aducanumab, which is the first drug in this category that was conditionally approved by the FDA but is now being taken off the market in 2021 and subsequently lecanemab, which is currently available. And I have everybody sign a consent form. I usually have the caregiver sign a consent form as well understanding that these drugs are not going to cause any improvement, that it's only going to slow progression. So that's a big difference. I also make them aware of the side effects and the possibility of death as a side effect which has occurred with Leqembi or lecanemab. And that while most side effects are generally asymptomatic, there is the possibility that they would have a serious one. So I'm very serious about it. I make sure there's a caregiver on board most of the time. I make sure everyone's aware.

- So the people who are leaving your office, if they were showing up in an emergency department, you think they would be saying things like, "My neurologist told me to come here, if I develop these problems."

- They would probably say that they called me already and I told them to go to the emergency room. So yes, we maintain very strict control, but that's not always the case, I must say.

- Good. So thanks a lot for that. So I think in summary it's clear that there's one approved agent out there already, another one probably on the way insurance is covering this more and more. And so for sure we're going to be seeing more of these patients in emergency departments. So back to our emerge colleagues before we go on to Dr. Chiang, Kevin and Jen. And perhaps well maybe start with Jen. When Dr. Devi's patients show up in our emergency department, what do you think we need to be doing differently? How do we need to change our system?

- Absolutely, the availability of these Amyloid-targeting therapies are going to impact how we manage these patients. And Don, if you wanna go to the next slide, I'll touch on two of the points that I wanted to bring up. And the first was that, and Kevin's already said this, we need to be prepared for these patients before the first one even arrives. And so that means going ahead and meeting with your ED leadership, your stroke coordinators, educating your ED physicians that are gonna take care of these patients when they roll in the door. And then as you start on modifying your protocols, I just wanted to bring up two points to address. So the first would be highlighting which patients are actually even on these medications, which I think we're gonna identify as a huge problem. And then two would be optimizing your electronic medical record for the management of them. So when it comes to the med reconciliation component, right now, as Dr. Devi said, patient and family member interviews are gonna be your most reliable

sources of information at this time. These drugs are given at IV infusion centers, they're not picked up at pharmacies. So a lot of the traditional methods that we use to get medication histories on this patients, we can't do. Their insurance companies are not gonna talk with our electronic medical record the same way. Likewise, if a patient is at a facility, it may not even show up on their facility MAR because they're not receiving that medication at the facility. So in current state, unfortunately interviewing the patient and family members is the best way to identify these patients. And then moving on to how we can optimize our electronic medical records for these patients, it's obviously gonna be dramatically different for every institution. So if you are at an academic medical center, you're the one giving these medications within your health system, it becomes a lot easier. You can do things like best practice alerts that are tied specifically to the medication or that patient. So every time they roll in, as soon as the provider opens their chart, they know the patient's on these medications and they're automatically flagged for the contraindications that we're gonna be later in the presentation. However, that's kind of like the best case scenario. I think a lot of times we're all in different practice settings and we may not have those luxuries of the medications being given within our system. You know, a patient may drive an hour or two to get these infusions, but if they call EMS for a stroke-like symptoms, they're probably gonna be going somewhere nearby. So I think it's looking at your electronic medical record, seeing what the capabilities are. If it just means, you know, adding allergies to the patient charts with the contraindicated medications so that way they flag that might be the best thing you can do. So I think it's just evaluating your institution's specific workflow issues and seeing what you can do within that system. And then also just being prepared for any changes. You know, we may get more data that changes how we manage these patients. We may have to alter our policies, they may become available subcutaneously, in which case that would change how we do med reconciliations as well. So those are just the two points I wanted to bring up for these protocol changes.

- So thanks a lot, Jen. It strikes me as this is sort of geriatric ED care 101 like establish a baseline with every older patient. Be sure that you involve other caregivers because our patient in this case probably was not able to give his own history. So make sure that you're reaching out to other family members and caregivers and people who know the patient best. And most importantly, make sure you've got an interdisciplinary team available to look after an older person because I'm sure Jen, you are going to be much better at tracking down all that information than the emergency physician whom you're working with. And on that note, I'll turn it over to Kevin. What do you have to say?

- First of all, we're incredibly fortunate to have Jen on the team. Taking care of complicated patients with multiple medical problems in time-sensitive conditions is truly an interdisciplinary sport. Don, I wanna go back just a second to make sure we've been crystal clear about the stroke issue here. So if someone is on an Amyloid monoclonal antibody, anti-Amyloid monoclonal antibody, and if they are having micro bleeding from it, it is highly likely that giving them TPA is a bad idea. Now there is debate right now whether it's an absolute contraindication or a relative contraindication, but certainly if their symptoms are coming from the bleeding, it's tricky, right? We wouldn't usually give a lytic to a hemorrhagic condition and expect to improve the outcome. And there are case reports out there of people that have received lytics when they presented like they had a stroke and they died. And so we need to keep this in mind and just think

about it, that patient that you talked about in that first scenario, they come in, they look like they're having a stroke, you're in a rush. They were last seemed normal, it was two and a half hours ago. Everyone's like, "Oh my goodness," you pull out your little card, they're not on anticoagulant, their creatinine's not greater than 1.8, their blood pressure's not higher than 180, whatever's on that little card. And you're like, "All right, give 'em TPA" and that's the patient that we have a risk of making them much worse by turning their little bleeding condition into a big bleeding condition, right? And so unclear whether the symptoms in this case were from actually an ischemic stroke on top of lecanemab or from the lecanemab itself. But either way, the fact that they're on an medication with a high likelihood of causing micro bleeding that you will not see on the CT is a great risk to this patient. So what do you need to do? You need to have a plan in advance. You need to have a plan in advance, right? I think at the very least we need to be asking our patients, their caregivers, anyone we can get ahold of, are they on these medications? Beyond that, you need to talk to your neurologists, right? So at UNC, we have a neurology department that is starting to give these medications and our emergency department team is starting to meet with our neurology team about how do we arrange care for these patients? How do we have our best chance of knowing they're on them? If you're in a smaller hospital, right? Then you need to reach out to the centers that are giving them, like let's say you're, I don't know, an hour outside of Manhattan, right? Maybe you're reaching out to some of the centers that are giving these medications in advance to make sure you're aware or know who to talk to. But you have to have a program in advance to increase the odds that you will know these patients are on their medications. When you pull out your little card of what to consider for whether you give lytics for a stroke, it needs to be listed on that card and you have to have someone in advance that you know to call to the best of your ability, "Hey I think I have someone on one of these new anti-Amyloid medications, help me talk through this." That's how we need to change our care patterns. And it all has to happen before that first patient rolls in because at two and a half hours last seen normal acute stroke where you're considering TPA and you don't have a complete medical history and the family hasn't gotten to the hospital yet, is a hard time to figure this out.

- Good, thanks for those points. We'd be interested to hear from the audience if you know that at your site you have done any of those things already. So before we go on to Dr. Chiang, we have a skill testing question here. Which of these following statements regarding Amyloid-related imaging abnormalities, which we're gonna be hearing about, is true? ARIA only occurs in patients taking Amyloid-targeting therapies. Most patients taking an Amyloid-targeting therapy will develop ARIA. Most cases of ARIA are asymptomatic. The most common clinical symptom of ARIA is vision impairment or I don't know. So I think we've got a bunch of smarty pants on the call here today. Most cases of ARIA are asymptomatic, which turns out to be the right answer and we might be interested in hearing a response to the first question there as well. So yes indeed it seems that most of these are asymptomatic. So given that we have this now serious condition on imaging, which might be asymptomatic, I think I'd like to hear from Dr. Chiang about what we should be doing to investigate that and what we need to know in the emergency department.

- Thanks, Don and so as we alluded to before, the main adverse effect of these Amyloid-targeting therapies is ARIA, which stands for Amyloid-related imaging abnormalities. And so there are two main types of ARIA. There's ARIA E, the E standing for emus or

edema. Basically you can see like in that first image, you have basically too much fluid in the brain parenchyma, or you could have fluid actually accumulating within the sulci of the brain, manifesting as the sulcal effusions. And then there's ARIA-H, which is more of the hemorrhagic type of ARIA where you can see in the circle these little punctate, little dots of microhemorrhages in the brain parenchyma, or you can see the arrows on this right side image are pointing to these linear areas of cirrhosis or basically chronic blood products in the sulci. So this is what we're looking for on those monitoring MRIs in these patients that are on these therapies.

- And just to be clear, these would not show up on a CT?

- And absolutely it's a question we get a lot actually. But unfortunately because CT is not as sensitive, particularly for this little tiny microhemorrhages, a CT is not sufficient for monitoring these patients. They have to get an MRI. And you know, going further into this. And so if you look at the clinical trials of the people who are on these therapies, about 30% of them did develop at least one of these forms of ARIA. But again, the vast majority were not symptomatic. Only 6% or fewer were symptomatic and they only knew about the ARIA because of these monitoring and MRIs that were taken while they were on therapy. Also, notable is that patients are actually at greater risk of ARIA within the first three months of therapy. So early on the therapy, that's when you're most closely monitoring for ARIA.

- And just to reiterate, you did say that and I guess Dr. Devi as well, patients on this new medication would be routinely getting MRIs on a regular basis every few months?

- That's right, so for example, for lecanemab, which is the main drug that's out in the market now, patients get a standard baseline MRI just to evaluate what their baseline status is in terms of hemorrhages, strokes, white matter hyperintensities, and then patients go on to get another MRI before the fifth infusion, before the seventh infusion and before the 14th infusion. And that's written on the label. It's sort of standard recommendation. And typically in our institution, our neurologists schedule these MRIs right at the baseline. So all the patients know when these followup MRIs will be right when they start the medication.

- Good, okay and so onto you or back to you Dr. Devi. So now we know that we've got this abnormality seen on imaging that may be asymptomatic. So how can we know what is actually a symptom when we are faced with patients with very non-specific symptoms?

- Sure, I mean, and just to add to what Gloria had mentioned on, you know, we have found that a slower titration schedule sometimes helps to reduce risk for the Amyloid-related imaging abnormalities. And I probably, in our practice, we have had so far about 40 patients who received this drug, the prior drug, aducanumab and now lecanemab over the last, since July of 2021. And we've had four patients who've developed Amyloid-related imaging abnormalities and none of the four did we have any symptoms, no headaches, no confusion, no dizziness, none of that. And we really only found out as Gloria said, because of routine monitoring. And the other thing too is when you titrate up on the dose is when the risk for bleeding from these drugs is the highest. And with the slower titration, we've found that, for example, one of our patients had ARIA at the end of the second year of treatment with a very, very slow titration schedule. So you wanna also keep that in mind, you know, are the patients being on a regular titration schedule, which is fairly rapid,

in which case most patients will have symptoms within the first eight months depending on the drug you're using, are you going to have symptoms later on. In terms of side effects, I mean obviously depending on where the pathology is, patients can have any number of side effects. And clinical mimics, we actually had one patient who was diagnosed as having acute ischemic stroke because it looked like a wedge-shaped infarct, which was found on an incidental MRI. And we spoke to a bunch of neurologists, decided it was a wedge-shaped infarct. And then when we did a follow-up RI and a few, and she was asymptomatic. When we did her follow-up MRI, it had disappeared. So it was a classic mimic of what looked like an acute ischemic stroke, but in fact was ARIA. Of course posterior reversible encephalopathy syndrome, but that presents very differently usually in patients who are hypertensive, eclamptic women, et cetera. And it reverses very quickly. It's usually in the back of the brain, in the back of the cerebra and then subarachnoid hemorrhage would probably be less likely in the situation. But those are all differentials you wanna keep in mind. But ischemic stroke I think would be the biggest problem in terms of a mimic.

- So as I understand it, you could be doing routine screening and find an ARIA, an Amyloid-related imaging abnormality. There's a really great question from our audience. So if that happens in your practice, Dr. Devi, when you're following this person, would you refer that person to the emergency department for in-hospital assessment?

- So I have not, I've not done that with any of my... In our practice, we actually examine every patient, every visit that they come in because just to be extra cautious. And none of these four patients had any clinical changes and none of them even had any clinical symptoms. In fact, the one patient who had the most dramatic ARIA with bilateral involvement traipsed off to Europe with his wife the week after, and we only held this Amyloid medication for a month, you know, that's really all we did. But everybody else has been on the same program. We haven't really made any changes because they were all asymptomatic and they didn't really have any clinical findings on examination and we just followed them carefully with MRIs.

- Dr. Devi, I'm gonna butt in for a sec, barge in for a second and ask a question. Let's say that one of your patients, I was working in Manhattan in the ER and one of your patients came to an ER with what looked, not imaging wise, imaging irrelevant clinically wise, like an acute stroke and they were on lecanemab. Do you think we know, I'm not actually trying to put you on the spot, it sounds unlikely that the acute stroke symptoms were caused by the lecanemab in this patient though possible, I don't know. Do you think we know whether in that case two hours now they can't move their right arm? They were throwing a, you know, they were moving their right arm fine with their grandchildren two and a half hours ago and now they're not. The amount of contraindication that TPAs in that patient, is it a relative, is an absolute, I'm calling you on the phone, "Hey, I've got your patient, I've figured out they're on lecanemab and that you're prescribing it and it looks like they had an acute stroke." And you say...

- I would say that a lot of patients with Alzheimer's have comorbidity for stroke, so they have already preexisting comorbidity. And if in fact it looks like an acute embolic stroke, ischemic stroke, then I would, despite the fact that they're on lecanemab, if it's an evolving stroke, I would personally, depending on the patient, again, it's individualized, consider TPA for that patient.

- Got it, and one way of paraphrasing that is to know it and practice shared decision-making in that case to the best of our ability there there's perhaps an increased chance of bleeding that's still being quantified. I want you to correct me at any point if I'm saying it wrong, we're still figuring it out. But these medications can cause small bleeds and I'm about to give you a medication that busts up a clot and can cause more bleeding. And so we could cause a bigger bleed but also could have a chance of making that stroke better in practice shared decision-making. Is that essentially?

- That is correct. And just to speak to that point, I mean, for example, I have one of a pair of identical twins, both of whom have Alzheimer's. And the one twin who's not in my practice has severe Alzheimer's. And the twin who's in my practice has a cardiac valve and therefore she needs to be on a blood thinner, but she's opted to be on monoclonal antibody and so she's on both and we're titrating her up so slowly and so far she's been good. But it really is a case by case decision and in this case the one twin decided that she would rather opt for this with the possibility of real bleeding.

- Got it. Well thank you for that.

- My pleasure.

- I'm gonna take it back down to the emergency department. Down 'cause emergency departments are always on the ground floor. So for you, Kevin and Jen, so it's becoming increasingly clear, it's complicated. We're on medications, medications cause imaging abnormalities, same medication can cause problems with symptoms. The two don't always correlate. So what are we supposed to do in the emergency department? Kevin, you go first.

- Call their neurologist and then call 'em again. I mean like, so whenever possible that decision today should be made in conjunction. Now I remain concerned because that's not always going to be possible. As Dr. Devi alluded to earlier, not every person prescribing these medications could, you know, tell you the middle names of all 40 patients that they've given them to so far and you know where they're living and that kind of thing. And so, and as more patients take them, obviously that will not be the case and as Jen alluded to when they go subq, but today the answer is talk to your neurologist in advance and figure out who to call and make sure that you arrive at a shared understanding that they really are on these medications. And then of course involve the patient in any decision-making. You know, I'd say that one, the stroke conversation, it has to be shared decision-making. I am aware that like for example in a large healthcare system on the west coast, they're considering TPA absolutely contraindicated today in the setting of these medications. I'm not saying that's right or wrong, I'm just saying that some places have made that decision. Some places have talked about having these conversations, but you have to know they're on it and then talk to the patients and then if they come in and they're not having a stroke but they're having a headache or they're dizzy or their vision changes or you know, all the neurological stuff that could be presenting in patients who are on these medications, I think the answer remains the same; call the neurologist. And then have their neurologist tell you or talk to Dr. Chiang or whoever it is and make sure that the MRI is sequenced correctly when possible because their neurologist is likely to suggest an MRI at that point, either in the ER or in close follow-up. So if it looks like a stroke, talk to the neurologist and the patient about, you know, about how you want to proceed with lytics or not. And I would be just very careful. And then if it doesn't look like a

stroke, again, we're trying to talk to the neurologist about how to further diagnose this and does it have to happen right now? Or especially if you're in an ER without a MRI, could they come to their clinic tomorrow. But again, that's a conversation I wanna have with that neurologist. I don't think I know enough today to make those decisions on my own.

- And I also think that patients really, patients and families, especially if you involve them early on, are very invested in making that decision with you, although it's obviously time-sensitive in the emergency room.

- Thanks. Gayatri, just be interested in your contribution around how do we improve processes of medication reconciliation?

- Sure, I think as we're working on this, you know, as our specialties move forward with all these drugs, it's good to think about ideal state and what that looks like in the future. So we always wanna give the right meds to the right patient at the right time. And when these patients fall into the ED, knowing from EMS what they're on would be very helpful. And as Dr. Devie touched on earlier, I think having a centralized registry could be something that we advocate for where it could be right at our fingertips. You know, I don't wanna memorize yet another login, but it would be really nice for a time-sensitive decision like this to have access to that information right away.

- Good, so medication reconciliation and then processes to try and figure out what the right imaging is supposed to be. Which brings us back to Dr. Chiang. Gloria coming back to this case, which we've already reviewed, we're now happy that CT scan is normal. This is now a rhetorical question also, is the CAT scan enough? And I think your answer is going to be no.

- - Right, so again, CT scan is not sufficient for these small changes in the brain compatible with ARIA. And so you really do need MRI and that's why it's sort of written into the label as a recommendation. And so you know as much as you can, I think it's very important for the administrative and the radiology team to come together and to have a standard way of ordering these MRIs as well as a standardized protocol that can actually identify the necessary findings on these MRIs. And so I would say, you know, most MRIs nowadays they have a slice thickness of at least five millimeters or less. But make sure for the ARIA-E component, looking for the edematous ARIA that you have a T2-FLAIR sequence that's the more fluid sensitive sequence. For the ARIA-H detection, it's important to have either a GRE, a gradient echo sequence or an SWI, a susceptibility weighted sequence. Both of these are blood sensitive sequences and you need these to look for those small areas of microhemorrhages. As we talked about, the symptoms can often mimic an acute ischemic stroke. And so oftentimes we get a diffusion weighted imaging sequence, which is very quick, it's usually less than a minute, just to make sure that we rule out a stroke because clinically ARIA symptoms could mimic an acute stroke.

- So as a simple-minded emergency physician, what do I need to know? Is there anything different about this MRI evaluation or the order that needs to be made in the unlikely event that I'm the person making the order or is this just like a regular brain MRI is mostly gonna get you the information that you need from the emergency department?

- Yeah, so I think it's institution dependent. I think I would say routine MRI protocols have these sequences. Most MRI protocols should already have the DWI to exclude for exclude infarct. Most have FLAIR already. A key one is this gradient

echo where SWI sequence. I think it's not always on all routine protocols. So just to make sure that you have one of these standard blood sensitive sequences. I think that's important. And the other thing is it's important to have a non-open MRI. So sometimes patients who are claustrophobic, they go to clinics that have these open very low Tesla, low field magnets and those are not sufficient in terms of having the right sequences to exclude ARIA at this point. And so it's important to get sort of, we typically recommend a three Tesla MRI but if you do it at 1.5 Tesla, that's okay as long as all these sequences are included.

- And Don, I would just say what that means to me, in thinking about helping run an ER is that when I have that meeting that I'm gonna have after this webinar where I call up my neurologist and say, "Hey, how are we gonna make sure we know patients are on lecanemab or anything else comes out?" I'm gonna invite our neuroradiologist to that meeting and the neurologist and the neuroradiologist are gonna talk about what kind of picture they need and then we're gonna make sure that it's an epic and it's gonna say, "All right, and I'm gonna click on that one." I mean like everything Dr. Chiang just said of course is incredibly correct and helpful and I'm not gonna remember it. Which is all the more reason why you've gotta plan before that patient comes in. So that in my institution, if it's 2:00 AM and I'm talking to the poor second year resident, they're not trying to figure out what that modality is. Rather it's already been decided in advance and we know we can find it under whatever we wanna label it as.

- Which I think brings us to this question that I was gonna ask, but I think it kind of gives us the answer. I mean we need to tell the radiologist that this person is on an ATT and we need to have already put in place a process that ensures the person can easily get the right study that they need. So what else do you need to know? Is there anything else we need to communicate with you Gloria?

- Right, so Kevin, you're absolutely right. So that's exactly how we have the process set up at our institution. We have an epic order, you know, anyone who's on this medication, they can click this order, get the MRI, because of that epic order, it triggers a standard protocol, we have an ARIA protocol so the right sequences are done and then the radiologist also knows to read it looking for ARIA. So you know, one thing to keep in mind is these findings that we're describing with ARIA, these microhemorrhages, these areas of edema, the siderosis, they're not specific to ARIA. So without that history of knowing that this person's on this therapy, the radiologist may not know, they could say, oh it's a microhemorrhages from anticoagulation or you know, trauma something else, right? So it is critically important to let the radiologist know they are on this Amyloid-targeting therapy. The other thing that's critically important is if you have prior imaging, if you could make that available to the radiologist, that would be very helpful because again, with each of these monitoring MRIs, we're trying to decide if there are new areas that are concerning for ARIA, new areas of microhemorrhages, new areas of edema. And so having that prior MRI would be very helpful. You know, understandably these patients move around, they're not always imaged in the same place. So sometimes images aren't available. But if there's a prior report say that says okay, the patient, you know, on the prior MRI, they had two microhemorrhages and then I'm reading the followup MRI and I'm seeing five, you know, that will also gimme an indication. Okay, three new microhemorrhages developed in the interim that's concerning for ARIA.

- Thanks a lot. And now in these next two slides we're coming to the final quarter

of the webinar and there's some very important things ahead. Dr. Chiang, if you could just spend a moment walking us through these images.

- Yeah, sure, so this is just to show you there are ways that we grade the severity of the ARIA. So for RAE for example, there's mild, moderate, severe and it's really dependent on how many locations are involved. If it's just one location or more than one and how large the abnormality is. And so it's considered mild if it's less than five centimeters and sort of that overall abnormality size, it's moderate if it's five to 10, and it's severe if it's greater than 10. And these are some examples of ARIA-E. Same with ARIA-H, again, we have mild, moderate and severe in terms of the staging. And again it depends on how many areas that are involved or in terms of microhemorrhages, the actual number of microhemorrhages. So like in my example, knowing that exact number of microhemorrhages from the prior exam is really crucial on the follow-up exam to know what has developed.

- Thanks a lot, Gloria. So Gayatri, now we've got the answer that we need from our excellent neuroradiologist. What is the management for these Amyloid-related imaging abnormalities?

- So as we discussed several times earlier, almost all of the Amyloid-related imaging abnormalities are asymptomatic and discovered incidentally on MRI scans. If they are symptomatic then if they're very mild then we don't do anything about it. If there's moderate symptoms, the person's got bad headaches, they're having real problems with ambulating et cetera, then we hold treatment and see how they do, repeat the MRI if if and watch to see what happens to symptoms. I mean so really employ common sense in this situation. And if it's asymptomatic, but they look severe on MRI, I think it really depends, you know, if it's severe, then yes you wanna hold the medication because there's a possibility that if you give the next dose you can actually cause a catastrophic situation. So you wanna hold the doses and then see how the patient progresses, repeat the MRI, if things are stable then you can proceed with treatment. The other kind of caveat, you know, nothing's ever simple in the world of medicine and certainly not in neurology, you know, microhemorrhages which are very, very small hemorrhages in the brain, microbleeds if you will, are actually common as we get older without ARIA. So up to 30% of older adults just have these, if you do fine enough imaging. So that complicates matters as well.

- So we're kind of talking about two groups of people who may have ARIA, those whom you are finding in your routine practice who come for their routine monitoring. And unless they have had catastrophic symptoms, they probably would never come to an emergency department.

- Right, that's right.

- And you wouldn't manage them. The people where it's gonna be relevant for emergency physicians are those people who have developed new symptoms, whether they be because of ARIA or because they have developed new neurological symptoms because there are complex potentially frail older people with other neurological conditions. And yet even in those cases, unless their symptoms are very severe, they likely are also going to be managed as an outpatient once we make the decision that this is not treatable, is that right?

- Right, I mean, yeah, that is correct, Don. And in the clinical studies as well, only a very, very small number of patients were actually hospitalized for and we're talking thousands of patients that were treated that had to be hospitalized for any kind of ARIA related problems. And those were

really the only reasons they were hospitalized. Some patients had just a response to the infusion itself, but that was, you know, much more manageable and very few deaths also in the studies which involved, as I said, altogether between the two drugs plus the new drug that might be soon, I think well over at least over 8,000 patients. So it's a small percentage but I always feel it's better to be safe than sorry, especially 'cause we have created a rent in the fabric of the blood-brain barrier by administering the monoclonal antibodies. So you wanna hold it for a couple of months if you need to, if you're not sure.

- Good, thanks, so the punchline on this is contact the neurologist to, you know, it clearly it it's gonna be shared decision-making between the physician, the treating physician and the patient, but also between the emergency physician and the neurologist. So I'm just gonna move on then to this topic that keeps coming up. Here's a final quiz, 77-year-old male receiving lecanemab, our patient, presents with a probable acute ischemic stroke. Would you, our audience out there in webinar land, would you administer an acute thrombolytic to this patient? And I'll give you a moment to give us your answers

- Don, this is assuming it was a high enough stroke scale stroke to have TPA be indicated just to throw that out there.

- Hey, there is our answer. It's pretty divided, let's call it even between yes, no and I don't know, which is sort of doesn't surprise me all that much. I am going to, Jen, what do you think about that answer and what do you, as the emergency department pharmacist whom I'm gonna be talking to as well as the neurologist, what do you have to say about that?

- I mean, it's a tough one because we just don't have a lot of data right now. So I think at this point in time the drug companies and everyone recommends not giving TPA, but it really is a patient by patient decision and it involves everyone in the multidisciplinary team and it also involves the family. You know, it's something that we need to assess the risk versus benefit and it's hard to give somebody an adequate risk when we really don't know the answer and allow them to have that informed consent. But I think this is gonna be an ongoing conversation for each patient specifically

- Gayatri, what do you have to add to that?

- I agree with Jen, I think it's really a case by case decision that you make the decision, you know, I mean I would say if you'd asked me a while ago, would I ever give lecanemab to a patient who is on Coumadin with a cardiac valve? I would say absolutely not. But now I am because we have a patient who's an identical twin who will surely get it and she's at a much earlier stage. So it really depends on a... And also getting the family to partner with you, having the patient partner with you. So we're all going in together with our eyes wide open, aware of the risks and possible benefits.

- Don a slight a agree, but to add a slight nuance, the decision that Dr. Devi made with that patient presumably took place over time. And some of these decisions that we have to make in the setting of stroke to lice or not to lice, that is the question, don't have that luxury. It may not have the family plugged in yet, may not have the amount of information. Of course shared decision-making remains the right avenue, but at the risk of being a broken record, I'm gonna say that you want to have these conversations with your neurological team in advance and have a standard approach to how you approach that shared decision-making. How you describe those risks and how you kind of approach that scenario because some of these patients aren't going to do well and you want to function

within the best practices that your institution came up with, with your input, not in the crisis moment. You gotta have a plan in advance because there's such time-sensitive decisions when they come to your door.

- So I'm struck that this is a kind of, again, a classic example of older person care in the emergency department, there's a lot of gray zone, there may not be very specific evidence that is going to be able to guide things. You absolutely need to involve other caregivers, you need to involve your interdisciplinary team. There's gonna be shared decision-making. So it's really another example of how we need to do things well for older people. Jen has really kind of touched on this and we have now four minutes remaining and I'm gonna move right on. You've covered most of that Dr. Devi. So Kevin, I'm gonna ask you to just summarize in the last few minutes the toolkit kit that is available to our participants and the how you think it could be helpful to them.

- Absolutely, so, you know, we will have cross-linked at the GEDC, the Geriatric Emergency Department Collaborative website and at the Efficient CME site access to this toolkit where essentially you have some of the key materials you need on education and training and the conversations, you can click through this, the conversations to have in advance. I would just say for purposes of time, go take a look, right? Like a lot of the materials that have been discussed here are relatively new to us. You don't need to memorize them all. If you've been frantically taking notes, I'm sorry for your hand, but instead we'll suggest that you should go and take a look and download some of these materials so that your team knows something about what these drugs are. You have some tools to converse with your patients around them. What are the images that you need? When might you consider treatment? And again, to the risk of being a broken record, how can you plan in advance before those patients arrive so that you have a consistent, optimal approach to taking care of what is still a fairly complicated patient group, early on using a new treatment.

- Good, as we're coming up to the end, any final comments? Dr. Chiang, in your interactions with your emergency department at your place, do you have any learning points that you'd like to share from there? I'm assuming you do it well.

- Well, you know, I would say we started giving the medication October, 2023. I would say, I think because of all the uncertainties, especially with Aducanumab, we're giving lecanemab, our neurologists are very, very conservative. So they're very conservative about giving the medication. They're very careful, just like Dr. Devi is very careful about giving the medication. They monitor them closely. And so sort of like what Dr. Devi mentioned, our ARIA rate has been exceedingly low. I would say definitely less than 10%. And as far as I know, knock on wood, no one has shown up in the ED just yet. So again, we've seen just a handful of ARIA cases. They've all been asymptomatic so far and they've just been managed by the neurologist and so far it hasn't gone to the ED.

- Good, we've got one last great question, which I suspect the answer is going to be, once again it depends and we're not sure, but in patients with PE, pulmonary embolus or deep vein thrombosis and on lecanemab, do you have recommendations for how to proceed if they require acute anticoagulation? Might be Dr. Devi who has the most experience.

- So I actually have a real patient with this problem. The only difference is that he had had a PE a few months before, so we put in a filter, got him off the medication and

then gave him the lecanemab. In case of an acute PE in someone with lecanemab, if going back to the same patient, I mean he had a massive episode with both his lungs. I would say it's one of those situations where do you operate on someone who's, you know, who's on an anticoagulant if it's an emergency? The answer would be yes. I would say in that particular situation I might actually consider it. But again, it's a case by case basis. But what the medication, what lecanemab has helped me do is in a lot of patients who are eligible for the drug and who are anxious to be on the drug, but who are not able to be on the drug because of anticoagulants, been able to put the, you know, they've had a WATCHMAN procedure for atrial fibrillation or like in this particular patient had a filter put in and went off the anticoagulant.

- Thanks for that. So we've dealt with that. As we're closing out right now, I would remind you that you're all going to be getting an evaluation post webinar. I'd encourage you to fill that out to give us some feedback. If you want to access the downloadable clinical toolkit, there's the QR code there and it's also on your tab. There will be a follow-up webinar, no sorry podcast available through the Geriatric ED Collaborative on GEMCast on this same topic. I would really like to thank our expert panel, Dr. Devi, Dr. Chiang, Dr. Sutherland and Dr. Biese. We've really learned a lot from all of you. It was really great having you. I learned a lot and I'm sure that everybody else listening did as well. So with that, I think we'll wrap up the webinar and hope that the rest of you have a good morning, afternoon, or evening. Bye for now.

- Bye bye.