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GLP-1 Use and AMD Risk

Barton Blackorby:
Welcome to the New Retina Radio Journal Club of VBS. My name is Barton Blackorby from the Retina Institute in St. Louis. I'm joined today by Kat Talcott from the Cleveland Clinic.

Kat Talcott:
Thanks so much for having me.

Barton Blackorby:
And Hong-Uyen Hua from the University of Miami.

Hong-Uyen Hua:
Hi, there. Thanks for having me.

Barton Blackorby:
And today we're going to be discussing a paper titled Glucagon-Like Peptide-1 Receptor Agonist Use and Risk of Neovascular Age-Related Macular Degeneration in a National Cohort Study. It was authored by Kevin Allan and colleagues and published online in Ophthalmology Retina in November of 2025. And we're very lucky today because we have an author from that paper today, Katherine Talcott. Can I throw it to you to summarize your paper?

Kat Talcott:
I would love to. So big shout out to Kevin Allan, who's one of our PGY3 residents who first authored this paper, and to my colleague, Dr. Rachitskaya, who did a great job. But this is a retrospective cohort study. It's using the TriNetX network that many of us in ophthalmology know that's increasingly being used to look at questions, but it was used to evaluate the association between GLP-1s and the risk of developing AMD to focus both on non-neovascular as well as neovascular AMD. We really wanted to be able to determine what the risk of developing neovascular and non-neovascular was in patients who are prescribed GLP-1s compared to other medications.

The database was queried to look for adults over the age of 60 with documented ophthalmology follow-up of at least one, two, or three years, as well as having medication prescription records. Patients were then grouped by the use of GLP-1s versus other glucose-lowering or lipid-lowering medications. And these patients were propensity matched based on demographics, chronic disease prevalence, as well as the severity of their disease at baseline. The main outcome was looking at the risk of developing AMD, including non-neovascular as well as neovascular AMD at one, two, and three years after the initial prescription of the medicine, comparing GLP-1 users as well as matched comparative users.

Overall, we found that, compared with alternative glucose-lowering medication, GLP-1 prescriptions was associated with a significant reduction in the risk of non-neovascular AMD at one, two, and three years. The hazard was very similar at these years and ranged from 0.75 to 0.79. We also found similar protective effects compared to lipid-lowering medications at two and three years. We found that GLP-1 use was associated with a significant reduction in the risk of neovascular AMD across all time points compared with comparator groups, but there was no significant impact on GLP-1 use on progression from non-neovascular to neovascular AMD among those patients who had non-neovascular AMD at baseline.

So overall, as a result of this analysis, we concluded that the use of GLP-1s was associated with a lower risk of non-neovascular and neovascular AMD, and that GLP-1 use did not show an increased risk of conversion from non-neovascular to neovascular in patients

who had dry AMD at baseline. But obviously prospective studies are needed to be able to confirm these observational findings. I'm really curious to hear your guys' thoughts on this paper, and thanks for discussing it.

Barton Blackorby:
Well, thanks for summarizing and publishing this paper. Dr. Hua, I'm going to start off with you. Do you think this paper, and others that we've seen, do we have enough longitudinal data to begin saying that we have a sense of how GLP-1s interact with patients with macular degeneration?

Hong-Uyen Hua:
I would say that the timeline of 3 years in this paper is a certainly a reasonable start to look at the longer-term effect of GLP-1 agonists and AMD risk, and that the clusters of other papers that show similar effect is a favorable trend. I do think it's interesting the juxtaposition or contradiction with the Ontario paper that many may be familiar with showing the opposite effect, but I would say that this paper makes more sense to me in terms of pathophysiology and possible mechanisms for decreased AMD risks.

Barton Blackorby:
Yeah, I think we're getting there. I think it's going to be difficult for us to have the gold standard, prospective, randomized clinical trial, it's such a slow -moving disease process, but this is really where I think big data and diving into that can shine because it may allow us to find these correlations.

So as we look at this, Dr. Talcott, when you went through this paper, what changed in your thinking of the risk and neovascularization in patients beyond just VEGF in terms of how this could be modulated by a GLP-1 modulator?

Kat Talcott:
Yeah, I think that's a really good question, and that's why there's so much interest in these agents, is that the pathogenesis for AMD is so multifactorial. We know that genetics plays a role, but also I think we're beginning to appreciate that inflammation actually plays a big role too. And if some medicines like GLP-1s or other things modulate some of those processes, oxidative stress, inflammation, whatever, that you might have decreased risk of developing disease. And we didn't find it here, but you would think, too, if you looked long enough or you had enough patients, that it might decrease your risk to developing end-stage disease as well. So I think associations like this really highlight that AMD is really a multifactorial process in terms of its development.

Hong-Uyen Hua:
And for me, I think GLP-1 receptor agonists really hearkens back and makes me think of the gut microbiome as well. And I think that's a burgeoning area of study within ophthalmology to see how other systems affect retinal pathology. And so it's always good to have more than one pathway to target with different disease pathways.

Barton Blackorby:
I think so. I think, as we're all going to be minors in biochemistry as we go into retina further, because we're going to see just how much all these pathways interact each other.

Dr. Hua, is the observed reduction in this development of macular degeneration more consistent, in your mind, with either anti-inflammatory, metabolic, or antiangiogenic effects from GLP-1s?

Hong-Uyen Hua:
I think it's hard to say specifically. We can't really pin a specific pathway just from this study. If I were to hypothesize, I would say perhaps this is more from an anti-inflammatory or antioxidant effect more than a VEGF pathway, but we would need more studies to look at that question specifically.

Barton Blackorby:
How about you, Dr. Talcott?

Kat Talcott:
Yeah. I mean, I agree. I think it's kind of hard to parse out all these individual things, especially because we know the GLP-1s can have an anti-inflammatory effect, antioxidant effect, but also just a neuroprotective effect overall. I think it's hard to tease out the individual things, but collectively, for sure, there seems to be sort of a signal.

I think that there's more interest, especially in the field of AMD, about thinking about how these other pathways like inflammation oxidation impact things. For instance, there have been papers looking at people who have autoimmune disease, that they're more likely to get AMD, and then potentially at younger ages. And so I think this kind of goes along with it. And then there was another TriNetX study that found that there's a decreased chance of having uveitis if you're on GLP-1s as well. So I think it's hard to parse out what's what, but I personally think that the inflammatory piece might be one of the key drivers here.

Barton Blackorby:
I agree with you. Yeah. I think, especially with what you're talking about with autoimmune, with what Dr. Hua was talking about these systemic conditions, other conditions such as the inhibition of mast cells and mast cell activation syndrome has attenuated their inflammation system-wide from these GLP-1 modulators. And I think we're probably seeing something in the eye where we just don't quite understand that, but there's something being affected pathways up that we're seeing the downstream effects. Worth further investigation in this.

So when we look at the GLP-1 receptors in terms of how they're going to potentially reduce the risk for macular degeneration, how do we compare that to known things that people can take that can reduce their risk of developing advanced macular degeneration, such as the AREDS 2 vitamins? Do you think this is going to eventually add on to an additional thing we'll recommend patients to take? I'll start with you, Dr. Hua.

Hong-Uyen Hua:
So I always think about this when these types of studies come out, how am I going to counsel my patients? So if a patient were to ask me, "Should I take a GLP-1 receptor agonist just for my macular degeneration?" That would give me pause. But I would say that it has many other good effects, especially with weight loss, with, in this study, decreasing possible development of macular degeneration. I would say that the benefits likely outweigh the risk in many of these scenarios, but we don't have enough to say that it's a definite preventer of macular degeneration at this time.

Barton Blackorby:
So Dr. Talcott, this paper was about big data. You guys dove through a massive database to do this, and I think that we're seeing a lot more papers as people dive through this. Can you talk a little bit about how big data is going to impact what we think about retinal conditions and interactions? There's the other paper, the Ontario paper, if you want to hit a little bit about that as well. Just how big data influences this?

Kat Talcott:
Yeah, I think it's a really good point. I think big data can give us a lot of information, especially databases like the TriNetX one, I think is really good at being able to look at the risk of ophthalmic disease or progression of ophthalmic disease when it comes to systemic conditions and systemic medications. Other databases like the IRIS Registry is great, and then you can actually look at individual charts a little bit more. With TriNetX you can't. But it's really robust in terms of those things.

But you have to be careful about how these... Although there's so many patients in these databases to be able to answer clinical questions, how the study is set up really can impact what you find. So you need to make sure that you're sort of controlling for any potential confounders, that your cohorts are very well-matched, and especially disease baseline. That's one of the concerns that I had when I read the Ontario paper is that they didn't control for AMD at baseline when they looked at the results.

And then when you get the results, like the hazard ratios, you have to think about, "Does this clinically make sense?" And so we found, in the paper that we presented, a modest risk reduction, but that makes sense to me clinically. You have to think if your risk of AMD is twofold or something, "Does this make sense? Is there something that I'm just not accounting for?" So I think big data is fantastic. It's really great for hypothesis-generating studies, doesn't replace, in my mind, prospective studies looking at individual charts and individual images. But by having so many numbers of patients in the studies, we can certainly answer questions quickly that would otherwise be difficult to answer.

Barton Blackorby:
I think one of the difficulties with big data, like you mentioned, there's all these variables. Nothing was ever put in clean. Dr. Hua, I'll ask you this question. As we move forward with big data, do you think we should mandate a structured data format to ensure that we have clean data for AI and as we mine through this in the future?

Hong-Uyen Hua:
I would say that the cleaner data, the better. But in these studies, it's really hard to control what people are doing and what people are charting. I think in these studies, it's important to have the propensity matching and try to really clean up all of the background data and noise that is present in big data studies. And so, for example, in this study, they creatively came up with a neutral diagnosis of stye to see if GLP-1 receptor agonists have a positive or negative effect on styes. And so being able to clean up any background noise in these big data studies and doing it in a standardized way moving forward, I think would be helpful for us to interpret big data studies moving forward.

Barton Blackorby:

So as we look towards the future of clinical trials, I'll ask both of you guys this, where do you think we're going to go with this? Do you think they're going to be partially or fully replaced by real-world registries and synthetic controls or are the old-school clinical trials still going to rain at the end of the day? Dr. Talcott, I'll start with you.

Kat Talcott:
Yeah, it's a great question. Really interesting. Depends on what the FDA tells us we're allowed to do and what they're not allowed to do. I think it'd be hard given the amount of questions that we have about big data and just not being able to see individual charts and verify images. It'd be hard to see it totally replaced by something like this. But as you guys know, to run any sort of clinical trials, crazy expensive, and it can be prohibitive to be able to do that. So I'm sure trials are going to change from where they are now, it's just hard to feel like we're at that place now, if that makes sense.

Barton Blackorby:
How about you, Dr. Hua?

Hong-Uyen Hua:
Yeah, I would have to agree. I don't think we're quite there yet. I think AI could possibly play a big role in terms of validating these big data studies or simulating control groups with AI or these big data studies compared to our old-school, classic, gold standard prospective studies. And I think the FDA, at the end of the day, makes the big decisions there.

Barton Blackorby:
I think the FDA's our big overlord there.

Hong-Uyen Hua:
Yes.

Barton Blackorby:
Well, Dr. Talcott, Dr. Hua, thank you so much for your expertise and your discussions. This is a fantastic review of this paper. Surely going to generate a lot more in the future.

To everyone out there, thank you for listening and joining the New Retina Radio Journal Club of VBS. Stay tuned for future episodes.