*(PLEASE NOTE: Transcribed automatically by Vimeo; mistakes are possible/likely. Our apologies.)*

TRANSCRIPT - GR 02 28 25 ***"Innovations and Gaps in CKD Clinical Trials"*** guest speaker Amy Mottl, MD MPH FASN, University of North Carolina at Chapel Hill

---

**Internal Medicine Grand Rounds**

- Welcome to medical. We are also invited to have Doctor Amy model here with us to talk about innovations and gaps in Ckd clinical trials today.
- Let's take this through. Our Cme accreditation slides and welcome up Dr. Marco Cusa, our division chief of Nephrology, to introduce the lecture
- for the faculty can see any credit you got this shot of this screen here.
- Welcome up, Dr. Okusa to introduce the Atook language.
- Well, thank you all for coming to medical grand rounds. I'm really pleased to introduce our lectureship, which is the lectureship, and Shana will then introduce our distinguished lecturer, Amy, model from the University of North Carolina.
- So darker, it's helpful.
- He was a fabulous nephrologist. He was from Turkey. He did his internship and residency at the University of Virginia, fellowship in nephrology and cardiovascular medicine. He then joined the faculty and was the 1st division head of nephrology. Back in 1976 we initiated the human dialysis program at Eca. And this in this paper here shows the 1st dialysis.
- His research interests was in the area of catecholamines, and he was very excited about this, and he had a clinical practice, one of the largest clinical practices that dealt with familial Plomocytoma. He published a number of studies on this line of blood since.
- And so today, we're really pleased to have Dr. Eva model from the University of North Carolina. I think Shane was going to do so. Good afternoon, everyone. It's my pleasure to introduce the grand round speaker for today. Dr. Amy Model, Dr. Model obtained her medical degree from Albert Einstein, College of medicine, and then went on to complete her Internal Medicine Residency and Nephrology fellowship at Unc. At Chapel Hill, where she is now a professor of medicine as an academic nephrologist. She works to identify pathogenetic factors and novel approaches in the treatment of diarrheatic kidney disease.
- Her clinical interests include the multidisciplinary care education and health equity for patients with Ckd glomerular and genetic treatments. She focuses on collaboration with primary care providers and specialists to deliver patient-centered guideline-driven care, expanding access to medications with cardio-renal benefits for contribut as well as medical weight loss therapies.
- In addition to her clinic for diabetes, vasculitis, and glomerular nephitis, she has a series of patients with fatal disease and other dominant sizes of kidneys.
- Her primary research interests rely on the heterogeneity of Dkd. And the distinct clinical and pathogenetic mechanisms that vary between individuals, even with the same diabetes type. These interests manifest in primary neurologic research and large cohorts with diabetes, analysis of clinical and research, giving biopsies from people with diabetes in the beginning and clinical trials. So we're very pleased to

have her speak with us today, and please join me in welcoming her thanks so much, Shaina. You all can hear me. Okay so it's a pleasure to to be here and an honor to commemorate Dr. Tuck's career.

- As Shaina said, talking about Ckd clinical trials. So we've just had an onslaught of Ckd medications that have come out over the last 1015 years and really have opened up avenues not only for clinical care, but also research to improve the lives of our patients with chronic kidney disease.
- These are my disclosure.
- And so here is the breakdown of my talk. I want to talk a little bit and show you the innovations that have happened over these years, as well as talk about why smoking matters so for those of us who are not in nephrology, I think, especially internal medicine, where we're bombarded by every chronic disease, it can be hard sometimes when somebody has very mild. Ckd, so I want to just refresh our memories of the high prevalence as well as the high morbidity and mortality in this population, and then go into really the innovations that we've seen over these last 10 to 15 years talking about Sglt, 2 inhibitors, non-steroidal Mras glp one agonists, and then refresh our memory as to why ace inhibitors and arb still matter, and then break into a little bit about what the gaps are at this point, and how we can trying to fill those gaps as we move forward.
- So here's a schematic of the breakthroughs and endpoints for Ckd. So I think a lot of us don't think about how this plays a huge role in the innovation in any given space in medicine. But prior to 2,000, you had to actually have proof of a reduction in end stage kidney disease for the FDA to approve your drug, and there was virtually nobody in that space and then in 2,001, they agreed to use doubling of creatine as a primary surrogate endpoint followed by a 40 to 50% reduction in 2012. And then some other landmark. Changes were looking at Egfr slope in some populations, looking at total kidney volume specific to autosomal, dominant, polycystic kidney disease, and most recently approving protonuria as a surrogate endpoint for iga nephropy.
- And so you can see Losartan and Erbisartan came out in 2,001 in our back-to-back idnt and renal trials, and then canagliflozin in 2019, followed by Venerinone, and then Empa and dapagliflozin as well and most recently last year. Sevaglutide. It's not yet approved, but it should be.
- And then just sticking with our other disease states that I'm not going to talk about today but tolvactan for poly disease.
- And then we also have Budesonide as well as sparsentin for hygiene properly.
- One of the things that I think are the gaps that we'll talk about later are really, how should we incorporate this? You know onslaught of therapies which one do we use, and which patient? How do we provide therapies, etc. And so I'm going to talk a little bit about hierarchical clinical endpoints, as well as this actually will open up avenues for decreased numbers and decreasing the period of time through which patients need to be followed.
- So, Ckd, why does it matter? It's really prevalent. So one in 7 adults in the United States has Ckd and one in 3 people with diabetes has Ckd, and you can see that people who are of African ancestry or Hispanic ethnicity have higher rates of Ckd, and this is Ckd one through 4. So if you're African American, you have about a 1.4 fold increased risk of Ckd compared to white counterparts. But then, if you look at end stage kidney disease, the red line, there is African Americans, whereas the dark blue line on the bottom is

- Caucasian people, and we're looking at end stage kidney disease over time. And here we see a sixfold increase. So this disease is predominantly affecting are ethnic and racial minorities.
- And so, about a year ago, the American Heart Association came out with a statement saying, Look, we really need to collaborate more and focus more on the syndrome, the vating Ckm or cardiovascular kidney metabolic disease from both a clinical as well as a research, perspective.
- Because we've learned over the years that these 3 entities are all tightly intertwined, partly because they all promote inflammation and oxidative stress but they also feed into one another. So if you have Ckd, chances are you're going to have cardiovascular disease and metabolic disease, and same for the other 2 as well.
- And so just to underscore that so cardiovascular disease is a huge risk in people with Ckd that worsens over time with worsening Gfr and albumura. And this is just a case in point, heart failure is the most common type of cardiovascular disease in kidney disease, and you can see that as you lose sorry as you lose. There you go. That's on it. Oh, yeah.
- As you lose. Gfr, your risk goes up as you increase your Alpineuria, your risk goes up, but these 2 points are additive. So if you look at both together, you'll have a better predictive model than if you look at any one of them individually.
- And so that's what conveys the huge mortality rate that we see in Ckd. So the red line up top shows us the mortality rate for patients who are on dialysis, green and brown lines are for people who have
- Stage 4 and 5 Ckd and the darker brown line below. That is for people with transplants.
- And so that's why it's really important for us to study, not only kidney disease, but also heart disease, because they go hand in hand. And we have to also remember when we're treating kidney disease, we're not just delaying the time until somebody needs dialysis or transplant, but we're probably also decreasing their risk for heart attack, stroke or cardiovascular death.
- And so again, back in 2,001, we had the initial kidney outcome trials, renal and idnt. And then out came the cardiovascular outcome. Trials for Sglt. 2 inhibitors glp, one s. And non-steroidal Mras. And that's when people said, Hey, you know what these people are actually having decreases in albumin Ra, and maybe even increases in Gfr slope. Maybe we should look at that. And hence out came all of the outcome trials.
- So here is meta-analysis, and you're going to see a few box plots. So I'm sorry it's not really for you to see the given individual lines, but just to kind of appreciate the gestal of how they all fall together. This is a meta-analysis of over 90,000 people who participated in clinical trials of Sglt, 2 inhibitors both for Ckd as well as heart failure. And looking at various outcomes, you can see on the left here. We're looking at kidney disease progression, and on the top here is just looking at diabetes alone. But we know that these drugs work for non-diabetic. Ckd as well, I put in acute kidney injury as well as you can see that there are signs that potentially these drugs may be a potential therapy for Aki, and those trials are actually in progress now, and that would be a late breaker, because we have nothing other than supportive care for Aki at this time. So sglt 2 inhibitors. We know there's probably some sort of common pathway, be it inflammatory or fibrosis that leads to progression of Ckd and the Dapa Ckd and the Empa kidney trials both showed us that because of the fact that they enrolled people not only with diabetic kidney

disease, but also non-diabetic kidney disease, and they actually included pretty much any kidney disease other than lupus or polycystic kidney disease.

- And when you look at the stratification according to the different type of kidney disease, we see diabetes, we see hypertension, even glomerulonephritis. So when you look at the Iga participants, there are actually quite a number of them that were enrolled in these trials. They also progress, or they also mitigated progression
- in that group as well. So now, it's actually a supportive care that's guideline driven for Iga as well. But basically any kidney disease other than the 4 matches.
- So the most recent study to come out was actually looking at epic kidney and looking at, how long do we get a mitigating effect after somebody has started this and then stopped it. And so, just to remind you the inclusion criteria. So these were people who had a Gfr. Of 20 to 45, or if they had a better Gfr. Of 45 to 90, they had to have some degree of albuminuria. So a Uacr greater than 200, and so the people were treated for about a median of 2 years, but then they continued to follow these people for another 2 to 3 years, and after the trial ended people could come off therapy or start therapy as they wanted. So if you look at during the active trial, of course, the vast majority of people they advised to was 90% versus post-trial dropped dramatically, which I found actually a little concerning that it dropped quite that low in that, you know, this was a proven drug. These people were on this in this trial, and yet they still only have about a 40 to 50% uptake.
- But the placebo group had about the same as well. So 37 to 42.
- And if you look you can see around 2 years. This is what I said is the about the median of the trial period. You can kind of appreciate the shaded region. So some people stopped earlier than others just due to whenever they got randomized.
- And you can see that those lines continue to separate. So over the trial period, there is a 3.8% absolute risk reduction. So that's a number needed to treat of 24. And after, when they each went on whatever drug or placebo that they wanted. The combine period was 4.1% over 4 years. The majority of that improvement that our continued improvement that they got was about a year after Israel ended. So basically, what we're saying is, the effects are long lasting for about a year up to 2 years after therapy.
- So another important question when it comes to sglt 2 s. Is whether albuminuria matters because a lot of the initial trials were only in people who had albuminuria. So in the kidneys trial. Specifically, they enrolled people who had no albuminuria as long as their Gfr. Was less than 45.
- And so, if you look at the absolute difference in their Gfr slope. So we're looking at the Gfr. Slopes here. So in those who had the Gfr. Of 20 to 30, and they were on placebo, they dropped almost 3% per year per year versus 40.7% per year
- for Albuminuria. If it was 300 to 1,000. It was 2.8 in placebo, 1.4 in the active trial. So you can see that as people had more albuminuria, they had greater benefit. The solid line is 0. This dotted line is the mean, absolute risk reduction.
- And so you can see that the same was true of the relative risk reduction. So now we're looking at the other side of 0 because we're looking at a decrease risk, we can see that those people who had less albuminuria actually benefited, greater because, while they had a slower drop in their or they had a lower slope in their Gfr. The relative risk was much better.
- So, even though they're less likely to progress within 3, 5, 10 years over the course of being on these drugs 1015, 20 years, they could potentially benefit even greater

than if we get it. Give it to people. Late stage just arguing again for early intervention.

- So I wanted to stop and talk a little bit about type, one diabetes, because a lot of people don't believe in giving Sglp 2 inhibitors to people with type, one diabetes because of the increased risk of a while. Sotogliflozin is the only Sglt 2. It's actually a Sglt, one and 2 inhibitor. That's been trialed specifically in type. One diabetes. But they haven't looked specifically at hard kidney endpoints, but what they did find was that people who were randomized to soda Mefluzin had better a 1. Cs. They had more time in range in terms of their Dkm. Which is crucial to mitigating risk reductions. They lost weight. Their blood pressure was better, but there was a greater risk of Dka. And so they were closed at 3% versus 0 point 6%.
- They also had greater reduction in Alpineuria. So this went up in front of the FDA in October of 2024, and FDA decided not to approve it because of this increased risk of Dia. And so it was put forth to them by their advisory committee.
- What are we supposed to do for people with type? One diabetes who have very severe Ckd. And they said, well, we can still use Dapagliflozin because they're approved for using this drug. And the committee was like, what are you talking about? We don't see that anywhere. And so they put out this statement and you can look it up online where it says that they have approved Dapagliflozin for people with Ckd and no type, 2 diabetes. And so this recommendation extends to those with type one which was so important because we have a hard time fighting with insurers about how to get them paid for for our patients. And now we can point to this.
- And so there are still some people who are a little concerned about it. So I put these numbers together. So if you extrapolate from Ccb. Diabetes with Sglp 2 inhibitors, these are the numbers in terms of risk reduction for kidney failure. So that's not doubling of crap. That's dialysis or transplant as well as cardiovascular mortality. So if you take those numbers, then we can actually come up with 3,500 cases of end-stage kidney disease, and 7,800 cardiovascular deaths that would be prevented per 100,000 person years treated with one of these drugs.
- Well, we know it increases the risk of Dka, so 3.6% 0 point 6%. It's estimated that there would be about 4,000 new cases of Dka per 100,000. And there's about in general a 0 point 4% mortality rate from Dka. So that would be 160 deaths per user.
- So you know, about 11,000 cases of end, stage kidney disease or death prevented 160 deaths caused.
- I'm just gonna leave it at that because people form their own.
- So now, moving to Finarinone this is the only non-steroidal mra that we have. It was tested in 2 big clinical trials. Fidelio and Figaro. Fidelio was looking at people with diabetes and album Ckd and then was looking at people with type, 2 diabetes and mild Ckd. And then they pooled these together to get the fidelity analysis. I don't know if it comes up with these names, but in any case we can see that the composite cardiovascular outcome was reduced by 14%. The composite kidney outcome by 23% death from any cause, 11% hospitalization mildly decreased. So this was approved as well. And so a lot of us are like, well, what's really the difference between Phenerinone versus Veronolactone and Implan.
- So there's only been a couple of head-to-head studies in the early phase Finerinone studies. And if you look at Fenarinone versus Furonalactone. The effect is pretty similar between the 2, as well as with the flarinone, but finerinone excuse. Meridone is superior to spironolactone, but it's equivalent to openeridome and we're in

reducing the ntprov levels numerically. When we looked at Openeridome there was a lower risk of hospitalization for heart failure, but it didn't reach significance. These were tiny little studies that they were just exploring whether there was an effect. So there was just a couple 100 people.

- We know that Fenarinone has a lower risk of Hyperkalemia than Smirnolactone, maybe a Clarinone, but definitely Spranolactone. But Fenarinone is the only one that has been tested in large numbers of people, and shown to have reductions in hard endpoints. So for me, I'll try and get it. If it's cost prohibitive, I will give patients a clarinone.
- Finally, glp one agonists for cardiovascular events. So these were the initial cardiovascular outcome trials. And the reason they had all these cardiovascular outcomes trials is because, if you remember way back, when, with Thizolidine Diomees they were approved just for glycemic control. But then it turned out they caused all this heart failure. And so that's why the FDA was like, you know, you really have to start testing these drugs after you get approval to make sure that they are safe. And so that's that's what led to all of this.
- And so you can see here again in our box block that there was about a 14% reduction in cardiovascular events, which was a composite of mi stroke and cardiovascular death and they looked at stratifying people with Gfr. Less than 60 versus greater than 60, and they found pretty much similar. Similar effects.
- The next came out was the award 7 study, and this was looking at specifically at people with advanced chronic kidney disease. So stage 3 and 4 Ckd. Who had albuminuria.
- And this was actually a trulicity study, and they compared trulicity at 2 different doses versus insulin. And then they looked at the proportion of participants with a 40 or 50% Gfr reduction dialysis before clean wound transplant. And you can see there was a dose dependent reduction with dulacletide or trulicity. And so to me this, this was pretty good evidence to start using trulicity. It does not carry a label. The FDA did not approve it very much, but in my practice this is what I use. And then finally came the ultimate study flow which came out last year, which is semaglutide. And again, these are people all with type, 2 diabetes who have albuminuria and looking at the major kidney disease events. Again, 50% decline and stage kidney disease.
- And you can see there was a 23.4% reduction for kidney events and an 18% reduction for 1st major cardiovascular event. So this is undergoing review by the FDA.
- Assuming there is an FDA coming to the see if we can use it for this, and then I also just wanted to quickly mention Terzapatide, because terzapatide is also being used a lot for diabetes and even obesity to itself.
- Cheers after time also hasn't hasn't gone to look and see if there are major endpoints in terms of reductions in kidney disease and cardiovascular death. But they do show some intriguing information. So 1st of all, weight change is superior, actually, compared to Semagne. And that's important, because we're all getting heavier and obesity is definitely a driving factor nowadays in progressive Ckd but also, if you look at the composite renal endpoints that included new onset, macroalbuminuria. So it was the other hard endpoints, but also, including macroalbumuria. That's severe albuminuria, greater than 300 milligrams per gram.
- You can see there was a significant reduction in risk. The reduction in risk. When you take out background. Humania does not reach statistical significance. But

again, this is not what this study was designed for, so it wasn't powered for it. And so this is kind of preamble evidence to potentially look at a future trial.

- So does raz and commission matter anymore. I've had this question a lot. And I think the answer is definitely yes, and we shouldn't forget the original trials, Ronel and idea in 2,001. I remember these so well because I was a fellow, and I remember I was so excited about this.
- It was the 1st treatment that we had for diabetes and chronic kidney disease. It looks like, maybe the lines aren't as impressive. But the reason is is because, as we see in the Sglt 2 and other trials. But the reason is is because they were honest rovers, and they kept the Y active you know, going all the way up to 50 rather than just condensing it on so similar risks specifically in idnt, superior probably to to amlodipine.
- And then we also know that if we stop ras inhibitors due to Hyperkalemia rather than just dose, reduce it.
- It's associated with a much higher risk of mortality. We also know that when we stop Ras inhibitors in the hospital from Aki, which I also am not sure we necessarily need to do, but if we do, it really needs to be restarted, if not on discharge, then, as soon as they follow up with their Pcp. Because otherwise they're much higher risk for coming back to the hospitals with various illnesses actually as well as as dying.
- So the only difference the only time, I would say, maybe resinhibition is less important is in very advanced Ckd, so I have qualms about this, but I thought I'd be honest and show you. So this came out a couple of years ago, and this is looking at people with an Egfr less than 30, and they were actually randomized to either stop their ras inhibitor or continue their ras inhibitor. And they looked at percentage of patients reaching end stage kidney disease. And the full group is the group who continued it. And so it was lower. But it wasn't statistically significant.
- I would argue that still matters, because if you continue the duration that you're followed may be able to statistical significance but you can see that it didn't matter what type of diabetes they had, what their blood pressure was what their proteinuria was or whether their Gfr. Was above 15. So I do say this because I know oftentimes we struggle when people have severe Hyperkalemia, which I define as greater than 6 and a half that we wonder if we can stop it safely. I think we can. I think the better way to go. This is just kidney events. It's not heart failure. Heart failure probably still makes a difference if we continue them on it.
- But you know, if people can't afford a potassium binder, then this is this is this is your path. In stopping a ras inhibitor. If if there's no other safe way to go.
- The other thing that I wanted to touch on is the Egfr dipping. So I get a ton of questions about this like, I just started my person on an Sglp. 2, and their Gfr. Has gone from 50 to 40. That's 10 points. That's too much. And I said, No, it's not. That's a normal, acute drop that we see because these drugs as do aces and arbs and Mras, and probably excuse me, probably even glp one agonists. They actually reduce the intraglomerular pressure because of alterations in aserent and arterial or caliber. And so you have less mechanical force. And so your creatinine is going up. But it's not in the urine and as soon as you take patients off of it it goes right back up. And so this is not something that we ever really need to worry about. They say the maximum is 30% I've seen higher than that and I've stopped it, and the cracking comes back down, and then I restart it and goes back up. But because it's clearly just a physiologic effect. I've chosen not to worry about it, and people have done fine.

- So that brings us to the question of like, well, how many of these drugs should we use? Should we use one drug, 2 drugs, 3 drugs, 4 drugs. And so this is data that's extrapolated from clinical trials. And it's showing us, I know this is a lot of boxes. But again, just look at the pattern. This top group here is mace hospitalization for heart failure, and then cardiovascular death.
- And the 1st 3 rows are the individual agents. But then, after that we're looking at combinations with the last row which is the farthest to the left, meaning greatest benefit. Having all 3 of these drugs together, and we actually see the same through Ckd, progression and all-cause mortality.
- So depending on the risk and the cost of these drugs because it's definitely a factor, you know I use all of these drugs, including Ras inhibitors for my high risk patients.
- So another way to go about this is to actually do a trial. So confidence is a trial that the top line results are due out at the European Renal Association Meeting in June.
- But this is a study where we enroll people and randomized them to just venerinone, just empilocan, or both, and they all take 2 pills. Just one of them may be a placebo and here's the schematic of the people. The primary endpoint is change in albuminuria. But we've seen over and over and over again that if you're reducing albuminuria and diabetes, you're improving, Gfr, and so we'll have that coming to you soon.
- So let's talk for a second about something new. I'm just curious.
- Is anybody familiar familiar with hierarchical clinical insights.
- Just Julie. Okay, so this is actually an endpoint that's been around for a decade, and cardiology has been using it for quite some time, but it is currently being looked at as a new approach to finding new medicines and new ways of combining medicines to treat patients.
- So a traditional composite endpoint is based on the clinical outcome with whatever happened first.st So if you get end stage kidney disease first, st that's your endpoint. If you die first, st that's your endpoint, and those are looked at as the same. You drop half your kidney function, same as dying.
- Okay? And so it's just time to 1st versus a hierarchical clinical endpoint that's based on clinical outcomes that are ranked according to their importance. So generally we would rank death first, st followed by kidney failure, replacement therapy, and then various declines in Gfr.
- And if none of those are hit, then a person will contribute to the analysis by whatever their Gfr slope is so you can do that continuously, or you can have thresholds like, did you lose more than 5 mils per minute per year? However, you want to design your study.
- And so the way that we analyze this data is either with win ratios or win odds. So the reason that this study design is helpful is because it brings a great degree of power, so it incorporates every pairwise comparison. So if you have 20 people 10 in each group, that's a hundred comparisons. So you can see how that has a lot more power. And so each comparison 2 individuals. It's either a win a loss or a tie.
- So the win experiences, the win active participant will experience a less severe event than the control participant, or if they both are experiencing the same event, it's whoever experiences it last and the total active group wins. Losses and ties are how we calculate this win odds. So it's the number of wins plus number of tie, half the number of ties divided by the number of losses, plus the other half, the number of ties.

- So when odds greater than one, so you can think of to, you know 2 athletic groups, right? So they play each other 10 times right? So there's 4 wins and 6 losses.
- So that would be 28, and that would be a watch it would be like and the numbers are in to what we normally save for hazard ratios in terms of how strongly positive or negative they are in terms of the strength of the clinical estimate but they should not be confused, because they are very different math equations. I'll just say that. So just as an example. So we have person A and person B and Person A is the control group B is the active group, so the circles are deaf and the diamonds are in stage kidney disease. So the person who wins in this 1st comparison is A. So, even though A died B got in stage kidney disease first.st So that's how that works, whereas here they both have the same endpoint. But a got it first.st So B wins for this one this 3rd one. Neither of them experienced an event. So we're going to contribute each of their slopes and the reason that this is important above and beyond power is that there's greater meaning to this right? So we're not. We're not just doing a time to event. We're we're talking about how important these events are. And I think that's really important from patient perspectives as well. So we actually had a meeting about this last month that was that was fostered by the National Kidney Foundation, and patients were there, and they really liked this.
- They didn't understand it, and they were like, if you guys say it works, it kind of looks cool. And we're okay with it. Because that was really important to us. It's also important because it includes more common. We don't just care about end stage kidney disease and death. We do also care about loss of kidney function.
- And for the same reason that I pointed out at the beginning of this, because, as you prevent loss of kidney function, you're probably preventing cardiovascular complications as well.
- And this is a great way to integrate both binomial. So 2 2 different types of options, as well as continuous endpoints like Gfr Slip.
- The problem is, as we saw. Nobody's familiar with this. But that can change. We just need to educate people follow up. Time is problematic. It depends on which, by a statistician, you ask, but that may be an issue because it changes how the values can be interpreted. Most people are contributing Gfr slope. So you got to get at this with the study design. Like, if you're looking at a population who's just not going to have end stage kidney disease or death, then don't do a hierarchical point. Do a Gfr slope study, and then some differences can be important, like a week between experiencing an endpoint or the difference in Gfr slope. But that's easy to deal with. You. Just define them as to whatever you think is clinically so with all that being said, we're looking here at the approved medications that we have here. We're looking at our ongoing phase, 3 studies. These are all just for Ckd and diabetes at the top, or with or without diabetes on the bottom, and there's just a whole slew of molecules that are under investigation, so some of them will make it hopefully. Some of them won't.
- But we are going to see more and more of these therapies come through. Come through. I'm sure that so, just to close off hopefully, I convey to you that Ckd is actually really important for us to think about commonness and its high morbidity, mortality, and that these innovations and trial design is really why we have all these therapies that have come down the pipeline, and how we're able to improve the lives of our patients. But there are still gaps. We don't know which drug for which patient how to combine the therapies which combination is best and the last one I don't know how to get this one how to pay for these medications, but also how to

mitigate side effects. So I'll close there. And if you have any questions that's awesome, Amy, thank you so much. I think we published a paper in Ajk in the last year or so that showed the Placebo group in clinical trials, for Ckd has gotten better over time. So I mean, you showed us it made me think about when you showed the renewal. And Id and T. That 50% of the people were having events. And now it's much lower. So we're obviously doing something right or enrolling much lower risk populations.

- Is there a point at which patients just won't take as many drugs if they're low risk.
- And how do you think that great question? It's true. Actually, the flow study took way longer than they expected, because there just weren't as many events as they thought there would be. I do think it's because we're doing something right. I think it is partly because we have these these drugs. There was a good number of people who are on Sglt, 2 inhibitors and ras inhibitors. I think of drugs as what I hope and I hope is a temporizing measure until we can get better education, better practice models so that we can have less people who get Ckd and less people who progress on and need.
- So you know, that's my my rosy picture. My less rosy picture is that you know, the poly pill is always going to be be an option. We're going other directions with therapies. We have weekly injectables that people don't mind. That will go to monthly. I think technology will take us in a direction that patients will probably be agreeable to taking lots of different drugs. You know as much as I invest in clinical trials and research.
- I just think you know, the money is prevention. The money is primary care. It's making sure you know not only how severe your kidney disease is, but why you have kidney disease, and you need to see a nephrologist to make sure that there's not something else going on to talking to patients? What are kidneys? And you know, what do they do? And why should you care about them? So I think education, education, and better health care, which I'm not sure.
- Gonna see it anytime soon. But that'll be my answer.
- I have a question in the chat. Do hce include things like quality of life? They can, they most certainly can. And that's the beauty of them. The question is really, how to combine that. Does it belong in the hierarchy, or does it belong as a secondary endpoint? And how do you prioritize that? Right?
- So it was interesting. We talked about polycystic kidney disease. And so a lot of patients have have cyst pain. So quality of life is huge. And so like a lot of patients. We we sent out surveys and asked people to rank things so like quality of life or increased pain was at the top.
- Transplant patients. They will prioritize graft failure over death, so they would rather die than go back on dialysis. Not all of them, but some of them. So so those are the things that are hard to settle out for this and require a lot of, I think, introspection and discussion with patients and providers.
- Yeah, and sort of question branching from that, then. So what is the process like for coming up with the Hcps and deciding like, who who all is at the table deciding those rankings?
- Yeah. So that's a very good question, too. So we're just entering this like this is literally just being talked about. And so, you know, when it comes to trial design, you know. No, industry is not going to spend, you know, 20 million dollars on a trial. If the FDA feels that their trial design isn't going to lead them to approval if they, if they find a positive outcome.

- So certainly discussions with the FDA and the FDA. Our FDA is pretty good people. They will want to hear from patients. They will want to hear from nephrologists, transplant nephrologists, cardiologists, diabetologists, you know. So I think this is just the beginning of this conversation, but at the end of the day the FDA decides.
- I'll let you ask your question.
- Okay? Sure. I really enjoyed your presentation. The question I have. It appears as though if you take 100 patients, I mean 100,000 mentions, you will have about 7,000 that continue to report on.
- So for the hce, yeah, yeah, for the so it's squared. It's the number of patients squared.
- Okay? So I'm just trying to look at your data. So if you put 10 patients on Sgrt 2 inhibitors, how many of those 10 are going to be healthy in terms of progression? Or, Oh, yeah. So the number needed to treat in general. Yeah, because I had the impression that from the 10 patients to have one to have one. So that's always going to be true with any drug and any chronic disease. So in in this climate where we're trying to cost, you know, cut costs and everything. I'm wondering whether we can do a better job in identifying who is going to be that one patient that that we can help. So right now we are sitting 10 patients and helping with 3 years. One patient? Yeah, no, that's a great question. So you're talking about precision medicine. And Julie and I were talking about this. So
- I think this is a long way to come. But I think we need better ways of phenotyping, if you will. Our patients. So you know what are the specific mechanisms at play in any given individual? And will this molecule potentially help? You know every day that particular mechanism? So the Neptune study is a glomerular disease. Study
- Fsgs membranous minimal change disease, and they have a Neptune match. So for patients who enroll in it, they do all this? Fancy, Schmancy multi analysis to see what are the main pathways that are upregulated or down, regulated, and then they contract with Pharma who are doing trials in those disease spaces, and they will give the patient and their clinician a printout of all the pathways, and how those match up with the various drugs that are available in clinical trials so that they can pick the one that they're most likely to benefit from. They'll still be randomized. That's where we're going.
- You know, we research is a sales sales pace. So I think that's probably 1020 years away or more. But that is definitely the goal.
- Another question in the chat. So given increasing use of combination of grass Noors and Mres and Ckd. What potassium threshold do you use for initiating a potassium, lowering agent or lowering the dose or discontinuing. Yeah. So the beauty of Sglt 2 inhibitors is that they lower your potassium. And so that's why it works really well in conjunction with multiple whereas inhibitors, including Canarinone and acrr. So that's just one tidbit. What's my threshold? We were talking about this as well, so in the nephrology space we are much less concerned by potassium. As our non-nephrologists. I tend to start somebody on potassium binder. If they're consistently above 5 and a half.
- I don't send people to hospitals till they're closer to 600.
- Thank you, Amy, for that wonderful lecture. It's really exciting to know that there are new drugs out there for kidney disease.
- My question goes back to one of your earlier slides where you had a slide which showed that if you stopped the Sglt, then there's a persistent effect to to have the

protective effect and we know that that you have a dynamic effect where there's a drop in.

- What is the mechanism? What do you think is the mechanism by which the protective effect is persistent? Yeah. So sglt, 2 inhibitors benefit. Go way above and beyond just hemodynamic effects. They are definitely anti-inflammatory. They improve their reactive oxygen profile. You know, when I read that article I thought of you know in diabetes how, if you control somebody's blood sugar for any period of time, it's long lasting study as well as in the Dcct. Trial, and those effects were hypothesized to be epigenetic in nature. You know. I'm sure there are other possibilities, but that would make sense to me here as well.
- Thank you.
- Thank you so much.