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

TRANSCRIPT - GR 03 25 22 Nuzhet O. Atuk Distinguished Lectureship - "Advances in diabetic kidney disease"" ***Ian de Boer, MD, MS,*** **from the University of Washington**

- 00:10:28Good afternoon, everybody.
- 00:10:31So thank you for joining us today for the news that it took to stay with lectureship here the Department of medicine at uva.
- 00:10:38This lectureship was established in 2006 to honor the legacy of Dr took in pioneering dialysis care in the State of Virginia founding or division and apology and ETA and providing low leadership scholarship and secondary.
- 00:10:59History background stuff after Medical School at the university assemble doctor took story brought him to Charlottesville, and 1951 pursue residency in internal medicine at uva just like many of you.
- 00:11:13This was followed by a fellowship at uva and cardiovascular medicine.
- 00:11:17During this period, this was the early 1950s it's really the dawn of the for ology and the beginning of time and dialysis was emerging as a lifesaving therapy for kidney failure it's really hard to blame them for took for becoming fascinated by the kidney and this time.
- 00:11:34enjoy the fact with Ada in 1950 cents becoming the first chief of the division of the project uva and leading the team that provided the first haemodialysis session in the State of Virginia 1959.
- 00:11:48served as a medical director on the dialysis unit subsequently.
- 00:11:52Throughout time university he served in other critical roles, including as affiliated faculty the division clinical pharmacology and as founding director of employee health over 20 years.
- 00:12:08Most of the enduring legacy of Dr is attributable to his foundational scholarship.
- 00:12:14As the director of the lab as I'm kind of colonies and the divisional clinical pharmacology he made major contributions to our understanding of catecholamines metabolism depicted here by one of many idioms.
- 00:12:29For delegated patient care and clinical investigation doctor took as a leader and feel promising Tillman and describe some of the initial relationships between feel promise a trauma and been able to now disease.
- 00:12:43He also helped us understand the genetic basis this case.
- 00:12:49So in honor of this legacy lectureship was established in 2006 but in addition to the project honor the outstanding contributions of science.
- 00:12:58Practice of medicine and the extraordinary local contributions to the University of Virginia school of medicine we're very pleased today to have Dr into board joining us for the 2022 distinguished lecture.
- 00:13:12Before as well equipped to fill the shoes, he is a professor of medicine adjunct Professor geology and associate they can be research institute at the University of Washington or he's risen through the ranks since joining faculty and do have access.

- 00:13:28After the war is under undeniably a global leader and vitamin D metabolism diabetic kidney disease and really driving clinical trials from prodigy because over 350 peer reviewed publications.
- 00:13:43Over the course of an extremely successful research career to date, Dr Boris lead eight major NIH research project grants recruiting for clinical trials.
- 00:13:52He also serves a multiple leadership roles in the international nephrology community, including as Co-Chair of the recent kd go clinical practice guidelines on the management of diabetic kidney disease.
- 00:14:05Chair of the American heart association kidney and heart disease scientific committee.
- 00:14:11debbie editor of the journal of the American society and prodigy and you mostly for the global kimmy platform trial network that's been developed by George clinical a major international CRM.
- 00:14:24So, again it's an honor to have you here today Thank you so much for joining us.

Ian de Boer

00:14:30Thank you so much for that kind introduction and for inviting me here for this lectureship I wish I could be there with you in person, but we'll have to do a zoom a little longer here, can you see my screen.

Unknown Speaker

00:14:44Yes.

Ian de Boer

00:14:45All right, great.

- 00:14:47It really is an honor to.
- 00:14:49present this as a lectureship I didn't know Dr took, of course, but I was inspired reading His story and hearing it again this morning.
- 00:15:00And he his career really did set a roadmap for how to advance science and clinical medicine and there were many parallels I saw to what he did in the 1950s, to what the field is still doing today and diabetic kidney disease.
- 00:15:16And that includes a focus on multidisciplinary science, he was a hematologist cardiologist nephrologist pharmacologists.
- 00:15:25And that's really what's brought kidney disease and diabetic kidney disease forward in this century as well, he focused on catacombs.
- 00:15:33metabolism catecholamines metabolism specifically but that's yielded great advances in diabetic kidney disease as well.
- 00:15:41And you really translated his work clinically through pharmacology and also for patient advocacy and application through dialysis, for example.

- 00:15:50And so that story I think is very inspiring and I think there are many parallels and what we've seen happen in diabetic kidney disease over the last 20 or more years as well.
- 00:16:01That is what I'll talk about today, and I have just one slide about the epidemiology and impact of diabetic kidney disease, because I spent suspect this audience already knows this quite well.
- 00:16:13On the left here is a map from the International diabetes federation, looking at the prevalence of diabetes Type one and two worldwide and then updated estimate is that there will be 783 million people with diabetes and.
- 00:16:29And in the middle, is a snapshot of some work that i'll expand on a little bit later from our group, looking at the epidemiology of diabetic kidney disease in the United States.
- 00:16:39and showing that, as the prevalence of diabetes has grown over time, the prevalence of kidney disease in diabetes has grown proportionally and really it is the predominant problem that we're seeing in nephrology clinics and really a huge impact.
- 00:16:55Worldwide, and then on the right, you can see data from the United States renal data system, looking at the prevalence of dying of.
- 00:17:04kidney failure that's dialysis or kidney transplantation by tas and diabetes is far and away the leading cause here and internationally.
- 00:17:13Half of all new end stage kidney disease cases are due to diabetes in this country and so.
- 00:17:19From both a personal perspective for individuals who have diabetes and kidney disease is a very morbid complication and from a public health standpoint.
- 00:17:30Reducing the impact of diabetic kidney disease is key to improving outcomes.
- 00:17:36Reducing dialysis and also not shown here, reducing cardiovascular disease, because kidney disease we know potently augments rest of cardiovascular disease for atherosclerosis disease and heart failure among people with diabetes.
- 00:17:50So there's lots to talk about with diabetic kidney disease, including diagnosis pathophysiology biomarkers but today i'm going to focus mainly on treatment.
- 00:18:01And i'll divide my talk into three sections one on the foundations of diabetic kidney disease prevention that's really close to mind control and treatment with Ras inhibition.
- 00:18:13A new standard of care that's emerging based on new drugs and new clinical trials supporting their benefits and being applied through clinical practice guidelines, as noted in the introduction.
- 00:18:26And then finally I'll shift and talk a little bit looking towards the future of diabetic kidney disease and the emerging pipeline of additional therapies that are available and how we can perhaps he's precision medicine to better target and advanced therapies for diabetic kidney disease.
- 00:18:43I do have some disclosures I have consulted for a number of companies that make, in particular the slt to inhibitors and gop one receptor agonist that I'll be talking about I'll try and provide a balanced overview of the risks and benefits, as I discussed them.
- 00:18:59I one slide here on glycemic control this is from the landmark diabetes control on complications trial or d-ct and it's observational follow up the edict study, this is a study that.
- 00:19:11started in 1983 before I was in medicine, but I have been fortunate to work with this research group for the last 20 years or so, focusing on kidney complications and type one diabetes.

- 00:19:23And the dcc T as you'll recall, was a study of 1441 people with relatively new onset type one diabetes.
- 00:19:32They were randomly assigned to intensive diabetes therapy, which is what we use today multiple daily injections of insulin or a pump.
- 00:19:39versus conventional therapy, which was to insulin injections daily aimed only to prevent hypoglycemia and the hemoglobin a one sea levels achieved by the two groups for 7% or 9%.
- 00:19:54And you can see, on the left of this table during the dcc T intensive diabetes therapy applied.
- 00:20:03On average over 6.5 years resulted in a 39% reduced risk of developing what we called micro albuminuria and 54% reduced risk of what we called macro albuminuria Alvin excretion rate of 300 milligrams per day or more.
- 00:20:21And then, at the end of the DC CT all participants were offered intensive diabetes therapy because of these benefits on the kidney as well as other outcomes like retinopathy.
- 00:20:31And they work continued to be followed and the really amazing thing about the decency to eat study was what happened during that observational follow up when you guys see me control was the same.
- 00:20:42And you can see here in the right part of the column, the risk reductions in micro macro albuminuria.
- 00:20:48Were 59% for people who have previously been assigned to intensive diabetes therapy and 84% for macro albuminuria, and these are despite current similar glycemic control, this has been called metabolic memory, or the long term effects of.
- 00:21:05Early glycemic control on subsequent development of clinical diabetes complications.
- 00:21:12And then on the right, you can see the in addition to albuminuria the other main manifestation of kidney disease, of course, is reduced egfr and these participants had normal egfr baseline.
- 00:21:22And during the six and a half years of the trial very few developed a low egfr defined as a persistent egfr less than 16 better only for such cases in the during the DC CT.
- 00:21:34And it was only after one or two decades of total follow up that participants began developing low egfr but with that long term follow up.
- 00:21:45In terms of diabetes therapy was shown to reduce the development of low egfr by 50%, so this is another manifestations of metabolic memory, the long term beneficial effects.
- 00:21:56And really it's important to note how large these effects are reducing risk reduction to 50% 59% 84%.
- 00:22:05They manifest over decades and really in type one diabetes and 10s of glycemic control is still the foundation for preventing long term complications.
- 00:22:15And that's important perspective when we talk about the new diabetes medications as well, I believe the effects of.
- 00:22:23Intensive diabetes therapy and glycine mixture are also equally important for type two diabetes.
- 00:22:29That we don't have any studies, like the dcc to eat activity and type two diabetes, to show the long term benefits.
- 00:22:35accord advanced the va diabetes trial all are much shorter and duration, they all showed benefits with regard to albuminuria.

- 00:22:43But these long term effects on egfr just can't be evaluated adequately and those studies, due to the duration of follow up and I believe that in type two diabetes glycemic control is also the foundation of prevention in that population.
- 00:22:58The other main intervention we've had, of course, for many years as Raza inhibition.
- 00:23:02And there are three seminal studies, the collaborative study group trial type one diabetes and then the Rhode island at and T study.
- 00:23:10Published now 20 years ago and people with type two diabetes that albuminuria and reduced egfr.
- 00:23:17And those trials showed comparable cboe or in the ID Mt also an active competitor and load up that Ras inhibition among people with prevalent kidney disease, reduce the progression of kidney disease stumbling a serum creating end stage kidney disease or death by 16 to 20%.
- 00:23:35So smaller but still clinically meaningful and important reductions that have established the standard of care Ras inhibition for secondary prevention of chronic kidney disease.
- 00:23:46Our group has looked a little bit at the epidemiology of diabetic kidney disease United States over time, and this is one of those studies.
- 00:23:54it's a little bit complicated these data are stratified by self reported race and ethnicity.
- 00:23:59But I like to look at the overall trends here and the use of these medications that were proven to be effective 20 to 30 years ago, and this is using enhance data so data that's representative of the United States population in snapshots over time, starting with.
- 00:24:18And proceeding in this study, up to the 2009 to 2014 evaluation period, these are different individuals, over time, but looking at the prevalence of drug use and clinical manifestations over time what you can see is that.
- 00:24:32There has been an increased use of glucose lowering medications among people with diabetes over this 30 year period.
- 00:24:41that's in part due to increase screening and awareness of diabetes in the United States the same time we've seen improvement and hemoglobin anyone see levels.
- 00:24:52Within increased risk are increased use of Ras inhibitors over the same period of time perhaps not as prevalent as we'd like to see Ras inhibitor use as established therapy for some of these people.
- 00:25:05But still, there has been updated with improve control systolic blood pressure and on the right, you can see, also increased use of status with better ldl cholesterol.
- 00:25:16Control and what's happened to kidney disease over the same period of time, while, on the left is the prevalence of albuminuria the columns are the.
- 00:25:25prevalence of any albuminuria 30 milligrams per gram in a spot urine collection or more or in this smaller shorter bars macro albuminuria 300 milligrams per gram or more, and you can see that, over time, this is improved.
- 00:25:39down from prevalence of about 21% to 16% and our estimates, account for looking at persistence of this this albuminuria so that would be expected with improved.
- 00:25:51glycemic control and improved blood pressure, control and mass inhibition, on the other hand, the prevalence of low egfr the other manifestation of kidney disease actually has increased over time.

- 00:26:02And this is a little puzzling we don't know exactly why this is it couldn't be a good thing and people with diabetes are living longer and that may allow.
- 00:26:12More development of kidney disease is a chronic complication we've hypothesized also it speaks to the need for additional treatments to target pathways that we're not adequately addressed through glycemic control mass inhibition alone.
- 00:26:25And on the right, you can see the prevalence of any chronic kidney disease remains above 25% for people with diabetes in the United States, and we really haven't made enough progress on reducing that over time.
- 00:26:40And that's consistent with clinical outcomes data from the United States population summarized here by Edward Greg.
- 00:26:47and which has shown market benefits for people with diabetes and reducing atherosclerotic cardiovascular disease myocardial infarction stroke, as well as amputation.
- 00:26:59Less hyper glycaemic crisis with better glucose control here on the bottom, but really only marginal if any benefits and prevention of kidney failure.
- 00:27:11So happily that's started to change or we hope it's going to change and what's really changed the landscape.
- 00:27:18Are the new trials and new glucose lowering drugs, and these were mandated in 2008 by the FDA and the AMA such that new glycemic control medications no longer.
- 00:27:28Could could stay approved based on glycemic lowering alone, but had to show cardiovascular safety and that spawned a large number of trials.
- 00:27:37summarize here, and in particular the ones that have been so impactful are those of the sgt two inhibitors shown what I think is a pink color there and the gop one receptor agonist shown and yellow here.
- 00:27:49And I'm going to summarize mckinney perspective just a little bit on that and then talk about how that is currently changing the standard of care for people with diabetes and kidney disease.
- 00:28:00So sgt two inhibitors, as you know, are small molecules that inhibit the sodium glucose transporter to present in a number of places, but most predominantly in the brush border of the proximal tubular cells of the kidney.
- 00:28:17In nephrology we've known about slt to numbers for a long time flora xen is one that has been used and research laboratory fees to explore Reno physiology.
- 00:28:27And it's been adapted now to a number of commercial products shown here.
- 00:28:32and any of these sgt two inhibitors are freely filtered at the colonialists they enter the urinary space they bind the SG lt to protein and inhibit reabsorption of sodium and glucose leading to glucose Syria and reduced blood glucose through that mechanism.
- 00:28:52There have now been 11 published cardiovascular other outcome studies of people have slt to inhibitors.
- 00:29:00that are relevant and I group them into three categories in blue here are studies of people with type two diabetes have high atherosclerotic cardiovascular disease risk which looked at cardiovascular outcomes, these are the FDA manage CV OTS.
- 00:29:16There are also a number of trials here and yellow looking at heart failure populations and testing effects of sgt two inhibitors on heart failure outcomes.

- 00:29:26And then for us in there for ology very important are these green studies that are enrolled people with prevalent chronic kidney disease and for the most part, have looked at chronic kidney disease progression as an outcome.
- 00:29:37And there I've noted with Asterix there to ongoing studies here that have not yet reported to liver and the kidney which actually was just stopped early for evidence of benefit, but we don't have data on that one just yet.
- 00:29:52And these trials have been evaluated and a number of Meta analyses and I, like this one, because it summarizes the effects of these drugs in the same way that I think about them on the prior slide.
- 00:30:04by the population, for example, heart failure here on top type two diabetes of high atherosclerotic.
- 00:30:11vascular disease risk and the middle increment kidney disease on the bottom and then within those categories by specific trial and drug.
- 00:30:18And what you can see, for most of these outcomes are clear class effects that.
- 00:30:24That are present or process across the populations so for hospitalization for heart failure or cardiovascular deaths john here on the left.
- 00:30:31Class effect consistent effects about a 23% reduction for these drugs compared to placebo for major adverse cardiovascular events that's Am I stroke or cardiovascular deaths.
- 00:30:45smaller reduction about 11% but still statistically significant for a ck the progression defined very ugly but usually is something like a 40 or 50% decline in egfr or kidney failure.
- 00:30:59there's a little bit more heterogeneity in the trial effects, but overall evidence of effective across the populations and drugs with a very large reduction and zeke at progression of 36%.
- 00:31:11Good that's about double what we've seen in the Renault trial, and this is generally seen on top of Ras inhibition which was used for most of the patients in this in these trials.
- 00:31:22and also a 40% reduction in cardiovascular deaths so very impressive benefits for a number of outcomes, particularly kidney disease progression and heart failure.
- 00:31:32And one trial that I will highlight in just a little more detail.
- 00:31:38The three big kidney trials, where the credence trial, the data see kitty trial shown here and the advocating trial, which I mentioned, where we're still hoping to hear more about soon.
- 00:31:48And the data security trial enrolled people who had type two diabetes and establish kidney disease with albuminuria 200 milligrams per gram or more.
- 00:31:58And randomly assign them to death, will flow Center placebo and looked at a primary composite outcome of sustained decline and gsr by 50%.
- 00:32:08And stage kidney disease or death from Reno or cardiovascular cause and and showed a 39% reduction man.
- 00:32:15And one thing I want to point out, with this slide is the time to effect and Compare that to what we saw in DC CTE deck which was.
- 00:32:22an effect that manifest over decades here, you can see it quite easily by two years, maybe even by one year, so this is an effect on kidney disease progression that happens, much more quickly than we expect for glycemic control alone.
- 00:32:36And on the right, you can see the effects for other secondary outcomes were similar to what I showed in the Meta analysis.

- 00:32:44And one thing that was really game changing about data to ck D was that two thirds of the population, I had type two diabetes, but one third of the population, did not have diabetes shown here in the red bar and while.
- 00:32:57There were fewer events lower event rate in that subset of the group, compared to those with type two diabetes.
- 00:33:05The relative benefits of kind of topical focus and versus placebo were at least as large as those with type two diabetes again speaking to the non glycaemic mechanisms of the drug and.
- 00:33:16More importantly, potentially extending these drugs to the care of people without diabetes and we're seeing that increasingly over time.
- 00:33:26I did want to speak just briefly about the mechanisms of kidney protection by sgt two inhibitors, why do we see such dramatic effects.
- 00:33:33For sgt two inhibitors and preventing ck the progression and we're still working on those to be honest, those are still a subject of inquiry.
- 00:33:42it's clear that these drugs cause modest weight loss and blood pressure reduction, though not nearly enough to explain the kidney or heart protective effects.
- 00:33:52One mechanism that seems quite clear as restoration of to be local mariela feedback and I've outlined, that in the schematic and the upper right here.
- 00:34:01And this goes with a tubular hypothesis of diabetes and that to be live offices is that when people filter a lot of glucose at the gold medalists.
- 00:34:11That glucose reabsorption is coupled with sodium reabsorption as I noted previously leading to decrease delivery of sodium through the nephrons to the distal to be able and immaculate denson.
- 00:34:23And that decreased delivery of distal sodium suppresses to be local mayor of feedback and leads to.
- 00:34:31Visa dilation of the ether and arterial the kidney increase blood flow and increased integral Mariano pressure which could drive the progression of diabetic kidney disease.
- 00:34:41So the thought here is that sgt two inhibitors reverse all those processes so by blocking reabsorption of sodium and glucose approximately it restores distal sodium flow that's sense to buy the macula denser.
- 00:34:59reactivating to be looking for feedback and leading to a fairly basic construction with decreasing the amount of pressure.
- 00:35:06So that's been shown in some very nice physiology studies and I think as part of the story it's probably not all of the story, to be honest.
- 00:35:14And some of the other mechanisms that have been proposed and evaluated in early studies are shown here on the left.
- 00:35:20I like the one shown in the third bullet, the idea that these drugs, reduce the work of the proximal tubular cells and kind of function is beta blockers of the kidney.
- 00:35:30In fact it's been estimated that about 12% of the energy expenditure of these proximal tabler cells.
- 00:35:38Are hardworking reabsorbed of cells is devoted to glucose reabsorption and so you can imagine that reducing that could reduce oxygen demand and reduce hypoxic damage in those cells it's also clear that there are systemic changes and metabolism, including a shift from glycaemic.

- 00:35:57carbohydrate metabolism to keep him body and lipid metabolism, which is more efficient and engagement of other transporters, including the sodium hydrogen exchanger notably these mechanisms of probably not needed by glycine MIA.
- 00:36:14i'm not going to spend too much time talking about gop interceptor agonists and other important new class of drugs.
- 00:36:20us, not just for type two diabetes, but also for weight loss, but I will know that they do have important effects throughout the body, including on the kidney.
- 00:36:28They also cause mild nature you're racist and dire races and also have effects on the base of constriction and visa dilation within the kidney that may lead to Kenny benefits.
- 00:36:40And secondary analyses of large trials and suggested some kidney benefits, we do not have the sort of data we have for sgt to inhibitors from primary kidney trials looking at kidney outcomes and gop one receptor agonist This is one.
- 00:36:55very interesting trial, looking at the kidney effects of a dlp interceptor agonist and do the blue tide performed by Kathy Tuttle one of my colleagues here at the University of Washington.
- 00:37:07And this trials, a word seven and two people with reduced egfr important area and type two diabetes.
- 00:37:14And randomly assign them to do a glue tired and as part insulin or an active competitor clergyman SLIM plus as part lunch line and looked over one year and change in jira far and, in fact.
- 00:37:25The rate of egfr loss was lower dose dependent factor with do a little tired vs clergy, so this is one piece of.
- 00:37:35accumulating body of evidence that gop one receptor agonists may be kidney protective there is now a phase three trial going on with some glue tied to test whether there are real clinical benefits and we're looking forward to those data, we do know that.
- 00:37:53gop one receptor agonist do reduce cardiovascular outcomes which I've noted, are very important for people with kidney disease and so that actually is another.
- 00:38:02actionable finding that can be used to guide care now.
- 00:38:07And so I'm going to talk now just a little bit about how clinical practice guidelines have incorporated some of these trials.
- 00:38:13And really established, I think, a new standard of care for people with diabetes and kidney disease and K Diego is the international kidney disease guideline.
- 00:38:24Writing group it organizes guidelines from everything from CJD definitions to anemia management and stage kidney disease to evaluation for kidney transplantation.
- 00:38:36And I was fortunate to co-chair the first such guideline from this group on diabetes and chronic kidney disease, along with Peter crossing from the steno diabetes Center in in.
- 00:38:47In Copenhagen, and it's been a bit of a Labor of love, we started in 2017 and published our first guideline and in.
- 00:38:56With a really great international work group that included endocrinologists nephrologists pharmacologist and internal medicine physician.
- 00:39:07nutritionist and, very importantly to patients, we insisted on having two patients involved in our writing group from the very beginning, they helped set our goals and questions and evaluate the evidence and helped with the writing.
- 00:39:20And we were supported by the Cochrane evidence review team from from Australia.

- 00:39:26We published our first guideline in 2020 and in fact we've just generated a revised.
- 00:39:35guideline, because the evidence is coming in, so fast for a number of drugs, in particular, and we summarize the evidence in this pyramid here.
- 00:39:47As an approach to guide care of people with diabetes and CJD, with a focus on on lifestyle therapy as a foundation key first line drug therapies.
- 00:39:57Including sgt two inhibitors and Ras inhibitors as I've discussed here with layered on top goal directed therapy this guideline is organized into five.
- 00:40:09chapters, one on comprehensive care and integrating all these aspects to optimize outcomes for people who have comorbidities with diabetes and chronic kidney disease.
- 00:40:19glycemic monitoring and targets lifestyle interventions and a hyper glycaemic therapy specifically and then approaches to management, including systems level approaches as well self management goals.
- 00:40:31With regard to.
- 00:40:33glycemic management, this is the central figure for management of people with type two diabetes and chronic kidney disease, again based on lifestyle and then the guideline recommends.
- 00:40:45Co first line therapy with metformin long considered our basis, as well as an SG lt two inhibitor, and this is not just for glycemic control, but for the kidney and cardiovascular outcomes that have been shown and trials.
- 00:41:01Initiating sgt two inhibitor down to an egfr of 20 mils per minute.
- 00:41:06given evidence from new trials, something we might discuss them in question and answers and continuing as glc two inhibitors even if.
- 00:41:14egfr drops below that threshold as long as tolerated or until the.
- 00:41:20initiation of dialysis so really expanding the population of people for who as Chelsea to nourish to be should be used.
- 00:41:27And then the kid ego guidelines do recommend a dlp round receptor agonist mainly for its cardiovascular benefits for people who have type two diabetes and ck D who's glucose is not controlled using this first line therapy or who can't take those first line therapies.
- 00:41:45there's been a criticism of guidelines in general that there are too many not something that I.
- 00:41:50Particularly empowered to do much about and sometimes that their conflicting.
- 00:41:56And that is something that we've tried to tackle head on and i'll note that our guidelines from kd go are very consistent with those are the American diabetes association which I.
- 00:42:05contributed to in years past as well, and so one thing we've done with the update here is form a partnership with the Ada.
- 00:42:15And we've written a consensus report, for the first time between the Ada and Kd ego outlining the similarities in clinical practice guidelines.
- 00:42:24which I think is very important to highlight and disseminate What we do know about optimal treatment.
- 00:42:30And this is a figure from that consensus report, which I hope will be published in June, it looks a little bit like the pyramid upside down and it is because, again, the Ada and Kd are so similar in their recommendations.

- 00:42:43And it's focusing on lifestyle management first line drug therapy which the Ada also agrees includes an SG lt two inhibitor Ras inhibition.
- 00:42:54And then other drugs as needed for targeted therapy and so I'm very pleased that there's consensus in the field, and I think now need to increasingly move towards implementation of proven therapies, to improve outcomes.
- 00:43:10And i'm not going to talk too much about specific additional therapy is on notice that right i'll know that right here in the middle, there is a new.
- 00:43:17Drug class nonsteroidal mineral hot Korean receptor antagonist that are recommended by both K Diego and Ada in the 2022 guidelines, this is an example of one new drug class.
- 00:43:28That is coming into the space to provide more options to treat people with diabetes and chronic kidney disease, and there are more in the pipeline as well that, hopefully, will increase our menu of available agents to treat people.
- 00:43:43And so that's leading to a nice problem to have, which is thinking about how to combine multiple effective therapies.
- 00:43:53Just 10 years ago, all we had was glucose lowering and Ras inhibition and now we're adding sgt two inhibitors dlp one receptor antagonist.
- 00:44:01been around for 40 receptor antagonist and I think there are more coming down so, how will we, how will we put these together for individual patient.
- 00:44:10And there are a number of options what I've shown in the schematic here on the right is the schematic from heart failure management with pillars of heart failure care can see St lt two inhibitors are there, too, but the cardiologists have envisioned this as multiple parallel.
- 00:44:27interventions to implement to improve outcomes another approach is layered therapy that's sort of what I've shown with a pyramid starting with base therapy and adding On top of that, and that's been advocated.
- 00:44:41By Kate ego and Ada largely because many of these drugs have human dynamic effects in our heart to start all at the same time, but ultimately, they should get to the same place of.
- 00:44:53Having all patients who have indications for drugs beyond the appropriate drugs.
- 00:44:58Another approach that I think, and I hope will be the wave of the future is targeting therapies and to specific patients, giving the right drug to the right patient at the right time that's precision medicine and so.
- 00:45:10i'm going to pivot for the last bit of my talk before we have questions and discussion to talk about the kidney precision medicine project or KPN P, which I think is a really exciting new.
- 00:45:22Project and in the field that I hope will be a game changer, and this is the visual abstract for the rationale design paper for for the kp MP.
- 00:45:32And I'll go through the design, briefly, is a new prospective cohort study that's based around a research kidney biopsy.
- 00:45:41And so there are actually three populations being studied and kp MP, one is the population people, diabetes and ck D I'm very excited about that, of course, also hypertension and ck D and hospitalized acute kidney injury all three of these are sort of bread and butter common.

- 00:45:59kidney disease presentations people who don't usually get kidney biopsies and for people for whom we really don't understand heterogeneity.
- 00:46:08or mechanisms we're getting there, but these are common presentations people not usually biopsied for whom you know kidney tissue analysis, we think, will lead to new insights.
- 00:46:20And so we're rolling people from these populations collecting clinical data pathology from the kidney biopsy omics and imaging.
- 00:46:31Very detailed molecular data from the kidney tissue and I'll talk a little bit more about that and clinical outcomes, with the goal of.
- 00:46:39Creating a kidney tissue atlas so a collection of cell types and cell states that can be used for researchers and others.
- 00:46:48To advanced science in any number of ways, develop mechanism based disease, sometimes so far as you've noticed I've only categorize tk D, for example, based on egfr and albuminuria and we hope.
- 00:47:00That we'll be able to go much more deep deeply than that to understand, not just where they are right now, but what mechanisms are driving individuals disease progression.
- 00:47:11And then also identify critical cells pathways and targets for novel therapies, to help improve and expand the menu of treatments, we have available to patients.
- 00:47:23The kp MP is organized with a central hub I sit in the central hub at the University of Washington university Michigan and mount Sinai are also part of this federated central hub, and it really is a national effort.
- 00:47:36With recruitment sites for ck D and aka across United States tissue interrogation sites that interrogate.
- 00:47:44The tissue that's obtained from the kidney biopsies in a number of opportunity pool funded sites that provide extended phenotype adding additional technologies and quality control metrics and on the left, I, this is a schematic of a patient here and.
- 00:48:02Like with the guideline, we have really taken great efforts to include patients from the very beginning.
- 00:48:09Because of the ethical considerations of of doing research kidney biopsies and really a desire to our to have our results be maximally impactful for people with.
- 00:48:20Patients with kidney disease, and they have participated in clinical protocol design they drafted our first informed consent form they said on all of our committees and he had published a number of papers.
- 00:48:31And we're really privileged to have them participate in this consortium, this is a flow diagram of what we do in the kp MP.
- 00:48:39So recruitment sites individual participants are identified, they undergo a kidney biopsy.
- 00:48:45With one core sent for clinical diagnosis, usually using the usual kidney pathology techniques that generates slides and.
- 00:48:56A pathology diagnosis, which is made locally and return to the KPMG participant for their own knowledge, we also take additional corps which we process in the biopsy sweeter operating room.
- 00:49:09Immediately those go to university of Michigan the central repository and then are disseminated to the various internal tissue interrogation sites.

- 00:49:19who generate data and all of this is entered into a data lake and as soon as data our quality control, these are promoted to an atlas that's freely available online.
- 00:49:32We really do cover the spectrum of today's technologies for.
- 00:49:38For molecular interrogation of kidney tissue including what we're missing epidemics right now hopefully it'll add that, but we have epigenetics.
- 00:49:48metabolite mix proteomics single cell and single Nicholas transcript omics spatial transcript onyx and proteomics and three dimensional imaging techniques that are all integrated in promoted to this.
- 00:50:02Integrated functional kidney map.
- 00:50:05we're over 150 participants now, you can see, we started our enrollments in the fall of 2019.
- 00:50:14We paused, as did.
- 00:50:18Many of us and research for the initial wave of coven but restarted in the fall of.
- 00:50:262020 and kovats still impacts.
- 00:50:29enrollment To be sure, but we are making progress with 94 participants with chronic kidney disease biopsy 32 with API and now we're also recruiting.
- 00:50:40People to donate healthy reference tissue either the time of donating a kidney for living kidney transplant or at the time of us a surgery for kidney stone or mobile.
- 00:50:52So what is KPMG observed so far and and we're really still in the early stages we're making anecdotal observations and preparing for larger increase as well.
- 00:51:05But each of this, the hundred and 50 people that we've biopsied has a dedicated clinical pathological review session, where we look at the tissue and come up with an adjudicated diagnosis, as the cause of the patients.
- 00:51:19kidney disease in this we've seen that unexpected clinical diagnoses are common, for example with API.
- 00:51:28most common causes are acute to necrosis and acute interstitial Freitas, but we clinicians are often wrong, based on the clinical history, compared to what we see and pathology.
- 00:51:38and ck D we've had two cases of fibber lyrical Marilyn Freitas so for the nephrologist in the room, we know that's a very uncommon cause and completely unexpected for these sort of run on the bill presentations of diabetes and hypertension.
- 00:51:55we've definitely seen substantial heterogeneity and kidney pathology so even with a relatively clinically homogenous sort of.
- 00:52:03Patient pool we're seeing all sorts of differences and kidney pathology in terms of where there's what compartments of the kidney there's disease, the Gomera lie or the tutorials the types of damage arterial damage matrix accumulation and all sorts of unusual presentations of.
- 00:52:23Diabetes or high potential related kidney disease it's very hard to actually describe what we're seeing in these kidney biopsy it's because the pathology nomenclature is designed to.
- 00:52:35to identify market abnormalities and the subtle 100 maladies oftentimes don't have adequate vocabulary or ontology is even to to describe and quantify what we're seeing another.

- 00:52:50Observation we've made a substantial overlap between see ck and Ai and I presented these as distinct populations, but in fact, in fact.
- 00:52:58In our ck the participants we're seeing lots of what would be called acute tubular injury, but these are chronic stable outpatients.
- 00:53:05Similarly, in patients who have API we see a lot of chronic changes that clearly preceded the acute event.
- 00:53:13And in early agnostic molecular analysis, where we put all these patients together and try and identify subgroups diagnostically we're actually seeing in those agnostic subgroups that ck and Ak oftentimes don't separate that the mechanistic subgroups overlap between those participants.
- 00:53:33One of the approaches we've taken to understanding the sort of data we see in kp MP, is an n equals one analysis of the clinical data pathology and molecular data we've seen.
- 00:53:44And that's been very insightful for us as a consortium and we're starting to publish those experiences as what we're calling clinical pathologic molecular correlations so an expansion of the classic CPC that we've all.
- 00:53:57used in training and has been used to understand the diseases, for decades, and this is the first one and i'll just walk through it.
- 00:54:05Briefly, as an example, so this is a 66 year old woman who had both type two diabetes and hypertension.
- 00:54:12she's a little unusual compared to most of our KPMG participants and that she also had a pair of protein identified and had she not participated in a KPN P, is a research participants.
- 00:54:23Her nephrologist was interested in pursuing a clinical kidney biopsy which is not usually the case for KPN p.
- 00:54:30she'd have type two diabetes for five years, with no complications Peter only with metformin hypertension for 30 years with no no complications to not only with candace certain.
- 00:54:40and her presentation was one of protein area with a normal Sierra granular level So what do we see in the biopsy.
- 00:54:48Well i'll start with what we didn't see and hear our goal Mary ally.
- 00:54:54In the kidney biopsy and they are normal so 18 out of 20 global relay were normal there was not expansion of museum there was not extra matrix their modules consistent with diabetes diabetic kidney disease and electron microscopy the Clara basement membrane which was normal.
- 00:55:13We did see a little bit of arteriosclerosis and perhaps from her that's the at symbol here, maybe from her hypertension and a little bit of interested it's rolling fibrosis and tubular atrophy which was nonspecific.
- 00:55:30To the left here to out of the twinkle Mary lie or globally sclerotic here.
- 00:55:36which we can see, for a number of reasons, and including hypertensive nephrons grossest and here's an example of what I was talking about.
- 00:55:45Your a tubular march T that are actually not normal again, this is a patient who does not have a clinical API but they have.

- 00:55:53Value realization of the tools which you can see here and electron microscopy as well, they have a typical blessing and attenuation of the brush border all findings that we see an API present in the cpt patient.
- 00:56:07and based on this constellation of findings there really wasn't great explanation for her protein area, to be honest, but what was absent was diabetic kidney disease or mild hypertensive changes so this patient.
- 00:56:18From a pathologic standpoint, it was labeled as having mild hypertensive kidney disease.
- 00:56:24So then, what we did is we looked at just one of the various technologies that was performed in this participant, and that was laser capture micro deception with bulk RNA seek.
- 00:56:36To see what's going on functionally under the surface and so what's done with this particular technology is.
- 00:56:43slides are prepared they're labeled with antibodies and using Amina fluorescence, for example, for mega Lin for proximal two bills you mind for the K sending limbs.
- 00:56:54We define this is an Indiana university we define sub segments of the kidney those are laser microsecond put together and then bulk RNA seek is done.
- 00:57:07And what we see, then, in these in these diagrams are pathways on the y axis here individual genes along the X axis and compared to controls, who, in this case we're nephrectomy donors.
- 00:57:22We look at whether individual genes were up regulated down regulated and So what do we see with this.
- 00:57:28we're looking first and the goal marissa lie, we saw some evidence of hypertension, hypertension related damage that is up regulation of the rain and angiotensin system up regulation of vascular smooth muscle cell.
- 00:57:44Growth up regulation of faisal constructors and down regulators down regulation and prostate gland is all really consistent with hypertension or hypertension related kidney disease.
- 00:57:55But we also saw more we saw evidence of insulin resistance and then go marry lie with decrease expression of irs to and glute for, among other enzymes.
- 00:58:05or other genes that have been implanted in the pathogenesis of diabetic kidney disease.
- 00:58:10We saw up regulation of glucose finger lifted synthesis.
- 00:58:15Which is related and part of the process of extracellular matrix formation, which we didn't see on the pathology but here we see functional evidence that those pathways related to diabetes are indeed activated along with a potosi's and practices.
- 00:58:30and other compartments the proximal to build, for example, we saw a market down regulation of glucose neo genesis.
- 00:58:37Which is seen in diabetes models as well, and then the interstitial we saw up regulation of glucose meter glycogen synthesis which is.
- 00:58:46which can be related to fibrosis and diabetic can you disease So what is this showing this is showing that, with just this one technology by looking under the hood we can learn a lot more functionally.
- 00:58:58Then we can see simply in the pathology to understand, we think what is going on mechanistic Lee in a patient beyond what's may in a traditional pathologic diagnosis.

- 00:59:13I noted that we're very centered on our patients and participants and K P amp G and actually our original patient advisors advise us to collect data on on how kp MP impacts our participants.
- 00:59:30We present this as a study where of course people is research, study we don't.
- 00:59:36tell people to anticipate any benefit, but it turns out lots of participants do learn from participating in the kp MP and in ways that I wouldn't have anticipated.
- 00:59:48Some are making changes to medications, but these are questions that our patients asked us to ask our participants.
- 00:59:55such as how much has KPMG changed the way you think your kidney about your kidneys we asked this one month in six months after participate after a kidney biopsy.
- 01:00:05And you can see that participating, including going through the informed consent process and getting results from the kidney biopsy.
- 01:00:12seems to have a market impact on on how people think about their kidneys but how they talk with their friends and family about their kidneys.
- 01:00:20And things that we as physicians we might not immediately think of as a downstream consequences of of knowledge or participation, such as physical activity and exercise.
- 01:00:32we've just finished the first five years of KPMG we've established our protocols we've developed a proof of concept kidney atlas there are data available online now for for open use that are quite rich.
- 01:00:47And we're now looking forward to the next five years, expanding to larger covert studies really amping up the size markedly and.
- 01:00:55starting to define disease subgroups and generalizable knowledge about the processes underlying these common diseases we do hope that ultimately.
- 01:01:06will go beyond what I've presented so far, which is classifying people by egfr and albumin area for diabetic kidney disease, for example.
- 01:01:14To use either kidney biopsy markers or biomarkers that reflect those and other emphasis of the study those biomarkers and your blood to look at overall risk and hopefully beyond overall risk at specific.
- 01:01:32Mechanisms underlying disease for Roman into trials in general and specific drug drug trials as well and, ultimately, hopefully, a couple that to enhance treatments in a precision medicine approach.
- 01:01:45So my conclusions here diabetic kidney disease is a growing public health priority.
- 01:01:52glycemic control on as inhibition remain the foundations of prevention and treatment and we can't forget that, even as we look at new agents and science.
- 01:02:03sgt to inhibition now clearly is the standard of care for people with type two diabetes and chronic kidney disease and is also expanding into non diabetic chronic kidney disease.
- 01:02:13Additional treatment options are needed, and they are emerging there's a robust pipeline and I do think that prison precision medicine offers a promising path forward.
- 01:02:23Both to identify new complementary therapies and tailor treatments to specific individuals so want to thank my research group.
- 01:02:31The DC edict that I spoke about the key Diego guideline group and the KPMG participants coordinators staff and investigators, who have helped so much that study, so I hope that we have a little bit of time for discussion, thank you.

UVA IMR

01:02:50Just open up to questions in a room.

- 01:02:53I forget if you can pick up the audio here but it's now run a MIC over again.
- 01:02:59yeah Thank you so much for given this wonderful.
- 01:03:05lecture so I really appreciate you taking the time with some 70 or make sure.
- 01:03:11I do have a question about that he had touched on earlier slides or double your size on.
- 01:03:17nonsteroidal 40% grant is, I wonder if you could comment on the rather than seeing how they compare to more traditional online.

Ian de Boer

01:03:30yeah that sounds like Dr Okusa if I recognize your voice.

- 01:03:35With a good question so.
- 01:03:39There, there are.
- 01:03:41Many of us have used mineral content query receptor antagonist for a long time it's been a lack tone we've used it for primary hyper aldosterone ISM refractory hypertension, for which it's very effective I use it all the time and for heart failure, particularly half RAF.
- 01:03:57There is this new class of nonsteroidal mineralogy or a quarter receptor antagonist and the one that has been advanced most is phenomenon and studied in two large clinical trials in which phenomenon added to.
- 01:04:12A certain air be so added to harass inhibitor.
- 01:04:16among people with type two diabetes and albuminuria reduced in these trials progression of ck and a composite kidney cardiovascular, how can focusing on heart failure and those reductions we're in the order of magnitude of 15 to 20% on top of Ras inhibition.
- 01:04:36So, similar to what Ras inhibitors do on their own.
- 01:04:41Added to that, not quite as large as the effects we've seen for sgt two inhibitors so based on those data both the Ada and the cage ego have made recommendations to us.
- 01:04:54To add those drugs to layer those drugs onto the therapy of people with type two diabetes and seek at when appropriate.
- 01:05:00And there's a lot of discussion about how to do that and I'm happy to do that more you asked specifically about how to use those drugs versus the existing Mrs.
- 01:05:13And I think, maybe I answered that question a little bit, at least from the guideline perspective so for hyper Alto and resistant hypertension and half rough that that's where spread a lactose is indicated.
- 01:05:25There is no data, there are no data long term for spreading lactose and destroy Mrs with regard to kidney disease progression so when you're looking at high risk kidney disease populations and trying to reduce risk on top of the therapies that I've outlined today.
- 01:05:43Really scenarios, the one that has the data and probably the one we should be reaching for people who have residual risk.
- 01:05:50Hope I answered your question.

UVA IMR

01:05:53Thank you.

- 01:05:55For that question in the chat does ACER art therapy increase expression on the rendering engine tends to system protein, we know that as or art therapy increases soon.

Ian de Boer

01:06:06yeah that's a great question and that's probably best understood we don't have KPMG data on that, so I can't address that, but it is certainly true that.

- 01:06:18Ras inhibition because of inhibiting feedback regulation does increase rena and expression and other upstream.
- 01:06:27components of the renewed energy 10s and cascade in general, we know that actually it's a good question to look at that in kp MP, we have patients and participants in KPMG who are in are not on Ras inhibitors and.
- 01:06:40that's a question, you might be able to address yourself actually those data are probably in the Atlas online and could be interrogated there.

UVA IMR

01:07:00yeah.

- 01:07:04If you mentioned, also the important facts of as Chelsea would to an editor's.
- 01:07:11oftentimes in our Father clinical practice we might get a patient who would come into a slate and within each year by that might be greater than.
- 01:07:20One of your degree, is there, do you have data that suggests that they are beneficial when you have when you start them late in the course of CD or DVD.

Ian de Boer

01:07:32yeah, thank you for that question, and that is a very important.

- 01:07:37Clinical question and we do have new data and that's a major change in the guideline the K D go guideline from 2022 to 2020 so.
- 01:07:47Earlier, is always better, of course, and you're likely to have more long term cumulative benefits starting early, but in nephrology clinic we do oftentimes see people who are progressing have egfr is less than 30.
- 01:08:02And what do we do there, so the 2022 K Diego guideline recommended initiating sgt two inhibitor for people with type two diabetes and ck D down to egfr 30 and the.
- 01:08:14guideline recommends initiating down to 20 so that group and the 20 to 29 range stage for chronic kidney disease.

- 01:08:23The new guidelines say that yes, that is, a population that should be treated with an s blt two inhibitor and that's based on emerging trials.
- 01:08:32That ever reduced in the Emperor preserved heart trailer trials both included people with egfr is down to 20 and demonstrated, safety and efficacy in that egfr arrange.
- 01:08:45The data ck D trial included people down with egfr as low as 25 and, in fact, some snuck in who had baseline levels lower than that and
- 01:08:57benefits and safety were consistent in that low group as well, and now we have the embassy epic kidney trial that I mentioned a couple of times.
- 01:09:05Coming out, which also included people down to an egfr of 20 and we're waiting those data, but hopefully they'll support this as well, so I think there's quite strong evidence now to support using an SG lt two inhibitor down to do, ours is as low as 20.

UVA IMR

01:09:26Fantastic right well another question and I don't know if you can pick it up, sometimes he's worked with not you can give it a try to follow up question about with you are.

- 01:09:38When do we expect the FDA to change their label as a cut off, because I know previously it used to be 60 now it's 45 based on a bunch the data and all the data that the renal outcomes.
- 01:09:51have shown that it goes, all the way down to 20 cc's per minute so any follow up on bendel decades instantly.

Ian de Boer

01:10:00So that's a very interesting question and.

- 01:10:04The FDA works differently than at least I think as a clinician because the FDA gives labels for outcomes I don't.
- 01:10:14categorize patients sitting in front of me according to their outcome, particularly people with diabetes and ck D for whom there are multiple outcomes to consider I see me a cardiovascular disease, kidney disease progression and.
- 01:10:30So the guidelines take the patient centered approach that the labels have changed already for topical flows and the label, there is a label for kidney disease progression down to an egfr of 25.
- 01:10:43For ethical flows and the label is for glycine me as down to 30 now and for heart failure is down to 20 so typical thousand does have an FDA indication for heart failure down to need you, for 20 it's not approved.
- 01:10:59To be transparent for the use of diet for kidney disease progression in that range perhaps that something I should have mentioned in response to the last question.
- 01:11:08So that would have officially be off label to use for that purpose, but it is approved for heart failure in that range and I and.

- 01:11:17Will we see changes to these labels, with the new trials, I think we will, and I think we'll see those coming soon this whole field has changed incredibly rapidly with new data new recommendations and new labels.
- 01:11:33Coming.
- 01:11:36Just rapid fire, which is why the guidelines have been updated so quickly as well.

UVA IMR

01:11:45Well it's one o'clock I really appreciate your time and fantastic presentation and.

- 01:11:50Thank you again.

Ian de Boer

01:11:54thanks for having me.