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TRANSCRIPT - GR 11 03 23 "Type 1 Diabetes and Cardiovascular Disease: Why the Endothelium Matters" guest speaker Kaitlin Love MD from University of Virginia

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- Hello, everyone. Welcome to Medicine brand rounds.
- I have the pleasure of introducing today's speaker, Dr. Caitlin love.
- Dr. Love first traveled to Uva for her Internal Medicine Residency. After completing her MD. At Florida State University. She then stayed on further for endocrinology, fellowship, and lucky for us, stayed on faculty in the division of endocrinology. She is a very productive researcher. Her scholarly work is focused on vascular insulin resistance and type. One diabetes pre diabetes and obesity.
- Additionally, her current research focuses on micro macrovascular endothelial dysfunction in type, one diabetes and response to GLP. One, agonism and exercise treatment.
- She is dedicated to team science and collaboration and is a co-investigator of multiple studies. For example, she has current collaborations with the Curry School of Education Division of Kinesiology, Department of Surgery and department of Pathology.
- She is known for her teaching skills and residents thoroughly, having her thoroughly enjoy having hers. They're attending on consults.
- Also she is an educator across the spectrum, starting with medical students during their very first course at Uva all the way to endocrinology, fellows. Thank you so much for joining us. We are excited to learn from you today. Please join me in welcoming Dr. Love.
- There we go, can you? Can you hear me? Okay? Okay, great. Well, thank you. So much for the introduction. I am grateful for the opportunity to be here today and chat with you about a topic that's very that I'm very passionate about, and get to share a little bit of that with you. I have no financial conflicts of interest. I do have research support through that nih, with a award and also dexcom allows me product support for some of the research that I'm doing and I'll tell you a little bit about that research at the end of the talk here today.
- But first I realized that not everyone here is seeing patients who have type, one diabetes on a daily basis, maybe not even on a weekly basis. And I wanted to say, you know something inspiring that was outside of type, one diabetes in particular.
- And you know, for those of you in here who are maybe budding researchers or budding academicians.
- I think that something that is so key to success in a career is to really have, you know, big dreams. And still remember what your big dreams are, what drew you into medicine, what drew you into the field to begin with, because there are a lot of up bumps in the road, especially when we're, you know, doing research and there, there are challenges, and frustrations. And it, you know, I think that when I was early on. II really thought that it was about, you know, kind of having a spark of genius, having great ideas, having really good mentorship, and those are all good things to have very nice to have, but I think even more important is perseverance and I was recently at the Wright Brothers Museum at Kitty Hawk in the outer banks over the summer, and if you've ever been there, it's kind of like this case. Study and perseverance cause they have so many unsuccessful flights. And you know, there's just a lot of background about them growing up. But II was thinking of this quote from Orville Wright, who said, The only a real stumbling block is fear of failure in

aviation as a life courage is the most important skill to possess to, you know, kind of constantly be pushing yourself, and to constantly be working on that perseverance. Because I think, if we well for people who are taking an airplane for the very first ride. I think courage is important, but I think for us researchers perseverance is really to get to how important.

- So today, diving into the talk, we'll talk about endothelial dysfunction type one diabetes. I'll tell you what I mean by that. We'll also talk about why that happens in type one diabetes, and we'll look at some interventions that may help with this endothelial dysfunction that we see in type one diabetes, but first a case. So there's you see, a 39 year old woman in clinic. She has a 30 year history of type, one diabetes, and her A. One C is pretty good. At 7 she has a history of mild background retinopathy. The only medication she takes is Novala. Through a hybrid closed loop insulin pub. So you know, state of the art technology. Her blood pressure is great. At 1, 18, over 62. Her Bmi is 25, and I invite you to just reflect over the course of this talk about what you might suggest for next steps with cardiovascular prevention for a patient like this, and at the end I'll go through and talk about what my approach would be.
- But first, some background. So type one diabetes is a hard disease to manage.
- I personally have type one diabetes. I was diagnosed when I was 4 so I've had over 30 years experience managing type, one diabetes.
- I also, you know, am an endocrinologist practicing in the real world and a type one diabetes researcher, and I still find type, one diabetes difficult to manage, and you know there are still curve balls in managing this disease. I was woken up by my low blood, glucose alarm at 40'clock in the morning this morning, and I'm like, not today diabetes. I have something important to do.
- But you know, I think it's also very much evidenced by the fact that 75% of people living with type, one diabetes are not achieving target glucose control.
- And of the, you know, small portion of people who do manage to achieve an A. One C below 7. There's still a threefold increased risk of cardiovascular death compared to the general population, and that you know, risk of cardiovascular death increases dramatically, exponentially with higher a one C, so that once someone has an A one C above 9.7. So 10 fold increased risk of cardiovascular death.
- So that's a lot. And then, you know, when looking at a younger population. So this was looking at a cohort of people who are 35 years with a mean duration of diabetes of 17 years, one in 5 of these young adults had elevated coronary artery, calcification scores when we fast forward another 10 years. By mid-forties. A majority of that cohort had evidence of increased coronary artery, calculation, 50% of women, 70% of men with type, one diabetes cardiovascular disease is the leading cause of death for people with type, one diabetes.
- But despite that. And you know, someone with type, one diabetes, and also someone who takes care of patients with type, one diabetes. I find it very frustrating to know that there are no randomized trials that have been specifically designed to look at the impact of cardiovascular risk reduction treatments for people with type, one diabetes, so everything that we recommend to help prevent cardiovascular disease and type. One diabetes is taken from a type, 2 diabetes population. Whether that is you know, something that we can really extrapolate accurately. I'm not sure. II think probably not. And you know why. Why is that? Because we do have so much cardiovascular outcome data in the type 2 diabetes, population.
- And I think it's really the exception that we do have so much of this cardiovascular outcome data for people with type 2 diabetes. And it's essentially because the FDA

mandates it in in 2,008, in response to evidence of vascular harm with a number of diabetes medications. The FDA started to require that any new type, 2 diabetes treatment, have evidence of really rigid cardiovascular outcome, safety data. And this is expensive. So, according to Sinofi, one of the drug manufacturers, this has dropped diabetes drug development by about 50% and it, you know, fortunately, the the regulations have slightly relaxed, but they're still very robust, and a typical cardiovascular outcome trial is gonna cost about 500 million dollars and to to sort of put that in perspective for the Nih trial I'm doing, which is a 5 year K Award, costing the Nh. About a million dollars. Then I just not generally shelling out 500 million dollars for studies.

- So it it really has to have buy in from a drug company. And if I were a drug company looking at cardiovascular outcomes for people with diabetes. Because I have to get this approved to, you know. Get my drug on the market and show safety. I wouldn't wanna include people with type one diabetes, anyway, either. Cause you know, there's a issues with safety. There may be less of an effect. So that that's kind of where we are that we just don't have a lot of cardiovascular outcome data. So how can we assess cardiovascular risk and risk reduction in a population with type one diabetes. So this is where I. My interest in endothelial dysfunction, has come from with type, one diabetes.
- So first of all, what? Just a little review, what's the endothelial cells that these are the cells that line the inside of blood vessels? They're sort of our first responders. They're gonna be in direct contact with plasma. Glucose hormones. Insulin is actually a vasoactive hormone. So it binds our receptor on the endothelial cell and causes endothelial cell to produce nitric oxide, which is a vasodilator. And vasodilation is important for insulin delivery. So you know, insulin is gonna vasodilate the vasculature and increase profusion to target tissues so that insulin and glucose delivery can happen and glucose uptake can happen. So it's important for insulin sensitivity. It's also important, for you know, muscle health in general, because it's increasing the delivery of those important nutrients to the muscle target tissues.
- But insulin can signal 2 different pathways in the endothelial cell. But the one pathway. That this sort of we can think of. This is the beneficial pathway involves nitric oxide and insulin by binding its receptor, activates this PI. 3. Kinase a KT. Endothelial nitric oxide synthase, which is the enos enzyme to make nitric oxide and then insulin resistant conditions like type, 2 diabetes obesity.
- And I'll also try to persuade you that type. One diabetes is one of those as well. This this advantageous, healthy pathway that generates nitric oxide is sort of selectively down, regulated. Instead, there's this shift to a more Vaso constrictive pathway that causes production of endotheline, one which causes Vasopon instead of dilation, so could be reducing profusion to the target tissues.
- For the purpose of this talk. I'm talking about nitric oxide dependent endothelial function, that endothelial cells have a lot of jobs. But I'm specifically talking about that role of producing nitric oxide. But I'm gonna shorten that to endothelial function and dysfunction, because it's really a mouthful. Say that 20 times during a talk.
- So there are 2 ways that we measure this in my lab, which is through contrast, enhanced ultrasound. Where we infuse this radiopa dye that we look at with an ultrasound. The definitive contrast has teeny little micro bubbles that are about the size of a red blood cell, and that allows the contrast to go throughout the Vascar, including into the microvascher, but not be released from the blood vessel. So it kind of allows us to make this roadmap of the vascular, and we use insulin to stimulate an increase in profusion. So we would typically see about a 30% increase in microvascular perfusion in response to insulin.

- This picture is a picture at the level of the heart. But we also look at skeletal muscle. Another way that we look at endothelial function is with Fmd or flow mediated dilation. And this is a technique that's well utilized in cardiovascular research and exercise research. Where? We're looking at a larger, more muscular vessel, the brachial artery.
- And in order to assess that we put a blood pressure cuff around a forearm and pump it up and hold it for 5 min to block blood flow, and then, after that 5 min, we, you know, quickly release the cuff. If you've ever had a blood pressure checked, you know that sort of whoosh of blood flow. Is would happen in that sheer stress on a blood vessel is what triggers calcium influx into the endothelial cell, and then activation of endothelial nitric oxide synthase are Enas similar to what the insulin signaling pathway would do and generate nitric oxide.
- Fmd is particularly useful because it's well validated. It's been shown to be a good predictor of cardiovascular disease in the future.
- And some. A number of men. Analyses have also shown that every 1% decrease in Fmd also corresponds with that 9% increase in cardiovascular events. So you know, a useful vascular tool as as sort of a predictive technique.
- So I mentioned that endothelial dysfunction happens in type one diabetes. So this is the part where II show you that that happens. So people for this. This is a study of children with type, one diabetes who have an average age of 11, and we see that that their healthy peers have a nice robust dilation response. And in type one diabetes that's impaired. And even within 5 years of diagnosis we see that one in 3 of these children already have evidence of endothelial dysfunction. So a lot and then, when we looked at this with the slightly older cohort in in the population where we were doing research. That was 60% of those adolescents with type, one diabetes who'd had a duration of diabetes a little over 10 years had this dysfunction and then, when we fast forward a little bit. So this is now at age 14 we see, you know. Not only is there reduced Fmd. But also reduced microvascular profusion. This was stimulated the smell to muscle by a meal and exogenous insulin. In the case of the children with type one diabetes, but we see that, unlike their healthy peers, who have a 30% increase in microvascular perfume they actually have a decrease in microvascular perfusion in response to the insulin and then, when we look at now, sort of a young adult population with a mean age of 24, we see that the the young adults have evidence of insulin resistance. That you glycaemic insulin clamp is sort of a gold standard way to measure insulin resistance, and we see that, compared to the healthy control population, the population here with type, one diabetes had a lower glucose infusion rate and also had really a a lack of increase in microvascular profusion in response to the insulin clean. So microvascular, endothelial dysfunction, too.
- So why? Why is that important? So the micro Vascar is, is particularly relevant when we think about whole body insulin resistance and insulin. Resistance is clearly independently associated with cardiovascular disease in people with type. One diabetes and this this has been very strongly examined throughout the years as a strong predictor of cardiovascular disease. So possibly this microvascular endothelial dysfunction may kind of have a direct relationship with cardiovascular disease, because we know that there is a relationship between this microvascular endothelial dysfunction and insulin resistance in a large cohort that it includes people with type, one diabetes. And we've also seen that there is in early relationship. This needs a little bit more definition. But between this microvascular endothelial dysfunction and endothelial dysfunction at the larger vessel, at the conduit artery level. And as I showed you in other populations impaired Fmd. Clearly corresponds to cardiovascular disease again, not extremely well studied for type. One diabetes, but

certainly there's an independent association with carotid artery plaque and impaired. Fmd. In children with type, one diabetes or people with type, one diabetes.

- So why does this happen? Why does endothelial dysfunction happen in type? One diabetes? I don't want the takeaway today for anyone to be that, the endocrinologist said hyperglycemia is not detrimental. Hyperglycemia is probably the leading problem when we think about endothelial dysfunction and type, one diabetes.
- But there are a number of other factors. So what I'm really considering is this land of residual risk, the fact that even when we get someone's a one C down below 7, there's still a threefold increased risk of this cardiovascular mortality. Cardiovascular disease. So why is that?
- Well, so we certainly know that there's this J curve relationship between essentially a one C's and risk of mortality in a population who has pre-existing coronary disease. People who've had a prior mi that when we drop anyone see below 6.5 there's an higher risk of mortality even compared to an A one C between 6.5 and 7 and 7 and 7.5 and so maybe hypoglycemia is part of the problem here.
- So this, this is one of my favorite studies. Actually, I know we shouldn't have favorites. I didn't do this study. So it's okay for me to see it. But I think it's really interesting. It'd be very difficult to get this, Irb approved, because what they did was randomize adults with type, one diabetes to 2 h of 2 conditions either severe hypoglycemia, with a blood sugar at 50 for 2 h, or severe hypoglycemia with a blood glucose of 250 for 2 h and under both conditions we see an impairment in Fmd. And the hypoglycemia is as bad, if not more severely impaired. Compared to that moderate, severe hyperglycemia, we also see an increase in plasma oxidative stress markers and some inflammatory cytokines under both conditions that are similar. So when I see a patient in clinic who is telling me? I don't. You know. I know I have a lot of lows like 10% below range. But you know, I'm just, I'm terrified of having a blood sugar above 180, because I know that it's gonna harm my blood vessels and cause complications. I talk to them about this study that you know I actually there is evidence of harm to the vascular with severe low blood sugars, just as we see with severe high blood sugars.
- And when we look at culture cell data, so this is from data of human umbilical vein, endothelial cells or flu vex cells. When these cells are exposed to declining glucose concentrations, we see an increase of oxidative stress at the endothelial cell level. And we also see a significant reduction in stimulated nitric oxide production. So it's causing endothelial dysfunction at the cellular level.
- Aside from the low glucoses and high glucoses, though there may be something particular about glycaemic variability, that ping ponging of blood sugars up and down, that is common for people who have type, one diabetes mostly because we we're really only using insulin to treat them so. It's sort of by necessity. We tend to see low blood sugars that we're getting good control.
- The top, the top panel here would be someone with high glycaemic variability where blood sugars are swinging really between fortys and 400, and then the lower panel B, we see lower glycemic variability where blood sugars are mostly fluctuating between 100 200 or 250, and they would, you know, in theory, have the same a. One C, but the top panel having higher glycaemic variability. So it it. It becomes tricky from a research perspective, though, to say, Well, maybe it's just all of this severe lows and all of this of your highs that's driving this. You know, problematic changes like cardiovascular disease.
- However, I think this is again an interesting study that really gets at that question of differences in blood sugars. So this his study looked at people who had type, 2 diabetes and people who had normal blood sugars, so healthy people, and it randomized them to 3

different conditions. And it was a crossover study. So 24 h of a blood sugar, 1 80 so kind of high within our target range for someone with type, 2 diabetes or type, one severe hyperglycemia with a blood glucose of 2 70, and then every 6 h, alternating between a normal blood sugar of 90 and a high blood sugar of 2, 70, and so like 6 h of 96 h of 2, 72, 76 h, 96 h of 2 70.

- And you know what I want to draw your attention to is the fact that if we were to average that 90 and 270, we would get the equivalent of 180. So this should be the same cumulative glucose exposure at the vessel for a 20 four-hour period.
- But not only do we see more endothelial dysfunction with a severe hyperglycemia so 270 is worse than 180, we see an even worse endothelial dysfunction and more oxidative stress when they're fluctuating between a glucose of 90 and 270.
- So something harmful about that fluctu fluctuation. The people with type 2 diabetes were slightly protected against this, so at least early, although later the condition was worse for everyone. And there was increased increase in oxytocin and that would suggest to me that perhaps there is some sort of antioxidant factor that is enhanced in in people with more chronic fluctuations of blood sugars. But you know, certainly to to me this suggests like variability, that fluctuation levels is harmful.
- And then 1 one other aspect is insulin resistance that can be harmful when we think about cardiovascular disease and microvascular complications. So this study shows that for people who have more insulin sensitivity with type, one diabetes have less progression, important artery, calcification, less diabetic retinopathy or retinopathy, and Lvue and area so fewer microvascular complications. So in summary, there are probably a lot of factors that cause endothelial dysfunction type, one diabetes high, glucose, certainly a big player again. I didn't extremely emphasize that, but just know it could be a whole talk about just high blood sugars and the detriment insulin resistance is harmful. Hypoglycemia seems to also be harmful and glycaemic variability as well.
- So again, insulin, signaling 2 different pathways, the good pathway would be the PI, 3 kinase a KT. Enos generating nitric oxide and these conditions seem to, you know, really stir up factors in the cell that are harmful. So I kinda think of these 2 elements protein, kinase c and nadph oxidase as saying one and thing 2. There are sort of reekers of havoc and mischief in the endothelial cell where, when protein kinase C is activated, that activates nadph oxidase or nox. And not only does it sort of turn off Enos from its typical producer of nitric oxide production function. But it also increases generation of reactive oxygen species. So it's like a light switch of like, okay. Now, now, it's a bad actor. Nadph! Oxide is also helps with consuming nitric oxide that's produced and then upstream. We're also seeing a reduction in the signaling pathway and then at the same time protein kinase C is possibly influential with Nf. Capa beta, and increasing transcription of inflammatory cytokines, and then also increasing adhesion molecules. So these sort of combined to increase risk of atherosclerosis. And so, you know, essentially, my argument would be that when we are seeing less nitric oxide bioavailable.
- This is an indicator that you know this is a trend towards atherosclerosis instead, and harm alright, so enough of the depressing talk of the harm. What interventions may actually be beneficial for people with type, one diabetes.
- So I am a big proponent of statins in type. One. Diabetes. Statins have shown benefit. They improve Fmd to separate studies and adults have shown this and remarkably consistent, both improved Fmd by 1.6 and then also the heart protection study is really what's used to justify that statins are very helpful for people with type, one diabetes. This study is unique in that. It actually included people who have type, one diabetes. So it was mostly a population who have type, 2 diabetes, but also about 600 people with type. One

diabetes were included, and while it was not powered to see a difference in cardiovascular events in a type I diabetes population. There was a similar proportion of improvement in cardiovascular events in the type one compared to the type, 2 diabetes population.

- Alright. So then, that brings me to an even more robust improver of endothelial function in type one. Diabetes which is exercise. So number of studies have shown benefit with exercise and a type, one diabetes. Population. And you know, we're seeing really big gains, you know, an Fmd improvement of 5.5 3 4.9, with high intensity, interval training and moderate continuous training.
- Not all exercise studies in the type one Ids population have shown improvement in Fmd, but that is probably methodologically related, because often in those studies. We're also not seeing improvements in vo. 2, Max. So that would indicate to me that they, you know, may not be adherent to exercise training regimen, or possibly not. Chat challenging them enough to see improvement.
- And the epidemiologic data is very consistent in a type. One diabetes population that exercise is beneficial. So 3 different pivotal, prospective cohort trials that involve type, one diabetes, populations, the Eurodiab, Pittsburgh and Finane studies all showed that less physical activity is associated with an increase in all cause. Mortality. So you know, said another way and you know what I talked to my patients about is you know it. Physical people who are physically active, who have type. One diabetes live longer, so exercise. But despite this that you know the fact that physical activity is helpful.
- We know that people with type, one diabetes tend to be a little bit less likely to exercise and obviously exercising is a problem throughout the United States. It's certainly not unique problem to a population with type, one diabetes. But there may be certain factors, for why people with type, one diabetes exercise less. And II, you know, personally think as someone who has type, one diabetes. It's kind of a case-by-case basis.
- But we do know that people with type. One Diabs tend to have a lower cardio respiratory fitness. And that's even when they're matched to people who have similar physical activity levels. And that could be related to tissue health, or possibly you know, perfusion issues. Possibly there's worries about hypoglycemia. That's certainly what anyone who looks at my grant seems to think but excuse me. But actually, when we look at survey data from people who have type one Diab, some people say they're worried about hyperglycing, and they're worried about blood sugars going up during exercise, or their one of their doctors at 1 point said that exercise is not good for someone with type one diab. So it really is important to be asking the patient wh. What is limiting them, and you know, to help if you can't give them some tools for managing blood sugar around the time of exercise to help encourage them and enable them to exercise and then, of course, you know type one diabetes can be time consuming. You know. I think that many of us don't really think about that, because it's so ingrained in our lives. But, you know that the burden of time management with disease may be another limiting factor with being able to exercise.
- So you may be thinking, well, what about the cardio? Protective medications for people with type? 2 diabetes, you know. Could that be helpful for people with type, one diabetes. I thought it might be useful to just briefly review what the cardioprotective medications are. First of all, for people with type, 2 diabetes.
- So you know II tried in true medication is metformin and I am very much pro pro metformin. I think I probably still am having a patient least once a week, asking me to come off of that, because there think it's fine. But it's a really good medication, and it's really good for cardiovascular disease. But the Uk pbs study showed a benefit with Metformin in. In that trial they had active comparators which we don't use anymore. They're off the market. But the spread Dyam CAD trial in 2,013 actually compared

Metformin to Galpaside. So it's an active comparator. Trial. Unlike many of the cardiovascular outcome trials now, which is just a placebo comparator. So they brought a one C to similar levels. It was about 7 in both group and they that still found a 14% reduction in cardiovascular disease with metformin compared to global beside and global design is generally thought of in the and to feel your cell community as like just being in. Or it just doesn't really do much to the vast majority. And then, of course, another up and coming drug class is the receptor agonist class, and that has a lot of, you know, really exciting data. When we think about ischemic events and cardiovascular mortality. So they've toze up with the leader trial. Ozmik in sustain 6 and trulicity and the rewind trial all showed cardiovascular benefit. Victosyosemic were sorry the leader and sustained 6 trial. We're really looking at people with very, very high cardiovascular risk. The trulicity study with rewind is slightly unique in this this category, in that there is a little bit less of pre-existing cardiovascular disease in that study. So it's been used to suggest a primary prevention role. For virtually. then, IA common misconception is that all sglt? 2 inhibitors have benefit when we think about cardio like ischemic events and cardiovascular mortality.

- That's not straight sticks.
- It's not, strictly speaking, the truth. I mean, certainly we have a lot of benefit when we talk about heart failure, readmission, and we have a lot of benefit when we're thinking about chronic kidney disease outcomes. But Jardians is unique in that cl 2 inhibitor class with the infrared trial showing benefit with ischemic disease, or like mace that excludes heart failure.
- Read emissions. So with that the remaining slides, I just have to highlight we'll talk about non, FDA approved or off labeled Use. I'm not necessarily recommending that we use these drugs for people with type one diabetes. I'm just showing you what the data has shown so far.
- So this trial looked at adults with type, one diabetes and randomized participants into one of 3 groups. One was impactful, flows in one was Metformin, and one was impactful. Flows in Metformin combined, and each of those 3 groups dropped saw improvement in Fmd. After 12 weeks of study intervention. It's a little bit confusing how they present this. But each of those groups were not significantly different from each other. They all had benefit compared to placebo. Okay also. But well, I should say, unfortunately, that longer term trials of Metformin have really yielded pretty disappointing results when we think about vascular benefit from that foreman. This was a 12 month trial in children with type, one diabetes, and it showed no improvement in Fmd. It showed no improvement in carotid or aortic intima media thickness for people with type, one diabetes.
- There are a number of studies looking at map foreman and outcomes like Fmd. And outcomes like, especially within the chronic kidney Disease realm. And those trials are ongoing and something to pay attention to in the next couple of years. But so far it just hasn't shown very impressive outcomes.
- But going back to that favorite study of mine. So G. Lp, one has shown some improvement. This was a study looking at just infusion. So it's not actually treatment with one of our G. Lp, one receptor agonists. It's just acute thank you. And infusion with GLP. One, and that again randomized people into these 2 groups of hypoglycemia and hyperglycemia, and we see that in with both dyslelycemic conditions, gl. P. One improves fmd, so with hypoglycemia and with hyperglycemia, and also improves some oxidative stress markers or reactive nitrogen species like nitro tyrosine is reduced in the setting of hypoan hypoglycemia Aid isoprosticly, and F. 2 is also improved.
- And this also squares. Let's see, let me get rid of that.

- That's chat. So and this also squares with data that my mentor, Doctor Zenchie Lou, has seen. He was evaluating people who have obesity but normal blood sugars, and you know, I think it's noteworthy that insulin fails to increase microvascular profusion in that population that he had studied, but adding a gl p. One infusion helps restore that insulin effect to increase microvascular perfusion so that, you know, has led me to have some interest in the receptor agonist class with type, one diabetes and vascular health. I did a review article, I guess, was published yeah, last year around this time. And II found a few things that are interesting one almost all of them at foreman data uses that forming concentrations that are about one hundred-fold, maybe a thousandfold higher than what would be pharmacologically relevant and totally toxic to humans.
- So likely with these mechanistic studies, we're seeing off target effects that are not relevant. When we're seeing improvement in vascular function. But when we looked at metformin concentrations that were pharmacologically relevant, we did see increase in Amp K mediated enos activity, and then a reduction in protein kinase, c activity or activation, and G, lp, one, which actually there, there are receptors for GLP. One. On endothelial cells. They're expressed abundantly throughout the vasculature glp. One seems to act through protein, kinase A and a M. Pk. Also to increase Enos activity, and possibly also may have some protein kinase C activation. So there's biologic plausibility. For you know why these medications may help with vascular function.
- So that brings me to the study that I am currently working on which you know. Hey? If if you anyone you know, or any patients that you have might be interested in a study like this, I, you know. Please send them my way.
- We're recruiting essentially pretty, healthy people with type one diabetes between the ages of 18 to 40 who are only using insulin for diabetes, treatment, and don't yet have any complications related to diabetes, cause that may confounder outcomes to some degree have an agency that's pretty well controlled as long as it's below 8.5 not have hypoglycemia unaware.
- And then we're including people with normal Vmi overweight Bmi or class, one obesity. But just Bmi lower than 35 for participation.
- And we plan to or and are randomizing these participants to one of 3 treatment arms. So trulicity for 14 weeks placebo injection or exercise training for a total of 14 weeks, and then we'll be studying before and after. We'll be looking at the vascular measures, especially that microvascular function and Fmd. And a number of other vascular studies. We'll be looking at body composition and cardio respiratory fitness before and after, and we'll be looking at continuous, glucose monitor data to associate that with some of our vascular outcomes as well and everyone will also have a an insulin clamp, which is again, that gold standard measure of insulin resistance. But also it's a way for us to stimulate the micro vascular and see the before and after effect and we'll also be, are working on a process for isolating endothelial cells to sort of look at proteins of interest relevant to endothelial function.
- So going back to the case. This is towards the end. Now. going back to the 39 year old patient who has retinopathy a 30 year. Diabetes duration has normal blood pressure. I didn't tell you her cholesterol sort of intentionally.
- Not that it doesn't matter, but it almost doesn't matter. And what I would think about starting her medication-wise. There are risk engines that can be used to calculate cardiovascular risk for people with type, one diabetes, I think, like many risk assessment calculators they tend to underestimate who would benefit from a statin. But this
- particular assessment center type. One risk engine has been validated against coronary artery, calcification for and crowded intimal thickness in people with type, one diabetes. So

if we were to plug in her numbers, we would get that, she would fall into a low risk, having less than 10% 10 year risk of cardiovascular disease. But you know, I in in hearing her history, a few things would make me think that a Sten could be appropriate. The American they Aj guidelines would recommend anyone with diabetes. Type one or type 2 between ages of 40 and 75 be started on a statin, and then, considering that if someone has risk enhancers at a younger age and so for her, she has a long duration of diabetes greater than 20 years would qualify for type, one diabetes and she also has a micro vascular complication, retinopathy. But micro album area chronic kidney disease, neuropathy and peripheral artery disease would also be considered a risk enhancer. So you know, II think that she has enough that I would be concerned, and certainly talk to her about statin, if that is fitting within her thinking for reproductive timing.

- So, and then I'd also, you know, certainly be as an endocrinologist, reviewing her blood sugars, making sure we're not seeing too many extremes, not seeing a lot of glycaemic variability and talking about exercise and the American Diabetes Association recommends 150 min of moderate intensity. Exercise per week for people with type, one diabetes, or 70 min of high intensity, exercise per week for people with type, one diabetes that and the exercise is good. Even hand grip exercises have been shown to improve insulin sensitivity for people with diabetes so just incorporating it, however, if they can. And those epidemiologic studies, they weren't like 150 min, you know, it was just any activity is beneficial. So that that is something that II really push at in clinic. So in summary endothelial dysfunction is very common in type, one diabetes and perceives the occurrence of cardiovascular disease. There are many factors in play that increase, risk of vascular dysfunction, hyperglycemia, hypoglycemic hypoglycemia, glycemic variability and insulin resistance. All appear to be important. Contributors, statins, and physical activity probably have the most evidence for improving cardiovascular risk, and we just need more studies to know if other adjuvant treatments may be helpful for people who have type, one diabetes.
- So with that, I just wanna express appreciation to my lab, my primary mentors at Chili, secondary Mentor, Sue Brown, as part of my K. Award art Weltman and Kerry morrow at the University of Colorado as well, and sort of the spine to buy research team, which is Linda Yann, Lee, Hartline, and Kevin Ailer, who are awesome and help me every day.
- and happy to take any questions. This I just wanted to once again highlight, that this study is posted on clinical trials at Uva. So, please, if you think anyone that you know might be interested. Please send them my way, and this is these are my children. I have a 5 year old, Oliver, and 3 year old or no 2 year old. Tidy. They're awesome. I was thinking of 3 years. Alright. Any questions that was fantastic. Thank you so much, I'll get us started, and one of my co-chairs, I think, is looking at the chat for us. This was great, I think, with our type 2 diabetics. We're great at about talking about exercise. But honestly, I don't think about that quite as much in my type ones.
- My question is. So we talked about exercise being helpful, statins being helpful. Better glycemic control. And then we talked about how maybe Gop ones are the answer. It's interesting to me that were so popular. But now we have these medicines like Trisepetide, and I apologize. Don't even know. I think there's a new one that has 3 mechanisms of action, kind of on the same pathway, and they keep proving more and more weight loss, and then honestly to a non end.
- The pathways are very confusing, and it's kind. It's kind of overwhelming. You're not even really sure where this cardiovascular risk protection is coming from, and I feel like you might be one of the first people that has explained it to me. And so I'm wondering, with these new medications are getting stronger and stronger and more weight loss, and they

seem to be targeting the same pathway. Are you assuming that if they did do the studies that those medicines would have even more effect on the end of vascular, and that we would have you know, better outcomes for cardiovascular. That's a great question. So it is a little bit. So I showed you data from 3 G. Lp, one receptor agonist studies. I don't know that each of them will have cardiovascular benefit. Because they there is such difference if they're each of the structures, and especially when we're adding Gip agonist to the G lp, one receptor agon, you know it's it might be different, and I wouldn't assume that there would just simply be a class effect.

- I it would make sense to me that with weight loss there would be less insulin resistance, and then that may be protective for people with type, one diabetes. But we really don't know and we don't even know is, is weight loss necessarily protective for people with type one diabetes. So I guess my argument would be we really need to see them being effective, but not all. G lp, one receptor agonists have shown cardiovascular protection. Like the shorter acting. G lp, one receptor agonist, have had disappointing results so II think it has to be assessed. Case by case.
- Great question.
- Thank you, Katie. That was awesome. I'm heading from here to Friday afternoon at Uma again, where we worked when you were resident. So let's go back to Uma. You talked about glycemic variability, which I think is something that especially in kind of the primary care space we we maybe don't love, and we don't think about so. Stepping back from some of the complexity of Cara's question. Yeah, what would you have us be looking at in terms of you know. Sort of what's some of the degrees of glycemic variability, or some of the ways that that you would sort of encourage. Our burgeoning pcps as you're looking at patients. Glycemic trends. You know what kept what should catch your eye? As in terms of hospitalist pcps in terms of glycemic variability, because don't think it's something we talk about as much coming through the training pipeline.
- Yeah. So for glycemic variability, there's a marker that is sometimes calculated for us in the Cgm. Reports, so if it would be very difficult to calculate it from just, you know, 3 blood sugar checks a day. But from Cgm. Reports, they will calculate coefficient of variation for us, which is a marker of glycaemic variability, and the threshold would be 36% or higher. You can also calculate it yourself. And I'm thinking that the formula is mean, glucose, standard deviation. I think that's right. But I mean, you could. You can look online. But yeah, you would. You could see coefficient variation. Dexcom reports actually define it for you. So you don't have to memorize any numbers, you just know, like, okay, that's 50% is a lot of but I mean, pro, maybe not that. But like forties, fifties. That would be very high glycaemic variability. And so II would talk to the patient. And you know, typically, my first step in addressing glycemic variability is looking at hypoglycemia because hypoglycemia is a really efficient way of spiking to hypoglycemia, because people tend to overcrack and eat a lot of sugar and so you know, one way to smooth out patterns is to limit the amount of severe hypoglycemia someone's seeing.
- Thank you for a great talk so it was interesting to me, using Fmd as sort of a short term outcome to study some of this in type one diabetics and definitely acknowledging the challenges you brought up at the beginning for studying this population. I'm curious if any of the studies using Fmd is it feasible to use sort of some of the more clinical outcomes for cardiovascular disease like Mace, or anything like that? Or is that time period just so long that we can't really get that data? Yeah, I think it. It really comes down to cost like an Fmd. Study, could be conducted over a 3 or 4 month interval, because we see these relatively acute changes whereas even using pulse wave velocity as a marker, which is, is more of an arterial stiffness measure, and that's thought of as like sort of a subclinical

atherosclerosis marker. Even that takes like 6 month study duration. So I think it really comes down to you need really large sample size of people who are very high risk of cardiovascular disease.

- And a lot of time like 3 to 5 years is going to be a typical for the duration of a cardiovascular outcome study? Yeah. Good question.
- Oh, I think we might have one more too long, but I loved the design of doing it that way to see if there was more of a synergy. And I think that if we see some successful outcomes, this would justify a crossover study combination study. But yeah, the way that we initially designed it was an exercise group who also gets a GLP. One receptor agonist, and someone or a group that just has placebo and then has exercise combined. But yeah, that then I said that for an early stage researcher they just didn't think it's doable, and they were probably right.
- Yes, hey, Katie? Great talk! Thank you. So are you worried about weight loss in the type ones? And if and you've got exercise going on, which is great, too. Are you measuring body? Comp, maybe with Dexo or something? Yeah, we're using bod pods. Well, so yes, that weight is an important confounder for the study. We designed it with that in mind to help reduce the influence of that by selecting trulicity as the glp. One receptor agonist with cardiovascular prevention which has the least amount of weight loss, so that hopefully, people don't lose a lot of weight.
- And we're adjusting for changes in weight as a adjustment. Covariant and we are also we. We initially designed it with people who had a normal Bmi, but just from a recruitment standpoint, we found that people were more interested in the study who were at higher Bmi categories. And so we're Bmi is part of our randomization scheme to try to, you know. Think about that, too. That's and a really important point, though.
- Alright. Well, thank you all so much for having me there really appreciate the ability to highlight that.