Preventing Strokes in Type Two Diabetes

Walter Kernan:	00:04	Thank you for joining this podcast on preventing strokes in patients with type 2 diabetes. We'll discuss risk factors for stroke, treatment and management options for stroke prevention, and the importance of multidisciplinary team care. This podcast is a continuation of our series to reduce cardiovascular deaths, heart attacks, heart failure, kidney disease, and strokes in patients living with type 2 diabetes and is based on the collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart.
	00:42	This series is brought to you by founding sponsor Novo Nordisk. I'm Walter Kernan. I'm a primary care physician at Yale School of Medicine where my career has involved research in the prevention of stroke among patients who already had one stroke. I'm joined today by Heather Ferris and by Alejandro Rabinstein. I'll ask them to introduce themselves. Heather let's start with you.
Heather Ferris:	01:08	Good morning. My name's Heather Ferris. I am the co-director of Diabetes Cardiovascular Clinic at the University of Virginia. I'm an endocrinologist and I focus on the care of patients with diabetes and cardiovascular disease.
Walter Kernan:	01:23	Alejandro?
Alejandro Rabinstein:	01:25	Yeah. Hi, I am Alejandro Rabinstein. I'm professor of neurology at Mayo Clinic in Rochester, Minnesota. I'm a practicing stroke neurologist with an interest in the interface between diabetes and stroke.
Walter Kernan:	01:41	Well, thank you. So, we're going to start right in on the topic and we're going to begin by asking the simple question, why are we here? I'm going to start by asking Alejandro to comment on what is the interest in caring for patients with diabetes to prevent brain illness?

Alejandro Rabinstein:	01:59	Well, because diabetes is extremely common in patients who end up with a stroke, and both diabetes and stroke are conditions that are becoming increasingly common in the general population. In people with diabetes, the risk of a stroke is increased approximately twofold compared with people without diabetes, even adjusting for age. Also, in patients with diabetes who have a stroke, the chances of worse stroke outcomes, worse outcomes after a stroke are greater, both in terms of the stroke deficits that we normally care about for daily function, but also in terms of cognitive abilities.
	02:53	So as I said, this is a common problem. The prevalence of diabetes in people with stroke is high. Approximately a third of patients with stroke, ischemic stroke in particular, have diabetes. The risk is a little bit lower in persons with the hemorrhagic stroke. I know that our focus is going to be on primary stroke prevention, but the rate of a stroke recurrence is also higher in patients with diabetes than in patients without diabetes, without one metanalysis indicating that increased risk may be as high as 50%. So, it truly matters.
Walter Kernan:	03:41	Thank you. Hey, Heather, I'm just going to ask you, how common is diabetes in the US population? What proportion of adults have diabetes and does that increase with age or what can we expect?
Heather Ferris:	03:55	So diabetes is absolutely a disease of aging, and we see more and more diabetes as people get older. Obviously as they age they have an increased exposure to hyperglycemia. They've had the diabetes for longer, and so they've had the opportunity to accumulate the risks from that diabetes for longer. So just as stroke is a disease of aging that is compounded by diabetes being a disease of aging.
Walter Kernan:	04:34	Thank you, that's helpful. So, I'll mention briefly why diabetes is related. Diabetes essentially is a disease of small and large blood vessels. That's how I think of it. It's the syndrome of disease of small and large vessels. How does it cause stroke? Well, because it damages large blood vessels, damages the aorta, it damages the heart, it damages the large blood vessel

		going to the brain and it damages the small blood vessels in the brain.
	05:01	How does it do it? Well, it starts with obesity, metabolic syndrome and insulin resistance, which are involved in intracellular pathways that result in hyperinsulinemia, insulin resistance, dyslipidemia, inflammation in blood vessels. It results in decreased nitric oxide, all of which leads to a pro-atherosclerotic environment. You compound the obesity metabolic syndrome with relative insulin deficiency, then people become hyperglycemic. Hyperglycemia independently leads to further blood vessel damage. So that's why we're here. It's this diabetes and its pathophysiology damage blood vessels.
	05:51	I'd like to turn now to what we can do about this. I view diabetes as an opportunity. It's an opportunity to help people with the condition to stay healthy. So, I want to turn first to Heather and say, thinking generally, got a patient with diabetes in front of you. What do you think sort of big buckets that you can bring to that patient to reduce their risk of stroke?
Heather Ferris:	06:19	So all the same things that we want to do to prevent stroke in the general population apply to patients with diabetes. We're talking about making sure that if they're smoking that you're helping them try and quit. We're keeping blood cholesterol under control, blood pressure under control, and really the only additional aspect for stroke prevention in someone with diabetes is trying to keep those blood sugars under control. Everything else is going to be exactly the same. When we're talking about all of these different risk factors, we also want to make sure that our patients are overall maintaining a healthy lifestyle. So exercise is going to be another key component to preventing stroke, but nothing special for diabetes.
Walter Kernan:	07:21	Okay. I want to press you on this a little bit. Alejandro, you may have an opinion. What about blood pressure? What is the blood pressure care in someone with diabetes? Is it the same as for a patient without diabetes and do you use the same drugs?

Alejandro Rabinstein:	07:35	Yeah, so yes and no because it used to be that we used the goal of 140 over 90 for all patients and 130 over 80 for patients with type 2 diabetes. Now we have all sort of gone down for all patients trying to reach that blood pressure, that 130 over 80. Some people, some colleagues may think, okay, how about the SPRINT (Systolic Blood Pressure Intervention Trial) trial and going below 120 systolic? Well, I mean that trial actually excluded patients with diabetes, so it may not apply. Certainly, beyond the recommendations, there is a fairly widespread opinion I would say among stroke clinicians that without risking hypotension, one is even stricter in patients with diabetes when it comes to blood pressure control.
	08:38	As to the agents, well, there is a higher, a greater value in starting ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers (ARBs) in patients with diabetes, particularly in those with proteinuria established coronary artery disease as opposed to other agents that are commonly used for blood pressure control. I would say that also using an ACE inhibitor or an ARB in addition to another agent in patients who are more refractory, at least I personally tend to start a second agent to improve blood pressure control earlier in patients with diabetes.
Walter Kernan:	09:27	Heather, do you agree that we should as a reflex go to an ACE and ARB first for blood pressure control in somebody, in all patients with type 2 diabetes?
Heather Ferris:	09:37	Yeah, I think that while we don't necessarily have to start there, the reality is that albuminuria is really common in patients with diabetes. As soon as they have albuminuria, you want them to be on an ACE inhibitor or an ARB. So, if you're going to start an agent for hypertension, I think that that's the place to start. I will mention that I think that there was a period of time where we would start an ACE or an ARB even in people without hypertension, and that we've walked away from. As Alejandro mentioned with the SPRINT trial, we're generally starting to move our notion of what hypertension is down some. In anyone with a blood pressure under 120 systolic, we don't use an ACE

		inhibitor for sort of kidney protection. Patients should have frank hypertension before it started.
Walter Kernan:	10:41	Thank you. As a primary care physician, I'm going to add that when you start a patient on treatment for high blood pressure or intensify it, they really need to be followed up within a month. I mean that should be I think a rule we stick by because you want to be sure they get to goal, and you can help a patient get to goal in two years or in two weeks and better to do it early because it's so important. All right, I want to press Heather. I'm going to press you on cholesterol. Alejandro, please feel free to pipe in. How is treating hypercholesterolemia different in a patient with diabetes compared to a patient without diabetes? Are there any differences?
Heather Ferris:	11:23	This is a place where there's some differences and maybe a little bit of disagreement among different societies as well. If you follow American Diabetes Association guidelines, those patients that are between the ages of 40 and 75 with diabetes, without known cardiovascular disease, we are going to recommend a moderate dose statin. That's regardless of what their LDL cholesterol is. That's regardless of doing any of the risk calculators. So once someone has established cardiovascular disease, then you would consider a high-intensity statin. The big difference between someone with diabetes and someone without is that reflexive use of a moderate statin.
	12:25	Now if you have somebody who is under the age of 40 with type 2 diabetes, which unfortunately is becoming more and more common, the guidelines are a little bit less clear. We're not quite so reflexive, but you could consider a moderate dose statin, particularly if somebody has a lot of other risk factors. It's not just hyperglycemia, but they're also smoking, or they have hypertension. In that case, you may also consider adding a moderate dose statin.
Walter Kernan:	12:56	Among people aged 40 to 75 who have diabetes, you mentioned that almost everybody should be on moderate dose statins. Who should be on intensive statins in that age group?

Heather Ferris:	13:07	So the intensive statins, those are going to be people who have evidence of existing cardiovascular disease. So, if they have peripheral artery disease, they've had a cardiac stent. This could also be patients who are smoking, have otherwise high levels of risk factors, but for the most part it's established cardiovascular disease.
Alejandro Rabinstein:	13:43	That certainly includes stroke. It's a given that we're going to give high intensity statins.
Walter Kernan:	13:50	Do either of you use PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitors in patients with diabetes who do not have established cardiovascular disease?
Heather Ferris:	14:03	So I would say that those are going to be pretty uncommon. These are going to be the patients who are truly, either they're intolerant of statins and you just can't get them on a statin, or despite your best efforts, they have really significantly elevated LDL cholesterols. For the most part I would say I lean on those for patients who do have established cardiovascular disease.
Walter Kernan:	14:36	Thank you. Okay. I want to turn to treating glycemia. I'm going to begin to ask if either of you could comment on what are the goals, what should be the glucose target for a patient with type 2 diabetes or type 1 diabetes to reduce their risk for stroke?
Alejandro Rabinstein:	14:59	Heather, this is all you.
Heather Ferris:	15:02	So this is an area that has evolved over time, and I think will continue to change, but really as anyone who takes care of diabetes knows getting to a particular target can be quite challenging depending on the patient. So, it's really always going to be a balance between risk for hypoglycemia, cost of medications and complexity of regimens.
15:39	That being said, 7% A1C is really sort of our starting place. Then if we can get people a little bit lower without risk of hypoglycemia, that's fantastic, but for the most part, we're really aiming for an A1C around seven. For our older adults who are on agents that can cause hypoglycemia, so they're on a sulphonylurea, they're on	

		insulin. We may want to target more like 7 to 7.5%. For patients who are frankly at very high risk of stroke but have limited life expectancy and poor functional status, if they're requiring insulin, we're probably going to have A1C targets that are even higher, above 7.5%, just because the risks of getting those A1Cs lower with insulin outweigh the benefits of stroke prevention.
Alejandro Rabinstein:	16:47	It is interesting that the glycemic control, particularly the tight glycemic control, doesn't seem to have a major influence in stroke rates. I've always been curious about that. So, it seems like diabetes causes an increased risk of a stroke by means other than directly related to hyperglycemia. So, I always rely on diabetes experts to take care of the hyperglycemia. On the other hand, I think that the treatment of diabetes as a vascular disease, particularly using medications that have a low risk of inducing hyperglycemia, is more a part of my job as well.
Heather Ferris:	17:49	I think that that's really important to recognize that the trials that we have where we were targeting particular A1C cutoffs for preventing stroke and for preventing heart disease, we're in the age where most of what we had were sulphonylureas and insulin and metformin. We're in a very different place right now. I think that the hyperglycemia is actually really important as far as a stroke risk, but I think a lot of that has to do with glycemic variability, which is one of the hardest things to manage.
	18:31	Where again, we've made huge advances in diabetes care of late. Now that we have continuous glucose monitors and more sophisticated ways to manage blood sugars, we may see that getting patient's A1Cs down in those lower ranges really does confer benefit, cardiovascular and cerebrovascular benefit, but we don't have those studies right now.
Walter Kernan:	19:00	Heather, I was very interested to see the American Association Clinical Endocrinologists (AACE), shoot for hemoglobin A1C less than 6.5% when you can, and their justification was with newer agents, it's possible to get lower safer. Would you agree with that?

Heather Ferris:	19:20	I think it's absolutely true that we can get lower safer. What I think we're missing right now is data to show that outcomes are improved. You have to remember that these are really expensive medications that we're using to get people lower. It's an open question.
Walter Kernan:	19:43	Okay. I want to turn if we could to how to lower blood glucose (sugar) in patients with diabetes. I think we'll focus on type 2 diabetes, understanding that in type 1 diabetes, really the option is insulin. So, let's talk about type 2 diabetes. All right, so we see an average patient in the office with type 2 diabetes. What's the right first drug to choose? I'm going to turn that to either one of you.
Heather Ferris:	20:15	So I think we have the best data for GLP-1 (glucagon-like peptide-1) receptor agonists. These are really great glucose-lowering drugs. They don't cause hypoglycemia. They help with weight loss, which in the long term is really going to help you out for the diabetes management and prevention of secondary outcomes. They have proven prevention, cardiac disease prevention. So, these are going to be probably our first line.
	20:57	Now the other group that has also really good cardiovascular prevention data are the SGLT2 (sodium-glucose transport protein 2) inhibitors. These have a specific niche, which is patients with heart failure and patients with chronic kidney disease. So that class of drugs, if you have somebody who's got proteinuria, I'm going to go to the SGLT2 inhibitors first. Or if I have somebody with heart failure, absolutely an SGLT2 inhibitor first because they just have such impressive outcomes in those areas. Where we don't have other medications with quite such potency in preventing chronic kidney disease and heart failure hospitalizations.
	21:50	The other group of medications or the other medication that I want to point out that I think has gotten forgotten is pioglitazone. So, pioglitazone is a thiazolidinedione (TZD) and is a really excellent generic diabetes medication that has good stroke prevention data. The TZD class of drugs got a bad rap many years ago, and rosiglitazone-related medication showed worse cardiovascular outcomes. This is the class of drugs, that's

		the reason that all diabetes drugs go through cardiovascular outcomes trials now, but pioglitazone does not carry that same risk.
	22:49	Again, the SGLT2 inhibitors and GLP-1 receptor agonists are really expensive medications. So, for a lot of patients, pioglitazone is going to be a really good first-line drug that has good cardiovascular outcomes data. Now it does cause some fluid retention, so you don't want to use it in someone who has significant heart failure, but it really is a potent, again, medication. It also is very helpful for managing triglycerides, another cardiovascular risk factor that we don't have great medications for.
Walter Kernan:	23:37	Heather, if I understand you correctly, you're saying pick a first agent or even a second agent based on patient care. You mentioned patients with heart failure, kidney disease, they might get an SGLT2 inhibitor first, get a GLP-1 receptor agonist first instead of say an SGLT2 inhibitor. Who would get that agent and who could get other agents?
Heather Ferris:	24:03	Yeah, so I mean I think someone with significant obesity is going to a GLP-1 receptor agonist is going to again, help them with multiple aspects of their risk. So that's the main group that I would look for with that. I also mentioned that we're focusing on type 2 diabetes, but for someone with type 1 diabetes at high cardiovascular risk, you can use a GLP-1 receptor agonist off-label. SGLT2 inhibitors, you should not be using in type 1 diabetes for sure. GLP-1 receptor agonists continuing alongside their insulin can be helpful for management of their diabetes and we presume also for cardiovascular risk reduction.
Alejandro Rabinstein:	25:05	So what I'm hearing correctly is this whole idea of you have to go through metformin before getting to one of these newer agents is no longer valid?
Heather Ferris:	25:19	So I would say that most people start with metformin, and we can start with metformin in the pre-diabetes range as well. It is still incredibly safe, effective and affordable and often required for insurance approval of other diabetes medications, but it

		doesn't have the same cardiovascular outcomes data that these other medications do. So, I would say all of my patients go through metformin, but maybe it's metformin plus one of these other agents if I think they're at high risk.
Walter Kernan:	26:00	It's worth pointing out that in the GLP-1 receptor agonist trials, the cardiovascular outcome trials, 70% or so of those patients were on metformin. So, a lot worked and that's allowed the ADA (American Diabetes Association) and the AACE to say, "Hey, you don't necessarily have to go through metformin, but it's an option." Heather, I wanted to do one more clarification. We're talking about primary prevention primarily today. So, for patients with diabetes who do not have a prior stroke or MI but are at high risk, those patients are also suitable for GLP-1 receptor agonists, if I'm correct.
Heather Ferris:	26:41	Yeah, absolutely.
Walter Kernan:	26:44	Where does weight consideration of patients with diabetes, how should we factor into that into our treatment? This will be our last section.
Alejandro Rabinstein:	26:55	Weight is important. Obesity is very common in patients who suffer strokes. There is no question that GLP-1 receptor agonists are very useful for weight reduction. Please don't forget diet and exercise.
Walter Kernan:	27:13	I would agree with that. Taking a little bit of a contrary view, diet and exercise are probably less effective than GLP-1 receptor agonists for people who really need weight loss. Do you agree with that?
Heather Ferris:	27:25	Yeah. Diet and exercise is hard. We know it is. It should be part of any plan for patients in conjunction with medications. I think we get patients sometimes who think that the GLP-1 is going to miraculously make all weight melt away, but they have much better success when they are working on a healthier diet and exercise. Importantly, when people are going through a lot of weight loss, exercise is key, so they're not losing muscle mass. So, I try to emphasize if nothing else that patients who are

losing weight need to really increase their exercise so that they don't have excess loss of muscle mass.

Alejandro Rabinstein:	28:24	Exercise in and by itself improves not only physical health but also cognitive health, any degree of aerobic exercise. So, I think that it has to be pointed out even if it is not as effective in terms of weight reduction.
Walter Kernan:	28:41	Thank you. This has been enormously informative. I'm going to make two final comments and then bring us to a close. One is that there are selected patients for bariatric surgery, selected patients with diabetes for whom bariatric surgery should be considered both. It can be effective for diabetes remission and for hyperglycemia control. There's some indirect evidence that it can reduce risk for cardiovascular disease. Alejandro, should every patient with diabetes be on aspirin regardless of their history of vascular disease?
Alejandro Rabinstein:	29:13	No, I don't think so. I think that they have to give me some vascular disease, then I tell them to be on aspirin.
Walter Kernan:	29:21	Thank you. This has been wonderful. I've really enjoyed speaking with both of you. This concludes the podcast, and we want to hear from you. If you have a suggestion for future content, email knowdiabetesbyheart@diabetes.org. It is our mission to reach as many listeners as possible with this lifesaving information. If you enjoyed this podcast and are listening on iTunes or Google Play, don't forget to leave us a rating and subscribe. Thank you very much for listening.