Dr. Eckel:	00:04	Welcome and thank you for joining the podcast on cardiovascular disease and diabetes for healthcare professionals. The purpose of this ongoing series is to reduce cardiovascular disease related deaths, heart attacks, strokes, and heart failure in people living with type II diabetes, and is based on the new collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart.
Dr. Eckel:	00:30	This series is brought to you by founding sponsors, Boehringer Ingelheim, and Eli Lilly and Company, Diabetes Alliance, and Novartis, and its national sponsors Sanofi and AstraZeneca.
Dr. Eckel:	00:45	I'm Dr. Robert Eckel, and joining me today is Dr. Chris Cannon, and we're going to be discussing the use of anti-hyperglycemic agents with CVD benefits. Chris, good to you have you.
Dr. Cannon:	00:57	Well, thanks very much, Bob. It's a delight to join this podcast.
Dr. Eckel:	01:01	Well, I think this podcast is really established by, I think, the last decade of clinical trials that relate to management of diabetes. I think have been surprisingly favorable.
Dr. Eckel:	01:12	I think this is providing a big shift in therapeutic approaches to treatment of patients with diabetes, in terms of the reduction of risk for cardiovascular disease, death, myocardial infarction, and many other CVD outcomes that have been really part of the primary and secondary outcomes of the trails that have been implemented.
Dr. Eckel:	01:30	Historically, diabetes management to prevent cardiovascular disease has been focused on glycemic control, and the FDA, historically, has approved new drugs for the treatment of diabetes based on their ability to lower levels of glycemia, and more recently, as I'm sure most of you know, the hemoglobin A1c has been used as a glycemic biomarker to assess the benefit of therapeutic interventions in patients with diabetes.
Dr. Eckel:	01:56	However, as I've just mentioned, I think we've rendered a whole new space of understanding how diabetes risk for cardiovascular disease can be improved by therapies that also lower glucose, that have many other manifestations of their mechanism of action that relate to the benefit in patients with diabetes.
Dr. Eckel:	02:16	I think it's important to say upfront that the studies at this point have been carried out exclusively in patients with type II

		diabetes, and we can't ignore the fact that we still have 1.3 million patients with type I diabetes, where in the kind of clinical trial evidence to reduce cardiovascular disease risk has not really clearly been demonstrated.
Dr. Eckel:	02:35	Our focus today is on managing diabetes in relationship to outcomes, specifically cardiovascular disease outcomes in patients with type II diabetes. Recently, the ADA has updated its guidelines, or better called I think recommendations, every three months approximately or when new data are made available.
Dr. Eckel:	02:56	This is unlike a history of diabetes recommendations previously stated just annually in the January issue of Diabetes Care. It's important for the practitioner to know that ultimately, they can turn to the updated standards of medical care guidelines for patients with diabetes on a regular basis and feel like they're updated with a current clinical trial related evidence for benefit, for all aspects of diabetes assessment and care.
Dr. Eckel:	03:24	Chris, let me begin the conversation here today by just opening up the door to kind of discuss the new trials. We've seen trials carried it out basically with two new classes of drugs, the SGLT2 inhibitor and also the glucagon-like peptide-1 receptor agonists. These trials again have opened new doors and get people like you in cardiology-space more interested and more hopefully capable of implementing these strategies in their own treatment paradigm. Chris, your thoughts?
Dr. Cannon:	03:56	Well, it's true that it really has been a wonderful era in really the last decade when these large trials have been done, where we really see what the outcomes are for patients and we've learned an enormous amount where the initial worry was safety and that started with rosiglitazone, then safety was shown with the DPP-4 class, but now the two classes you've just mentioned are showing benefit in reducing a wide range of cardiovascular events.
Dr. Cannon:	04:25	And so, this is now drawn us in in cardiology to say that we need to start offering this and treating our patients to get these cardiovascular benefits. A really exciting time.
Dr. Eckel:	04:38	You're a clinical trialist yourself and been involved in many major cardiovascular disease outcome trials. The primary outcomes are similar but differ to some extent. Do you want to reflect on how the decision for primary and maybe even

		secondary outcomes relate to the interpretation by the practicing physician?
Dr. Cannon:	04:56	It's a good point, and the rigor of doing cardiovascular outcome trials has been well established in various areas of antithrombotic therapies, lipid management and now diabetes management. We've done them over and over.
Dr. Cannon:	05:12	And so, the main idea is to establish a primary end point and that becomes the key takeaway. But then, we also will specify two or three key secondary end points where if we've pre-specified it, have enough power to make sure that they're well robust answers, that we can include those in really the key messages from the trials, and then all the other secondary end points, we try and adjudicate the important end points, we learn from them, and indeed in this first two rounds of trials, this has spurned a second round of trials focused on heart failure, where initially, these trials were showing safety from cardiovascular death, MI or stroke showing benefits, but then seeing a huge benefit on heart failure that has now turned into a second round of trials again in patients starting with heart failure to look at those outcomes.
Dr. Cannon:	06:10	So both count, but we can really take to our guideline committees, these primary and the first key secondary end points, and we're now seeing that incorporated into the standards of care and other guidelines across cardiology and nephrology and in diabetes.
Dr. Eckel:	06:30	The recent update on the medical care guidelines for patients with type II diabetes relate to kind of beginning with metformin, that's been around for a long time now, and we know that metformin is fairly well tolerated, effective in modifying glycemic burden, but yet, the clinical trial evidence for metformin isn't all that good.
Dr. Eckel:	06:49	I don't know, Greg Schwartz, one of my colleagues here in Denver is running a trial in prediabetes, looking at the benefit of metformin. But, in your opinion, as a practicing cardiologist, are you comfortable with metformin being the primary therapy and then considering other agents' individualization of prescriptions to follow?
Dr. Cannon:	07:07	I think so. It's been in practice for so long and it does provide a good glycemic control, seems to be a benefit and is widely accepted. We're really sort of tiptoeing into this field because we see the benefits, but we're sort of learning how all the drugs

		work and who should get them and when. So, we're not quite at a position to question that so, but I think that's been perfectly well accepted.
Dr. Cannon:	07:35	Of note in all the trials, only about three quarters of patients are able to be on metformin. There are a substantial proportion of patients who don't tolerate it and I've certainly had some myself where then we'd be moving to the next classes of drugs in people who are not on metformin. But, it's reasonable to have it be the starting point, I think.
Dr. Cannon:	07:56	One nuance on that question has come up in the patients where we're about to discuss with say, documented atherosclerotic cardiovascular disease where you'd like to add one of the new agents and they're on metformin and they're glycemic control is good, do you add the cardiovascular protective agents anyway?
Dr. Cannon:	08:17	And so, that's kind of a hot topic, I'd say, regarding metformin. And, does that prevent you from using some of these newer classes that have documented clear cardiovascular benefit?
Dr. Eckel:	08:29	Well, let me extend that thought a bit with you now, and we have a patient who's had a recent acute coronary syndrome and you're seeing them post MI, say, six weeks later in your preventive cardiology clinic, how might you choose whether that patient might be best benefited by a GLP-1 receptor agonist versus an SGLT-2 inhibitor?
Dr. Eckel:	08:50	And secondly, does the presence of kidney disease influence your decision?
Dr. Cannon:	08:55	Well, the first step is to get patients with, especially the very high-risk patient, of someone early post MI, to be thinking about either of the agents. And so, most people are not on these agents. We had a paper just presented and published at ADA where only about 15% of patients with diabetes and documented atherosclerotic cardiovascular disease were on one or the other agent.
Dr. Cannon:	09:25	Going from not on to on one of them is the key first step. Deciding between the two classes, I think their renal disease is certainly one that would tilt towards the SGLT-2, although there are benefits of both classes for renal disease, but the CREDENCE trial was just completed and published in patients with macro albuminuria and renal disease and found a significant reduction in the need for dialysis and development of end-stage kidney

		disease and all the other benefits, cardiovascular death and et cetera.
Dr. Cannon:	10:02	There, you get a big benefit with SGLT-2, you see reductions in albuminuria or progression of albuminuria with the GLP-1 receptor agonists, so either of the classes are good. Both of them are very helpful for the post MI patients. I think, trying to get them onto one of them is really the first goal, I would say of us as cardiologists.
Dr. Eckel:	10:26	Is the cardiologist not interested at all in control of glycemia? Is that something that they should dismiss in their practice or are we talking about a teamed approach here, which would also involve the endocrine community?
Dr. Cannon:	10:39	Well, I have seen it really as there are now two goals in management. One is to get good glycemic control, but the second is to offer the drugs that provide cardiovascular and renal benefit. Those two goals intersect in these glycemic control agents because they do both, but we still have two goals and we want to accomplish both the goals, and hence we want to get glycemic control by titrating and adding appropriate therapies, but then want to offer the classes of drugs that provide cardiovascular benefit.
Dr. Cannon:	11:18	And so, an analogy is the ACE inhibitors where they lower blood pressure, but often we're adding them for renal protection and cardiovascular protection, not necessarily because the blood pressure was too high. And so, that concept is now shifting over to these two classes of drugs where we are looking to add them and not necessarily because we need them for glycemic control, but that we want to get them on and the patient could always benefit from a little bit more glycemic control.
Dr. Cannon:	11:50	It's keeping those two goals in mind, in parallel, than I think we approach the management, and then for us as cardiologists, we're again still learning the side effects of the drugs and the nuances of dosing, and so, we really need help from the endocrine community and primary care physicians who have often been managing the patient's diabetes for five or 10 or more years already.
Dr. Cannon:	12:16	Building that collaboration is really the step that we're at now, I think.
Dr. Eckel:	12:22	I've seen some recent data in this space that relates to the percent of prescriptions for GLP-1 receptor agonist and the

		SGLT-2 inhibitors that are occurring in a primary care setting versus by endocrinologist versus by cardiologist. Your subspecialty, Chris, less than 5% of prescriptions for these two classes of drugs come from cardiologists. This is an expanded need for the cardiology community to get more informed about this benefit.
Dr. Eckel:	12:51	I think you mentioned the 15% figure before, so we got all a lot of room to play here to get people on optimal therapy.
Dr. Cannon:	12:59	And, we have a lot to learn, and so this podcast series and all the information slides and the guideline updates, we really need to absorb all this information. We're actually doing a little program here at our hospital to try and teach cardiologists how to prescribe this and it's amazingly difficult to get over the hump of prescribing a new class of drugs and being comfortable doing that.
Dr. Cannon:	13:27	And so, reaching out for support from our endocrine community has really been a great help in teaching myself and other colleagues here.
Dr. Eckel:	13:36	I think teamwork for the next five to 10 years is going to be very necessary, and I think you and I have talked about this previously, but the idea of a cardio-metabolic subspecialty in medicine is something that Mike Blaha from Hopkins and I are promoting, have a paper and press on that and ultimately may be a decade-related capability that doesn't exist currently.
Dr. Eckel:	13:56	Let me ask you a little bit more about mechanisms. I think, increasingly we're thinking the SGLT-2s have the mechanisms that relates to hemoconcentration and some form of a diuretic benefit. Whereas, the GLP-1 receptor agonists have been kind of promoted as anti-atherosclerotic agents. Are you convinced about either one or both of those mechanisms?
Dr. Cannon:	14:18	I've come away with the thought that there are multiple mechanisms of both of these different classes and that we're just starting to learn all of them, and so accepting, I think the multiple mechanisms concept, maybe how there's such a broad number of benefits. To see the diuretic component make sense in that there's a reduction in heart failure with the SGLT-2 inhibitors, but not with the GLP-1 receptor agonists, I've been very impressed in the renal benefits, especially of SGLT-2 and reductions in intraglomerular pressure have been part of the touted mechanism by which we would see benefit, and so I

		think that is probably a key aspect of how the class of drugs works.
Dr. Cannon:	15:10	The glycemic benefit probably contributes some, that's probably of benefit, the effect on atherosclerosis, there are multiple hormonal changes I think with both the classes of drugs that impact in a beneficial way. It's a lot of different positive mechanisms, reductions in blood pressure and loss in weight, many beneficial factors all contribute to then big clinical benefit, which is of course driving all of our excitement to start using these more broadly.
Dr. Eckel:	15:44	Do you know if the American Heart Association in their heart failure guidelines has now placed SGLT-2 inhibitors as a therapeutic choice for practicing cardiologist?
Dr. Cannon:	15:54	Well, I think that the document is very well written and reviews beautifully all of the data and does stick to the point you made earlier of what counts in the clinical trials. And so, as has been seen as a secondary endpoint in just about every single trial, huge and consistent, 35% 40% reductions in hospitalization for heart failure in otherwise pretty stable patients without heart failure.
Dr. Cannon:	16:26	But, there hasn't been to date a study in patients with documented heart failure at baseline to look at what are the effects, and so this has been a secondary endpoint that's been consistent that now the prospective trials are well underway to try and study that as a new indication.
Dr. Cannon:	16:46	And so, the document, I think, nicely words this that these agents should be considered in patients at risk of developing heart failure, but that the main indication comes from the traditional guidelines. It would be a consideration, not a mandate that you really should use this in heart failure. That may come with the prospective trials, depending on how the data look.
Dr. Eckel:	17:10	Well, I'd like to try to extend that thought of yours a bit further, and let's say I'm a primary care physician or let's take someone who is a primary care physician, either an internist, more likely perhaps than a family doc, who then patient's short of breath and they'd gotten a chest X-ray and it looks okay, and they decided to order an echocardiogram and they get a reading of a normal left ventricular ejection fraction, but a reading of diastolic dysfunction.

Dr. Eckel:	17:36	When should this physician, who's taking care of a patient with type II diabetes, with that scenario, be willing and capable of referring that patient to you?
Dr. Cannon:	17:45	Well, it's a very reasonable patient to refer. I think heart failure is common and obviously of great morbidity from multiple hospitalizations and higher mortality. There are lots of good therapies to think about. To try and have someone who thinks every day about heart failure and issues would be a good reason to get a consultation and work in parallel.
Dr. Cannon:	18:12	With regard to the glycemic management, this would be something that they could say, "There's edema, heart failure, shortness of breath, I could start thinking about the SGLT-2 class as I'm choosing my agents," so that would be sort of a consideration in the glycemic management, but certainly reasonable to refer and get other expertise and what other agents would you get on, spironolactone as a diuretic and push the ACE inhibitor as a key therapy and get that to the higher doses as used in the clinical trials, would be some of the things that we would do. Beta blockers often can be indicated.
Dr. Eckel:	18:51	Well, that patient with HFpEF, though that have preserved ejection fractions, we don't really know the mechanism for that so well, do we? We don't have clinical trial evidence that would be necessary to have that patient be seen by you. What are your thoughts in that space?
Dr. Cannon:	19:08	All very true, and it's one of the more vexing diagnoses in that it's very common, high morbidity, and there are few sort of dedicated trial and interventions that have been shown to fall on the list. And so, this is where some of the nuance of clinical practice can come into play, but good blood pressure management is key. I think we rely heavily on the ACE inhibitors since that they have broad benefit.
Dr. Cannon:	19:36	Spironolactone in the TOPCAT trial had looked promising and other data supports that, and fortunately there'll be more trials coming in that space, but that can be something in a difficult patient who's, say, had hospitalizations that one might think about, and then just simply diuretic management to try and keep them from getting fluid overloaded.
Dr. Eckel:	19:58	I think one of the more recent trials that was just presented a week ago at the ADA is the CREDENCE trial, and I think if you look at the primary outcome, the statistical significance of benefit, they have far outweighed any other trial that's been

		done in patients with type II diabetes. And of course, as you've already stated, these are people with more advanced renal disease and also moderately high-risk for another cardiovascular disease, have had many who had secondary interventions or very high-risk who are entered into the trial.
Dr. Eckel:	20:25	The primary outcome really included the renal outcome and the cardiovascular disease outcome. If you look at some of the components, CVD death was reduced statistically, and the composite of MI and stroke were reduced significantly, but no effect on all-cause mortality. How important in being a physician of patients with type II diabetes and heart disease is convincing our patient of all-cause mortality benefit, and how do you address that with a patient if she or he asks, "Doctor, am I going to live longer because of this intervention?"
Dr. Cannon:	20:58	Well, it's often a reasonable consideration. I think, in this situation, patients with renal disease have a lot of competing risks, and so they often are older and will have other things that contribute to non-cardiovascular related death that we can't impact, but obviously, we try and impact the other things.
Dr. Cannon:	21:18	I was delighted to be a part of this study and really was so impressed at the outcomes, and I think the focus on the benefit in renal disease has been seen as secondary end points in all the other trials was sort of a bit of a surprise, but then to have this prospective trial show on the hard renal endpoints like need for dialysis or developing end-stage kidney disease being significantly reduced by 30% was really dramatic.
Dr. Cannon:	21:50	Of course, having people avoid or potentially delay, if you'd take a long-term view of it, dialysis would have huge cost and quality of life benefits. The consistency with the other trials on cardiovascular death and heart failure on the MACE (Major Adverse Cardiovascular Events) cardiovascular death, MI stroke is also very encouraging, and as you noted, there were both people with prior cardiovascular disease, about half and half were primary prevention, and Ken Mahaffey just presented this, equal benefit in the primary and secondary benefit groups.
Dr. Cannon:	22:25	And so, to have these prospective data reaffirming all the things we've seen, but then really putting an exclamation point on the renal benefit introduces, this is really the first thing since ACE and ARB therapy that can prevent progression to renal failure. This really ratchets up, and I think the ADA is in the process of writing the updated recommendation regarding, we already put

		in the 2019 document strong consideration of SGLT-2 for renal benefit.
Dr. Cannon:	22:57	But, now we've got it where it might become really a Class I, you should do this for patients with evidence of albuminuria and CKD. But that recommendation is being worked on and will come as one of those updates.
Dr. Eckel:	23:11	Well, one thing that was comforting at a CREDENCE, the drug was canagliflozin and the amputation risk and the risk for bone disease, et cetera, was not seen in that trial. That provides a little bit more comfort for prescribing physicians. In the REWIND study using dulaglutide, which had a primary outcome that was also favorable, and that was a lesser risk population also.
Dr. Eckel:	23:32	I think we can start to be more comfortable and at least in a moderately high-risk patient without known atherosclerotic cardiovascular disease of using these agents to effectively manage their CVD risk in addition to their glycemia.
Dr. Cannon:	23:46	It's a very key point. Cardiovascular risk is really a spectrum, and it makes sense that the highest risk patients, you'll see the biggest benefit, but we now do see benefit in both these classes. The GLP-1 and SGLT-2s in the primary prevention population. It is a key thing that we want to think about, turning to these classes earlier than we otherwise might have.
Dr. Eckel:	24:13	I'm trying to put my shoes on as you wear them and think about being a preventive cardiologist, which I kind of am, but I'm not a certified cardiologist, but my clinic's been in the heart center for many, many years now. But, is the cardiology community who is going to be likely more encouraged to consider these therapeutic choices in treatment of type II diabetes, are they ready to take care of diabetic ketoacidosis with a modest increase in plasma glucose or this increasing evidence that may be not only genital infections, but this Fournier gangrene is a really pretty serious disorder?
Dr. Eckel:	24:47	That's rare, but the analysts just published a paper a couple of months ago on 55 cases on SGLT-2s where this occurred. I think, the cardiologist who gets into this area of prescribing needs to be prepared. What are your thoughts about that?
Dr. Cannon:	25:02	I think this is where we will quickly get out of our comfort zone and rely appropriately on a collaboration, and we do this for all the different diseases our patients share. But it becomes our responsibility to help monitor for side effects of drugs that we

		have. We have to be aware of what to look for and what to ask. For men, the genital infections are more in uncircumcised men.
Dr. Cannon:	25:29	For the first time, I'm asking my patients if it's relevant, are they circumcised or not? And, talking about the potential side effect and importance of hygiene if starting an SGLT-2. We have to be aware, communicate some of the risks and how to monitor, but then continue to work together with our primary care and endocrine colleagues.
Dr. Eckel:	25:51	Now, one thing we shouldn't forget, whether it's a primary care physician, you in the cardiology community or us as endocrinologists, we need to have appropriate lipid altering therapy and blood pressure control too. Many patients, obviously, need platelet inhibitors or other antithrombotic therapy.
Dr. Cannon:	26:07	It's a key point, and the number of beneficial classes of drugs that we have is so broad and broadening each year that the embarrassment of riches often leads to our under treatment with some of these things that if you asked us on a test, "Would you use this?" Of course, we'd say yes, but then, in the busy day to day practice, you're managing one thing and you forget about some of the other things.
Dr. Cannon:	26:32	So having sort of the checklist of making sure, "Have I got the lipids, how's the blood pressure? What about renal function?" Antiplatelet therapy, as you note, and making sure that the different bases are covered is a key part of our assessment.
Dr. Cannon:	26:49	In the 2019 guideline, we actually included in the medical history page a new table of what things to summarize in your assessment and plan. Not just the laundry list of things to check in the physical, but to say, "What's the cardiovascular risk? What stage is the kidney disease?"
Dr. Cannon:	27:07	So that, in asking the question, then you can say, "Wait a minute, what therapies do I need to think about that? What are the lipids? Is the patient on a statin? They should be, what's their LDL? Do I need to intensify therapy?"
Dr. Cannon:	27:21	One of the updates that was just added talked about the use of the icosapent ethyl, the omega-3 high-dose preparation for patients with high triglycerides. That's a new class of drugs that's added to the list of things that we need to think about. Running down the list and offering all these beneficial therapies will have big impact for our patients.

Dr. Cannon:	27:47	And so, it's a wonderful opportunity to really maximize their preventive care.
Dr. Eckel:	27:52	The REDUCE-IT trial was quite interesting, and I think we still don't quite understand the mechanism and I think it's important for the prescribing physician to know that ultimately, the triglyceride reduction did not appear to relate to the outcome, so we're looking at other possible mechanisms by which at least that product, icosapent ethyl works.
Dr. Eckel:	28:11	So, let's remind ourselves in concluding here that we need to individualize therapy. I think the ADA and the EASD (European Association for the Study of Diabetes) has for a decade now, approached patient care in patients with type II diabetes, and by the way, type I diabetes too, and individualization.
Dr. Eckel:	28:28	We're taking someone who's older and who may be on insulin and has already known cardiovascular disease, to consider therapy to be a little less aggressive in terms of maintenance of a lower level of A1C, and in patients who are younger and recently diagnosed and have no disease, I think that the glycemic control needs to be focused in on more intently up front.
Dr. Eckel:	28:50	What are your thoughts about this individualization in care? I'm sure you do it all the time in cardiology.
Dr. Cannon:	28:56	Yeah, I think those are points of individualizing the goal of glycemic, how strict, but then the individualization by the patient characteristics was really the big new thing in the 2019 standard of care and the EASD locked onto that as well, where you start asking, "Does the patient have atherosclerotic cardiovascular disease? Do they have CKD? What's their heart failure risk? What's their hypoglycemia risk? Do they need weight loss?"
Dr. Cannon:	29:25	Those clinical factors end up driving different class choices in therapy. Using the patient characteristics to drive different classes of therapies is really the big new idea for the guideline and one that will really help get maximum benefit of different and appropriate agents.
Dr. Eckel:	29:45	Right, then that individualization is a balancing act between various components of diabetes care and that relates to weight gain, hypoglycemic risk, cost of medications, and most importantly, clinical trial evidence of what works and what

		appears to be more neutral or potentially carry some negative issues related to its prescribing.
Dr. Eckel:	30:07	Thanks, Dr Chris Cannon, for our conversation here today, and want to thank you as a listening audience for being tuned to this and upcoming podcasts are going to follow. Again, this is Dr. Bob Eckel, Dr. Chris Cannon from the Brigham and Women's in Boston. This is Know Diabetes by Heart™. Thank you for tuning in.